atom, so the spectrum obtained is actually that of the corresponding hypoxanthine.

Biological data. Some of the 7-substituted-7*H*-purines which we have screened have shown cell cytotoxicity (H. Ep-2) and activity against Adenocarcinoma 755. A comparison of the activity of the corresponding 7- and 9-substituted purines can now be made.

EXPERIMENTAL

Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer or a Beckman DK-2 (optical densities at the maxima with a Beckman DU).

Preparation of N-(4-amino-5-pyrimidinyl)formamides. A dry sample of the 4,5-diaminopyrimidine was dissolved in an excess of 98% formic acid and the formylation reaction allowed to proceed under the appropriate conditions. The reaction mixture was then evaporated to dryness *in vacuo* with additions of ethanol, before it was transferred to a sintered glass funnel and triturated with several small portions of ethanol. The insoluble solid was dried by ether trituration, then *in vacuo*, to give the crude product, which was recrystallized, if necessary, from ethanol. Details of the individual reactions are given in Table I.

Alkylation of N-(4-amino-5-pyrimidinyl)formamides. The 5-pyrimidinylformamide was dissolved in *N,N*-dimethylformamide with an equivalent (mole/mole) of anhydrous potassium carbonate (or 1.5 equivalents of sodium hydride) and the reaction mixture stirred vigorously. Two equivalents of *o*-chlorotoluene (or iodoalkane) were added to the reaction mixture and the resulting mixture stirred vigorously at room temperature.

After the reaction was complete, the mixture was evaporated to dryness and the residue triturated with water. The insoluble solid was collected by filtration, washed with ethanol and ether, and dried *in vacuo*. The crude product was recrystallized from ethanol if necessary. Details of individual reactions are given in Table I.

Cyclization of N-(4-amino-5-pyrimidinyl)-N-substituted formamides. A. In N,N-dimethylformamide. The *N*-(4-amino-5-pyrimidinyl)-*N*-substituted formamide, with or without previous isolation, was allowed to react in *N,N*-dimethylformamide containing 1 equivalent of anhydrous potassium carbonate. The mixture was stirred vigorously under anhydrous conditions until cyclization was complete, and then poured into ice water from which the crude product that precipitated was collected by filtration, washed with water and dried with ethyl alcohol and ether to give the 7-substituted purine. If necessary, the crude product was recrystallized from ethyl alcohol. Details of each reaction are given in Table I.

B. In 98% formic acid. A solution of dry *N*-(4-amino-5-pyrimidinyl)-*N*-alkylformamide in a large excess of 98% formic acid was refluxed until hydrolysis of the chlorine atoms and cyclization were complete, as indicated by the ultraviolet spectrum of reaction aliquots. The reaction mixture was then evaporated to dryness *in vacuo* several times with additions of ethyl alcohol to give the crude hypoxanthine which was recrystallized from water. Details of the individual reactions are given in Table I.

7-Benzyl-6-(benzylthio)-7H-purine (XVII). A solution of *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]-*N*-benzylformamide (50 mg., 0.16 mmole) in formamide (5 ml.) was refluxed for 30 min. After being cooled to room temperature, the reaction mixture was diluted with two volumes of cold water and the insoluble grey solid that precipitated was collected by filtration and air dried. The solid was triturated in boiling cyclohexane, the mixture filtered to remove insoluble material, and the filtrate allowed to stand in the cold until crystallization was complete. The white solid was collected by filtration and dried *in vacuo*; yield, 24 mg. (51%) of purified product.

Acknowledgment. The authors are indebted to Dr. W. J. Barrett and the members of the Analytical Section of Southern Research Institute who performed the spectral and most of the analytical determinations reported. Some of the analyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ROOSEVELT UNIVERSITY]

Synthesis and Properties of 5-(Substituted) Mercaptotetrazoles[1]

EUGENE LIEBER[2] AND TAKASHI ENKOJI[3]

Received November 8, 1960

Improved procedures for the synthesis of aryl thiocyanates have been developed. A series of alkyl and aryl thiocyanates has been converted to 5-(substituted) mercaptotetrazoles by reaction with azide ion in dimethylformamide in the presence of ammonium chloride. The 5-(substituted) mercaptotetrazoles undergo decomposition, at or near their melting points, to hydrazoic acid and the corresponding thiocyanate. The ultraviolet spectra indicates that the tetrazolyl sulfide group is electron donating. The 5-(substituted) mercaptotetrazoles are acids with pK_a values in the range 3.08–4.53 and their acidities are influenced by the electron-donating or -withdrawing nature of the R substituent on the sulfur atom.

A recent study by Finnegan[4] has shown that when aliphatic and aromatic nitriles are treated with azide ion in the presence of a suitable catalyst, using dimethylformamide (DMF) as a solvent, 5-(substituted) tetrazoles (I) are obtained in excellent yields. They also reported that when benzyl thiocyanate was used instead of the nitrile, the primary reaction was that of displacement although a substantial amount of 5-benzylmercaptotetrazole (I.

(1) Sponsored by the Office of Ordnance Research, U. S. Army.

(2) To whom all correspondence should be addressed.

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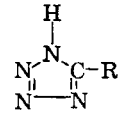
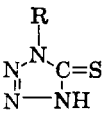
(4) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Org. Chem.*, 80, 3908 (1958).

R = $C_6H_5CH_2S$) was obtained. Methyl thiocyanate gave an excellent yield of 5-methylmercaptotetrazole (I. R = CH_3S).

