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HALOALKYLTETRAZOLE AND AMINOALKYLTETRAZOLE DERIVATIVES

EDWARD K. HARVILL[1], ROBERT M. HERBST,[2] AND ELIZABETH G. SCHREINER[3]

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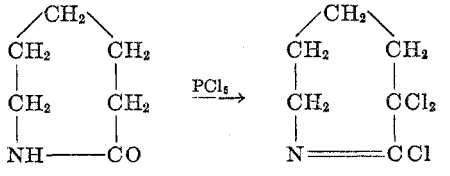
A previous communication from this laboratory described the preparation of a series of 1-alkyl-5-alkylaminotetrazoles (1), a group of compounds characterized by a more or less profound central nervous stimulatory action (2) but which failed to exhibit the respiratory stimulation essential to true analeptic agents. Earlier work with 1,5-dialkyltetrazoles (3, 4) had led to several compounds with pronounced analeptic action whose usefulness was, however, limited by a lack of water-solubility. To explore the possibility of producing water-soluble compounds by the introduction of a salt-forming group the preparation of a number of 1,5-disubstituted tetrazoles was undertaken in which an alkylated amino group was introduced in the *alpha* position of an alkyl substituent at position 5 of the tetrazole nucleus.

The preparation of 1,5-disubstituted tetrazoles can be accomplished easily by treating the imide chlorides of N-substituted amides with hydrazoic acid under anhydrous conditions (3). The direct application of this procedure to the synthesis of tetrazoles with a substituted amino group on the *alpha* carbon atom of the 5-alkyl substituent would require as intermediates the N-substituted amides of a series of *alpha* amino acids. Much more attractive was the possibility of synthesizing a group of 5-haloalkyltetrazoles which would permit the preparation of a variety of mono- and di-alkylamino derivatives from a single intermediate.

The literature failed to reveal descriptions of any tetrazole derivatives with a halogen-substituted alkyl group in the 5 position, although von Braun and Rudolph (5) have described a 1-methyl-5-*p*-bromomethylphenyltetrazole which they obtained by bromination of 1-methyl-5-*p*-tolyltetrazole. Bromination studies of 1,5-disubstituted tetrazoles with an alkyl group in position 5 have not been reported. The formation of an α-dichloro-imino chloride by treatment of the lactam of ϵ-aminocaproic acid with phosphorus pentachloride at elevated temperature has been claimed (6). Treatment of this compound with sodium azide led, apparently, to a chlorine-substituted pentamethylenetetrazole from which the chlorine was removed by reduction.



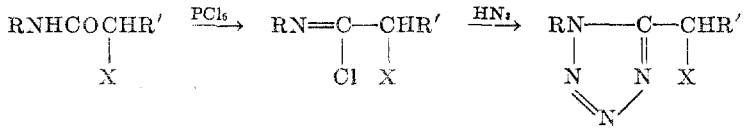
[1] Present address: Ernst Bischoff Company, Inc., Ivoryton, Connecticut.

[2] Present address: Kedzie Chemical Laboratory, Michigan State College, East Lansing, Michigan.

[3] Present address: E. Merck, Inc., Rahway, New Jersey.

As intermediates for the synthesis of a group of 5-haloalkyltetrazoles a number of N-substituted α- and β-haloacid amides was prepared by interaction of various α- and β-haloacid chlorides with different primary amines. In general, when primary aromatic amines were employed best results were obtained by addition of the haloacid chloride to a benzene solution or suspension of an equimolar amount of the amine followed by heating the mixture under reflux until the reaction was complete as evidenced by the cessation of hydrogen chloride evolution. When pyridine or an excess of the amine was used to take up the hydrogen chloride formed in the reaction, it was frequently difficult to separate the ammonium salt from the amide except by prolonged periods of digestion with water. In Table I are listed the N-substituted haloacid amides prepared in the course of this work. It should be pointed out that many of these compounds are irritants, some of which cause painful cracking of the skin and swelling of the hands. Even minute amounts of dust such as might result from grinding small samples for melting-point determinations sufficed in some instances to cause annoying irritation of the nasal passages and a burning sensation of the eyelids.

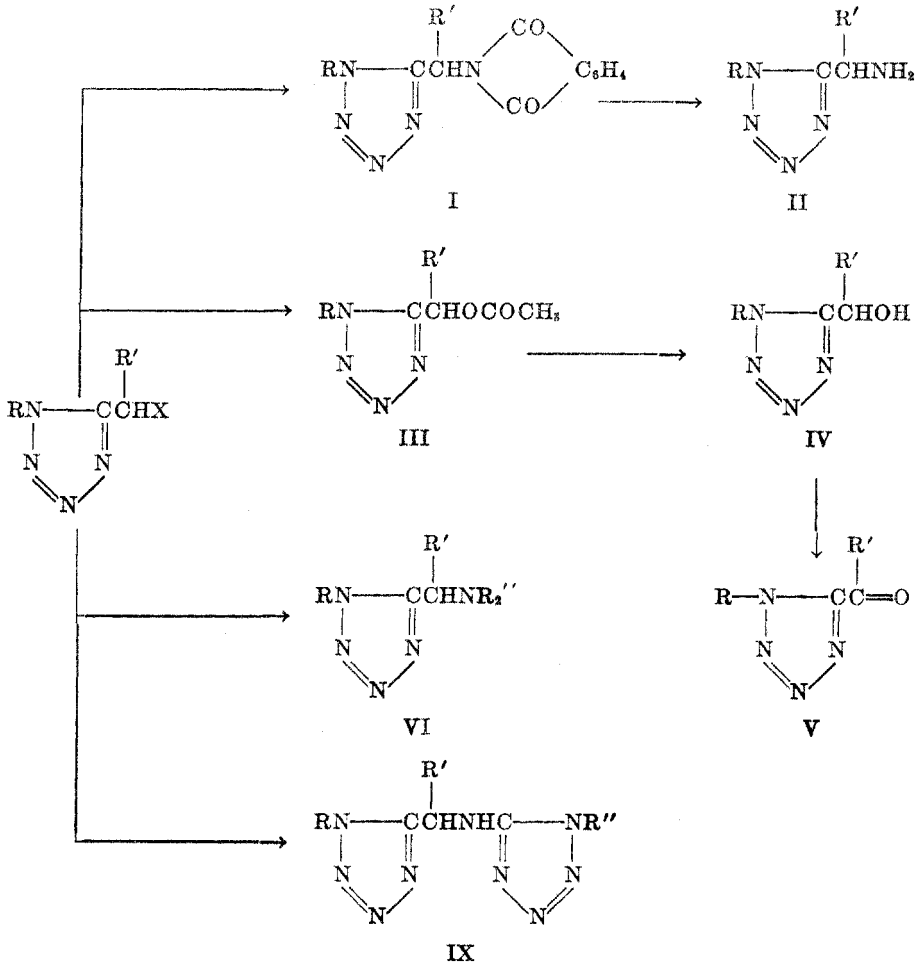
The N-substituted haloacid amides were converted into the corresponding 1-substituted 5-haloalkyltetrazoles by treatment successively with phosphorus pentachloride and hydrazoic acid in benzene solution (3, 7). It had been indicated by von Braun and coworkers that the imide chlorides formed from the anilides of aliphatic acids were quite unstable (8, 9) and that they could be isolated only when derived from anilides in which the aromatic residue contained an *ortho* substituent as, for instance, the *o*-toluidides, *o*-chloranilides, and *o*-bromoanilides (10). It was suggested that the rearrangement and self-condensation of the imide chlorides was inhibited by steric hindrance attributed to the *ortho* substituent. It might be concluded from von Braun's work that only the imide chlorides derived from N-substituted benzamides are stable; that those derived from anilides are stable only when the proximity of other ring substituents exerts a stabilizing effect. Although we have not attempted to isolate the imide chlorides in any instance, it has been our observation that these intermediates, even when formed from anilides, are sufficiently stable in benzene solution or suspension to permit their preparation and use in synthetic procedures. The results of our experiments also indicate that the halogen of the imide chloride linkage is very much more reactive than the halogen attached to the *alpha* or *beta* carbon of the acyl group. In no instance were there any indications of interaction between hydrazoic acid and the *alpha* or *beta* halogen. All of the haloalkyltetrazoles prepared during the course of this work are listed in Table II. Most of the compounds were irritants and care should be exercised when handling them to avoid contact with the skin.



