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THE SYNTHESIS OF NITRO- AND AMINO-PHENYLTETRAZOLES

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Recently the synthesis of certain derivatives of 1-alkyl-5-aminotetrazole (1) and of 1-aryl-5-dialkylaminomethyltetrazole (2) has been described. The compounds in these groups appeared to be, respectively, central nervous stimulants (3) and substances showing rather a mixed stimulatory and depressant effect (4) upon the central nervous system. In both instances a rather high degree of potency was achieved, an observation which made it desirable to study the effect of other modes of attachment of the amino group upon the pharmacological action of the tetrazole derivatives.

In an earlier communication (5) the preparation of a number of 1,5-disubstituted tetrazoles was described. When administered in dibutyl succinate solution, the simpler compounds of this type, such as 1-phenyl-5-methyltetrazole and the isomeric 1-methyl-5-phenyltetrazole, exhibited a moderate degree of activity as central nervous stimulants (6), although this effect rapidly disappeared as the size of the alkyl groups was increased. In view of the possibility of enhancing the water-solubility of the resulting compounds, it appeared desirable to attempt the synthesis of a number of aminophenyl substituted tetrazole derivatives. A moderate degree of water-solubility could be anticipated for salts of compounds of this type.

The simplest approach to the synthesis of aminophenyltetrazoles seemed to reside in the reduction of the corresponding nitro compounds. A search of the literature revealed that only few nitrophenyltetrazole derivatives had been described and that still fewer, actually seven, aminophenyltetrazoles were known. Furthermore, most of the known aminophenyltetrazoles were derivatives of the relatively difficultly accessible 2,5-diphenyltetrazole. Wedekind (7) had prepared 2-phenyl-5-*p*-nitrophenyltetrazole by heating N-phenyl-N′-guanyl-C-(*p*-nitrophenyl)-formazan with nitric acid. Reduction of the nitro compound led to 2-phenyl-5-*p*-aminophenyltetrazole. The isomeric 2-aminophenyl-5-phenyltetrazoles were prepared by Ponzio and Macciotta (8) by treatment of the nitrophenylhydrazones of phenylnitroformaldehyde with hydrazine hydrate in alcoholic solution followed by reduction of the nitro derivatives. A number of isomeric 1- and 5-nitrophenyltetrazoles have been prepared by direct nitration of the appropriate phenyltetrazole (9, 10, 11) or by treatment of nitrobenzamidrazones with nitrous acid (12). In several instances (11) the corresponding aminophenyltetrazoles were prepared by reduction of the nitro compound. By

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the interaction of phenyl-*p*-nitrophenyldichloromethane and silver azide Schroeter (13) prepared a compound later shown to be 1-phenyl-5-nitrophenyltetrazole (14).

An interesting synthesis of disubstituted tetrazoles involving the condensation of aromatic diazonium salts with acyl hydrazines was described by Dimroth and de Montmollin (14). An initial condensation of the reactants to form diazohydrazides was followed by conversion of the latter into tetrazole derivatives by treatment with aqueous alkali. The reaction seemed to be rather widely applicable since a variety of diazonium salts were employed as examples and the acyl hydrazines could be derived either from aliphatic or aromatic acids. Among the compounds so prepared were 1-*p*-nitrophenyl-5-methyltetrazole and 1-*p*-nitrophenyl-5-phenyltetrazole.

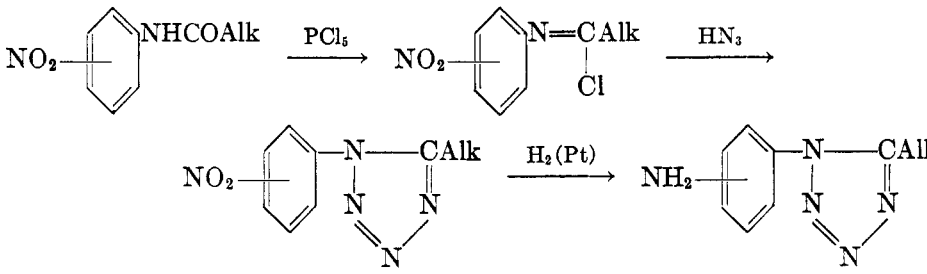
More recently von Braun and Rudolph (15) described a particularly convenient method for the preparation of 1,5-disubstituted tetrazoles which involved the interaction of imide chlorides with hydrazoic acid. A variety of isomeric phenylnitrophenyl- and bisnitrophenyl-tetrazoles were prepared by these authors as

reference compounds for a study of the nitration of 1,5-diphenyltetrazole. It should be observed that von Braun and Rudolph applied this synthesis only to amides in which R′ or both R and R′ represented aromatic groups. Other procedures for the synthesis of 1,5-disubstituted tetrazoles have been summarized by Benson (16).