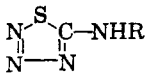
The present investigation relates to the reactions of a series of organic thiocyanates with sodium azide substantially under the conditions previously described.[4] The resulting 5-(substituted) mercaptotetrazoles were desired for comparison with the isomeric 1-(substituted) tetrazoline-5-thiones[5,6] (II) and 5-(substituted) amino-1,2,3,4-thiatriazoles[7] (III):



I

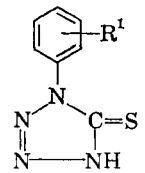


II

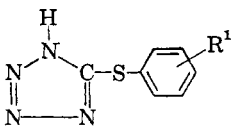


III

Lieber[6] studied the ultraviolet absorption spectra acidities of II and III. The electron-donating or withdrawing nature of substituents (IV. R^1) on the phenyl ring had a measurable effect on the acidity. The Hammett *sigma* values of these substituents exhibited a linear relationship when plotted against pK_a values. It was then one of the objectives of this study to determine whether the isomeric 5-(substituted aryl)mercaptotetrazoles(V) were similarly effected by substituent R^1 on the phenyl ring.

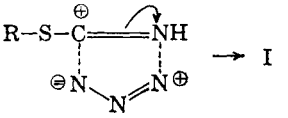


IV



V

Lieber *et al.*[5] found that water could be used in the condensation of methyl and benzylthiocyanate, respectively with azide ion. In the present study water was found not to be a suitable solvent for the condensation of more complex thiocyanates. While the condensation can be carried out in the absence of acidic catalyst, it is evident (Table I) that acidic catalysis leads to improved yields. The present study has revealed that mixtures of dioxane and water represent a convenient solvent for this reaction. It is also evident (Table I) that an optimum temperature exists. This fact is significant as this study has revealed that V was found to decompose at or slightly above their melting points to yield hydrazoic acid and the original thiocyanate. The reaction temperature for many of these condensations (Table II) was at the reflux temperature of dimethylformamide (*ca.* 150°) which is actually higher than the decomposition points of the expected products. This factor may account for the lack of correlation observed in the present study on the electronegativity of the substituent of the arylthiocyanate with yield of V. Finnegan *et al.*[4] observed that increasing electron-withdrawing substituents of aryl nitriles increased the yield of I at a condensation temperature of 100°. There is no doubt but that the mechanism suggested by Finnegan *et al.*[4] for the acid-catalyzed condensation of azide ion with organic nitriles is directly applicable to thiocyanates and need not be elaborated here. However, it is suggested that it is not necessary to assume an imino azide, —C(NH)N_3, as precursor, as the formation of I can arise by simple neutralization of charges:



the bent azido-moiety, representing the reactive intermediate of the rigid linear azido group. A comparison of the melting points of the 5-(substituted) mercaptotetrazoles with the isomeric 5-(substituted) amino-1,2,3,4-thiatriazoles and 1-(substituted) tetrazoline-5-thiones in Table III shows that the 5-(substituted) mercaptotetrazoles generally melt higher than the other two.

It has been demonstrated in this investigation that 5-(substituted) mercaptotetrazoles, upon heating at or slightly over their melting points, yield hydrazoic acid and the corresponding organic thiocyanates. In some instances, a considerable amount of tars are formed which are insoluble in chloroform. Upon heating, the compound probably undergoes a heterolytic bond cleavage. It is obvious that a cleavage of the 1,2-bond would result in the same intermediate as a cleavage of the 3,4-bond. A

TABLE I

COMPARATIVE STUDIES IN THE REACTION OF BENZYL THIOCYANATE WITH SODIUM AZIDE[a]

Solvent	Catalyst	Time, Hr.	Temp.	Yield,[b] %
DMF	NH_4Cl	6	95	22.0[c]
DMF	NH_4Cl	6	125	13.5
DMF	NH_4Cl	6	152	4.7
50% Aqueous dioxane	None	6	89	1.9
80% Aqueous dioxane	None	6	89	5.4
67% Aqueous dioxane	NH_4Cl	20	89	11.6
80% Aqueous dioxane	NH_4Cl	6	89	26.6
Water	NH_4Cl	6	100	4.7

[a] One-tenth mole of reagents, and 100 ml. of solvent used in all runs. [b] Based on recrystallized 5-benzylmercaptotetrazole, m.p. (from toluene) 134–135°. [c] *Anal.* Calcd. for $C_8H_8N_4S$: N, 29.16; S, 16.687. Found: N, 29.50; S, 16.50. Finnegan *et al.*[4] report a m.p. of 137.5–138.5°, Lieber *et al.*[5] report 138–138.5°.

(5) E. Lieber and J. Ramachandran, *Can. J. Chem.*, **37**, 101 (1959).

(6) E. Lieber, J. Ramachandran, C. N. R. Rao, and C. N. Pillai, *Can. J. Chem.*, **37**, 563 (1959).

(7) E. Lieber, C. N. Pillai, and R. D. Hites, *Can. J. Chem.*, **35**, 832 (1957).

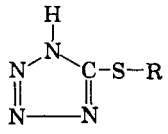
TABLE II. 5-(SUBSTITUTED) MERCAPTOTETRAZOLES[a] RSCHN$_4$