The 5-haloalkyltetrazole derivatives exhibited the characteristic behavior of alkyl halides in their reactions and permitted the preparation of a variety of substituted tetrazole derivatives of hitherto unknown types. It has been possible by interaction with potassium phthalimide to form the anticipated phthalimido derivatives (I) which could in turn be hydrolyzed to the corresponding primary amines (II). With potassium acetate acetoxy derivatives (III) were formed easily. The latter could be hydrolyzed without difficulty to the corresponding alcohols (IV) and acetic acid. When the substituent in the 5 position was a chloromethyl group, tetrazoles with a primary alcohol group in that position resulted from this sequence of reactions. If the 5 substituent was a 1-haloethyl group, secondary alcohols were formed and the latter could be oxidized to tetrazolyl methyl ketones (V). Interaction of the chloroalkyltetrazoles with *p*-nitrophenol in alkaline medium led to the anticipated *p*-nitrophenoxymethyl derivatives. By interaction with various primary and secondary amines the haloalkyltetrazoles were readily converted into a variety of secondary and tertiary aminoalkyltetrazoles (VI). An interesting sequence of reactions took place when 1-cyclohexyl-5-chloromethyltetrazole was heated with 2-methylamino-6-methyl-5-heptene. Apparently the initial reaction involved alkylation of the secondary amino group. When the resulting tertiary amine (VII) hydrochloride was heated in aqueous acid solution, hydration of the unsaturated linkage in the aliphatic substituent occurred with the formation of an amino alcohol (VIII). This behavior is completely analogous to the hydration of 2-methylamino-6-methyl-5-heptene in aqueous acid solution with the formation of 2-methylamino-6-hydroxy-6-methylheptane (27).

With 5-aminotetrazole derivatives typical exothermic reactions took place on heating (1) with the formation of tetrazolylaminoalkyltetrazole derivatives (IX). A typical dehydrohalogenation reaction was also observed with the formation of a 5-isobutenyl tetrazole derivative (XI) when 1-phenyl-5-(1-bromo-2-methylpropyl)tetrazole (X) was heated with a number of different secondary amines. The dehydrohalogenation was due in part to the reactivity of the hydrogen on an adjacent tertiary carbon atom since neither the 5-(1-haloethyl)- nor the 5-(2-haloethyl)-tetrazole derivatives were observed to undergo dehydrohalogenation under similar conditions.

Particular emphasis was placed upon the preparation of compounds of the type shown in formula VI in view of the probable water-solubility of salts of products of this general structure (11). In Tables III–VI are listed the compounds of this type prepared during the course of this work. The general action of most of these compounds upon intraperitoneal administration to albino rats has been described (12). The effects ranged from almost purely depressant to purely stimulatory while a mixed stimulatory and depressant action was reported in many instances. An attempt to associate ultraviolet absorption spectra and resonance effects with pharmacological activity in this group has been made (13), but insufficient data are given in the published results to permit a critical evaluation of the conclusions.



I

II

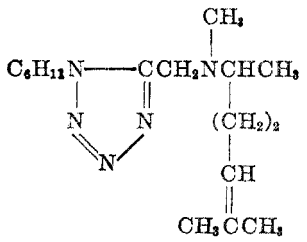
III

IV

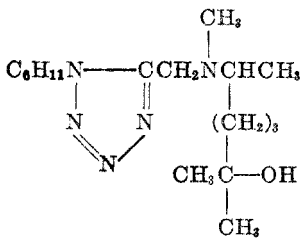
V

VI

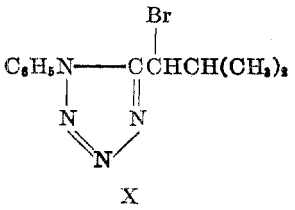
IX



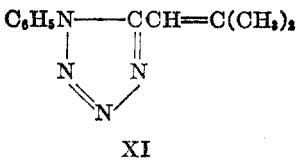
VII



VIII



X



XI

EXPERIMENTAL[4, 5]

N-SUBSTITUTED HALOACID AMIDES

The *haloacid amides* were prepared by standard procedures involving the interaction of primary amines and haloacid chlorides. Details for the preparation of several new compounds will illustrate the techniques employed. Physical constants for all the haloacid amides and analytical data for the new compounds are recorded in Table I. Most of these compounds are irritants and should be handled with suitable precautions.

3-Chloroacetylaminophenanthrene. (*Method A*) A solution of 11.5 g. (0.06 mole) of 3-aminophenanthrene (28, 29) and 5.1 g. (0.06 mole) of pyridine in 125 ml. of benzene was treated with 7.3 g. (0.06 mole) of chloroacetyl chloride. The mixture was stirred continuously until the heat of reaction was dissipated after which an equal volume of water was added and the benzene was removed under diminished pressure. The insoluble amide was filtered from the water layer and recrystallized twice from a mixture of toluene and heptane.

Liquid haloacid amides were purified by distillation under diminished pressure of the residue remaining upon evaporation of the benzene solution.

N-Cyclohexyl-α-chloropropionamide. (*Method B*) α-Chloropropionyl chloride (102 g., 0.8 mole) was added dropwise with stirring and cooling to a solution of 158 g. (1.6 moles) of cyclohexylamine in 1 l. of benzene. After completion of the reaction the mixture was diluted with water and the benzene was removed by distillation under reduced pressure. The water-insoluble amide was recrystallized from aqueous methanol.

m-Nitro-β-chloropropionanilide. (*Method C*) *m*-Nitroaniline (145 g., 1.05 moles) was suspended in a solution of 150 g. (1.18 moles) of β-chloropropionyl chloride in 1 l. of benzene and boiled under reflux until hydrogen chloride evolution ceased. The solvent was then removed under diminished pressure. The residual material, which solidified on cooling and scratching, was recrystallized twice from 70% methanol.

In similar reactions involving chloroacetyl chloride and α-bromopropionyl bromide these reagents should be added slowly to the solution or suspension of the amine in benzene.

5-HALOALKYLTETRAZOLES[6]

In general the preparation of the 1-substituted 5-haloalkyltetrazoles involved the treatment of the appropriate N-substituted haloacid amide first with phosphorus pentachloride and then with hydrazoic acid in benzene as a diluent. The preparation of several compounds of this type is described to provide typical examples of the procedures employed. All the haloalkyltetrazoles are listed in Table II together with analytical data, physical constants, and other pertinent data. The haloalkyltetrazoles are *irritants* and should be handled with proper precautions to avoid contact with the skin or mucous membranes.

