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

THE REACTION OF NITRILES WITH HYDRAZOIC ACID: SYNTHESIS OF MONOSUBSTITUTED TETRAZOLES

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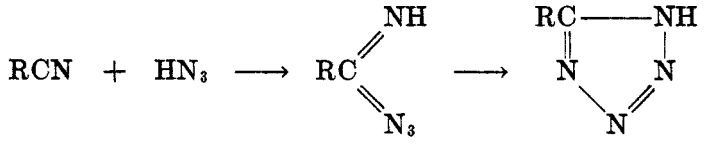
The addition of hydrazoic acid to the cyanide group with the formation of 5-substituted tetrazole derivatives was first observed by Hantzsch and Vagt (1) who prepared 5-aminotetrazole by the interaction of hydrazoic acid and cyanamide. Some twenty years later Stollé (2) showed that the same product could be prepared from the more readily accessible dicyandiamide and hydrazoic acid. Presumably the dicyandiamide dissociated under the conditions of the reaction so that the process was essentially the same as that described by Hantzsch and Vagt. The synthesis of the parent heterocycle was accomplished by Dimroth and Fester (3) by the interaction of hydrazoic acid and hydrocyanic acid in alcoholic solution. These authors suggested that tetrazole formation took place through the formation of an imide azide which immediately cyclized as indicated in the following general reaction:



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R = H, NH_2, CN, $COOC_2H_5$, $CON(C_2H_5)_2$, Br

Using the same general reaction Oliveri-Mandalà (4) succeeded in preparing 5-bromo-, 5-cyano-, and 5-carbethoxy-tetrazole by the interaction of hydrazoic acid with cyanogen bromide, cyanogen, and ethyl cyanoformate, respectively. More recently the preparation of tetrazole-5-diethylcarboxamide from hydrazoic acid and cyanodiethylformamide has also been described (5). It should be noted that no condensing agents or catalysts were required to bring about interaction of these nitriles with hydrazoic acid and that the reactions took place at relatively low temperatures, in boiling ether, except in the case of hydrocyanic acid. Other methods of preparing 5-substituted tetrazoles have been reviewed recently (6).

In 1932 von Braun and Keller (7) reported attempts to bring about reaction of hydrazoic acid with a number of alkyl and aryl cyanides in the presence of concentrated sulfuric acid. Under these conditions a reaction between two moles of hydrazoic acid and one of the nitrile took place and the formation of 1-alkyl or aryl-5-aminotetrazole derivatives indicated that a rearrangement of the nitrile with a shift of the alkyl group from carbon to nitrogen had taken place during the reaction. They suggested that the reaction involved the addition of an imine radical (HN=) to the cyanide group to form an intermediate which after

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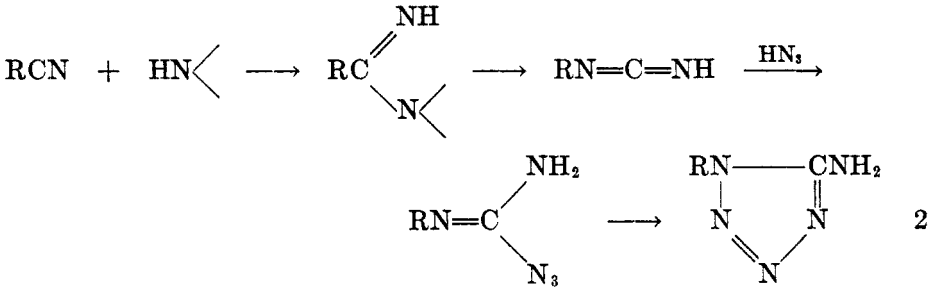
rearrangement added a molecule of hydrazoic acid and cyclized to form the 5-aminotetrazole derivative. The assumption of the existence of the imine radical



was based on the work of Schmidt (8) who had suggested its formation during the decomposition of hydrazoic acid in the presence of sulfuric acid. Since they failed to isolate any 5-alkyl- or 5-aryl-tetrazoles from the reaction, von Braun and Keller concluded that hydrazoic acid would not add to the cyanide group of the nitriles of carboxylic acids.

