Pharmacology.—The local anesthetic action was determined by the infiltration technique in guinea pigs. Five-hundredths of a cubic centimeter of a 1% solution of the hydrochloride of the test substance, buffered to a *p*H of 6–7.4, was injected intradermally and the response to a stimulus was determined at five-minute intervals. Each substance was tested on a minimum of four animals.

N′-Cinnamoyl-N,N-diethylethylenediamine (no. 1) had an average local anesthetic action, as determined by this test, of 25–30 minutes duration. The introduction of a substituent on the amide nitrogen resulted in a marked increase in the duration of local anesthesia. N′-Benzyl-N′-cinnamoyl-N,N-diethylethylenediamine (no. 5) was the most active compound in this series, with an activity lasting 240–300 minutes. Compounds with substituents in the aromatic ring (no. 6, 7, 8, 9) or on the alpha carbon atom of the cinnamic acid (no. 10, 11, 12) decreased the local anesthetic activity to approximately $^1/_2$ to $^2/_3$ that of the parent compound, no. 5. A similar effect was noticed in the replacement of the N,N-diethyl group by the N,N-dimethyl group (no. 4, 13). The N′-hydrocinnamoyl-N′-benzyl-N,N-diethylethylenediamine and N-β-(α-furyl)-acryloyl - N - benzoyl - N′,N′ - diethylethylenediamine had activities lasting 135–180 minutes and 118–126 minutes, respectively, as compared with 240–300 minutes for No. 5.

Experimental

The N′-phenyl and N′-benzyl substituted N,N-disubstituted ethylenediamines were obtained by the methods previously described.[3] N′-(*n*-Propyl)-N,N-diethylethylenediamine was prepared by the method of Kermack.[4] The substituted cinnamic acids were obtained by known procedures.[5]

N′-(*p*-Chlorocinnamoyl)-N′-benzyl-N,N-diethylethylenediamine.—Fifty milliliters of purified thionyl chloride was added slowly with occasional shaking to 9.1 g. (0.05 mole) of *p*-chlorocinnamic acid, and the mixture was then refluxed for two hours on the steam-bath. The excess thionyl chloride was distilled off under vacuum, 50 ml. of anhydrous benzene was added, and the benzene was removed under vacuum. To the residue, a solution of 4 g. of dry pyridine in 50 ml. of anhydrous benzene was added, the mixture was cooled to 10–15° and a solution of N′-benzyl-N,N-diethylethylenediamine in 50 ml. of anhydrous benzene was added dropwise with occasional shaking. The resulting mixture was heated under reflux for six hours and kept overnight at room temperature. The dark red mixture was poured into ice-water, made alkaline with dilute sodium hydroxide and extracted with ether. The ether extract was extracted with 10% hydrochloric acid, and the acid phase was then made alkaline with dilute sodium hydroxide. The red oil which precipitated was taken up in ether and the solution was dried over anhydrous sodium sulfate and distilled.

N′-Hydrocinnamoyl-N′-benzyl-N,N-diethylethylenediamine: b.p. 210–213° (2 mm.), $n^{24}D$ 1.5518, yield 58%.

Anal. Calcd. for $C_{22}H_{30}ON_2$: N, 8.28. Found: N, 8.42.

N-β-(α-Furyl)-acryloyl-N′-benzyl-N′,N′-diethylethylenediamine: b.p. 205–208° (1 mm.), $n^{24}D$ 1.5798, yield 64%.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.54.

N′-(*p*-Aminocinnamoyl)-N-benzyl-N,N-diethylethylenediamine.—Thirty-eight and six-tenths grams (0.2 mole) of *p*-nitrocinnamic acid was converted into the acid chloride by the method described in the preceding paragraph. The acid chloride was treated with a solution of 16 g. of dry pyridine, 39.2 g. (0.2 mole) N′-benzyl-N,N-diethylethylenediamine and 250 ml. of dry benzene and processed as described above. On neutralization of the hydrochloric acid extracts the product precipitated as a brownish-black crystalline mass (72 g.), which was difficult to purify. A small sample was recrystallized for analysis from a large volume of dilute ethanol.