R	M.P.	Yield,[b] %	Reaction Temp.,[c]	Reaction Solvent	Method of Work-up[d]	Recrystn. Solvent	Cryst. From	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
CH_3	144–146	71	95	DMF	A	Dioxane	Prisms	$C_2H_4N_4S$	48.26	47.90		
C_2H_5	86–88	15	89	DW[e]	B	Toluene	Plates	$C_3H_6N_4S$	43.04	42.90	24.64	24.30
i-C_3H_7	61–63	25	125	DMF	B	Carbon tetrachloride	Needles	$C_4H_8N_4S$	38.85	39.40	22.26	22.00
CH_2=$CHCH_2$	65–67	4	95	DMF	C	Cyclohexane	Prisms	$C_4H_6N_4S$	39.40	39.70	22.65	22.20
n-C_4H_9	96–97	33	125	DMF	C	Toluene	Needles[f]	$C_5H_{10}N_4S$	35.41	35.00	20.26	19.70
$C_6H_5CH_2$	134–135	27	89	DW	A	Toluene	Feathers	$C_8H_8N_4S$	29.16	29.50	16.68	16.50
4-$NH_2C_6H_4$	199–200	25	Reflux	DMF	A	*n*-Propyl alcohol	Powder[g]	$C_7H_7N_5S$	36.52	36.60	16.60	16.60
4-$(CH_3)_2NC_6H_4$	192–193	15	"	"	A	Ethyl acetate	Needles	$C_9H_{11}N_5S$	31.65	31.40	14.49	14.28
4-$CH_3OC_6H_4$	163–164	62	"	"	A	Toluene	Needles	$C_8H_8N_4OS$	26.91	27.10	15.40	15.88
4-$CH_3C_6H_4$	172–173	70	"	"	A	Ethyl acetate	Needles	$C_8H_8N_4S$	29.14	29.43	16.68	16.45
C_6H_5	92–93	25	"	"	D	Toluene	Prisms	$C_7H_6N_4S$	31.44	31.00	17.99	17.80
4-FC_6H_4	142–143	32	"	"	E	Toluene	Needles	$C_7H_5N_4SF$	28.56	28.61	16.34	16.80
3-$CH_3OC_6H_4$	158–159	14	"	"	E	Ethanol toluene	Needles	$C_8H_8N_4OS$	26.91	27.00	15.40	15.45
4-ClC_6H_4	157–158	38	"	"	A	Toluene	Needles	$C_7H_5N_4SCl$	26.34	26.60	15.07	15.10
4-BrC_6H_4	176–177	56	"	"	A	Ethyl acetate	Needles	$C_7H_5N_4SBr$	21.79	21.96	12.47	12.47
4-IC_6H_4	190.5–191	38	"	"	A	Ethylene dichloride	Needles	$C_7H_5N_4SI$	18.42	18.50	10.54	10.47
3-$F_3CC_6H_4$	105–106	31	"	"	E	Toluene	Plates	$C_8H_5N_4SF_3$	22.76	22.60	13.02	13.45
4-$(COOC_2H_5)C_6H_4$	103–104	27	"	"	F	Toluene	Prisms	$C_{10}H_{10}N_4O_2S$	22.39	22.20	12.81	12.35
4-$NO_2C_6H_4$	189–191	68	"	"	E	Ethyl acetate	Needles[h]	$C_7H_5N_5O_2S$	31.65	31.40	14.12	14.30

[a] All new compounds except R = CH_3 and $C_6H_5CH_2$. [b] Based on product having a m.p. of ±2° of analytical sample. [c] Reaction time of 6 hr. [d] For *Methods A*, *B*, and *C* see ref. 4; for *Methods D*, *E*, and *F* see Expl. section. [e] 80% dioxane–20% water. [f] Cream color. [g] Tan color. [h] Yellow.

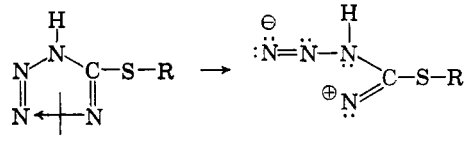
TABLE III

SUMMARY OF ISOMERIC 5-(SUBSTITUTED) AMINOTHIATRIAZOLES, 1-(SUBSTITUTED) TETRAZOLINE-5-THIONES, AND 5-(SUBSTITUTED) MERCAPTOTETRAZOLES

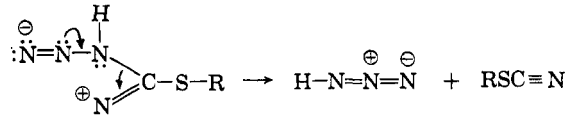


III II

R	M.P.[7]	M.P.[5]	M.P.
CH_3	93–96	125–126	144–146
C_2H_5	66–67	50	86–88
n-C_4H_9	40–41	Oil	96–97
CH_2=$CHCH_2$	53–53.5	69	65–67
$C_6H_5CH_2$	80.5–81	144	134–135
C_6H_5	142–143	150	92–93
p-CH_3—C_6H_4	142–144	153	172–173
p-Cl—C_6H_4	145–147	156–157	157–158
p-F—C_6H_4	127–128	154–155	142–143
p-NO_2—C_6H_4	152–153	148	189–191
p-$(CH_3)_2N$—C_6H_4	140	180	192–193



cleavage of the 2,3-bond would not yield the known products. After initial cleavage, the resulting intermediate undergoes rearrangement with the formation of the thiocyanate and evolution of hydrazoic acid. The loss of hydrazoic acid eliminates the possibility of the reformation of the tetrazole ring driving the reaction in one direction.



It has been reported[8] that tetrazole and its alkyl-substituted derivatives do not exhibit characteristic absorption in the 220–340-mμ region. A similar situation exists in other five-numbered, conjugated, heterocyclic nitrogen systems such as pyrazole,[9] imidazole,[10] 1,2,3-triazole,[11] and 1,2,4-triazole.[12] Some of the 5-alkylmercaptotetrazoles exhibit expected ultraviolet absorption characteristics in that no maxima are observed (Table IV, Fig. 1). However, 5-ethylmercaptotetrazole and 5-isopropylmercaptotetrazole both exhibit a definite but

(8) F. W. Schueler, S. C. Wand, R. M. Featherstone, and E. G. Gross, *J. Pharmacol. Exper. Therapy*, **97**, 226 (1949).

(9) D. M. Cassoni, D. Mangini, and R. Passerini, *Boll. Sci. Fac. Chim. Ind. (Bologna)*, **12**, 147 (1954).