Repetition of Dimroth's preparation of tetrazole in benzene solution rather than in alcoholic solution as originally suggested has made it possible to develop this procedure into a useful preparative method. Furthermore, a study of the interaction of hydrazoic acid with dicyandiamide in aqueous solution showed this reaction to take place with such remarkable ease that it could be used for the preparation of 5-aminotetrazole in excellent yield in almost any desired quantity. These observations suggested the desirability of studying again the interaction of alkyl and aryl cyanides with hydrazoic acid in the absence of reagents such as sulfuric acid. This was particularly desirable in view of the work of Newman and Gildenhorn (9) and Smith (10) which had demonstrated the readiness with which rearrangement of addition products of hydrazoic acid and unsaturated groupings took place in the presence of proton donors.

When alkyl or aryl nitriles were heated with benzene solutions of hydrazoic acid at temperatures of 120–150° for periods of 96–120 hours, excellent yields of the 5-alkyl- or 5-aryl-tetrazoles were obtained. In many instances the reaction could be carried out equally successfully in isopropyl alcohol solution using equivalent amounts of sodium azide and acetic acid, thus obviating the need of preparing benzene solutions of hydrazoic acid. A series of 5-alkyl- and 5-aryl-tetrazoles prepared in this manner are listed in Table I. Of this group the 5-phenyl-, 5-*p*-tolyl-, and 5-methyl-tetrazoles had been previously described. The first two had been prepared by Pinner (11, 12) by the interaction of benzimino ethyl ether and hydrazine and treatment of the amidrazone so formed with nitrous acid. 5-Methyltetrazole had been prepared in an analogous manner from acetonitrile (13). We have repeated the preparation of these three compounds from benzonitrile, *p*-tolunitrile, and acetonitrile, respectively, by way of the imino ethers and the amidrazones and the products so obtained were identical in every respect with the tetrazoles formed by direct addition of hydrazoic acid to the respective nitriles.

Our results indicate that the conclusion of von Braun and Keller concerning the non-addition of hydrazoic acid to alkyl and aryl cyanides is invalid. The formation of 5-substituted tetrazoles by interaction of hydrazoic acid and nitriles may be explained most easily by the assumption of an intermediate imide azide which rapidly cyclizes to form the tetrazole as suggested by Dimroth and Fester. Although it is unlikely that the imide azide would be stable at the elevated temperature employed, the formation of such an intermediate seems reasonable since Thiele (14) had succeeded in isolating guanyl azide by the interaction of aminoguanidine and nitrous acid and had observed its cyclization to 5-aminotetrazole in boiling aqueous solution. In Reaction 1, the group R may now be considered to include alkyl and aryl groups in addition to those already indicated.

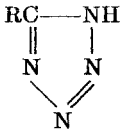
All of the 5-substituted tetrazoles described in Table I are acidic substances. The lower members of the series are quite soluble in water and their aqueous solutions will displace carbonic acid from the alkali bicarbonates. The higher members of the series dissolve readily in water upon addition of alkalies, alkali carbonates or ammonia. The calcium, strontium, and barium salts of the compounds are quite soluble in water and do not lend themselves easily to the characterization of the substances. All the 5-substituted tetrazoles form silver salts that are insoluble in water or dilute nitric acid. In the preparation of the silver salts care should be exercised to avoid an excess of silver nitrate since the precipitates appear to occlude or adsorb excess reagent. The silver salts are light-sensitive and decompose with a flash when heated on a spatula. They do not seem to be sensitive to shock. Two of the products, 5-benzyl- and 5-β-phenylethyltetrazole formed well crystallized complex salts with mercuric chloride in alcoholic solution. Analysis indicated that these compounds were mercuric chloride complex salts of the mercurichloride derivatives, $RHgCl \cdot HgCl_2$. In none of the other cases could characteristic crystalline derivatives be obtained with mercuric chloride.

Dissociation constants and neutralization equivalents of all the 5-alkyl- and 5-aryl tetrazoles were determined potentiometrically. The titration curve for each of the compounds was typical of a weak acid; no abnormalities were observed. The results are summarized in Table I. In most instances the dissociation constants of the tetrazoles were smaller by a factor of about ten than those of the corresponding carboxylic acids in which the carboxyl group replaced the tetrazole ring. The dissociation constant of tetrazole ($K = 1.62 \times 10^{-5}$ at 25°) determined in this way was in good agreement with the value ($K = 1.54 \times 10^{-5}$ at 25°) calculated from conductivity data by Oliveri-Mandalà (15). The most acidic compounds in the group in the order of decreasing strength are 5-phenyltetrazole, 5-*m*-tolyltetrazole, 5-*o*-tolyltetrazole, tetrazole, and 5-*p*-tolyltetrazole.