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[4] Micro-analyses were done on all compounds by Mr. William Saschek.

[5] Melting points were determined in open capillary tubes; temperatures are corrected.

[6] In view of the toxicity of hydrazoic acid all operations involving this substance should be carried out in a good hood with suitable precautions to avoid inhalation of the vapors. Solutions of hydrazoic acid in benzene can be made conveniently by adding concentrated sulfuric acid slowly to a cooled and well stirred mixture of equal weights of sodium azide and water under a layer of benzene. The concentration of the benzene-hydrazoic acid solution is dependent on the amount of sodium azide and the volume of benzene. After separation of the benzene layer and drying over sodium sulfate the hydrazoic acid concentration is determined by titration with standard sodium hydroxide solution using phenolphthalein as indicator.

TABLE I

N-SUBSTITUTED HALOACID AMIDES

AMIDES	METHOD	M.P. (B.P.), °C.	YIELD, %	CRYSTALLIZED FROM	REF.	FORMULA	N	
							Calc'd	Found
N-Methylchloroacetamide	A	(112/14 mm.)	22	—	19	—	—	—
N-Isoamylchloroacetamide	A	(122/11 mm.)	80	—	—	$C_7H_{14}ClNO$	8.5	8.2
Chloroacetanilide	B	131.5–133.5	60	Benzene-methanol	16	—	—	—
N-Cyclohexylchloroacetamide	B	108–109	42	2-Propanol	—	$C_8H_{14}ClNO$	8.0	7.9 8.0
m-Nitrochloroacetanilide	A	101–102	77	75% Methanol	22	—	—	—
p-Nitrochloroacetanilide	C	184–185	62	Methanol	18	—	—	—
Chloroacet-*p*-toluidide	A	163	55	50% 2-Propanol	26	—	—	—
N-Benzylchloroacetamide	B	93–94.5	39	Benzene	21	—	—	—
Chloroacet-α-naphthalide	C	163	42	80% Methanol	17	—	—	—
Chloroacet-β-naphthalide	C	120–121	53	Toluene	20	—	—	—
o-Phenylchloroacetanilide	A	101–103	84	Methanol	—	$C_{14}H_{12}ClNO$	5.7	5.8
p-Phenylchloroacetanilide	C	181–182	83	2-Propanol	—	$C_{14}H_{12}ClNO$	5.7	5.6
Chloroacetyl-3-aminophenanthrene	A	182–183	92	Heptane-toluene	—	$C_{16}H_{12}ClNO$	5.2	5.3

α-Chloropropionanilide	B	90–92	86	Heptane	24	—	—	—
N-Cyclohexyl-α-chloropropionamide	B	105–106.5	75	Methanol	—	$C_9H_{16}ClNO$	7.4	6.9
m-Nitro-α-chloropropionanilide	C	90–92	66	2-Propanol	—	$C_9H_9ClN_2O_3$	12.3	12.6
p-Nitro-α-chloropropionanilide	C	138.5–140	83	Benzene	—	$C_9H_9ClN_2O_3$	12.3	12.6
α-Chloropropio-α-naphthalide	C	146.5–147.5	72	2-Propanol	—	$C_{13}H_{12}ClNO$	6.0	6.2
α-Chloropropio-β-naphthalide	C	154–156	80	Benzene	—	$C_{13}H_{12}ClNO$	6.0	6.3
α-Bromopropionanilide	B	101–102	95	70% Methanol	15	—	—	—
N-Cyclohexyl-α-bromopropionamide	B	131–132	76	55% Methanol	—	$C_9H_{16}BrNO$	6.1	5.9
m-Nitro-α-bromopropionanilide	C	110–112	64	Methanol	23	—	—	—
p-Nitro-α-bromopropionanilide	C	148–152	75	2-Propanol	23	—	—	—
α-Bromopropio-α-naphthalide	C	157.5–159	62	Methanol	15	—	—	—
β-Chloropropionanilide	B	119.5–120.5	79	Propylene chloride	25	—	—	—
m-Nitro-β-chloropropionanilide	C	95–97	77	70% Methanol	—	$C_9H_9ClN_2O_3$	12.3	12.6
α-Bromoisovaleranilide	B	113	51	Ether-petroleum ether	14	—	—	—

TABLE II

HALOALKYL TETRAZOLES

TETRAZOLE	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	FORMULA	N	
					Calc'd	Found
1-Methyl-5-chloromethyl	34	65–66.5	Ether	$C_3H_5ClN_4$	42.3	42.1
1-Isoamyl-5-chloromethyl	48	[a]	—	$C_7H_{13}ClN_4$	[a]	
1-Phenyl-5-chloromethyl	90	76–77	Methanol	$C_8H_7ClN_4$	28.8	29.1[b]
1-Cyclohexyl-5-chloromethyl	80	108.5–109	75% Methanol	$C_8H_{13}ClN_4$	27.9	27.9[c]
1-*m*-Nitrophenyl-5-chloromethyl	73	117.5–118	Propylene chloride	$C_8H_6ClN_5O_2$	29.2	29.3
1-*p*-Nitrophenyl-5-chloromethyl	70	120–121	2-Propanol	$C_8H_6ClN_5O_2$	29.2	29.4
1-Benzyl-5-chloromethyl	52	67–68	Heptane-2-propanol	$C_9H_9ClN_4$	26.9	26.6
1-α-Naphthyl-5-chloromethyl	48	103–104	70% Methanol	$C_{12}H_9ClN_4$	22.9	22.8[d]
1-β-Naphthyl-5-chloromethyl	66	80–82.5	Methanol	$C_{12}H_9ClN_4$	22.9	22.8
1-*o*-Diphenyl-5-chloromethyl	51	99–100	Heptane-2-propanol	$C_{14}H_{11}ClN_4$	20.7	20.3
1-*p*-Diphenyl-5-chloromethyl	72	150.5–151.5	2-Propanol	$C_{14}H_{11}ClN_4$	20.7	20.7
1-(3-Phenanthryl)-5-chloromethyl	56	131.5–133	Toluene-heptane	$C_{16}H_{11}ClN_4$	19.0	19.0
1-Phenyl-5-(1-chloroethyl)	72	96–97	2-Propanol	$C_9H_9ClN_4$	26.9	26.6
1-Cyclohexyl-5-(1-chloroethyl)	71	124.5–125.5	2-Propanol	$C_9H_{15}ClN_4$	26.1	26.1

1-*m*-Nitrophenyl-5-(1-chloroethyl)	59	150–152	Benzene	$C_9H_8ClN_5O_2$	27.6	27.3
1-*p*-Nitrophenyl-5-(1-chloroethyl)	14	121–122.5	2-Propanol	$C_9H_8ClN_5O_2$	27.6	27.6
1-*α*-Naphthyl-5-(1-chloroethyl)	60	104.5–105.5	Methanol	$C_{13}H_{11}ClN_4$	21.7	21.5
1-*β*-Naphthyl-5-(1-chloroethyl)	73	96.5–97.5	2-Propanol	$C_{13}H_{11}ClN_4$	21.7	21.1
1-Phenyl-5-(1-bromoethyl)	88	96–97.5	Methanol	$C_9H_9BrN_4$	22.1	22.1[e]
1-Cyclohexyl-5-(1-bromoethyl)	38	125.5–126.5	75% Methanol	$C_9H_{15}BrN_4$	21.8	23.4[f]
1-*m*-Nitrophenyl-5-(1-bromoethyl)	63	160–161.5	Benzene	$C_9H_8BrN_5O_2$	23.5	23.4
1-*p*-Nitrophenyl-5-(1-bromoethyl)	90	124–125.5	Methanol	$C_9H_8BrN_5O_2$	23.5	23.8
1-*α*-Naphthyl-5-(1-bromoethyl)	55	110–111	Methanol	$C_{13}H_{11}BrN_4$	18.5	18.2
1-*m*-Nitrophenyl-5-(2-chloroethyl)	67	95.5–96.5	Methanol	$C_9H_8ClN_5O_2$	27.6	27.6
1-Phenyl-5-(1-bromo-2-methylpropyl)	86	72.5–73.5	Ether-pet. ether	$C_{11}H_{13}BrN_4$	19.9	20.2[g]

