TABLE III

1-*n*-OCTYL-4-BENZYL-5-IMINOTETRAZOLINIUM SULFONATES

Sulfonic acid	M.P., °C.	Formula	Analyses							
			Calcd.				Found			
			C	H	N	S	C	H	N	S
Methane[a]	116–117	$C_{17}H_{29}N_5O_3S$	53.2	7.6	18.3	8.4	53.6	7.8	18.5	8.3
Ethane[a]	98–99	$C_{18}H_{31}N_5O_3S$	54.4	7.9	17.6	8.1	54.4	7.9	17.9	8.0
2-Propane[a]	108–110	$C_{19}H_{33}N_5O_3S$	55.4	8.1	17.0	7.8	55.9	8.0	17.3	7.8
1-Butane[b]	125	$C_{20}H_{35}N_5O_3S$	56.4	8.3	16.5	7.5	56.5	8.3	16.5	7.4
3-Methyl-1-butane[c]	132–133	$C_{21}H_{37}N_5O_3S$	57.4	8.5	15.9	7.3	57.3	8.7	16.0	7.3
Benzene[d]	129	$C_{22}H_{31}N_5O_3S$	59.3	7.0	15.7	7.2	59.3	6.9	16.0	7.1
p-Toluene[d]	172–173	$C_{23}H_{33}N_5O_3S$	60.1	7.2	15.2	7.0	60.0	7.1	15.3	6.9
2,4-Dimethylbenzene[a]	91–92	$C_{24}H_{35}N_5O_3S$	60.9	7.5	14.8	6.8	60.8	7.6	14.8	7.0
2,5-Dimethylbenzene[a]	102–103	$C_{24}H_{35}N_5O_3S$	60.9	7.5	14.8	6.8	61.0	7.5	14.8	7.0
p-Chlorobenzene[d,e]	159–160	$C_{22}H_{30}ClN_5O_3S$	55.0	6.3	14.6	6.9	55.2	6.5	14.7	6.8
2,4-Dichlorobenzene[d,f]	134–135	$C_{22}H_{29}Cl_2N_5O_3S$	51.4	5.7	13.6	6.2	51.3	5.7	13.4	6.0
p-Bromobenzene[d,g]	162–163	$C_{22}H_{30}BrN_5O_3S$	50.4	5.8	13.4	6.1	50.5	5.7	13.4	6.0
p-Phenol[d]	114–115	$C_{22}H_{31}N_5O_4S$	57.2	6.8	15.2	7.0	57.3	6.8	15.0	7.1
m-Nitrobenzene[d]	138–139	$C_{22}H_{30}N_6O_5S$	53.9	6.2	17.1	6.5	54.0	6.4	16.9	6.6
p-Nitrobenzene[d]	171–172	$C_{22}H_{30}N_6O_5S$	53.9	6.2	17.1	6.5	54.2	6.3	17.2	6.3
Orthanilic[d]	134–135	$C_{22}H_{32}N_6O_3S$	57.4	7.0	18.3	7.0	57.7	6.9	18.3	6.7
Metanilic[a]	107–108	$C_{22}H_{32}N_6O_3S$	57.4	7.0	18.3	7.0	57.7	7.1	18.2	6.7
Sulfanilic[h]	154–155	$C_{22}H_{32}N_6O_3S$	57.4	7.0	18.3	7.0	57.5	7.2	18.0	6.8
m-Sulfobenzoic[d]	200–201	$C_{23}H_{31}N_5O_5S$	56.4	6.4	14.3	6.6	56.4	6.5	14.3	6.6
5-Sulfosalicylic[d]	169–170[i]	$C_{23}H_{31}N_5O_6S$	54.6	6.2	13.9	6.3	54.8	6.2	13.6	6.4
m-Benzenedi-[j,k]	143–144	$C_{38}H_{56}N_{10}O_6S_2$	56.1	6.9	17.2	7.9	56.0	7.0	17.2	8.1
4,4′-Biphenyldi-[d,j]	244–245	$C_{44}H_{60}N_{10}O_6S_2$	59.4	6.8	15.8	7.2	59.4	6.6	16.0	7.3
dl-10-Camphor[b]	146–147	$C_{26}H_{41}N_5O_4S$	60.1	8.0	13.5	6.2	60.4	8.1	13.3	6.3
d-10-Camphor[b]	144–145	$C_{26}H_{41}N_5O_4S$	60.1	8.0	13.5	6.2	60.1	8.0	13.3	6.1
2-Naphthalene[d]	146–147	$C_{26}H_{33}N_5O_3S$	63.0	6.7	14.1	6.5	63.2	6.8	14.3	6.6
4-Amino-1-naphthalene[k]	131–132	$C_{26}H_{34}N_6O_3S$	61.2	6.7	16.5	6.3	61.1	6.8	16.6	6.1
4-Acetamido-1-naphthalene[d]	148–149	$C_{28}H_{36}N_6O_4S$	60.9	6.6	15.2	5.8	61 0	6.7	15.0	5.7
1,5-Naphthalenedi-[d,j]	213–214	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.5	6.7	16.2	7.5
2,6-Naphthalenedi-[d,j]	253–254	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.9	6.8	16.3	7.6
2,7-Naphthalenedi-[d,j]	210–211	$C_{42}H_{58}N_{10}O_6S_2$	58.5	6.8	16.2	7.4	58.3	6.7	16.3	7.7