In an attempt to obtain characteristic derivatives 5-phenyl- and 5-β-cyclohexylethyl-tetrazole were treated with *p*-nitrobenzyl bromide in alkaline, aqueous alcoholic solution. Easily crystallizable, neutral products that gave correct nitrogen analyses for the *p*-nitrobenzyl-5-phenyl- and 5-β-cyclohexylethyl-tetrazoles were formed. In order to determine whether the benzyl group occupied the 1 or the 2 position on the ring the same reaction was carried out with benzyl

TABLE I

5-SUBSTITUTED TETRAZOLES



R	YIELD, %	M.P., °C. (CORR.)	REACTION TIME, HOURS	CRYSTALLIZED FROM	POTENTIOMETRIC TITRATION			
					Average Apparent K × 10⁶	Equivalent Weight		Solvent[a]
						Calc'd	Found	
Hydrogen	42	157.5–158	96	Ethyl acetate	16.2	70.7	70.3	Water
Methyl	76	148–148.5	100	Amyl acetate	2.74	84.1	84.4	Water
Ethyl	66	98–99	75	Ethyl acetate	2.56	98.1	99.0	Water
n-Propyl	76	64–65	108	Isopropyl ether	2.47	112	113	Water
Isopropyl	87	113–114	104	Ethylene chloride	2.80	112	112	Water
n-Butyl	56	47.5–48.5	106	Petroleum ether-ether	2.38	126	126	25% Methanol
Isobutyl	70	53.5–54	104	Isopropyl ether	2.45	126	126	25% Methanol
n-Amyl	77	41–42	109	Acetonitrile	2.22	140	141	25% Methanol
Isoamyl	53	95–96	109	Petroleum ether-ether	1.97	140	141	25% Methanol
n-Hexyl	78	46.5–47.5	125	Acetonitrile	2.12	154	155	23% Methanol
n-Heptyl	56	41.5–42.5	110	Acetonitrile	2.00	168	169	25% Methanol
n-Octyl	84	41.5–42.5	102	Ethyl acetate	1.85	182	184	34% Methanol
Phenyl	75	217–218	101	Water	29.8	146	147	44.4% Methanol
Benzyl	73	125.5–126	103	Ethylene chloride	8.92	160	161	20% Methanol
β-Phenylethyl	86	100.5–101	110	Benzene	3.92	174	176	20% Methanol
γ-Phenylpropyl	59	92.5–93.5	102	Toluene	3.10	188	190	20% Methanol
o-Tolyl	29	157–158	134	Water	23.9	160	162	23% Methanol
m-Tolyl	88	152–152.5	168	Water	25.5	160	162	33% Methanol
p-Tolyl	88	250–250.5	102	Ethanol	12.3	160	162	50% Methanol
Cyclohexyl	61	134–135	102	Water	1.85	152	153	25% Methanol
Cyclohexylmethyl	75	109.5–110	150	Ethyl acetate	2.01	166	167	25% Methanol
β-Cyclohexylethyl	85	143–143.5	120	Ethyl acetate	1.73	180	181	37.5% Methanol
γ-Cyclohexylpropyl	68	94–95	102	Ethyl acetate	1.61	194	195	41% Methanol
δ-Cyclohexylbutyl	67	65.5–66	108	Acetonitrile	1.40	208	210	47.4% Methanol
ε-Cyclohexylamyl	60	71.5–72.5	108	Ethyl acetate	1.18	222	224	56.5% Methanol

[a] Composition of aqueous methanol expressed as percent by weight of methanol.

bromide and 5-phenyltetrazole. A benzyl-5-phenyltetrazole was obtained as glistening needles which melted at 65.5–66°. To check the identity of this compound 1-benzyl-5-phenyltetrazole was prepared from N-benzylbenzamide by a procedure based on the general method of von Braun and Rudolph (16, 17) which involved conversion of the amide to the imide chloride and treatment of the latter with hydrazoic acid. The 1-benzyl-5-phenyltetrazole so obtained crystallized as coarse, granular prisms melting at 92.5–93° and caused depression of the melting point of the lower-melting benzyl derivative. In view of the dissimilarity of the products it is likely that the compounds formed by benzylation and nitrobenzylation of the 5-substituted tetrazoles are the 2-benzyl-5-phenyltetrazole and the 2-*p*-nitrobenzyl derivatives. However, further verification of these structures is necessary before they may be considered unequivocally established.