It has been shown in this laboratory that von Braun's procedure is much more widely applicable than had been indicated. The method is not limited to amides in which R′ is aromatic, but can be applied to amides where either R or R′ is aromatic while the other substituent is aliphatic. In fact, by careful adjustment of the conditions for the first step in the reaction the synthesis can be applied to purely aliphatic amides where both R and R′ represent alkyl groups (5). The method has now been extended to the preparation of several series of isomeric 1-nitrophenyl-5-alkyltetrazoles and 1-alkyl-5-nitrophenyltetrazoles in which either substituent, R or R′, may be an alkyl group while the other substituent is a nitrophenyl group. Imide chlorides were prepared by treatment of the appropriate N-alkyl nitrobenzamides or acyl nitroanilines with phosphorus pentachloride in dry benzene and conversion of these, without isolation, into the desired alkylnitrophenyltetrazoles by treatment with a benzene solution of hydrazoic acid. The positions of the alkyl group and the nitrophenyl group in the formulas may be reversed to give the isomeric series of compounds. We can confirm the observation of von Braun and Rudolph that the orientation of the nitro group (*o*, *m*, or *p*) does not appear to effect the yield of tetrazole.

The corresponding aminophenyltetrazoles could be readily prepared by catalytic hydrogenation of the appropriate nitro compounds at a hydrogen pressure

of two to three atmospheres in the presence of Adams' platinum oxide catalyst. There was no evidence of destruction of the tetrazole ring during the hydrogenation of the nitro compounds comparable to that observed by Roblin, *et al.*,



(17) during the reduction of 5-*p*-nitrobenzenesulfonamidotetrazole. In all cases the reduction proceeded smoothly and rapidly. The isolation of several *o*-aminophenyl derivatives proved to be difficult due to the formation of small amounts of highly pigmented by-products from which they could be separated only with inordinately large losses of the desired products. The aminophenyltetrazoles were further characterized by preparation of their hydrochlorides and acetyl derivatives.

Pharmacological investigations of the alkylaminophenyltetrazoles have been reported elsewhere (18). It is interesting to note that the *p*-aminophenyl derivatives do not appear to be characterized by any outstanding gross pharmacological effects while the *m*-aminophenyl compounds are moderately effective as sedative agents. The 1-*m*-aminophenyl-5-alkyltetrazoles seem to be more active than the isomeric 1-alkyl-5-*m*-aminophenyltetrazoles. In both series the potency increased as the size of the alkyl group was increased; generally, the normal chain compounds were more active than the branched chain compounds of the same molecular weight.

EXPERIMENTAL[4]

Nitrophenylamides. The nitrophenylamides were prepared by standard procedures such as the interaction of the nitrobenzoyl chlorides[5] with various aliphatic primary amines in the presence either of an excess of amine or of pyridine depending upon the availability of the amine. Nitro substituted anilides were prepared from the nitroanilines by interaction with aliphatic acid anhydrides or acid chlorides. The products were purified by crystallization from the solvents indicated in Table I and in two instances after distillation under reduced pressure as noted. A number of the nitrophenylamides prepared as intermediates had not been previously described in the literature. These are listed in Table I together with their physical constants and analytical data.

1,5-Alkylnitrophenyltetrazoles. All the alkylnitrophenyltetrazoles were prepared by essentially the same procedure for which the synthesis of 1-*m*-nitrophenyl-5-isopropyltetrazole may serve as an example. The apparatus and technique employed in the synthesis of tetrazoles from N-substituted amides has been described in detail in an earlier paper (5).

[4] Microanalyses on all compounds were carried out by Mr. William Saschek.

[5] *o*-Nitrobenzoyl chloride was prepared by treatment of *o*-nitrobenzoic acid with thionyl chloride and was used as a crude product after removal of the excess thionyl chloride under reduced pressure. Although the *meta* and *para* isomers can be distilled without difficulty, *o*-nitrobenzoyl chloride decomposes violently at elevated temperatures (19).