A solution of 306 g. of ferrous sulfate heptahydrate in 1.5 liters of water and 200 ml. of ammonium hydroxide was heated to 85–90°, while a solution of 70 g. (0.18 mole) of the crude nitro compound in 750 ml. of ethanol was added slowly with constant stirring. The mixture was kept alkaline by the occasional addition of ammonium hydroxide, and maintained at 85–90° for one hour. After filtering, the alcohol was removed by distillation under vacuum and the residue was thoroughly extracted with ethyl acetate. After drying, the solvent was removed and the residue was distilled. The distillation was accompanied by excessive charring and decomposition.

BLOOMFIELD, NEW JERSEY

(4) W. O. Kermack and T. W. Wight, *J. Chem. Soc.*, 1421 (1935).

(5) See Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 210–265.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

Thermal Isomerization of Substituted 5-Aminotetrazoles[1]

BY RONALD A. HENRY, WILLIAM G. FINNEGAN AND EUGENE LIEBER

RECEIVED MAY 29, 1953

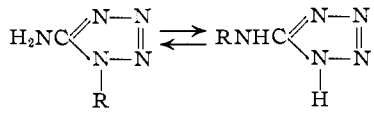
The isomerization of 1-substituted 5-aminotetrazole to 5-substituted aminotetrazoles, or *vice versa*, at 180 to 200° in homogeneous systems has been investigated and found to reach an equilibrium. The position of equilibrium is shifted toward the 5-substituted aminotetrazole as the electronegativity of the substituent is increased. An approximately linear relationship exists between the position of equilibrium and the pK_a of the 5-substituted aminotetrazole. In addition there is an excellent correlation between the logarithms of the equilibrium constants and Hammett's σ-values for groups. A mechanism of the isomerization, which involves the distribution of charge on a substituted guanyl azide intermediate, is proposed.

In a previous investigation[2] the isomerization of 5-alkylamino-, 1-aryl-5-amino- and 1-aryl-5-alkylaminotetrazoles at 180–200° to 1-alkyl-5-amino-, 5-arylamino- and 1-alkyl-5-arylaminotetrazoles, respectively, was described. Some evidence was reported which indicated that the isomerizations involved an equilibrium, although essentially quantitative conversions were frequently obtained. Since the isomerized product melted higher than the isomerization temperature in many cases, the equilibrium would be continuously displaced toward the isomerized product by solidification of the melt. A more careful study of the isomerization of monosubstituted 5-aminotetrazoles in homogeneous systems (undisturbed melt or solution in ethylene glycol) definitely confirms this idea of an equilib-

(1) Presented at the 123rd Meeting of the American Chemical Society, March 15–19, 1953.

(2) W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

rium, which can be expressed by the general equation



Experimentally, the equilibrium can be reached starting with either the 1-substituted 5-aminotetrazole or the 5-substituted aminotetrazole and is conveniently determined by titrating the latter compound, which is an acid comparable to acetic acid in strength. For example, either 1-phenyl-5-aminotetrazole or 5-phenylaminotetrazole, on heating to 194° in boiling ethylene glycol, yields a mixture of both products, which contains 55.3% of 5-phenylaminotetrazole. Further examples are given in Table I.

TABLE I

PROOF OF EQUILIBRIUM IN HOMOGENEOUS MELTS AT 199–201°

Starting tetrazole derivative	5-Sub. aminotetrazole in equil. melt, %	Starting tetrazole derivative	5-Sub. aminotetrazole in equil. melt, %
1-Ethyl-5-amino-	3.8[a]	1-(4-Tolyl)-5-amino-	36.8
5-Ethylamino-	3.5[a]	5-(4-Tolyl)-amino-	37.4
1-Benzyl-5-amino-	7.7	1-Phenyl-5-amino-	42.0
5-Benzylamino-	7.6	5-Phenylamino-	43.8
1-(4-Anisyl)-5-amino-	27.0	1-(2-Anisyl)-5-amino-	58.9[b]
5-(4-Anisyl)-amino-	27.2	5-(2-Anisyl)-amino-	58.6[b]

[a] Determined at 189–191°. [b] Determined in boiling ethylene glycol at 193–194°.