TABLE II

CYCLOHEXANEALKANOIC ACID CHLORIDES $C_6H_{11}(CH_2)_nCOCl$

n	B.P., °C./MM.	YIELD, %	ANALYSIS		REF.
			Chlorine		
			Calc'd	Found	
1	95–96/21	59	—	—	19
2	109–111/19	88	—	—	20
3	123–124/17	90	18.8	18.8 18.7	
4	143/18	78	—	—	21
5	150–152/17	93	16.4	16.3 16.4	

The nitriles used as intermediates for the tetrazole syntheses were generally available with the exception of those derived from the cyclohexanealkanoic acids. These were prepared from the acids by way of the acid chlorides and amides. Dehydration of the amides was accomplished very smoothly and usually in good yields by treatment with phosphorus oxychloride in the presence of sodium bisulfite (18).

EXPERIMENTAL

PREPARATION OF INTERMEDIATES

Cyclohexanealkanoic acid chlorides. The acid chlorides were prepared by the method of Darzens and Rost (19). In a typical example 274 g. (1.75 moles) of β-cyclohexanepropionic acid was added dropwise to 297 g. (2.5 moles) of boiling thionyl chloride. The mixture was refluxed for an hour after complete addition of the acid when the excess thionyl chloride was removed and the residual acid chloride was distilled under reduced pressure. Physical constants and analyses of the acid chlorides are given in Table II.

Amides of the cyclohexanealkanoic acids. The amides were prepared by a modification of the procedure of Katsnel'son and Dubinin (21). In a typical preparation 250 g. (1.33 moles)

of γ-cyclohexanebutyryl chloride was added dropwise with stirring to a cooled, saturated solution of ammonia in 3 l. of benzene. The mixture was kept below 10° and ammonia was bubbled through the mixture continuously during the addition of the acid chloride. Stirring was continued for an hour after complete addition of the reactants after which the precipitated ammonium chloride was filtered off and thoroughly extracted with benzene. Upon concentration of the combined benzene solutions, the amide separated as colorless plates. Physical properties and nitrogen analyses (Kjeldahl) are recorded in Table III.

TABLE III

AMIDES OF CYCLOHEXANEALKANOIC ACIDS $C_6H_{11}(CH_2)_nCONH_2$

n	M.P., °C.	YIELD, %	ANALYSIS		REF.
			Nitrogen		
			Calc'd	Found	
1	170–171	40	—	—	22
2	120	42	—	—	23
3	112–113	95	8.3	8.4 8.5	
4	124–125	92	—	—	21
5	119–119.5	95	7.1	7.4 7.5	

TABLE IV

NITRILES OF CYCLOHEXANEALKANOIC ACIDS $C_6H_{11}(CH_2)_nCN$

n	B.P., °C./MM.	YIELD, %	ANALYSIS		REF.
			Nitrogen		
			Calc'd	Found	
1	210–212/741	64	—	—	22
2	116.5–117/22	36	10.2	10.1 10.2	
3	132/22	59	9.3	9.3 9.4	
4	141–143/18	81	8.5	8.4 8.5	
5	154/17	77	7.8	7.9 7.9	

Nitriles of the cyclohexanealkanoic acids. Dehydration of the amides was carried out as recommended by Fahrenbach (18). For example, 200 g. (1.09 moles) of δ-cyclohexanevaleramide, 1000 g. (6.54 moles) of phosphorus oxychloride, and 125 g. (0.65 mole) of sodium metabisulfite were mixed in a three-necked flask. The mixture was warmed to 70° on a water bath when the reaction began. The temperature was slowly raised to 96° where it was maintained for two hours. After quenching the reaction with ice, the nitrile was extracted with ether and dried over sodium sulfate. The liquid left upon evaporation of the solvent was distilled under reduced pressure. Physical properties and nitrogen analyses (Kjeldahl) for the nitriles prepared in this manner are reported in Table IV.