(10) E. A. Braude, *Ann. Repts. Chem. Soc.*, **42**, 105 (1954).

(11) L. W. Hartzel and F. R. Benson, *J. Am. Chem. Soc.*, **76**, 668 (1954).

(12) M. R. Atkinson, E. A. Parkes, and J. B. Polya, *J. Chem. Soc.*, **1954**, 4256.

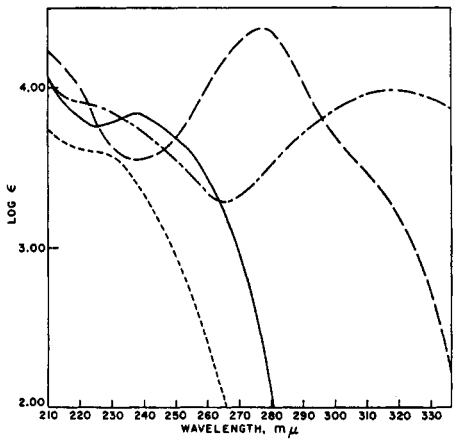
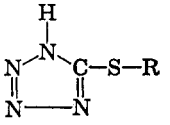


Fig. 1. The ultraviolet absorption of 5-(substituted) mercaptotetrazoles in methanol

5-Methylmercaptotetrazole ———
5-Phenylmercaptotetrazole ———
5-(*p*-*N*,*N*-Dimethylaminophenyl)-mercaptotetrazole - - - -
5-(*p*-Nitrophenyl)mercaptotetrazole — — —

TABLE IV

ULTRAVIOLET ABSORPTION OF 5-(SUBSTITUTED) MERCAPTOTETRAZOLES



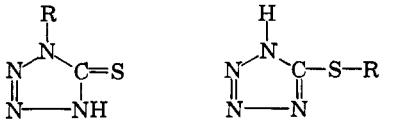
R	λ_{max}	λ_{min}	Log ϵ_{max}	Log ϵ_{min}
Methyl	228[a]		3.42	
Ethyl	237	229	3.46	3.28
Isopropyl	237	229	3.18	3.15
Allyl	247	221	4.06	3.52
n-Butyl	228[a]		3.47	
Benzyl	243[a]		3.47	
p-NH_2-Phenyl	260	226	4.08	3.49
p-$(CH_3)_2N$-Phenyl	275	235	4.40	3.64
p-CH_3O-Phenyl	234	218	4.09	3.90
p-CH_3-Phenyl	241	233	3.93	3.89
Phenyl	248	225	3.89	3.76
p-F-Phenyl	235	226	3.81	3.77
	220	237	4.14	3.64
	240	268	3.65	2.52
m-CH_3O-Phenyl	283	287	3.36	3.25
	290		3.30	
p-Cl-Phenyl	222	235	3.87	3.81
	244		3.89	
p-Br-Phenyl	233	238	3.94	3.93
	247		3.99	
p-I-Phenyl	257	222	4.14	3.80
m-F_3C-Phenyl	240	227	3.90	3.77
	250	246	3.88	3.87
p-$COOC_2H_5$-Phenyl	224	248	3.75	3.50
	277		4.14	
p-NO_2-Phenyl	315	264	4.02	3.42

[a] Appears as a shoulder.

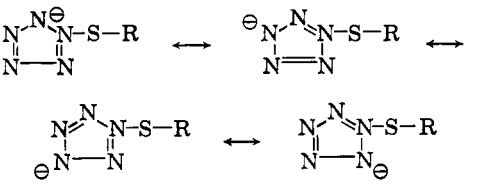
poorly defined maxima. It is possible that these alkylmercapto groups are interacting with the tetrazole ring through hyperconjugation. The fact that the 5 - alkylmercaptotetrazoles are moderately strong acids (Table V) is undoubtedly due to resonance stabilization of the anion, resulting in a fair degree of ionization:

TABLE V

COMPARATIVE ACIDITIES OF ISOMERIC 1-(SUBSTITUTED) TETRAZOLINE-5-THIONES[6] AND 5-(SUBSTITUTED) MERCAPTOTETRAZOLES



R	pK_a	
p-NO_2-Phenyl	3.36	3.15
p-F-Phenyl	3.61	3.69
p-Cl-Phenyl	3.62	3.58
Phenyl	3.65	3.78
p-CH_3-Phenyl	3.75	3.83
p-CH_3O-Phenyl	3.78	4.00
Benzyl	3.80	4.08
Ethyl	3.85	4.28
Methyl	3.86	4.27
Allyl	3.91	3.77
p-$(CH_3)_2N$-Phenyl	4.09	4.53



The case of 5-allylmercaptotetrazole is unique in that because of the unsaturation in the side chain, there is even greater mutual electronic interaction, giving rise to a net bathochromic effect on the ultraviolet absorption. This is also evident from the greater acidity of 5-allylmercaptotetrazole. These effects were also observed in 5-benzylmercaptotetrazole, although to a lesser extent. The 5-alkylmercaptotetrazoles absorb in the 228–247-mμ range and have pK_a values in the range of 3.77–4.28. The 5-arylmercaptotetrazoles may be considered disubstituted derivatives of benzene for the purpose of studying their ultraviolet absorption. It can be seen from Table IV that all of the aryl compounds exhibit definite absorption maxima in the 234–275-mμ region. Inasmuch as the tetrazole ring itself exhibits no maximum, these maxima must be attributed to the benzene rings. By comparison of these spectra with those of monosubstituted benzenes bearing similar substituents, it was possible to identify the E-bands. On this basis a correlation of the $\Delta\lambda$ values[13] with the Hammett sigma values was attempted (Table VI). Here it was found that the correlation was reasonably good for 5-arylmercaptotetrazoles with electron-withdrawing groups on the benzene ring, whereas, compounds with electron-donating groups gave poor correlation

(13) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947); **71**, 2414 (1949).