When the substituent is strongly electronegative, the 5-substituted aminotetrazole appears to be the major product when a substituted guanyl azide is ring closed in solution.[3] This suggested that electronegative substitution on the benzene ring of 1-phenyl-5-aminotetrazole would shift the position of equilibrium toward the 5-arylaminotetrazole and electropositive substitution toward the 1-aryl-5-aminotetrazole. The results obtained (Table II) confirm this idea when *m*- and *p*-substituents are employed. The results are more difficult to interpret when strictly electronegative effects are considered in the case of *o*-substituents, due to *o*-effects and hydrogen bonding. A number of alkyl and benzyl substituted 5-aminotetrazoles were studied as additional examples of electropositively substituted 5-aminotetrazoles. Generally, as the electronegativity of the substituent increased, the pK_a of the 5-substituted aminotetrazole decreased and the position of equilibrium shifted toward the 5-substituted aminotetrazole (Fig. 1). In addition an approximately linear relationship exists between the pK_a and Hammett's σ-values[4] for the substituent on the benzene ring (Fig. 2), and also between the logarithm of the equilibrium constant and Hammett's σ-values (Fig. 3).

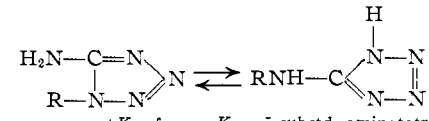
In order to explain the pronounced influence of the ring substituent on the acidity of the 5-arylaminotetrazoles, one can assume that an *o*- or *p*-

(3) See for example, the ring closure of nitroguanyl azide. E. Lieber, E. Sherman, R. A. Henry and J. Cohen, THIS JOURNAL, **73**, 2327 (1951).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

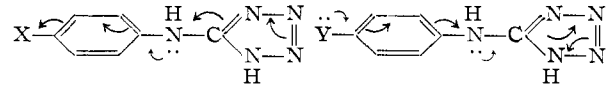
TABLE II

EQUILIBRIUM CONSTANTS



R	pK_a of 5-substituted aminotetrazole	K = 5-substd. aminotetrazole/1-substd. 5-aminotetrazole, Melt at 189–191°	Melt at 199–200°	In boiling ethylene glycol (193–194°)
CH_3	6.69	...	...	0.042
C_2H_5	6.68	0.038	...	...
n-C_7H_{15}	..	.047	...	...
n-$C_{10}H_{21}$	..	.045	...	...
Cyclo-C_6H_{11}	6.78	...	...	0.067
CH_2=$CHCH_2$	..	.072	...	.087
$C_6H_5CH_2$	6.64	.080	0.082	.10
2,6-$(CH_3)_2C_6H_3$	..	...	.13	.14
4-$NH_2C_6H_4$	6.53	...	...	.21
2,4-$Cl_2C_6H_3CH_2$	..	...	...	.22
2-HOC_6H_4	..	...	...	.28
2,4-$(CH_3)_2C_6H_3$	..	...	.30	.30
4-HOC_6H_4	..	...	...	.34
2-$CH_3C_6H_4$	6.08	.44	.46	.47
4-$CH_3OC_6H_4$	6.00	...	.37	.52
4-$CH_3C_6H_4$	5.95	.60	.59	.75
2-$C_6H_5C_6H_4$	..	...	...	.77
3-$NH_2C_6H_4$	6.02	...	...	.81
3-$CH_3C_6H_4$	5.94	...	...	1.02
C_6H_5	5.81	.86	0.72, 0.78	1.24
2-$CH_3OC_6H_4$	5.71	...	0.86	1.44
3-$CH_3OC_6H_4$	5.78	...	...	1.51
2-$C_{10}H_7$	..	...	...	1.63
4-ClC_6H_4	..	...	...	2.62
3-ClC_6H_4	5.42	...	...	3.72
2-ClC_6H_4	5.27	...	...	4.27
3-$NO_2C_6H_4$	5.17	...	...	5.67
3-$CF_3C_6H_4$	..	...	...	5.85
4-$NO_2C_6H_4$	4.87	...	...	15.23

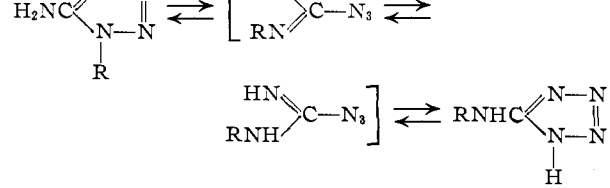
substituent is placed in conjugation with the tetrazole ring by resonance through the amino group.



X is electronegative Y is electropositive

The inductive effect, the only influence exerted in the case of a *m*-substituent, can also alter the electronic charge of the bridging nitrogen atom and thus increase or decrease the acidity of the tetrazole.