[a] Recrystallized from benzene–petroleum ether or benzene–hexane [b] Recrystallized from ethyl acetate–cyclohexane [c] Recrystallized from ethyl acetate [d] Recrystallized from aqueous ethanol. [e] Calcd.: Cl, 7.4. Found: Cl, 7.4. [f] Calcd.: Cl, 13.8. Found: Cl, 13.9. [g] Calcd.: Br, 15.2. Found: Br, 15.3. [h] Recrystallized from water. [i] Melts partially at 150–151°, resolidifies and remelts at 169–170°. [j] Neutral salt. [k] Recrystallized from benzene.

ing the mixture to boiling. The product which separated in sheaf-like clusters of crystals on cooling was recrystallized from 30% aqueous acetone, yield 3.5 g. (72%), m.p. 159–161°.

Anal. Calcd. for $C_{22}H_{31}ClN_6O_3S$: Cl, 7.2; N, 17.0; S, 6.5. Found: Cl, 7.1; N, 17.0; S, 6.3.

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

Apparent Acidic Dissociation of Some 5-Aryltetrazoles[1]

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Received February 27, 1957

An improved procedure has been developed for the preparation of 5-aryltetrazoles in which solutions of the aryl cyanides, sodium azide, and acetic acid in *n*-butyl alcohol are heated under reflux. The isomeric 5-chlorophenyl-, 5-bromophenyl-, and 5-methoxyphenyltetrazoles were prepared, their apparent acidic dissociation constants and ultraviolet absorption spectra determined and compared with those of the correspondingly substituted benzoic acids. With the exception of the *ortho* substituted compounds, the 5-aryltetrazoles appear to be stronger acids than the correspondingly substituted benzoic acids.

Tetrazole derivatives in which the hydrogen atom attached to the ring nitrogens has not been replaced generally behave as acidic substances.[2,3,4]

(1) Based on a thesis submitted by Kenneth R. Wilson to Michigan State University in 1955 in partial fulfillment of the requirements for the degree of Master of Science.

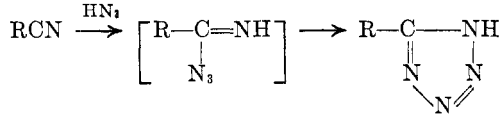
(2) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(3) E. Oliveri-Mandalà, *Gazz. chim. ital.*, **44**, II, 175 (1914).

(4) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1023, 1269 (1953).

The apparent acidic dissociation constants of 5-alkyltetrazoles (R—CN_4H) have been found to be about a fifth to a tenth as large as those of the corresponding aliphatic carboxylic acids (R—COOH) and variations in the apparent acidic dissociation due to the structure of the alkyl groups are quite parallel in both series. Apparent acidic dissociation constants have been reported for 5-phenyl-, and the 5-tolyltetrazoles[2] from which it appeared that these compounds were stronger acids than benzoic and the respective toluic acids. Furthermore, the apparent dissociation constants of the 5-tolyltetrazoles increased in the order *ortho* < *para* < *meta*, while those of the toluic acids increased in the order *para* < *meta* < *ortho*. The preparation and determination of apparent acidic dissociation constants of other 5-aryltetrazoles was undertaken to help explain this situation.

Recently it was shown that 5-substituted tetrazoles could be prepared in a single step by heating alkyl or aryl cyanides in sealed tubes at 150° with hydrazoic acid in benzene solution.[2] A similar reaction took place when the cyanide was heated under the same conditions in isopropyl alcohol solution with equivalent amounts of sodium azide and acetic acid.