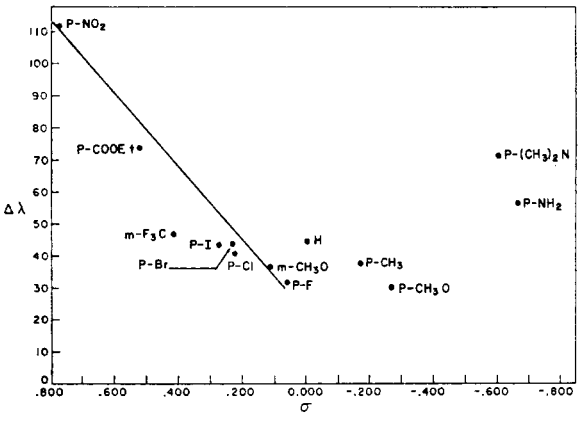


Fig. 2. Plot of Δλ of 5-(substituted) mercaptotetrazoles *vs.* Hammett sigma values

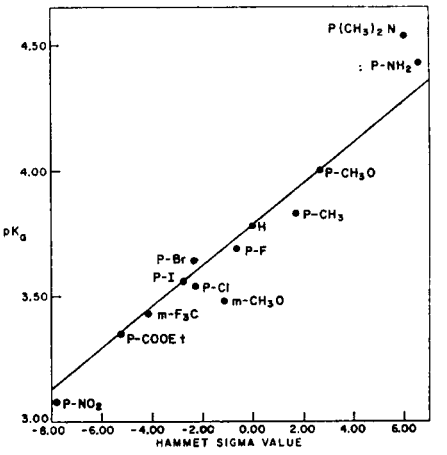
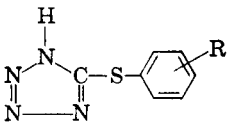


Fig. 3. Plot of pK_a of 5-(substituted) mercaptotetrazoles versus sigma values for groups

TABLE VI

HAMMETT SIGMA VALUES AND Δλ OF 5-(SUBSTITUTED) MERCAPTOTETRAZOLES



R	σ	λ_{max}	Δλ
p-NH_2	−0.660	260	56.5
p-$(CH_3)_2N$	−0.600	275	71.5
p-CH_3O	−0.268	234	30.5
p-CH_3	−0.170	241	37.5
H	0.000	248	44.5
p-F	0.062	235	31.5
m-CH_3O	0.115	240	36.5
p-Cl	0.226	244	40.5
p-Br	0.232	247	43.5
p-I	0.276	257	53.5
m-F_3C	0.415	250	46.5
p-$COOC_2H_5$	0.522	277	73.5
p-NO_2	0.778	315	111.5

(Fig. 2). In view of Rao's[14] observation that compounds with substituents of opposite charge give good correlation, it must be concluded on this basis that the mercaptotetrazoyl group is electron donating in nature, and to a greater extent than the thiocyano group.

It can be seen that the replacement of the alkyl group in 5-alkylmercaptotetrazoles with a phenyl ring greatly enhances the acidity of 5-(substituted) mercaptotetrazoles (Table V). A comparison shows that 5-phenylmercaptotetrazole has a pK_a value of 3.78 as compared to an average value of 4.27 for nonconjugated 5-alkylmercaptotetrazoles. As in 5-allylmercaptotetrazole, there is considerable electronic interaction between the benzene ring and the tetrazole ring. The addition of a nitro group to the benzene nucleus increases the acidity even further to give a pK_a value of 3.08 for 5-(*p*-nitrophenyl)-mercaptotetrazole. The addition of an electron-donating group has an opposite effect in that it decreases the acidity, so that 5-(*p*-aminophenyl)-mercaptotetrazole has a pK_a of 4.43. This compound is not only less acidic than the unsubstituted 5-phenylmercaptotetrazole, but even less than the 5-alkylmercaptotetrazoles. Fig. 3 presents a correlation of pK_a versus the sigma values for groups.

Tables VII and VIII tabulate the frequencies of the recurring bands in the infrared region. The more interesting aspects of the infrared study were of the cyclic N—N=N band, the skeletal vibrations of the tetrazole ring and C—S stretching band. All of the nineteen 5-(substituted) mercaptotetrazoles studies exhibited a medium to strong intensity band in the 1335–1277-cm.$^{-1}$ range. On the basis of a study of a series of tetrazole derivatives by Lieber, Levering, and Patterson,[15] and further study of a number of tetrazolinethiones and thiatriazoles, Lieber *et al.*[16] were able to make a tentative frequency assignment for the cyclic N—N=N linkage. In the case of the 5-alkylmercaptotetrazoles, a band of strong intensity was found in the 1319–1299-cm.$^{-1}$ region. With the 5-arylmercaptotetrazoles, the range was somewhat wider at 1335–1277 cm.$^{-1}$ and the intensity was medium to strong. Lieber,[15,16] after extensive study of many five-membered heterocyclic compounds containing at least three adjacent nitrogen atoms in the ring, suggested the assignment of the 1300–1270-cm.$^{-1}$ region for the cyclic N—N=N group. It is interesting to note that the variable symmetric vibration of the azido group N_3, has been assigned the 1343–1177-cm.$^{-1}$ range by Sheinker and Syrkin.[17] Lieber has assigned the 1297–1256-cm.$^{-1}$ region for this symmetric vibration band.

In the 5-(substituted) mercaptotetrazoles, three distinct series of bands were observed in the 1085–977-cm.$^{-1}$ region. Each band was found to lie within the relatively narrow ranges of 1085–1068, 1041–

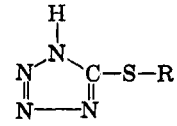
(14) C. N. R. Rao, *Chem. & Ind.*, 666 (1956).