[a] B.P. 163–165° at 4.5 mm. Calc'd: Cl, 18.8. Found: Cl, 18.4. [b] Calc'd: C, 49.5; H, 3.6. Found: C, 49.4; H, 3.8. [c] Calc'd: C, 48.0; H, 6.5. Found: C, 48.0; H, 6.5. [d] Calc'd: C, 59.0; H, 3.7. Found: C, 59.1; H, 3.9. [e] Calc'd: C, 42.7; H, 3.6. Found: C, 43.4;H, 3.5. [f] Repeated crystallizations did not improve the analyses. Possibly contaminated with the chloro derivative or partially hydrolyzed to the hydroxyderivative. [g] Calc'd: C, 47.0; H, 4.6. Found: C, 47.0; H. 4.8.

1-Phenyl-5-chloromethyltetrazole. Phosphorus pentachloride (72 g., 0.35 mole) was added in portions with stirring and cooling to a suspension of 56 g. (0.33 mole) of chloroacetanilide in 500 ml. of dry benzene. The initially vigorous reaction, accompanied by hydrogen chloride evolution, was complete in 45 minutes after which about one-half of the solvent was evaporated under diminished pressure on a warm (50°) water-bath. A solution of 23 g. (0.53 mole) of hydrazoic acid in 350 ml. of benzene was then added in portions with cooling and stirring. The mixture was allowed to stand overnight after which it was heated slowly to reflux temperature and maintained there for three hours or until evolution of hydrogen chloride was complete. The solvent was then removed under reduced pressure. The residue was treated with about 500 g. of ice and after the ice had melted the aqueous suspension was boiled under reflux for half an hour. The product was extracted from the cooled suspension with benzene and the extract was dried over sodium sulfate before the solvent was evaporated under diminished pressure. The residue solidified on cooling and was recrystallized twice from methanol.

1-β-Naphthyl-5-chloromethyltetrazole. A suspension of 81 g. (0.37 mole) of chloroacet-β-naphthalide in 1 l. of benzene was treated with 80 g. (0.38 mole) of phosphorus pentachloride added portionwise with stirring. No heat was evolved on mixing the reactants and hydrogen chloride was evolved only slowly as the reactants gradually dissolved. When a clear solution had formed, the hydrogen chloride was expelled by warming the reaction mixture gently under diminished pressure. The reaction with hydrazoic acid followed the procedure of the preceding example.

1-p-Nitrophenyl-5-(1-bromoethyl)tetrazole. To a solution of 130 g. (0.48 mole) of *p*-nitro-α-bromopropionanilide in 1 l. of benzene 100 g. (0.48 mole) of phosphorus pentachloride was added portionwise with stirring. Complete interaction was achieved only after stirring and gently warming the mixture for four hours when a clear solution resulted. The reaction with hydrazoic acid was done as in the preceding examples.

1-m-Nitrophenyl-5-(2-chloroethyl)tetrazole. A suspension of 75 g. (0.33 mole) of *m*-nitro-β-chloropropionanilide in 1 l. of benzene was treated with 69 g. (0.33 mole) of phosphorus pentachloride added in several portions with vigorous stirring. The reactants dissolved rapidly to form a clear solution. Without removing hydrogen chloride a solution of 16 g. (0.37 mole) of hydrazoic acid in 200 ml. of benzene was added after which the reaction was completed as previously described.

REACTIONS OF THE HALOALKYLTETRAZOLES

1-Phenyl-5-phthalimidomethyltetrazole. A mixture of 25 g. of 1-phenyl-5-chloromethyltetrazole and 25 g. of potassium phthalimide in 250 ml. of xylene was boiled under reflux for six hours. The phthalimido derivative crystallized from the clear, hot, filtered xylene solution. By recrystallization from toluene the product was obtained as small, coarse prisms, m.p. 142–144°, yield 33 g.

Anal. Calc'd for $C_{16}H_{11}N_5O_2$: N, 22.9. Found: N, 23.2.

1-Phenyl-5-aminomethyltetrazole hydrochloride. 1-Phenyl-5-phthalimidomethyltetrazole (28 g.) was hydrolyzed in boiling 48% hydrobromic acid solution. Phthalic acid separated from the hydrolysate on cooling and was removed. The clear solution was evaporated to dryness, the residue was treated with aqueous sodium hydroxide, and the base was extracted with benzene. The base remained as a liquid on evaporation of the benzene and was converted into the hydrochloride in a 99% isopropyl alcohol solution with dry hydrogen chloride. The *hydrochloride* separated as the *monohydrate* on crystallization from 95% isopropyl alcohol, m.p. 211–212° with decomposition, yield 12.5 g.

Anal. Calc'd for $C_8H_{10}ClN_5 \cdot H_2O$: H_2O, 7.8. Found: H_2O, 7.6.

Calc'd for $C_8H_{10}ClN_5$: N, 33.2. Found: N, 33.1.

1-Cyclohexyl-5-phthalimidomethyltetrazole. A mixture of 30 g. of 1-cyclohexyl-5-chloromethyltetrazole and 30 g. of potassium phthalimide in 350 ml. of xylene was boiled under reflux for three hours. The reaction appeared to be quite rapid during the early stages and much of the material dissolved. The hot suspension was filtered to remove potassium chlo-

ride and the product separated from the filtrate on cooling. After several recrystallizations from xylene a pure product was obtained, yield 36.5 g., m.p. 174.5–175.5°.

Anal. Calc'd for $C_{16}H_{17}N_5O_2$: N, 22.5. Found: N, 22.6.

1-Cyclohexyl-5-aminomethyltetrazole. A suspension of 8 g. of 1-cyclohexyl-5-phthalimidomethyltetrazole in 100 ml. of 48% hydrobromic acid was boiled under reflux for four hours. Phthalic acid was filtered from the cooled reaction mixture after which the solution was evaporated to dryness. The residue of *hydrobromide* was crystallized from 99% isopropyl alcohol. Yield 5.5 g., m.p. 244° with decomposition.

Anal. Calc'd for $C_8H_{16}BrN_5$: N, 26.7. Found: N, 26.1.

The liquid *base* liberated from the hydrobromide was converted into the hydrochloride in 99% isopropyl alcohol with dry hydrogen chloride. The *hydrochloride* was recrystallized from 99% isopropyl alcohol, m.p. 231° with decomposition.

Anal. Calc'd for $C_8H_{16}ClN_5$: N, 32.3. Found: N, 32.3.

1-Cyclohexyl-5-acetoxymethyltetrazole. A mixture of 25 g. of 1-cyclohexyl-5-chloromethyltetrazole and 15 g. of potassium acetate was boiled under reflux for two hours in 100 ml. of glacial acetic acid. The solution was evaporated to dryness under diminished pressure and the residue was suspended in water and neutralized with sodium bicarbonate. The crude ester was extracted from the aqueous suspension with benzene and the benzene solution was again evaporated to dryness. The residue crystallized on cooling and was recrystallized first from heptane-ethyl acetate and then from ether-petroleum ether from which it separated as massive prisms, m.p. 48–49°, yield 17 g.