PREPARATION OF TETRAZOLES

Tetrazole. Tetrazole was prepared by the interaction of hydrazoic acid and hydrocyanic acid in benzene solution (24). An alternative procedure was also employed. A Pyrex combustion tube was charged with 5.9 g. (0.12 mole) of sodium cyanide, 19 g. (0.3 mole) of sodium azide, 24 ml. of acetic acid, and 35 ml. of isopropyl alcohol. After sealing, the tube was heated for 96 hours at 110°. The contents of the tube were then dissolved in warm water, acidified with nitric acid, and treated with silver nitrate to precipitate silver tetrazole. This was washed and suspended in warm water without drying. After precipitation of the silver with hydrogen sulfide, the aqueous solution was evaporated to dryness and the residual crude tetrazole was recrystallized from ethyl acetate, small needles, m.p. 157.5–158°. The yield was 3.5 g., 42%.

5-Aminotetrazole. The procedure of Stollé (2) for the preparation of this compound was simplified. A suspension of 82 g. (1 mole) of dicyandiamide and 117 g. (1.8 moles) of sodium azide in 200 ml. of water was warmed to 65° on the water-bath under a reflux condenser when 150 ml. (1.8 moles) of concentrated hydrochloric acid was added in small portions with frequent manual agitation. After complete addition of the acid the mixture was kept at 65–70° on the water-bath for 6 hours during which the product began to crystallize. The semi-solid mass was allowed to stand overnight and was chilled thoroughly before the product was filtered off and washed with ice water. The crude 5-aminotetrazole was recrystallized from boiling water, coarse prisms of the monohydrate. The yield was 135 g., 73%, m.p. 206.5–207.5° decompn.

5-Alkyl and 5-aryl-tetrazoles. All the 5-monosubstituted tetrazoles were prepared in a similar manner. The appropriate nitriles and hydrazoic acid in about 1:1.15 molar ratio were heated in benzene solution in a sealed tube at 150° for 96–120 hours. On completion of the reaction the contents of the tube were transferred to a beaker, the solution evaporated to dryness, and the residue taken up in ethanol and decolorized with charcoal. From this point on three different procedures for the isolation and purification of the tetrazoles were employed.

(A) The alcohol was completely evaporated on a steam-bath after which the crude tetrazole was recrystallized twice from the solvent indicated in Table I. This method was employed when the original nitrile had a sufficiently low boiling point to permit complete removal on the steam-bath. The following products were purified in this manner: 5-methyl-, 5-ethyl-, 5-*n*-propyl-, 5-isopropyl-, 5-*n*-butyl-, and 5-isoamyl-tetrazole.

(B) The ethanol was removed by distillation and the residue was distilled under reduced pressure. The tetrazole fraction in the distillate usually solidified and could be purified further by crystallization from suitable solvents. 5-Isobutyltetrazole (b.p. 156–158°/3.5 mm.), 5-*n*-amyltetrazole (b.p. 158–159°/2 mm.), and 5-*n*-hexyltetrazole (b.p. 167.5–168.5°/2.1 mm.) were purified in this manner. The 5-*n*-heptyltetrazole could not be distilled under reduced pressure without extensive decomposition.

(C) The alcoholic solution of the crude product was evaporated to dryness and the residue subjected to steam-distillation to remove unreacted nitrile. After evaporating the water from the aqueous suspension of the non-volatile material, the residue of crude tetrazole was purified by recrystallizing twice from an appropriate solvent. In addition to the 5-*n*-heptyl- and 5-*n*-octyl-tetrazoles, all of the 5-aryl- and 5-cyclohexylalkyl-tetrazoles were isolated in this way.

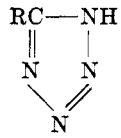
A typical example is the preparation of 5-benzyltetrazole. Benzyl cyanide (23.4 g., 0.2 mole) and 55 ml. of a 20.6% solution of hydrazoic acid (0.27 mole) in benzene were sealed into a Pyrex combustion tube and heated for 102 hours at 150°. After completion of the reaction the contents of the tube were washed into a beaker with ethanol and the solvent removed by evaporation. The residue was taken up in 100 ml. of ethanol, decolorized with charcoal, and the solution again evaporated to dryness. The crude product was then subjected to steam-distillation to remove unreacted benzyl cyanide and after evaporation of the water from the aqueous suspension, the residual 5-benzyltetrazole was twice re-

crystallized from the minimum amount of ethylene dichloride from which it separated as coarse, colorless prisms, m.p. 125.5–126°.