TABLE I

N-ALKYL NITROBENZAMIDES AND ACYL NITROANILINES R—NHCO—R′

R	R′	M.P., °C.	YIELD, %	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
m-$NO_2C_6H_4$	C_2H_5	104–104.5	85	99% Isopropyl alc.	$C_9H_{10}N_2O_3$	14.4	14.8
m-$NO_2C_6H_4$	*n*-C_3H_7	59–59.5[d]	74	Ether-petrol. ether	$C_{10}H_{12}N_2O_3$	13.5	13.9
m-$NO_2C_6H_4$	iso-C_3H_7	[a]	86	Methanol	$C_{10}H_{12}N_2O_3$	13.5	13.4
m-$NO_2C_6H_4$	*n*-C_4H_9	67.5–68	68	50% Methanol	$C_{11}H_{14}N_2O_3$	12.6	12.6
o-$NO_2C_6H_4$	iso-C_4H_9	73–73.5	41	Heptane	$C_{11}H_{14}N_2O_3$	12.6	12.8
m-$NO_2C_6H_4$	iso-C_4H_9	95–96[c]	76	Ether-petrol. ether	$C_{11}H_{14}N_2O_3$	12.6	12.5
p-$NO_2C_6H_4$	iso-C_4H_9	126.5–128	86	Toluene	$C_{11}H_{14}N_2O_3$	12.6	12.8
m-$NO_2C_6H_4$	*n*-C_5H_{11}	63–64	80	Ether-petrol. ether	$C_{12}H_{16}N_2O_3$	11.9	11.9
m-$NO_2C_6H_4$	iso-C_5H_{11}	77.5–78.5	85	Toluene-heptane	$C_{12}H_{16}N_2O_3$	11.9	11.9
p-$NO_2C_6H_4$	iso-C_5H_{11}	73–74.5	88	Toluene	$C_{12}H_{16}N_2O_3$	11.9	12.4
m-$NO_2C_6H_4$	$CH(C_2H_5)_2$	122.5–123.5	91	Benzene	$C_{12}H_{16}N_2O_3$	11.9	11.8
m-$NO_2C_6H_4$	*n*-C_6H_{13}	54–55.5	52	Ether-petrol. ether	$C_{13}H_{18}N_2O_3$	11.2	11.2
m-$NO_2C_6H_4$	*n*-C_7H_{15}	69.5–70.5	75	50% Isopropyl alc.	$C_{14}H_{20}N_2O_3$	10.6	10.9
m-$NO_2C_6H_4$	$CH(C_2H_5)C_4H_9$	90.5–91.5	83	Toluene	$C_{14}H_{20}N_2O_3$	10.6	10.6
o-$NO_2C_6H_4$	cyclo-C_6H_{11}	79.5–80.5	85	Toluene-heptane	$C_{13}H_{16}N_2O_3$	11.3	11.2
m-$NO_2C_6H_4$	cyclo-C_6H_{11}	128–129	85	Toluene	$C_{13}H_{16}N_2O_3$	11.3	11.3
p-$NO_2C_6H_4$	cyclo-C_6H_{11}	162–163	80	Toluene	$C_{13}H_{16}N_2O_3$	11.3	11.2
CH_3	*o*-$NO_2C_6H_4$	109–110	48[b]	Toluene	$C_8H_8N_2O_3$	15.6	15.9
n-C_3H_7	*m*-$NO_2C_6H_4$	77–78	76	50% Isopropyl alc.	$C_{10}H_{12}N_2O_3$	13.5	13.3
iso-C_3H_7	*m*-$NO_2C_6H_4$	131–131.5	85	Methanol	$C_{10}H_{12}N_2O_3$	13.5	13.3
n-C_4H_9	*m*-$NO_2C_6H_4$	73–74	90	Methanol	$C_{11}H_{14}N_2O_3$	12.6	12.5
iso-C_4H_9	*o*-$NO_2C_6H_4$	79.5–80.5	68[b]	50% Isopropyl alc.	$C_{11}H_{14}N_2O_3$	12.6	12.6
iso-C_4H_9	*m*-$NO_2C_6H_4$	123–124.5	91	Methanol	$C_{11}H_{14}N_2O_3$	12.6	12.4
iso-C_4H_9	*p*-$NO_2C_6H_4$	121.5–122	68	Methanol	$C_{11}H_{14}N_2O_3$	12.6	12.8

[a] Melts at 95.5–96.5° then solidifies and remelts at 103–104°. Apparently polymorphic since either form can be obtained by appropriate seeding of the saturated solution. [b] Yield based on *o*-nitrobenzoic acid since the acid chloride was not purified. [c] B.p. 207–209° at 2 mm. [d] B.p. 206–207 at 4 mm.