(15) E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(16) E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958).

TABLE VII

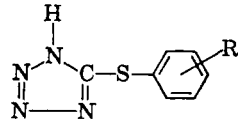
INFRARED SPECTRA OF 5-ALKYLMERCAPTOTETRAZOLES



R	Cyclic N—N=N	Skeletal			C—S—C	Other Bands		
Methyl	1299 S	1064 M	1044 S	987 S	679 M	1520 S	1348 M	725 M
Ethyl	1310 S	1085 M	1044 S	981 M	688 M	1520 S	1355 S	765 S
Isopropyl	1319 S	1083 M	1033 S	980 M	688 M	1520 S	1368 S	714 W
n-Butyl	1312 S	1078 M	1040 S	983 M	688 M	1520 S	1353 S	741 M
Allyl	1299 S	1074 W	1050 S	987 S	667 M	1488 S	1344 S	764 S
Benzyl	1316 S	1078 S	1035 S	978 M	702 S	1534 S		773 M

TABLE VIII

INFRARED SPECTRA OF 5-ARYLMERCAPTOTETRAZOLES



R	Cyclic N—N=N	Skeletal			Phenyl		Disubst. Phenyl	C—S—C
p-NH_2	1330 S	1082 W	1039 M		1620 M	1488 S	1016 W	693 W
p-$(CH_3)_2N$	1302 M	1082 W	1036 M	977 W	1590 S	1497 M	990 W	
p-CH_3O	1300 S	1073 W	1022 S	980 M	1590 S	1488 S	1000 M	680 W
p-CH_3	1312 S	1076 M	1025 S	978 M	1590 W	1515 S	1012 S	686 W
H	1314 S	1076 M	1030 S	978 M	1623 W	1515 S	998 M	
p-F	1305 S	1085 S	1041 S	980 M	1534 M	1488 S	1010 M	691 W
m-CH_3O	1304 S	1073 S	1031 S		1595 S	1488 S	991 S	670 M
p-Cl	1312 S	1085 S	1033 S	980 M	1541 M	1510 M	1009 S	687 W
p-Br	1304 M	1083 M	1032 M	981 M	1529 M	1473 M	1004 S	691 W
p-I	1305 S	1085 M	1029 M	980 M	1536 W	1508 M	1000 S	
m-F_3C	1312 S	1068 S	1036 M		1603 VW	1497 W		693 S
p-$COOC_2H_5$	1277 S		1019 S		1603 S	1475 M	1000 W	685 M
p-NO_2	1355 S	1083 M	1031 M		1603 M	1522 S	1002 W	694 W

1019, and 981–977 cm.$^{-1}$ A similar series of three or more bands were reported by Lieber *et al.*[15] for a number of other tetrazoles and 1-(substituted)-tetrazoline-5-thiones,[16] who attributed these to the skeletal vibrations of the tetrazole ring. Although these bands were also observed in other five-membered heterocyclic compounds such as 5-(substituted) amino-1,2,3,4-thiatriazoles[17] and vicinal-triazole derivatives,[18] they were generally found to be weak or variable in intensity. In this present investigation, as well as others mentioned above in which the tetrazole ring was involved, these bands were generally of medium to strong intensity. It can be said then that these bands are undoubtedly due to the skeletal vibrations of the tetrazole ring.

The 5-alkylmercaptotetrazoles exhibit a medium to strong intensity band in the neighborhood of 700 cm.$^{-1}$ Inasmuch as there are no aromatic bands in these compounds, it is a certainty that this band, 702–679 cm.$^{-1}$, is due to the C—S stretching vibration. This band is of variable intensity in the 5-arylmercaptotetrazoles, and lies between 694–670 cm.$^{-1}$ These findings are in agreement with that of Trotter[19] and Thompson[20] and also of Sheppard[21] who studied a number of alkyl mercaptans, sulfides, and disulfides. They are also in agreement with a study by Cymerman and Willis[22] who have worked with aromatic compounds. These latter workers have assigned the C—S frequency of aromatic compounds to the 702–673-cm.$^{-1}$ range.

A definite band was observed at 1534–1473 cm.$^{-1}$ in the 5-(substituted) mercaptotetrazoles. During preliminary examinations, it was felt that this was a band usually associated with aromatic compounds. However, when its presence was observed subsequently in the 5-alkylmercaptotetrazoles, other

(17) Y. M. Sheinker and Y. K. Syrkin, *Izvest. Akad. Nauk. S.S.S.R. Ser. Fiz.*, **14**, 478 (1950); *Chem. Abstr.*, **45**, 3246 (1951).

(18) E. Lieber, C. N. R. Rao, T. S. Chao, and H. Rubinstein, *Can. J. Chem.*, **36**, 1442 (1958).

(19) I. F. Trotter and H. W. Thompson, *J. Chem. Soc.*, 481 (1946).

(20) H. W. Thompson and D. J. Dupré, *Trans. Faraday Soc.*, **36**, 805 (1940).

(21) N. Sheppard, *Trans. Faraday Soc.*, **46**, 429 (1950).

(22) J. Cymerman and D. Willis, *J. Chem. Soc.*, 1951, 1332.

possibilities were explored. The C=N absorptions of conjugated cyclic systems have been assigned to the 1660–1480-cm.$^{-1}$ range by Bellamy.[23] Because of the uncertainty associated with this band, no definite assignment was made.