Anal. Calc'd for $C_{10}H_{16}N_4O_2$: N, 25.0. Found: N, 25.1.

1-Cyclohexyl-5-hydroxymethyltetrazole. A suspension of 11 g. of 1-cyclohexyl-5-acetoxymethyltetrazole in 150 ml. of 10% sodium hydroxide solution was boiled under reflux for five hours. The resulting solution was evaporated to about one-third of its volume when the alcohol crystallized on cooling. The alcohol was recrystallized from ether, yield 4 g., m.p. 100–100.5°.

Anal. Calc'd for $C_8H_{14}N_4O$: N, 30.8. Found: N, 30.8.

1-Cyclohexyl-5-p-nitrophenoxymethyltetrazole. p-Nitrophenol (13.9 g.) and 20 g. of 1-cyclohexyl-5-chloromethyltetrazole were added to 2.3 g. of sodium in 100 ml. of absolute methanol. The solution was heated under reflux for six hours during which a copious precipitate formed. After cooling and diluting with two volumes of water the insoluble product was separated and recrystallized first from methanol and then from toluene. Yield 7 g., m.p. 154–155°; (7 g. of the chloromethyltetrazole was also recovered).

Anal. Calc'd for $C_{14}H_{17}N_5O_3$: N, 23.1. Found N, 23.0.

1-Phenyl-5-(1-hydroxyethyl)tetrazole. A mixture of 41 g. of 1-phenyl-5-(1-chloroethyl)-tetrazole and 25 g. of fused sodium acetate in 100 ml. of ethanol was boiled under reflux for eight hours. The reaction mixture was evaporated to dryness under reduced pressure, the residue was suspended in water, and the crude acetoxy derivative was extracted with ether. On evaporation of the dried ether solution the acetoxy derivative remained as a viscous liquid that could not be induced to crystallize. Saponification of 20 g. of the crude acetoxy derivative with 10% aqueous sodium hydroxide liberated the alcohol which was extracted from the hydrolysate with benzene. Evaporation of the benzene extract left a solid that was crystallized first from a 99% isopropyl alcohol-heptane mixture, then from xylene, and finally from an ethyl acetate-heptane mixture. Yield 10.5 g., m.p. 108–109°.

Anal. Calc'd for $C_9H_{10}N_4O$: N, 29.5. Found: N, 29.5, 29.8.

1-m-Nitrophenyl-5-acetoxymethyltetrazole. A mixture of 23 g. of 1-*m*-nitrophenyl-5-chloromethyltetrazole and 10 g. of potassium acetate in 50 ml. of glacial acetic acid was heated under reflux for five hours. After evaporation of the solvent under diminished pressure, the residual material was suspended in water and the product extracted with benzene. The benzene extract was washed first with sodium bicarbonate solution and then with water and evaporated to dryness. The solid residue was recrystallized twice from toluene. Yield 16 g., m.p. 86.5–87.5°.

Anal. Calc'd for $C_{10}H_9N_5O_4$: N, 26.6. Found: N, 26.8.

1-m-Nitrophenyl-5-hydroxymethyltetrazole. A solution of 15 g. of 1-*m*-nitrophenyl-5-acetoxymethyltetrazole in 200 ml. of methanol and 20 ml. of concentrated hydrochloric acid was boiled under reflux for three hours after which about one-half of the solvent was evaporated. On chilling the product separated as dense prisms that could be recrystallized from water. Yield 10.5 g., m.p. 154–155°.

Anal. Calc'd for $C_8H_7N_5O_3$: N, 31.7. Found: N, 31.5.

1-m-Aminophenyl-5-hydroxymethyltetrazole. Hydrogenation of 10 g. of 1-*m*-nitrophenyl-5-hydroxymethyltetrazole was carried out in glacial acetic acid solution in the presence of Adams' platinum oxide catalyst at an initial hydrogen pressure of 50 p.s.i. After complete reduction of the nitro group the acetic acid solution was evaporated to dryness, the residue taken up in dilute hydrochloric acid, and the base liberated and taken up in ether. The ethereal solution, after drying, was treated with dry hydrogen chloride and the precipitated hydrochloride was twice recrystallized from 99% isopropyl alcohol. Yield of *hydrochloride* 4.5 g., m.p. 231–232° with decomposition.

Anal. Calc'd for $C_8H_{10}ClN_5O$: C, 42.2; H, 4.4; N, 30.8.
Found: C, 42.0; H, 4.4; N, 30.4.

1-Cyclohexyl-5-(1-acetoxyethyl)tetrazole. A mixture of 25 g. of 1-cyclohexyl-5-(1-bromoethyl)tetrazole and 10 g. of fused sodium acetate in 100 ml. of glacial acetic acid was boiled under reflux for five hours. A copious precipitate gradually separated from the hot, initially clear solution. The solvent was removed under diminished pressure and the residue was suspended in water, neutralized with sodium bicarbonate solution, and the product taken up in benzene. After removal of the solvent from the benzene extract the residual material was crystallized first from ether, then from ether-petroleum ether, and finally from heptane. Yield 15 g., m.p. 54–57°.

Anal. Calc'd for $C_{11}H_{18}N_4O_2$: N, 23.5. Found: N, 23.7.

1-Cyclohexyl-5-(1-hydroxyethyl)tetrazole. A solution of 13 g. of 1-cyclohexyl-5-(1-acetoxyethyl)tetrazole in a mixture of 100 ml. of methanol, 15 ml. of water, and 5 g. of sodium hydroxide was boiled under reflux for 2.5 hours. The clear solution was evaporated to dryness under diminished pressure, the residue suspended in water and the insoluble product extracted with benzene. After evaporation of the benzene, the product was crystallized from ether-petroleum ether. Yield 5 g., m.p. 91–92.5°.

Anal. Calc'd for $C_9H_{16}N_4O$: N, 28.6. Found: N, 28.5.

1-Cyclohexyl-5-acetyltetrazole. 1-Cyclohexyl-5-(1-hydroxyethyl)tetrazole (5 g.) was oxidized in aqueous solution with potassium dichromate and sulfuric acid. The product was extracted from the reaction mixture with ether and crystallized from ether by addition of petroleum ether. Yield 3 g., m.p. 71–72°.

Anal. Calc'd for $C_9H_{14}N_4O$: C, 55.7; H. 7.3; N, 28.9.
Found: C, 55.8; H, 7.5; N, 29.0.

1-Cyclohexyl-5-(1'-cyclohexyltetrazolyl-5'-aminomethyl)tetrazole. A mixture of 8.4 g. of 1-cyclohexyl-5-aminotetrazole (1) and 10 g. of 1-cyclohexyl-5-chloromethyltetrazole was heated in an oil-bath at 150–160°. The mixture melted partially and then resolidified. Heating was continued for an hour after apparent interaction ceased. The crude *hydrochloride* was recrystallized twice from 70% isopropyl alcohol. Yield 9 g., m.p. 251° with decomposition.

Anal. Calc'd for $C_{15}H_{26}ClN_9$: C, 49.0; H, 7.1; N, 34.3.
Found: C, 48.7; H, 7.2; N, 34.4.