The preparation would be greatly simplified if the reaction could be done in an open system and with liberation of hydrazoic acid from sodium azide in the reaction mixture. The problem was to find a solvent of sufficiently high boiling point so that the reaction would proceed at a reasonable rate and in which a weak acid such as acetic would react with sodium azide. Earlier work in closed systems[2] had shown that alcohols might be suitable. To determine the best conditions the preparation of 5-phenyltetrazole from benzonitrile, sodium azide, and acetic acid was studied in boiling isopropyl, *sec* butyl, and *n*-butyl alcohol. With all other conditions the same, the yields of 5-phenyltetrazole in the boiling alcohols were 64, 84, and 91%, respectively. The crude product obtained in *n*-butyl alcohol solution was also less pigmented and of higher melting point than when the lower boiling alcohols were used. The method eliminated the use of sealed tubes and made possible the use of larger quantities of reactants. All the 5-aryltetrazoles listed in Table III were prepared in boiling *n*-butyl alcohol from the respective aryl cyanides, sodium azide, and acetic acid; 5-phenyl-,[2,5,6,7] 5-*o*-chlorophenyl-,[8] and 5-*p*-methoxyphenyltetrazole[9] have been previously described. A 5-bromophenyltetrazole of undetermined orientation was obtained by Lossen and Statius[10] by treatment of 5-phenyltetrazole with bromine water at elevated temperature. The compound appears to be identical with the 5-*p*-bromophenyltetrazole prepared from *p*-bromobenzonitrile in this study.

The 5-aryltetrazoles listed in Table III are colorless, acidic substances; they are soluble in aqueous alkalies, alkali carbonates and bicarbonates, and aqueous ammonia. Their melting points follow the order found for substituted benzoic acids, *i.e.*, rise in the order *meta* < *ortho* < *para*. They form insoluble salts with silver nitrate in hot aqueous ethanol. Attempts to decompose the silver salts by digestion with concentrated nitric acid[11] were not successful and precluded estimation of silver by the Volhard method. Salts formed with benzylamine, ethylenediamine, 2-aminopyridine, piperidine, and *n*-hexylamine did not lend themselves to characterization of the tetrazoles since they did not crystallize well nor did they show sharp melting points.

Apparent acidic dissociation constants (Table I) and neutralization equivalents (Table III) of the 5-aryltetrazoles were determined potentiometrically in 50% or 75% aqueous methanol. Typical weak acid titration curves were obtained. For comparison apparent acidic dissociation constants of similarly substituted benzoic acids in the same solvents are included in Table I. It may be noted that the apparent acidic dissociation constant of 5-phenyltetrazole is larger than that of tetrazole[2] while

TABLE I

APPARENT ACIDIC DISSOCIATION CONSTANTS OF 5-ARYLTETRAZOLES AND THE CORRESPONDING ARYL CARBOXYLIC ACIDS

R	R—$C_6H_4CN_4H$[a] K × 10^6	R—C_6H_4COOH[a] K × 10^6
H	29 (13)[b]	8.0
o-CH_3	15.2[c]	9.33[c]
m-CH_3	20.0[c]	4.27[c]
p-CH_3	15.2[c]	3.55[c]
o-Cl	57 (25)[b]	70.8[d]
m-Cl	87	14.5[d]
p-Cl	(32)[b]	10.0[d]
o-Br	60	70.8[d]
m-Br	92 (42)[b]	13.5[d]
p-Br	(30)[b]	9.33[d]
o-CH_3O	1.2	6.5
p-CH_3O	14	2.8

[a] All values determined in 50% by volume methanol at 25° except as otherwise noted. [b] Values in parentheses were determined in 75% by volume methanol at 25°. [c] Reference 12. [d] Determined at 18–22°, reference 13.

(5) A. Pinner, *Ann.*, **297**, 229 (1897).
(6) A. Pinner, *Ber.*, **27**, 990 (1894).
(7) W. Lossen and C. Lossen, *Ann.*, **298**, 104 (1897).
(8) R. Stollé, A. Netz, O. Kramer, S. Rothschild, H. Erbe, and O. Schick, *J. prakt. Chem.*, (2) **138**, 1 (1933).
(9) W. Lossen and J. Colman, *Ann.*, **298**, 107 (1897).
(10) W. Lossen and F. Statius, *Ann.*, **298**, 91 (1897).
(11) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1003 (1953).
(12) Titrations done in this laboratory by Dr. James A. Garrison.
(13) R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 3, 31 (1928).

benzoic acid appears to be weaker than formic acid. Furthermore, 5-phenyltetrazole and its *meta* and *para* substituted derivatives appear to be stronger acids than the corresponding benzoic acids while *ortho* substituted 5-phenyltetrazoles are weaker than the *ortho* substituted benzoic acids. An interpretation of these differences has been published.[14]