To a suspension of 52 g. (0.25 mole) of *m*-nitroisobutyranilide in 500 ml. of dry benzene 52 g. (0.25 mole) of phosphorus pentachloride was added portionwise during 20–30 minutes with continuous, vigorous stirring. The mixture was stirred for 30 minutes at room temperature after complete addition of the phosphorus pentachloride, or until a clear, homogeneous solution formed after which dry air was drawn through the reaction mixture for a half-hour to remove most of the hydrogen chloride. (In several instances both the amide and the imide chloride were insoluble in benzene at room temperature. Warming the reaction mixture to not above 50° hastened interaction in these cases.) The solution (or suspension) of the imide chloride was then treated with 200 ml. of a 7.5% solution of hydrazoic acid in benzene[6] added portionwise with continuous stirring during 15 minutes. Stirring was continued at room temperature for two hours during which a solid precipitated. The reaction mixture was then slowly warmed to the boiling point and maintained at reflux temperature for two hours. The solid disappeared during the heating period. The solvent was then removed under diminished pressure and the residue was treated with 200 ml. of water. After the careful addition of 200 ml. of concentrated hydrochloric acid, the mixture was boiled under reflux for two hours in order to destroy any unreacted amide which would interfere with the subsequent purification of the product. The tetrazole melted in the boiling, aqueous suspension but solidified on chilling after which it was filtered by suction and washed thoroughly with water. The crude product was crystallized first from 70% aqueous methanol and then from 99% isopropyl alcohol from which it separated as very pale yellow needles, m.p. 115°; yield 51 g., 87%.

In the preparation of tetrazoles from N-alkylnitrobenzamides it was frequently advantageous to reflux the crude product with aqueous sodium hydroxide rather than with aqueous acid to hydrolyze the unreacted amide.

All of the alkylnitrophenyltetrazoles exhibited a pale yellow color even after careful purification. Their physical properties together with pertinent analytical data are recorded in Table II.

1,5-Alkylaminophenyltetrazoles. This group of compounds was prepared by the catalytic hydrogenation of the corresponding nitrophenyltetrazoles. The preparation of 1-*m*-aminophenyl-5-isopropyltetrazole is described as an example of the reduction of a nitrophenyltetrazole.

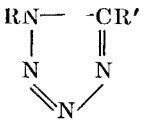
To a solution of 11.7 g. (0.05 mole) of 1-*m*-nitrophenyl-5-isopropyltetrazole in 100 ml. of glacial acetic acid, 0.1 g. of Adams' platinum oxide catalyst was added. Reduction was carried out in a Burgess-Parr low pressure hydrogenation apparatus at an initial pressure of 50 lbs./sq. in., and was complete in about 40 minutes. After removal of the catalyst, the solution was evaporated to dryness under reduced pressure on a water-bath. The residual material was taken up in 200 ml. of hot water containing about 5 ml. of concentrated hydrochloric acid, boiled for a few minutes, chilled, and filtered to remove a small amount of insoluble material. The clear filtrate was made distinctly alkaline to litmus by addition of concentrated aqueous ammonia and again thoroughly chilled before filtering off the precipitated product and washing the latter with cold water. The crude base was recrystallized first from 75% methanol and then from 99% isopropyl alcohol from which it separated as colorless needles, m.p. 103–103.5°. The yield was 9.2 g. (90%).

In some instances the nitrophenyltetrazoles, especially when the alkyl groups were small, were not completely soluble in glacial acetic acid at room temperature. In such instances the solid was pulverized and suspended in glacial acetic acid together with the catalyst. Reduction proceeded smoothly and the solid dissolved rapidly as hydrogenation progressed. This technique was also successful in the preparation of larger amounts of the aminophenyltetrazoles in the limited volume of solvent that could be used in the hydrogenation apparatus. The reduction of 0.2–0.25 mole of the nitrophenyltetrazoles could be conveniently

[6] Solutions of hydrazoic acid in benzene can be prepared conveniently by the method of von Braun (20). Because of its toxic character reactions involving hydrazoic acid should be carried out in a good hood.