In the 5-alkylmercaptotetrazoles, a band of variable intensity was observed in the 773–714-cm.$^{-1}$ region. A similar absorption band is present in a variety of compounds of high nitrogen studied by Lieber, Levering, and Patterson.[15] This region is normally associated with the out-of-plane deformation frequencies of the hydrogen atoms on an aromatic ring. Inasmuch as these compounds are not aromatic, and as they are found in other types of nitrogen compounds, this band may be associated in some way with compounds of high nitrogen content.

EXPERIMENTAL[24]

Alkyl thiocyanates. Methyl, ethyl, isopropyl, *n*-butyl, and benzylthiocyanate, respectively, were prepared commercially and used without further purification. *Allyl thiocyanate* was prepared *in situ* from allyl bromide and potassium thiocyanate in dimethylformamide.

Aryl thiocyanates (Table IX). The aromatic thiocyanates used in this study were synthesized by one of three general methods.

Method 1 is an adaptation of the procedure described by Gattermann and Hausknecht[25] in which aryldiazonium salts are treated with a mixture of cuprous and potassium thiocyanates. Considerable improvements in yields were effected by avoiding steam distillation in the recovery of the product. Three variations in methods of recovery were developed.

Method A-1 is illustrated by the preparation of *p-fluorophenyl thiocyanate*, a new compound. A solution of 47.0 ml. (1 mole) of concd. sulfuric acid in 300 ml. of water was cooled to 5° with stirring in an ice-salt bath. To this was slowly added 44.4 g. (0.4 mole) of *p*-fluoroaniline. A solution of 27.6 g. (0.4 mole) of sodium nitrite in 100 ml. of water was added by means of a dropping funnel at a rate to maintain the temperature at 5–10°. When addition was completed, stirring was continued for 30 min., and the diazonium solution was added in portions to a stirred suspension of 48.6 g. (0.4 mole) of cuprous thiocyanate and 200 ml. of water. The thiocyanate suspension was precooled to 5°. Stirring was continued for 30 min. at 5–10° and then overnight at room temperature. The aqueous solution was carefully decanted from the semisolid mass, and the remaining solid was stirred with 1 l. of ethanol until a uniform suspension was obtained. The mixture was filtered and the insoluble material was washed with an additional 200 ml. of ethanol. The combined ethanol filtrates were distilled to near dryness under vacuum at steam bath temperature, and the residue extracted with 500 ml. of chloroform. The chloroform extract was washed with water and dried over magnesium sulfate. The residue from this extract was distilled at 14 mm. pressure (20-cm. Vigreux) and the fraction, b.p., 101–103°, was collected to yield 19.4 g. (32%).

Anal. Calcd. for C_7H_4FNS: N, 9.15 S, 20.93. Found: N, 9.25; S, 20.60.

Method A-2. The residue of the ethanol extraction was taken up in chloroform, the chloroform extract washed with water, dried, and filtered. The filtrate was distilled to remove the solvent and the residue steam distilled. The distillate (usually crystalline) collected and recrystallized from *n*-hexane.

Method A-3. The combined ethanol extracts were filtered hot, cooled in an ice bath, the crystals collected, dried, and sublimed at 90–100°/25 mm.

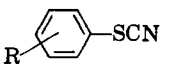
Method 2. This comprised direct thiocyanation.[26,27]

Method 3. The product of *Method 2* was converted to the desired product by the Sandmeyer reaction.[27,28]

Reaction of methyl thiocyanate with sodium azide. The reaction mixture comprised 0.1 mole each of methyl thiocyanate, sodium azide, and ammonium chloride in 100 ml. of dimethylformamide. Individual runs were made at 95°, 125°, and 152° for 6 hr. After removal of the dimethylformamide by vacuum distillation the product was recovered by *Method A* of Finnegan, Henry, and Lofquist.[4] The yields of *5-methylmercaptotetrazole* were 71, 62, and 58%. A similar run made with no ammonium chloride gave a zero yield. The melting point of the recrystallized product was 144–146°.[4,6,29]

TABLE IX

AROMATIC THIOCYANATES



R	Method	Yield[a]	M.P. B.P./Mm.
4-NH_2[b]	2	70	58–59[d]
4-$(CH_3)_2N$[c]	2	65	72–74[e]
4-CH_3O[b,f]	A-2	9	35–36[g]
4-CH_3[b]	A-1	25	130–132/19
H[b]	A-1	27	82–82.5/5
4-Cl[b]	3	48	36–38[h]
4-Br[b]	A-2	13	53–54[g]
4-I[b]	3	54	49–51[i]
4-F[j,k]	A 1	32	101–103/14
3-F_3C[l]	A-1	42	92–93/9
4-C_2H_5OOC—[j,m]	A-1	16	77–78[e]
4-O_2N[n]	A-3	66	131–132
3-CH_3O	A-1	27[o]	—

[a] Starting with 0.4 mole of amine and calcd. on purified product. [b] Ref. 26, 27. [c] R. W. Brewster and W. Schroeder, *Org. Syntheses*, **Coll. Vol. II**, 574 (1943). [d] Yellow prisms. [e] Yellow needles. [f] J. W. Dienski, *Rev. trav. chim.*, **50**, 1 (1931). [g] Colorless needles. [h] Prisms. [i] Flakes. [j] New compound. [k] See Exptl. section for analysis. [l] *Anal.* Calcd. for $C_8H_4F_3NS$: N, 6.90; S, 15.78. Found: N, 6.61; S, 15.69. [m] *Anal.* Calcd. for $C_{10}H_9NO_2S$: N, 6.76; S, 15.47. Found: N, 6.91; S, 15.21. [n] Ref. 28. [o] A viscous oil which could not be purified, however, an analytically acceptable tetrazole was obtained (Table II).

(23) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., 1954, p. 279.