An alternative procedure was especially useful with those tetrazoles which were quite insoluble in water and which were relatively high melting. A mixture of 7 g. (0.108 mole) of sodium azide, 11.7 g. (0.1 mole) of *p*-tolunitrile, 8.5 ml. (0.14 mole) of glacial acetic acid, and 25 ml. of absolute isopropyl alcohol was sealed into a combustion tube and heated at 150°

TABLE V

ANALYTICAL DATA FOR THE 5-SUBSTITUTED TETRAZOLES AND THEIR SILVER SALTS



R	TETRAZOLES			SILVER SALTS		
	Empirical Formula	N		Empirical Formula	N	
		Calc'd	Found		Calc'd	Found
Methyl	$C_2H_4N_4$	66.6	66.8	$C_2H_3AgN_4$	29.4	29.3
Ethyl	$C_3H_6N_4$	57.1	56.8	$C_3H_5AgN_4$	27.3	27.1
n-Propyl	$C_4H_8N_4$	50.0	49.7	$C_4H_7AgN_4$	25.6	25.3
Isopropyl	$C_4H_8N_4$	50.0	50.1	$C_4H_7AgN_4$	25.6	25.5
n-Butyl	$C_5H_{10}N_4$	44.4	44.1	$C_5H_9AgN_4$	24.1	23.8
Isobutyl	$C_5H_{10}N_4$	44.4	44.4	$C_5H_9AgN_4$	24.1	24.0
n-Amyl	$C_6H_{12}N_4$	40.0	40.0	$C_6H_{11}AgN_4$	22.7	22.5
Isoamyl	$C_6H_{12}N_4$	40.0	40.0	$C_6H_{11}AgN_4$	22.7	22.7
n-Hexyl	$C_7H_{14}N_4$	36.3	36.3	$C_7H_{13}AgN_4$	21.5	21.7
n-Heptyl	$C_8H_{16}N_4$	33.3	33.1	$C_8H_{15}AgN_4$	20.4	20.2
n-Octyl	$C_9H_{18}N_4$	30.7	30.4	$C_9H_{17}AgN_4$	19.4	19.5
Phenyl	$C_7H_6N_4$	38.3	38.4	—	—	—
Benzyl	$C_8H_8N_4$	35.0	35.0	$C_8H_7AgN_4$	21.0	21.0
β-Phenylethyl	$C_9H_{10}N_4$	32.1	31.8	$C_9H_9AgN_4$	19.9	20.0
γ-Phenylpropyl	$C_{10}H_{12}N_4$	29.8	29.5	$C_{10}H_{11}AgN_4$	19.0	19.0
o-Tolyl	$C_8H_8N_4$	35.0	35.0	$C_8H_7AgN_4$	21.0	20.7
m-Tolyl	$C_8H_8N_4$	35.0	34.9	$C_8H_7AgN_4$	21.0	20.7
p-Tolyl	$C_8H_8N_4$	35.0	34.7	—	—	—
Cyclohexyl	$C_7H_{12}N_4$	36.8	36.9	$C_7H_{11}AgN_4$	21.6	21.4
Cyclohexylmethyl	$C_8H_{14}N_4$	33.7	33.6	$C_8H_{13}AgN_4$	20.5	20.2
β-Cyclohexylethyl	$C_9H_{16}N_4$	31.1	31.0	$C_9H_{15}AgN_4$	19.5	19.4
γ-Cyclohexylpropyl	$C_{10}H_{18}N_4$	28.3	28.8	$C_{10}H_{17}AgN_4$	18.7	18.6
δ-Cyclohexylbutyl	$C_{11}H_{20}N_4$	26.9	26.9	$C_{11}H_{19}AgN_4$	17.8	17.5
ε-Cyclohexylamyl	$C_{12}H_{22}N_4$	25.1	24.8	$C_{12}H_{21}AgN_4$	17.0	17.3

for 108 hours. After completion of the reaction the solvent was evaporated and the residue was taken up in hot water. Upon acidification with hydrochloric acid 5-*p*-tolyltetrazole precipitated from the aqueous solution. The product was recrystallized from 95% ethanol from which it separated as fine, colorless needles, m.p. 250–250.5°. 5-Phenyl-, 5-*o*-tolyl-, 5-*m*-tolyl-, and 5-*p*-tolyl-tetrazole were prepared by the procedure just outlined as well as by the interaction of the appropriate nitriles with hydrazoic acid in benzene solution.