The ultraviolet absorption spectra of the 5-aryltetrazoles do not show the peaks of either of the components, benzene or tetrazole. The interaction of the phenyl group with the tetrazole ring produces a new chromophore that shows a single absorption band with a maximum at 241 mμ (Table II). Elpern and Nachod[15] have reported an identical absorption spectrum for 5-phenyltetrazole. Introduction of bromine or chlorine at the *para* position of 5-phenyltetrazole produces a shift of the band to longer wave lengths and an increase in the extinction coefficient while the same substituents in the *meta* position cause only a slight shift of the maximum toward longer wave lengths with a decrease in the extinction coefficient. With chlorine in the *ortho* position the band is shifted to shorter wave lengths and the extinction coefficient is lowered; bromine in the *ortho* position causes an even greater shift of the band to shorter wave lengths, maximum below 220 mμ. The hypsochromic shift caused by halogens in the *ortho* position may be a steric effect of the *ortho* substituent which makes attainment of coplanarity of the two ring systems difficult and disturbs the resonance interaction of the phenyl and tetrazoles rings. The same reasoning may explain the comparatively low apparent acidic dissociation constants of the *ortho* substituted 5-phenyltetrazoles.

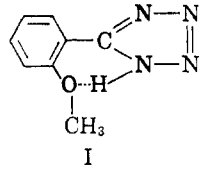


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TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF 5-ARYLTETRAZOLES

Compound	Maxima, mμ	Extinction Coefficient
5-Phenyltetrazole	241	15,900
5-*o*-Chlorophenyltetrazole	234	9,600
5-*m*-Chlorophenyltetrazole	242	14,000
5-*p*-Chlorophenyltetrazole	247	20,400
5-*o*-Bromophenyltetrazole	<220	—
5-*m*-Bromophenyltetrazole	243	13,300
5-*p*-Bromophenyltetrazole	251	21,200
5-*o*-Methoxyphenyltetrazole	294	4,900
	246	11,600
5-*p*-Methoxyphenyltetrazole	259	16,900

(14) R. M. Herbst in S. Graff, *Essays in Biochemistry*, John Wiley & Sons, Inc., New York, 1956, p. 141.

(15) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

TABLE III

5-ARYLTETRAZOLES

R	Cryst. from	Yield, %[a]	M.P., °C.	Formula	Analyses								
					Calculated				Neut. Equiv.	Found			Neut. Equiv.
					C	H	Hal	N		C	H	Hal	N	
H	Water	91	217–218	$C_7H_6N_4$	Ref. 2				146					147
o-Cl	20% A[b]	73	179–180	$C_6H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.7	2.9	19.7	31.3	181
m-Cl	20% A[b]	94	139–140	$C_7H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.6	3.0	19.7	31.1	181
p-Cl	80% A[b]	87	262–263	$C_7H_5ClN_4$	46.6	2.8	19.6	31.0	181	46.7	2.9	19.6	31.1	181
o-Br	20% A[b]	74	183–184	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	35.7	25.1	225
m-Br	25% A[b]	93	154–155	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	36.0	24.9	226
p-Br	95% A[b]	84	278–279 d.	$C_7H_5BrN_4$	37.4	2.2	35.5	24.9	225	37.6	2.3	35.5	25.2	225
o-CH_3O	10% A[b]	52	159–160	$C_8H_8N_4O$	54.5	4.6		31.8	176	54.8	4.6		31.8	177
p-CH_3O	20% A[b]	81	238–239	$C_8H_8N_4O$	54.5	4.6		31.8	176	54.5	4.6		31.9	177

[a] Allowing for recovered nitrile. [b] Aqueous isopropyl alcohol.

The methoxyl group in the *para* position produces a large shift of the absorption band to longer wave lengths and a small increase in the extinction coefficient. However, in the *ortho* position the methoxyl group causes the appearance of a second band with maximum at 294 mμ; the strong band at 246 mμ probably corresponds to the principal band noted for the other compounds. The second band at 294 mμ may be associated with hydrogen bonding; such bonding could also account for the relatively low apparent dissociation constant of 5-*o*-methoxyphenyltetrazole (I).