(24) Microanalyses by Drs. G. Weiler and F. B. Straus, Oxford, England. Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer double-beam spectrophotometer equipped with sodium chloride optics. Spectra were obtained on pure liquids: solids, by solution (5%) in chloroform, mulls, or 1% potassium bromide wafers. Ultraviolet spectra were determined on a Cary Model N spectrophotometer with automatic scanning and recording attachments. Spectra were obtained in absolute methanol in matched quartz cells of one cm. path length and a scanning rate of 5–10 Å per second.

(25) L. Gattermann and W. Hausknecht, *Ber.*, **23**, 138 (1890).

(26) H. P. Kaufmann and W. Oering, *Ber.*, **59**, 189 (1926).

(27) R. Riemschneider, F. Wojahn, and G. Orlick, *J. Am. Chem. Soc.*, **73**, 5906 (1951).

(28) F. Challenger and A. D. Collins, *J. Chem. Soc.*, **125**, 1378 (1924).

(29) M. Freund and T. Paradies, *Ber.*, **28**, 74 (1895).

Anal. (for product at 95°): Calcd. for $C_2H_4N_4S$: N, 48.26. Found: N, 47.90.

Reaction of benzyl thiocyanate with sodium azide (Table I). The variations studied were solvent, catalyst, time, and temperature. *Method A*[4] recovery was used. The data are summarized in Table I.

5-(Substituted) mercaptotetrazoles. Table II.

5-Allylmercaptotetrazole (I. R = CH_2=$CHCH_2S$). *Allyl thiocyanate* was prepared *in situ*, by reaction of 24.2 g. (0.2 mole) of allyl bromide, 19.4 g. (0.2 mole) of potassium thiocyanate and 200 ml. of dimethylformamide as solvent at steam-bath temperature, with occasional stirring for 30 min. After cooling, the mixture was filtered and to the filtrate was added 13.0 g. (0.2 mole) of sodium azide and 10.8 g. (0.2 mole) of ammonium chloride. The reaction was carried out at 90–95° for 6 hr. with stirring. Method C[4] recovery was used. The colorless crystals were recrystallized from cyclohexane to obtain 1.0 g. (3% based on allyl bromide) of product melting at 65–67°. For analysis see Table II.

5-Arylmercaptotetrazoles. Typical procedures and methods of recovery are illustrated by the following preparations of *new compounds*. Table II summarizes the data for all of the compounds prepared.

5-Phenylmercaptotetrazole. Method D. The reactants comprised 0.026 mole each of phenyl thiocyanate, sodium azide, and 40 ml. of dimethylformamide. The mixture was refluxed with stirring for 6 hr. After removal of the solvent by vacuum distillation, 40 ml. of water was added and the *p*H adjusted to 11. The insoluble material was removed by extraction with two portions of chloroform and the aqueous layer acidified to *p*H 1. The oil which separated was extracted with chloroform and the extracts washed with water and dried. After removal of the chloroform, the oil remaining was solidified in the refrigerator and the resulting waxy material recrystallized from toluene. For properties and analysis see Table II.

5-(4-Fluorophenyl)mercaptotetrazole. Method E. The purification required two successive solutions in alkali and reprecipitation by acid. Recrystallization was effected from toluene.

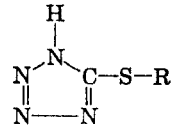
5-(4-Carbethoxylphenyl)mercaptotetrazole. Method F. The reaction residue obtained upon removal of the dimethylformamide was suspended in water and acidified. The solid, after drying, was extracted with ethyl acetate. The residue, obtained on removal of the ethyl acetate was extracted with chloroform. The chloroform extracts were combined and extracted twice with 0.1*N* sodium hydroxide. The alkali extracts were washed with chloroform, filtered and acidified to *p*H 1. The precipitate was collected and dried. Recrystallization was effected from toluene.

Thermal decomposition. The volatile product of the thermal degradation was identified as hydrozoic acid. The corresponding organic thiocyanate was extracted from the dark residues by chloroform extraction. Very qualitative experiments demonstrated that the rates of *pyrolytic decomposition* was in the order, for I, R, alkyl > R, aryl.

Comparative acidities. (Table X). The method of Lieber *et al.*[6] was used. The complete data for all of the tetrazoles are summarized in Table X, while Table V gives the comparative acidity with structure II as far as comparisons can be made. Fig. 3 presents the pK_a versus sigma values for substituents.

TABLE X

APPARENT DISSOCIATION CONSTANTS OF 5-(SUBSTITUTED) MERCAPTOTETRAZOLES



R	pK_a 1	2	3	Mean Value
Methyl	4.24	4.27	4.30	4.27
Ethyl	4.30	4.30	4.24	4.28
Isopropyl	4.27	4.28	4.27	4.27
Allyl	3.78	3.75	—	3.77
Butyl	4.33	4.37	4.30	4.33
Benzyl	4.12	4.06	4.07	4.08
p-NH_2—Phenyl	4.40	4.45	4.45	4.43
p-$(CH_3)_2N$—Phenyl	4.51	4.53	4.55	4.53
p-CH_3O—Phenyl	3.99	4.00	4.00	4.00
p-CH_3—Phenyl	3.78	3.84	3.86	3.83
Phenyl	3.75	3.78	3.82	3.78
p-F—Phenyl	3.68	3.68	3.70	3.69
m-CH_3O—Phenyl	3.46	3.55	3.45	3.48
p-Cl—Phenyl	3.46	3.58	3.58	3.54
p-Br—Phenyl	3.65	3.70	3.57	3.64
p-I—Phenyl	3.56	3.53	3.58	3.56
m-F_3C—Phenyl	3.42	3.45	3.42	3.43
p-$COOC_2H_5$—Phenyl	3.33	3.38	3.38	3.36
p-NO_2—Phenyl	2.93	3.15	3.15	3.08

CHICAGO 5, ILL.