All of the 5-substituted tetrazoles prepared by these procedures are described in Table I. Analytical data for all the compounds are summarized in Table V.

For reference purposes 5-phenyltetrazole and 5-*p*-tolyltetrazole were also prepared by the procedure described by Pinner (11, 12). The nitriles were converted into the imino ethyl ethers and interaction of the latter with hydrazine gave the amidrazones. Conversion to the respective tetrazoles was accomplished by treatment of the amidrazones with nitrous acid. The products were identical in every respect with the tetrazoles made by direct addition of hydrazoic acid to the nitriles and no depression was observed when mixed melting points were taken.

Silver salts of the tetrazoles. The silver salts of the 5-substituted tetrazoles were prepared by dissolving a weighed amount of the tetrazole in ethanol and adding the equivalent amount of a standard silver nitrate solution. Excess of either component was avoided since its adsorption or occlusion on the precipitate gave rise to erroneous nitrogen values. The precipitated silver salt of the tetrazole was digested for two hours in the supernatant liquid, filtered hot, washed with hot 50% ethanol, and dried for analysis for two hours at 90°. Analytical data are recorded in Table V. None of the silver salts listed in Table V could be detonated by shock. All of them were stable to sharp blows with a hammer on an anvil. On heating over a flame on a spatula all of them eventually decomposed with a flash, but they could be burned in the usual micro-Dumas apparatus without special precautions. On exposure to daylight most of the silver salts discolored rapidly.

Mercuric chloride complexes of the tetrazoles. On addition of an alcoholic solution of mercuric chloride to an alcoholic solution of 5-benzyltetrazole a complex of mercuric chloride with the mercurichloride derivative of the tetrazole separated as fine, colorless needles, m.p. 223° decompn.

Anal. Calc'd for $C_8H_7N_4 \cdot HgCl \cdot HgCl_2$: N, 8.4. Found: N, 8.3.

The mercuric chloride complex of 5-β-phenylethyltetrazole mercurichloride separated from alcoholic solution slowly in the form of very small, colorless prisms, m.p. 206° decompn.

Anal. Calc'd for $C_9H_9N_4 \cdot HgCl \cdot HgCl_2$: N, 8.2. Found: N, 8.2.

Although most of the other tetrazoles formed precipitates with mercuric chloride in aqueous or aqueous-alcoholic solution, the products were not crystalline and did not lend themselves to the characterization of the compounds.

p-Nitrobenzyl-5-phenyltetrazole. A solution of the potassium salt of 5-phenyltetrazole was prepared by dissolving 1.46 g. of the tetrazole in a small amount of ethanol and adding 0.7 g. of potassium carbonate and sufficient water to form a clear solution. After addition of 2 g. of *p*-nitrobenzyl bromide the mixture was refluxed for 3 hours. On cooling the product separated as needles which were recrystallized from methanol, m.p. 121.5–122°.

Anal. Calc'd for $C_{14}H_{11}N_5O_2$: N, 24.9. Found: N, 24.7.

p-Nitrobenzyl-5-β-cyclohexylethyltetrazole. A solution of the potassium salt of 5-β-cyclohexylethyltetrazole prepared by dissolving 1.8 g. of the tetrazole and 0.7 g. of potassium carbonate in aqueous alcohol was treated with 2 g. of *p*-nitrobenzyl bromide. After boiling under reflux for 3 hours the product separated as small yellow plates on cooling and was recrystallized from methanol, m.p. 82–82.5°.

Anal. Calc'd for $C_{16}H_{21}N_5O_2$: N, 22.2. Found: N, 21.9.

Benzyl-5-phenyltetrazole. A solution of 1.46 g. of 5-phenyltetrazole and 0.7 g. of potassium carbonate in aqueous ethanol was prepared. After addition of 1.7 g. of benzyl bromide the solution was boiled under reflux for 3 hours. The product separated as an oil which solidified on cooling. Recrystallization was effected from methanol from which it separated as glistening needles, m.p. 65.5–66°.