EXPERIMENTAL[16]

Substituted benzoyl chlorides were prepared by refluxing the substituted benzoic acids with thionyl chloride for several hours, removing excess thionyl chloride by distillation and fractionating the product under reduced pressure. The following substituted benzoyl chlorides were prepared: *m*-chlorobenzoyl chloride, 93%, b.p. 103–104° at 14 mm.;[17] *o*-bromobenzoyl chloride, 85%, b.p. 120–122° at 14 mm.;[18] *m*-bromobenzoyl chloride, 91%, b.p. 119–122° at 13 mm.;[19] *p*-bromobenzoyl chloride, 95%, b.p. 123–126° at 15 mm.;[19] *o*-methoxybenzoyl chloride, 90%, b.p. 135–138° at 13 mm.[20]

Substituted benzamides were prepared by slow addition of the substituted benzoyl chlorides to a large excess of cold, concentrated aqueous ammonia with vigorous stirring. The following amides were prepared: *m*-chlorobenzamide, 95%, m.p. 135.5–137°;[21] *o*-bromobenzamide, 92%, m.p. 160.5–161.5°;[18] *m*-bromobenzamide, 99%, m.p. 153–155°;[22] *p*-bromobenzamide, 99%, m.p. 192–192.5°;[22] *o*-methoxybenzamide, 87%, m.p. 130–131°.[22]

Substituted benzonitriles were prepared by the method of Fahrenbach[23] by interaction of the amide with a large excess of phosphorus oxychloride in the presence of sodium metabisulfite. The following nitriles were prepared in the yields indicated; where a boiling point is given the product was distilled: *m*-chlorobenzonitrile, 76%, b.p. 99–100° at 15 mm., m.p. 40–41°;[24] *o*-bromobenzonitrile, 84%, m.p. 55–55.5°;[18] *m*-bromobenzonitrile, 81%, b.p. 112–114° at 14 mm., m.p. 39–40°;[25] *p*-bromobenzonitrile, 89%, m.p. 114–114.5°;[25] *o*-methoxybenzonitrile, 89%, b.p. 147–149° at 24 mm.[26] Other substituted benzonitriles were obtained from commercial sources.

5-Aryltetrazoles. All of the tetrazoles were prepared from the appropriate nitriles, sodium azide and acetic acid in about 3:4:4 molar ratio by heating under reflux in *n*-butyl alcohol for 6 days in a well-ventilated hood. On the fourth day small amounts of sodium azide and acetic acid were added. A typical example is described in detail.

5-p-Methoxyphenyltetrazole. A mixture of 33 g. (0.25 mole) of *p*-methoxybenzonitrile, 22 g. (0.33 mole) of sodium azide, 20 g. (0.33 mole) of glacial acetic acid and 100 ml. of *n*-butyl alcohol was boiled under reflux for 4 days at which time 5 g. of sodium azide, 10 g. of glacial acetic acid, and 10 ml. of *n*-butyl alcohol were added and heating continued for 2 days. On completion of the reaction 300 ml. of water was added and all but about 100 ml. of the solvents was removed by distillation under reduced pressure. The residual suspension was made basic by addition of 10% sodium hydroxide. A small amount of insoluble solid was removed by filtration and the filtrate was extracted twice with 50-ml. portions of benzene. From the solid and the benzene extracts about a gram of unreacted nitrile was recovered. The aqueous alkaline solution was acidified with dilute hydrochloric acid and the precipitate was collected on a filter, washed thoroughly with cold water, and recrystallized twice from 20% isopropyl alcohol to yield long, thin needles.

Physical constants, yields, and analytical data for all the 5-aryltetrazoles are given in Table III.

Two preparations of 5-phenyltetrazole were made using isopropyl alcohol and *sec* butyl alcohol in yields of 64 and 84%, respectively. The quantities of reagents, reaction periods, and isolation procedure were as just described. Both preparations gave a product, m.p. 218° after one crystallization from water, that was somewhat more discolored in the crude state than when *n*-butyl alcohol was used as solvent.

All the 5-aryltetrazoles gave precipitates with silver nitrate in ethanol solution. Attempts to decompose the silver salts by digesting them with concentrated nitric acid[11] so that the silver could be estimated by the Volhard technique were unsuccessful. None of the salts were sensitive to shock although they decomposed with a flash when heated over a flame on a spatula. Exposure to daylight did not cause discoloration of the salts. Attempts to prepare salts of several of the 5-aryltetrazoles with ethylene diamine, 2-aminopyridine, benzylamine, piperidine, and *n*-hexylamine in ethanol-ether solution gave white powdery precipitates that melted over a wide range of temperature. Recrystallization from ethanol or ethanol-hexane solution gave either oils or solids with indefinite melting points.

Apparent acidic dissociation constants of all the tetrazoles were determined potentiometrically by titration of weighed samples in aqueous methanol solutions with standard alkali at 25° ± 1° using a Beckman *p*H Meter, Model G. Apparent acidic dissociation constants and neutralization equivalents are given in Tables I and III, respectively.

Ultraviolet absorption spectra of the 5-aryltetrazoles were determined in 95% ethanol using a Beckman Model D-U spectrophotometer. Absorption maxima and extinction coefficients are given in Table II.

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(16) Analyses were done by Micro-Tech Laboratories, Skokie, Ill.

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