TABLE II

ALKYLNITROPHENYLTETRAZOLES

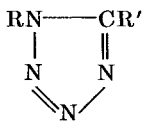


R	R′	M.P., °C.	YIELD, %	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
o-$NO_2C_6H_4$	CH_3	116.5–117	47	Benzene	$C_8H_7N_5O_2$	34.1	34.1
m-$NO_2C_6H_4$	CH_3	148–150	57	87% Isopropyl alc.	$C_8H_7N_5O_2$	34.1	33.8
p-$NO_2C_6H_4$	CH_3	130–133	58	87% Isopropyl alc.	$C_8H_7N_5O_2$	34.1	34.2
m-$NO_2C_6H_4$	C_2H_5	120–122	66	87% Isopropyl alc.	$C_9H_9N_5O_2$	32.0	32.1
m-$NO_2C_6H_4$	*n*-C_3H_7	55–56	47	60% Isopropyl alc.	$C_{10}H_{11}N_5O_2$	30.0	29.9
m-$NO_2C_6H_4$	iso-C_3H_7	115	87	99% Isopropyl alc.	$C_{10}H_{11}N_5O_2$	30.0	30.0
m-$NO_2C_6H_4$	*n*-C_4H_9	oil	63[a]	—	$C_{11}H_{13}N_5O_2$	28.3	—
o-$NO_2C_6H_4$	iso-C_4H_9	108–109	65	Toluene-heptane	$C_{11}H_{13}N_5O_2$	28.3	28.3
m-$NO_2C_6H_4$	iso-C_4H_9	80.5–81	85	90% Methanol	$C_{11}H_{13}N_5O_2$	28.3	28.3
p-$NO_2C_6H_4$	iso-C_4H_9	89.5–90.5	84	99% Isopropyl alc.	$C_{11}H_{13}N_5O_2$	28.3	28.3
m-$NO_2C_6H_4$	*n*-C_5H_{11}	51–51.5	70	99% Isopropyl alc.	$C_{12}H_{15}N_5O_2$	26.8	26.7
m-$NO_2C_6H_4$	iso-C_5H_{11}	41–41.5	70	99% Isopropyl alc.	$C_{12}H_{15}N_5O_2$	26.8	26.4
p-$NO_2C_6H_4$	iso-C_5H_{11}	oil	78[a]	—	$C_{12}H_{15}N_5O_2$	26.8	—
m-$NO_2C_6H_4$	$CH(C_2H_5)_2$	77.5–78.5	65	Benzene-heptane	$C_{12}H_{15}N_5O_2$	26.8	27.0
m-$NO_2C_6H_4$	*n*-C_6H_{13}	52–53	80	99% Isopropyl alc.	$C_{13}H_{17}N_5O_2$	25.4	25.8
m-$NO_2C_6H_4$	*n*-C_7H_{15}	33–34	51	99% Isopropyl alc.	$C_{14}H_{19}N_5O_2$	24.2	24.1
m-$NO_2C_6H_4$	$CH(C_2H_5)C_4H_9$	oil	85[a]	—	$C_{14}H_{19}N_5O_2$	24.2	—
o-$NO_2C_6H_4$	cyclo-C_6H_{11}	138–139	41	Benzene	$C_{13}H_{15}N_5O_2$	25.6	25.7
m-$NO_2C_6H_4$	cyclo-C_6H_{11}	135–136	88	99% Isopropyl alc.	$C_{13}H_{15}N_5O_2$	25.6	25.9
p-$NO_2C_6H_4$	cyclo-C_6H_{11}	113.5–114.5	81	99% Isopropyl alc.	$C_{13}H_{15}N_5O_2$	25.6	26.1
CH_3	*o*-$NO_2C_6H_4$	89–90	77	Toluene-heptane	$C_8H_7N_5O_2$	34.1	33.6
CH_3	*m*-$NO_2C_6H_4$	146–148	60	87% Isopropyl alc.	$C_8H_7N_5O_2$	34.1	34.1
CH_3	*p*-$NO_2C_6H_4$	123–126	72	87% Isopropyl alc.	$C_8H_7N_5O_2$	34.1	34.3
C_2H_5	*m*-$NO_2C_6H_4$	88–88.5	38	87% Isopropyl alc.	$C_9H_9N_5O_2$	32.0	31.9
n-C_3H_7	*m*-$NO_2C_6H_4$	61.5–62	68	60% Isopropyl alc.	$C_{10}H_{11}N_5O_2$	30.0	30.0
iso-C_3H_7	*m*-$NO_2C_6H_4$	111–112	90	90% Methanol	$C_{10}H_{11}N_5O_2$	30.0	30.1
n-C_4H_9	*m*-$NO_2C_6H_4$	oil	83[a]	—	$C_{11}H_{13}N_5O_2$	28.3	—
iso-C_4H_9	*o*-$NO_2C_6H_4$	106.5–107	87	99% Isopropyl alc.	$C_{11}H_{13}N_5O_2$	28.3	28.2
iso-C_4H_9	*m*-$NO_2C_6H_4$	82–83.5	89	75% Isopropyl alc.	$C_{11}H_{13}N_5O_2$	28.3	28.4
iso-C_4H_9	*p*-$NO_2C_6H_4$	108–108.5	81	99% Isopropyl alc.	$C_{11}H_{13}N_5O_2$	28.3	28.5

[a] Crude product.