A possible mechanism has been proposed for the isomerization which involves a thermal opening of the tetrazole ring to a substituted guanylazide and reclosing to the equilibrated mixture. This is represented simply by the equations



The mechanism of ring closure of the guanylazide

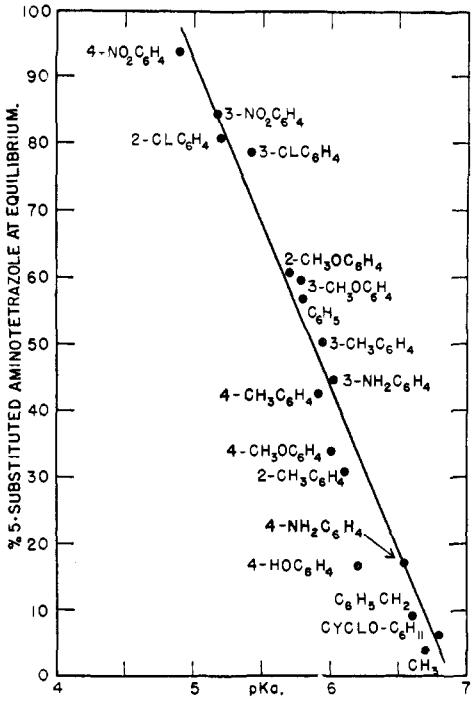


Fig. 1.—Correlation between position of equilibrium and pKa of the 5-substituted aminotetrazole.

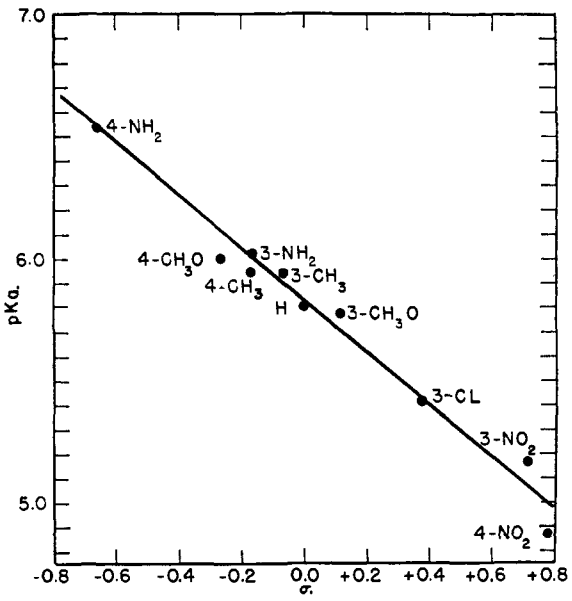
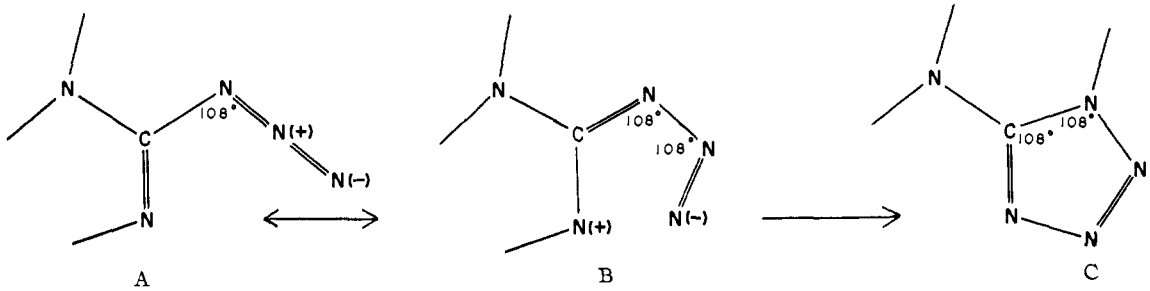


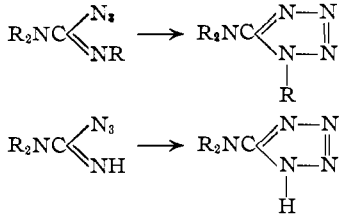
Fig. 2.—Correlation between pKa's of 5-(substituted aryl)-aminotetrazoles and Hammett's σ-values.

may involve the shift of electrons from an imino group to the azido group, followed by formation of the nitrogen–nitrogen bond and the tetrazole ring.

group cannot be brought sufficiently close to the imino nitrogen to form a new nitrogen–nitrogen bond (A). However, in the proposed activated state the grouping —C=N—N=N has a conjugate double bond system and can exist in either a chair or boat type configuration. In the latter configuration (used in B) the terminal nitrogen of the azido group is in close proximity to the imino nitrogen and ring closure can occur.