Anal. Calc'd for $C_{14}H_{12}N_4$: N, 23.7. Found: N, 23.1.

1-Benzyl-5-phenyltetrazole. A solution of 54 g. (0.25 mole) of N-benzylbenzamide in 600 ml. of benzene was prepared in a 2 l. three-necked flask equipped with a reflux condenser, benzene-sealed stirrer, and an addition tube. To the stirred solution 52 g. (0.25 mole) of phosphorus pentachloride was added. After the pentachloride had dissolved completely, 100 ml. of a 16% solution of hydrazoic acid in benzene was added in several small portions. Stirring was continued for 2 hours when the solution was gradually warmed to the boiling

point and allowed to reflux for 3 hours. The solvent was now removed under reduced pressure and the residue was treated with about 500 g. of ice and water. The aqueous suspension was gradually warmed and then boiled under reflux for 3 hours. After cooling the mixture the aqueous layer was decanted and the oily residue was boiled under reflux with 300 ml. of 10% sodium hydroxide solution. The insoluble material was taken up in benzene, the benzene solution washed with water, dried, and the solvent removed under reduced pressure. The crude product remained as a viscous oil which crystallized slowly. After three recrystallizations from ethanol the product was obtained as colorless, dense prisms, m.p. 92.5–93°. The yield was 29 g., 50%. The product depresses the melting point of the benzyl-5-phenyltetrazole prepared by benzylation of 5-phenyltetrazole.

Anal. Calc'd for $C_{14}H_{12}N_4$: N, 23.7. Found: N, 23.7.

DETERMINATION OF DISSOCIATION CONSTANTS OF THE 5-SUBSTITUTED TETRAZOLES

The acid dissociation constants of all the tetrazoles described in Table I were determined by titration of a weighed sample of the compound in aqueous or aqueous methanolic solution with standard alkali. Titration was carried out in a thermostat at 25° and the *p*H was determined after each addition of alkali with a Beckman *p*H Meter, Model G. From these data acid dissociation constants were calculated using the following expression (25):

$$K = C_{H^+}\left(\frac{x}{x_e - x}\right)$$

where C_{H^+} is the hydrogen ion concentration calculated from the *p*H corresponding to the addition of x ml. of alkali. The symbol x_e expresses the number of ml. of alkali required for neutralization of the acid.

The apparent acidic dissociation constants and equivalent weights of all the 5-substituted tetrazoles are recorded in Table I. Each dissociation constant is an average of at least six values calculated from different points near the region of half neutralization of the compound. In each instance the titration curve exhibited the form normally obtained with a weak acid.[2]

The equivalent weight of each of the tetrazoles, calculated from the value for x_e, is recorded in Table I.

SUMMARY

1. A new method for the preparation of 5-alkyl- and 5-aryl-tetrazoles by the interaction of hydrazoic acid and the nitriles of carboxylic acids in benzene or alcoholic solution has been described.

2. A group of twenty-one new 5-alkyl- and 5-aryl-tetrazoles has been prepared and characterized. The silver salts of all the compounds have been prepared and in several instances characteristic mercuric chloride complexes have been described.

3. The 5-substituted tetrazoles are weak acids. The acid dissociation constants of all the compounds have been determined and the effect of various substituent groups in the 5 position on the strength of the compounds as acids has been discussed.

4. Alkylation of a number of 5-substituted tetrazoles with *p*-nitrobenzyl bromide and benzyl bromide is described. Comparison of the products with the

[2] The apparent dissociation constant of 5-methyltetrazole at 25° was 2.74×10^{-6} in water, 2.43×10^{-6} in 25% by weight methanol, and 1.82×10^{-6} in 50% methanol. These values indicate that the tetrazoles may be expected to behave as weaker acids in aqueous methanol solution.

isomeric 1-benzyl-5-substituted compounds indicated that benzylation probably took place in the 2 position on the ring.

5. The preparation of 1-benzyl-5-phenyltetrazole from N-benzylbenzamide has been described.

6. A simple procedure for the preparation of 5-aminotetrazole by the interaction of dicyandiamide and sodium azide in aqueous acid solution has been described.

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