TABLE III

ALKYLAMINOPHENYLTETRAZOLES

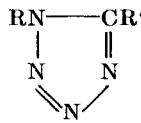


R	R′	M.P., °C.	YIELD, %	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
o-$NH_2C_6H_4$	CH_3	102.5–103.5	40	Water	$C_8H_9N_5$	40.0	39.8
m-$NH_2C_6H_4$	CH_3	122–124	69	Water	$C_8H_9N_5$	40.0	39.9
p-$NH_2C_6H_4$	CH_3	146.5–147	63	Water	$C_8H_9N_5$	40.0	40.3
m-$NH_2C_6H_4$	C_2H_5	114–114.5	90	Water	$C_9H_{11}N_5$	37.0	37.4
m-$NH_2C_6H_4$	*n*-C_3H_7	124.5–125	78	Water	$C_{10}H_{13}N_5$	34.5	34.5
m-$NH_2C_6H_4$	iso-C_3H_7	103–103.5	90	99% Isopropyl alc.	$C_{10}H_{13}N_5$	34.5	34.6
m-$NH_2C_6H_4$	*n*-C_4H_9	112.5–113.5	73	Water	$C_{11}H_{15}N_5$	32.2	32.4
m-$NH_2C_6H_4$	iso-C_4H_9	87.5–88	51	50% Methanol	$C_{11}H_{15}N_5$	32.2	32.1
p-$NH_2C_6H_4$	iso-C_4H_9	106.5–107.5	78	90% Methanol	$C_{11}H_{15}N_5$	32.2	32.3
m-$NH_2C_6H_4$	*n*-C_5H_{11}	98–99	73	99% Isopropyl alc.	$C_{12}H_{17}N_5$	30.3	30.7
m-$NH_2C_6H_4$	iso-C_5H_{11}	102–103	75	99% Isopropyl alc.	$C_{12}H_{17}N_5$	30.3	30.6
p-$NH_2C_6H_4$	iso-C_5H_{11}	oil	85[a]	—	$C_{12}H_{17}N_5$	30.3	—
m-$NH_2C_6H_4$	$CH(C_2H_5)_2$	139–140	65	99% Isopropyl alc.	$C_{12}H_{17}N_5$	30.3	30.4
m-$NH_2C_6H_4$	*n*-C_6H_{13}	76–77	95	50% Isopropyl alc.	$C_{13}H_{19}N_5$	28.6	28.5
m-$NH_2C_6H_4$	*n*-C_7H_{15}	96–96.5	77	Toluene-heptane	$C_{14}H_{21}N_5$	27.0	26.9
m-$NH_2C_6H_4$	$CH(C_2H_5)C_4H_9$	139–140	77	99% Isopropyl alc.	$C_{14}H_{21}N_5$	27.0	27.0
m-$NH_2C_6H_4$	cyclo-C_6H_{11}	158–159	96	75% Isopropyl alc.	$C_{13}H_{17}N_5$	28.8	28.7
p-$NH_2C_6H_4$	cyclo-C_6H_{11}	152.5–153	86	75% Isopropyl alc.	$C_{13}H_{17}N_5$	28.8	29.0
CH_3	*o*-$NH_2C_6H_4$	94	68	Benzene	$C_8H_9N_5$	40.0	39.8
CH_3	*m*-$NH_2C_6H_4$	157–159	51	Water	$C_8H_9N_5$	40.0	39.9
CH_3	*p*-$NH_2C_6H_4$	157–158	69	Water	$C_8H_9N_5$	40.0	40.0
C_2H_5	*m*-$NH_2C_6H_4$	119.5–120.5	71	Water	$C_9H_{11}N_5$	37.0	37.0
n-C_3H_7	*m*-$NH_2C_6H_4$	90–91	87	Water	$C_{10}N_{13}N_5$	34.5	34.5
iso-C_3H_7	*m*-$NH_2C_6H_4$	81.5–82.5	50	50% Methanol	$C_{10}H_{13}N_5$	34.5	34.5
n-C_4H_9	*m*-$NH_2C_6H_4$	87–88	58	Water	$C_{11}H_{15}N_5$	32.2	32.3
iso-C_4H_9	*o*-$NH_2C_6H_4$	oil	85[a]	—	$C_{11}H_{15}N_5$	32.2	—
iso-C_4H_9	*m*-$NH_2C_6H_4$	88–88.5	63	50% Isopropyl alc.	$C_{11}H_{15}N_5$	32.2	32.4
iso-C_4H_9	*p*-$NH_2C_6H_4$	119–120	65	Methanol	$C_{11}H_{15}N_5$	32.2	32.3

[a] Crude product.