The *base* was liberated from a small quantity of the hydrochloride and treated with phenyl isothiocyanate to form the *phenylthiourea derivative*, m.p. 162–163°.

Anal. Calc'd for $C_{22}H_{30}N_{10}S$: N, 30.0. Found: N, 30.3.

1-Cyclohexyl-5-(1'-ethyltetrazolyl-5'-aminomethyl)tetrazole. An intimate mixture of 5.7 g. of 1-ethyl-5-aminotetrazole (1) and 10 g. of 1-cyclohexyl-5-chloromethyltetrazole was heated at 150° in an oil-bath. Just below this temperature a homogeneous melt was formed followed by an exothermic reaction during which the mixture solidified again. Heating was continued for half an hour after the exothermic reaction subsided. The crude hydrochloride

TABLE III

1-ALKYL-5-AMINOMETHYLTETRAZOLES

TETRAZOLE	COMPOUND ISOLATED	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
1-Methyl-5-diethylaminomethyl	Base	35	[a]	—	$C_7H_{15}N_5$	41.4	41.3[a]
1-Isoamyl-5-(1-piperidyl)methyl	Hydrochloride	48	166–166.5	Ethyl acetate-2-propanol	$C_{12}H_{24}ClN_5$	25.6	25.4[b]
1-Cyclohexyl-5-allylaminomethyl	Hydrochloride	78	175.5–176	2-Propanol-ether	$C_{11}H_{20}ClN_5$	27.2	26.9
1-Cyclohexyl-5-*n*-propylaminomethyl	Hydrochloride	40	210 dec.	2-Propanol	$C_{11}H_{22}ClN_5$	27.0	26.5
1-Cyclohexyl-5-cyclohexylaminomethyl	Base	90	83–84	Heptane	$C_{14}H_{25}N_5$	26.6	26.4
	Acetyl	—	121–122	Water	$C_{16}H_{27}N_5O$	22.9	22.7
	Phenylthiourea	—	130.5–131.5	Xylene	$C_{21}H_{30}N_6S$	21.1	20.8
1-Cyclohexyl-5-(N-allyl-N-2-heptylaminomethyl)	Base	45	[c]	—	$C_{18}H_{33}N_5$	21.9	22.2[c]
1-Cyclohexyl-5-(N-methyl-N-2-phenyl-*n*-propylaminomethyl)	Base	—		2-Propanol	$C_{18}H_{27}N_5$	22.4	22.5
	Hydrochloride	52	191–192 d.	2-Propanol	$C_{18}H_{28}ClN_5$	20.0	20.1
1-Cyclohexyl-5-dimethylaminomethyl	Base	76	60–61.5	Heptane	$C_{10}H_{19}N_5$	33.5	33.6
	Hydrochloride	—	198–198.5	2-Propanol	$C_{10}H_{20}ClN_5$	28.5	28.6
1-Cyclohexyl-5-(N-methyl-N-2-(6-hydroxy-6-methylheptyl)aminomethyl)	Base	53	80–81	Benzene-pet. ether	$C_{17}H_{33}N_5O$	21.7	21.5
	Hydrochloride	—	172.5–173.5 d.	2-Propanol-ether	$C_{17}H_{34}ClN_5O$	19.5	19.6
1-Benzyl-5-diethylaminomethyl	Hydrochloride	70	145–146	Ethyl acetate-2-propanol	$C_{13}H_{20}ClN_5$	24.9	24.8

[a] B.P. 134–136° at 2.5 mm. Calc'd: C, 49.7; H, 8.9. Found: C, 49.5; H, 9.1. [b] Calc'd: C, 52.8; H, 8.8. Found: C, 52.8; H, 8.7. [c] B.P. 191–193° at 3 mm. Calc'd: C, 67.7; H, 10.3. Found: C, 67.7; H, 10.5.

TABLE IV

1-PHENYL-5-AMINOALKYLTETRAZOLES

TETRAZOLE	COMPOUND ISOLATED	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
1-Phenyl-5-methylaminomethyl	Hydrochloride	45	226–227 d.	Aqueous acetone	$C_9H_{12}ClN_5$	31.0	30.9
1-Phenyl-5-ethylaminomethyl	Hydrochloride	80	206 d.	2-Propanol	$C_{10}H_{14}ClN_5$	29.2	29.2
	Phenylthiourea	—	80–83	Propylene chloride	$C_{17}H_{18}N_6S$	24.8	25.2
1-Phenyl-5-isopropylaminomethyl	Hydrochloride	79	151.5–152.5	2-Propanol	$C_{11}H_{16}ClN_5$	27.6	27.2
	Phenylthiourea	—	135–136	Propylene chloride	$C_{18}H_{20}N_6S$	23.9	24.1
1-Phenyl-5-allylaminomethyl	Hydrochloride	78	189–190 d.	2-Propanol	$C_{11}H_{14}ClN_5$	27.8	27.5
	Phenylthiourea	—	65–68	Benzene	$C_{18}H_{18}N_6S$	24.5	24.8
1-Phenyl-5-isobutylaminomethyl	Hydrochloride	71	167–168 d.	Acetone	$C_{12}H_{18}ClN_5$	26.2	26.0
	Phenylthiourea	—	137–138	Propylene chloride	$C_{19}H_{22}N_6S$	22.9	22.7
1-Phenyl-5-isoamylaminomethyl	Hydrochloride	21	143–144 d.	Acetone	$C_{13}H_{20}ClN_5$	24.5	24.2
1-Phenyl-5-benzylaminomethyl	Hydrochloride	90	218.5 d.	2-Propanol	$C_{15}H_{16}ClN_5$	23.2	23.3
	Phenylthiourea	—	141.5	Propylene chloride	$C_{22}H_{20}N_6S$	21.0	21.0
1-Phenyl-5-(2-hydroxyethylaminomethyl)	Hydrochloride	58	150–151 d.	2-Propanol	$C_{10}H_{14}ClN_5O$	27.4	27.0
1-Phenyl-5-[2-(1-hydroxybutyl)aminomethyl]	Base	72	117–118	Water	$C_{12}H_{17}N_5O$	28.4	28.5
	Phenylthiourea	—	132–134	Propylene chloride	$C_{19}H_{22}N_6OS$	22.0	21.6

1-Phenyl-5-diethylaminomethyl.....	Base	87	[a]	—	$C_{12}H_{17}N_5$	—	—
	Hydrochloride	—	162–162.5	Ethyl acetate-2-propanol	$C_{12}H_{18}ClN_5$	26.2	25.9
1-Phenyl-5-(1-piperidyl)methyl.....	Base	62	90.5–91.5	Ether	$C_{13}H_{17}N_5$	28.8	29.1[b]
	Hydrochloride	—	[g]	2-Propanol	$C_{13}H_{18}ClN_5$	25.1	24.9
1-Phenyl-5-(4-morpholinyl)methyl.....	Base	60	96–97	Ether	$C_{12}H_{15}N_5O$	28.6	28.9
1-Phenyl-5-(N-ethyl-N-phenylaminomethyl).....	Base	75	72.5–73.5	2-Propanol-pet. ether	$C_{16}H_{17}N_5$	25.1	25.2[c]
1-Phenyl-5-[N-methyl-N-(2-heptyl)-aminomethyl].....	Hydrochloride	21	145–146 d.	Ethyl acetate-2-propanol	$C_{17}H_{28}ClN_5$	20.7	20.6[d]
1-Phenyl-5-(1-methylaminoethyl).....	Hydrochloride	70	195–196 d.	2-Propanol	$C_{10}H_{14}ClN_5$	29.2	29.2
	Phenylthiourea	—	138–139	Propylene chloride	$C_{17}H_{18}N_6S$	24.8	25.1
1-Phenyl-5-(1-diethylaminoethyl).....	Hydrochloride	63	156–157 d.	Acetone-ether	$C_{13}H_{20}ClN_5$	24.9	24.8
1-Phenyl-5-[1-(1-piperidyl)ethyl].....	Base	38	74.5–76	Benzene-pet. ether	$C_{14}H_{19}N_5$	27.2	27.2[e]
1-Phenyl-5-[1-(4-morpholinyl)ethyl].....	Base	66	80–81	Ether	$C_{13}H_{17}N_5O$	27.0	27.4
	Hydrochloride	—	177–178 d.	Ethyl acetate-2-propanol	$C_{13}H_{18}ClN_5O$	23.7	23.4
1-Phenyl-5-(2-diethylaminoethyl).....	Base	49	[f]	—	$C_{13}H_{19}N_5$	28.6	28.8