TABLE IV

HYDROCHLORIDES AND ACETYL DERIVATIVES OF THE ALKYLAMINOPHENYLTETRAZOLES



R	R′	HYDROCHLORIDES				ACETYL DERIVATIVES			
		M.p., °C.	Formula	N		M.p., °C.	Formula	N	
				Calc'd	Found			Calc'd	Found
o-$NH_2C_6H_4$	CH_3	190–192 d.	$C_8H_{10}ClN_5$	33.1	33.0	139.5–140	$C_{10}H_{11}N_5O$	32.2	32.1
m-$NH_2C_6H_4$	CH_3	202–203 d.	$C_8H_{10}ClN_5$	33.1	32.6	170–171	$C_{10}H_{11}N_5O$	32.2	31.8
p-$NH_2C_6H_4$	CH_3	197–198 d.	$C_8H_{10}ClN_5$	33.1	32.8	146–147	$C_{10}H_{11}N_5O$	32.2	32.4
m-$NH_2C_6H_4$	C_2H_5	187–188 d.	$C_9H_{12}ClN_5$	31.0	31.0	145.5–146.5	$C_{11}H_{13}N_5O$	30.3	30.2
m-$NH_2C_6H_4$	*n*-C_3H_7	170–172	$C_{10}H_{14}ClN_5$	29.2	28.8	140.5–141	$C_{12}H_{15}N_5O$	28.6	28.4
m-$NH_2C_6H_4$	iso-C_3H_7	[a]	$C_{10}H_{14}ClN_5$	29.2	29.0	152.5–153.5	$C_{12}H_{15}N_5O$	28.6	28.5
m-$NH_2C_6H_4$	*n*-C_4H_9	143–144[b]	$C_{11}H_{16}ClN_5$	27.6	27.3	111–112	$C_{13}H_{17}N_5O$	27.0	27.0
m-$NH_2C_6H_4$	iso-C_4H_9	150–152	$C_{11}H_{16}ClN_5$	27.6	27.3	126.5–127.5	$C_{13}H_{17}N_5O$	27.0	26.9
p-$NH_2C_6H_4$	iso-C_4H_9	193–195 d.	$C_{11}H_{16}ClN_5$	27.6	27.4	111–112	$C_{13}H_{17}N_5O$	27.0	26.8
m-$NH_2C_6H_4$	*n*-C_5H_{11}	161–162	$C_{12}H_{18}ClN_5$	26.2	26.0	81–82	$C_{14}H_{19}N_5O$	25.6	25.4
m-$NH_2C_6H_4$	iso-C_5H_{11}	176–178	$C_{12}H_{18}ClN_5$	26.2	26.0	108–109	$C_{14}H_{19}N_5O$	25.6	25.6
p-$NH_2C_6H_4$	iso-C_5H_{11}	189–191	$C_{12}H_{18}ClN_5$	26.2	26.1	114–115	$C_{14}H_{19}N_5O$	25.6	25.3
m-$NH_2C_6H_4$	$CH(C_2H_5)_2$	—	—	—	—	188–189	$C_{14}H_{19}N_5O$	25.6	25.4
m-$NH_2C_6H_4$	*n*-C_6H_{13}	155–157	$C_{13}H_{20}ClN_5$	24.9	24.9	93–94	$C_{15}H_{21}N_5O$	24.4	24.2
m-$NH_2C_6H_4$	*n*-C_7H_{15}	161–162	$C_{14}H_{22}ClN_5$	23.7	23.8	94–95	$C_{16}H_{23}N_5O$	23.2	23.0
m-$NH_2C_6H_4$	$CH(C_2H_5)C_4H_9$	—	—	—	—	120.5–121	$C_{16}H_{23}N_5O$	23.2	23.1
m-$NH_2C_6H_4$	cyclo-C_6H_{11}	122–124[b]	$C_{13}H_{18}ClN_5$	25.0	25.0	196–197	$C_{15}H_{19}N_5O$	24.6	24.3
p-$NH_2C_6H_4$	cyclo-C_6H_{11}	179–181	$C_{13}H_{18}ClN_5$	25.0	25.1	96–97[c]	$C_{15}H_{19}N_5O$	24.6	24.3
CH_3	*o*-$NH_2C_6H_4$	202–204 d.	$C_8H_{10}ClN_5$	33.1	33.2	120–121	$C_{10}H_{11}N_5O$	32.2	32.4
CH_3	*m*-$NH_2C_6H_4$	207–208 d.	$C_8H_{10}ClN_5$	33.1	33.2	173–174	$C_{10}H_{11}N_5O$	32.2	32.2
CH_3	*p*-$NH_2C_6H_4$	207–208 d.	$C_8H_{10}ClN_5$	33.1	33.5	208–209	$C_{10}H_{11}N_5O$	32.2	32.2
C_2H_5	*m*-$NH_2C_6H_4$	218–220 d.	$C_9H_{12}ClH_5$	31.0	30.6	108–109	$C_{11}H_{13}N_5O$	30.3	30.4
n-C_3H_7	*m*-$NH_2C_6H_4$	188–190 d.	$C_{10}H_{14}ClN_5$	29.2	29.1	143–143.5	$C_{12}H_{15}N_5O$	28.6	28.5
iso-C_3H_7	*m*-$NH_2C_6H_4$	224–225 d.	$C_{10}H_{14}ClN_5$	29.2	28.9	80.5–81.5	$C_{12}H_{15}N_5O$	28.6	28.5
n-C_4H_9	*m*-$NH_2C_6H_4$	116–117	$C_{11}H_{16}ClN_5$	27.6	27.6	98–99	$C_{13}H_{17}N_5O$	27.0	26.9
iso-C_4H_9	*o*-$NH_2C_6H_4$	160–162	$C_{11}H_{16}ClN_5$	27.6	27.5	118–119	$C_{13}H_{17}N_5O$	27.0	27.0
iso-C_4H_9	*m*-$NH_2C_6H_4$	197–199 d.	$C_{11}H_{16}ClN_5$	27.6	27.5	105–106	$C_{13}H_{17}N_5O$	27.0	26.9
iso-C_4H_9	*p*-$NH_2C_6H_4$	169–170	$C_{11}H_{16}ClN_5$	27.6	27.2	76–77[c]	$C_{13}H_{17}N_5O$	27.0	27.2

[a] Crystallizes from 95% isopropyl alcohol as a monohydrate, m.p. 90–92°. Anhydrous, m.p. 125–126°. [b] Crystallizes from 95% isopropyl alcohol-ether as monohydrate. Melting point for anhydrous product given. [c] Melting point of a monohydrate given.

handled in this manner but required refilling of the hydrogen reservoir during the hydrogenation.

The aminophenyltetrazoles were usually accompanied by small amounts of colored by-products that could be removed easily by adsorption on charcoal during the recrystallization. Occasionally the colored by-products appeared to be present in larger amount and persisted even after several treatments with charcoal. The speed with which reduction was completed seemed to influence the amount of colored materials since they were bothersome only when reduction had been slow. Generally the colored impurities could be removed by boiling an aqueous acid solution of the aminophenyltetrazole for a few minutes with a few granules of zinc.

The aminophenyltetrazoles prepared in this manner are listed in Table III where their melting points, solvents used for recrystallization and analytical data are also recorded.

Hydrochlorides of the aminophenyltetrazoles were prepared by treating solutions of the bases in absolute isopropyl alcohol with a slight excess of concentrated hydrochloric acid. In most instances the hydrochlorides crystallized from this solvent, but when they failed to do so the addition of ether usually sufficed to induce crystallization of the salt.

Acetyl derivatives were prepared by boiling the bases with acetic anhydride. Generally acetylation was complete within a few minutes, but a few bases required prolonged boiling with acetic anhydride for complete acetylation.

Melting points and analytical data for the hydrochlorides and acetyl derivatives are recorded in Table IV.

SUMMARY

1. A series of N-alkylnitrobenzamides and acyl nitroanilines has been prepared to serve as intermediates for the synthesis of a group of tetrazole derivatives.

2. The von Braun tetrazole synthesis has been extended to include the preparation of a variety of 1,5-alkyl-nitrophenyltetrazoles from N-alkyl nitrobenzamides and acyl nitroanilines.

3. A group of 1,5-alkyl-aminophenyltetrazoles has been prepared by the catalytic hydrogenation of the corresponding nitrophenyltetrazoles. Hydrochlorides and acetyl derivatives of the new aminophenyltetrazoles are described.

4. In the compounds under consideration the nitro group was more susceptible to hydrogenation than the tetrazole ring. No evidence of rupture of the tetrazole ring was observed during hydrogenation.

5. The aminophenyltetrazoles have been subjected to pharmacological testing and a brief statement of their action is included.

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