[a] B.P. 181° at 3 mm. [b] Calc'd: C, 64.2; H, 7.0. Found: C, 64.0; H, 6.9. [c] Calc'd: C, 68.8; H, 6.1. Found: C, 68.6; H, 6.0. [d] Calc'd: C, 60.5; H, 8.3. Found: C, 60.5; H, 8.2. [e] Calc'd: C, 65.4; H, 7.4. Found: C, 65.5; H, 7.6. [f] B.P. 176–178° at 3 mm. [g] Crystallizes as a monohydrate, m.p. 124–125°; anhydrous, m.p. 200° with decomposition.

was recrystallized first from 50% isopropyl alcohol and then from 70% isopropyl alcohol from which it separated as colorless needles, m.p. 234° with decomposition, yield 7.5 g.

Anal. Calc'd for $C_{11}H_{20}ClN_9$: N, 40.2. Found: N, 40.3.

The *base* was liberated from a small quantity of the hydrochloride and treated with phenyl isothiocyanate to form the *phenylthiourea derivative*, m.p. 164–165°.

Anal. Calc'd for $C_{18}H_{24}N_{10}S$: N, 34.0. Found: N, 33.9.

1-Phenyl-5-isobutenyltetrazole. A solution of 14 g. of 1-phenyl-5-(1-bromo-2-methylpropyl)tetrazole and 20 ml. of piperidine in 100 ml. of benzene was boiled under reflux for five hours. After removal of the solvent under diminished pressure, the residue was shaken thoroughly with water and the insoluble solid filtered off and air-dried. After two recrystallizations from benzene-petroleum ether 4.5 g. of product was obtained as needles, m.p. 65–66°. The product behaved as an unsaturated compound and decolorized aqueous potassium permanganate solution.

Anal. Calc'd for $C_{11}H_{12}N_4$: N, 28.0. Found: N, 27.9, 28.0.

The same product was also formed when 1-phenyl-5-(1-bromo-2-methylpropyl)tetrazole was heated with dibutylamine and with 2-allylaminoheptane in benzene solution.

Catalytic hydrogenation of the compound converted it into 1-phenyl-5-isobutyltetrazole, m.p. 55–56°, which proved to be identical with a sample prepared by an independent method of synthesis (3).

5-ALKYLAMINOALKYLTETRAZOLES

A large number of tetrazole derivatives substituted in the 1 position with alkyl or aryl groups and in the 5 position with a variety of secondary and tertiary alkylaminoalkyl groups was prepared. Although these compounds were all prepared by the same type of reaction, the interaction of an alkyl halide with a primary or a secondary amine, the conditions for this reaction were subject to variation in specific instances. A number of specific examples have been selected and described in detail to illustrate the techniques employed. Analytical data, physical constants, and other pertinent data for all the amines, their hydrochlorides, and other derivatives are collected in Tables III–VI.

1-Methyl-5-diethylaminomethyltetrazole. A solution of 18 g. of 1-methyl-5-chloromethyltetrazole and 30 ml. of diethylamine in 300 ml. of benzene was boiled under reflux for four hours. Benzene and unreacted amine were removed by distillation after the addition of an equal volume of water. The aqueous solution was made strongly alkaline with sodium hydroxide and evaporated to a small volume to remove excess diethylamine. The product was extracted from the aqueous suspension with ether, dried over potassium carbonate, and distilled under diminished pressure.

1-Cyclohexyl-5-dimethylaminomethyltetrazole. A solution of 20 g. of 1-cyclohexyl-5-chloromethyltetrazole in 150 ml. of benzene was boiled gently under reflux for six hours while a slow stream of dimethylamine was passed into the solution continuously. On completion of the reaction an equal volume of water was added and benzene and unreacted amine were removed by distillation. The aqueous solution was made distinctly acid to Congo Red with hydrochloric acid and decolorized with charcoal. The base was liberated from the clear solution, taken up in ether, and dried over potassium carbonate. On evaporation of the solvent the residual base solidified and could be recrystallized from heptane.

1-Cyclohexyl-5-cyclohexylaminomethyltetrazole. A mixture of 20 g. of 1-cyclohexyl-5-chloromethyltetrazole, 39 g. of cyclohexylamine, and 9.5 g. of sodium bicarbonate was heated to 120–125° and maintained at that temperature for three hours. Frothing during the heating period was probably due to carbon dioxide evolution. The reaction mixture was dissolved in an aqueous citric acid solution and filtered to remove insoluble material. The filtrate was made alkaline and steam-distilled to remove unreacted cyclohexylamine. On cooling the non-volatile, insoluble product solidified and was recrystallized from heptane. On treatment of the base with acetic anhydride an acetyl derivative was formed; with phenyl isothiocyanate a *phenylthiourea* derivative was formed.

TABLE V

1-SUBSTITUTED PHENYL-5-AMINOALKYLTETRAZOLES

TETRAZOLE	COMPOUND ISOLATED	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
1-*p*-Tolyl-5-diethylaminomethyl	Base	58	[a]	—	$C_{13}H_{19}N_5$	28.5	28.1
1-*p*-Methoxyphenyl-5-diethylaminomethyl	Hydrochloride	67	176.5–177	87% 2-propanol	$C_{13}H_{20}ClN_5O$	23.5	23.3
1-*p*-Hydroxyphenyl-5-diethylaminomethyl	Hydrochloride	45	226–227 d.	Aqueous acetone	$C_{12}H_{18}ClN_5O$	24.7	24.5
1-*m*-Nitrophenyl-5-diethylaminomethyl	Base	64	94.5–96.5	Methanol	$C_{12}H_{16}N_6O_2$	30.4	30.4
1-*p*-Nitrophenyl-5-diethylaminomethyl	Base	80	72–73	Methanol	$C_{12}H_{16}N_6O_2$	30.4	30.6
	Hydrobromide	—	181–182 d.	Ethanol	$C_{12}H_{17}BrN_6O_2$	23.5	23.9
1-*m*-Aminophenyl-5-diethylaminomethyl	Base	77	71–72.5	Acetone-pet. ether	$C_{12}H_{18}N_6$	34.1	34.1
1-*o*-Diphenyl-5-diethylaminomethyl	Hydrochloride	45	151–152	2-Propanol-ether	$C_{18}H_{22}ClN_5$	20.4	20.3
1-*o*-Diphenyl-5-(4-morpholinyl)methyl	Hydrochloride	24	204–205 d.	2-Propanol	$C_{18}H_{20}ClN_5O$	19.6	19.6
1-*p*-Diphenyl-5-diethylaminomethyl	Base	75	86.5–87.5	Aqueous-2-propanol	$C_{18}H_{21}N_5$	22.8	23.0
1-*p*-Diphenyl-5-(1-piperidyl)methyl	Base	67	106.5–107.5	Heptane	$C_{19}H_{21}N_5$	21.9	22.1
1-*p*-Diphenyl-5-(4-morpholinyl)methyl	Base	70	143–144	2-Propanol-heptane	$C_{18}H_{19}N_5O$	21.8	21.9
1-*m*-Nitrophenyl-5-(2-diethylaminoethyl)	Hydrochloride	42	209–210 d.	Methanol-ethyl acetate	$C_{13}H_{19}ClN_6O_2$	25.7	25.6

[a] B.P. 179–180° at 5 mm.

TABLE VI

1-NAPHTHYL AND 1-PHENANTHRYL-5-AMINOALKYLTETRAZOLES

TETRAZOLE	COMPOUND ISOLATED	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
1-α-Naphthyl-5-dimethylaminomethyl	Hydrochloride	34	188–189 d.	2-Propanol	$C_{14}H_{16}ClN_5$	24.2	24.1
1-α-Naphthyl-5-diethylaminomethyl	Base	98	68–69	Heptane	$C_{16}H_{19}N_5$	24.9	24.9
	Hydrochloride	—	190–191 d.	2-Propanol	$C_{16}H_{20}ClN_5$	22.0	22.1
1-α-Naphthyl-5-(1-piperidyl)methyl	Base	72	91–92	Heptane	$C_{17}H_{19}N_5$	23.9	23.9
1-α-Naphthyl-5-(4-morpholinyl)methyl	Base	55	108.5–109.5	Heptane	$C_{16}H_{17}N_5O$	23.7	23.7
1-α-Naphthyl-5-(1-diethylaminoethyl)	Base	23	88.5–89.5	Heptane	$C_{17}H_{21}N_5$	23.7	23.9
1-β-Naphthyl-5-methylaminomethyl	Hydrochloride	51	242–243 d.	Water	$C_{13}H_{14}ClN_5$	25.4	25.0
	Phenylthiourea	—	122–123	Benzene	$C_{20}H_{18}N_6S$	22.5	22.3
1-β-Naphthyl-5-ethylaminomethyl	Base	63	79–80.5	2-Propanol-heptane	$C_{14}H_{15}N_5$	27.7	27.5
	Phenylthiourea	—	114–115	Toluene	$C_{21}H_{20}N_6S$		
1-β-Naphthyl-5-allylaminomethyl	Base	80	76.5–78	Ethanol-heptane	$C_{15}H_{15}N_5$	26.4	26.2
	Hydrochloride	—	205–206	Methanol	$C_{15}H_{16}ClN_5$	23.2	23.0
	Phenylthiourea	—	103–105	Toluene	$C_{22}H_{20}N_6S$	21.0	21.1
1-β-Naphthyl-5-(2-hydroxyethylaminomethyl)	Base	72	105.5–106.5	Ethyl acetate	$C_{14}H_{15}N_5O$	26.0	25.7
	Hydrochloride	—	183–185 d.	2-Propanol	$C_{14}H_{16}ClN_5O$	22.9	23.1
	Phenylthiourea	—	103–105	Xylene	$C_{21}H_{20}N_6OS$	20.8	20.1
1-β-Naphthyl-5-diethylaminomethyl	Hydrochloride	61	151.5–152.5	Acetone-2-propanol	$C_{16}H_{20}ClN_5$	22.0	22.2
1-β-Naphthyl-5-(1-diethylaminoethyl)	Hydrochloride	30	168–169 d.	Ether-2-propanol	$C_{17}H_{22}ClN_5$	21.1	21.0[a]
1-(3-Phenanthryl)-5-diethylaminomethyl	Base	64	119.5–120.5	Methanol	$C_{20}H_{21}N_5$		
	Hydrochloride	—	193–194 d.	2-Propanol	$C_{20}H_{22}ClN_5$	19.0	19.0

[a] Calc'd: C, 61.5; H, 6.6. Found: C, 61.4; H, 6.6.

1-Cyclohexyl-5-[N-methyl-N-2-(6-hydroxy-6-methylheptyl)aminomethyl]tetrazole. An intimate mixture of 20 g. of 1-cyclohexyl-5-chloromethyltetrazole and 45 g. of 2-methylamino-6-methyl-5-heptene was heated slowly to 160° and kept at this temperature for four hours. Unreacted amine was removed by steam-distillation after suspending the reaction mixture in water. The aqueous suspension was acidified with hydrochloric acid and decolorized with charcoal. Apparently, during this process the unsaturated linkage in the heptene chain was hydrated (27). The clear solution was then made alkaline with sodium hydroxide and again steam-distilled. On cooling the base separated as a viscous, insoluble liquid that gradually solidified on standing at room temperature and could be recrystallized from benzene-petroleum ether.

1-Phenyl-5-(1-piperidylmethyl)tetrazole. A solution of 15 g. of 1-phenyl-5-chloromethyltetrazole and 20 ml. of piperidine in 200 ml. of benzene was boiled under reflux for five hours. After addition of an equal volume of water and 5 g. of sodium hydroxide the mixture was distilled to remove benzene and unreacted piperidine. The product was insoluble in the aqueous, alkaline medium and solidified on cooling the mixture. The base was recrystallized from anhydrous ether.

1-m-Aminophenyl-5-diethylaminomethyltetrazole. A solution of 13.8 g. of 1-*m*-nitrophenyl-5-diethylaminomethyltetrazole, prepared from 1-*m*-nitrophenyl-5-chloromethyltetrazole and diethylamine in isopropyl alcohol solution, in 150 ml. of glacial acetic acid was shaken with hydrogen at an initial pressure of 50 p.s.i. in the presence of 0.1 g. of Adams' platinum oxide catalyst. The calculated amount of hydrogen for the reduction of the nitro group was taken up in about 40 minutes. After removal of the catalyst the solution was evaporated to dryness under diminished pressure and the residue was dissolved in 100 ml. of 10% hydrochloric acid. The aqueous, acid solution was filtered to remove a trace of insoluble material and then made alkaline with aqueous ammonia. The base precipitated as a brownish, granular material which was decolorized by treatment with charcoal in aqueous acid solution, reprecipitated with aqueous ammonia, and recrystallized from acetone-petroleum ether.

SUMMARY

1. A procedure has been developed for the preparation of tetrazole derivatives substituted in the 5 position with haloalkyl groups. A series of such compounds is described with various substituents in the 1 position and chloromethyl, 1-bromoethyl, 1-chloroethyl, 2-chloroethyl, and 1-bromo-2-methylpropyl groups in the 5 position.

2. The behavior of the haloalkyltetrazole derivatives has been studied in reactions involving replacement of the halogen by the phthalimido, acetoxy, hydroxy, phenoxy, and amino groups. Tetrazole derivatives with side chain functions as primary, secondary, and tertiary amines; primary and secondary alcohols; ketones; ethers; and esters have been described. Tetrazole derivatives with unsaturated side chains have also been formed by dehydrohalogenation of the haloalkyl compounds.

3. An extensive series of secondary and tertiary aminoalkyl tetrazoles has been prepared for study of the pharmacological properties of these structures.

ORANGE, NEW JERSEY

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