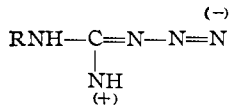
Evidence to support the idea that ring closure most likely involves the carbon–nitrogen double bond is found in the observation that N,N-disubstituted and N,N,N′-trisubstituted guanylazides cyclize to the corresponding tetrazoles.[2]



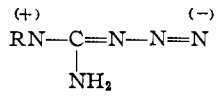
Structurally, the activated guanylazide intermediate B also satisfies the spacial requirements necessary to effect ring closure. Normally, the azido group with its allene type system of bonds is strictly linear[5]; in such a form the terminal nitrogen of this

During the isomerization the tetrazole ring probably opens to the activated guanylazide B. This intermediate can then either recyclize to the same imino nitrogen atom, or can cyclize to the other imino nitrogen after suitable charge redistribution and rotation of the azido group. Since experimentally the process has been demonstrated to reach an equilibrium, both modes of cyclization must occur. The position of equilibrium must, therefore, be dependent on the degree of positivity of the two guanyl nitrogen atoms as determined by the relative electronegativity of R *vs.* H. Substitution on the group R of monosubstituted guanylazides will affect the distribution of charge in the activated intermediate by induction or resonance. Electronegative substitution will decrease the electron availability around the nitrogen to which R is bonded, increase the importance of

(5) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 200.



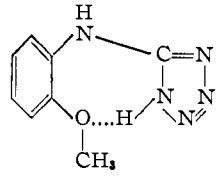
as a contributing structure and thus increase the amount of the 5-substituted aminotetrazole at equilibrium. Electropositive substitution would have the opposite effect, increasing the importance of



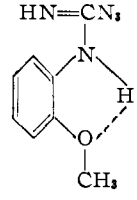
as a contributing structure and increasing the amount of 1-substituted 5-aminotetrazole at equilibrium. In other words, the distribution of isomeric tetrazoles is a direct measure of the distribution of the tautomeric guanylazides at equilibrium.

Experimentally, the proposed guanylazide intermediate has not been demonstrated to have an independent existence; perhaps it is present only momentarily as a transition state or activated complex. Indirect support for this type of intermediate is found, however, in the behavior of these substituted aminotetrazoles during their degradation in acid or in acetic anhydride at temperatures comparable to those employed in these isomerization studies. The products formed are those predicted for the decomposition and rearrangement of a substituted guanylazide.[6]

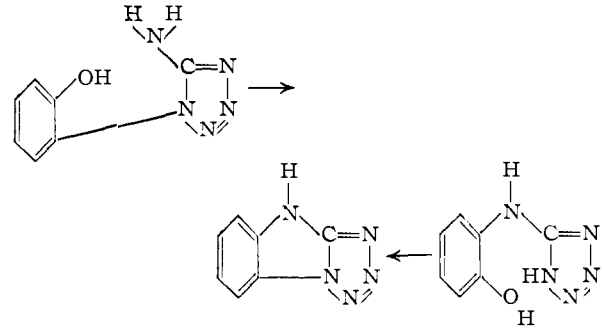
From electronegativity considerations, 1-(2-anisyl)-5-aminotetrazole should isomerize to a lesser extent than does 1-phenyl-5-aminotetrazole. Experimentally, the reverse is true. This increased tendency to isomerize may be due in part to internal hydrogen bonding in the acidic isomer and in



part to internal hydrogen bonding in the intermediate guanylazide tautomers.



The former idea is supported by the observation that 5-(2-anisylamino)-tetrazole is a stronger acid than 5-phenylaminotetrazole. If this is true, then 1-(2-hydroxyphenyl)-5-aminotetrazole occupies an anomalous position inasmuch as isomerization and titration shows only 21.6% of 5-(2-hydroxyphenylamino)-tetrazole in the equilibrium mixture. This anomaly may be due to ring closure by dehydration, as



This possibility is being investigated currently.

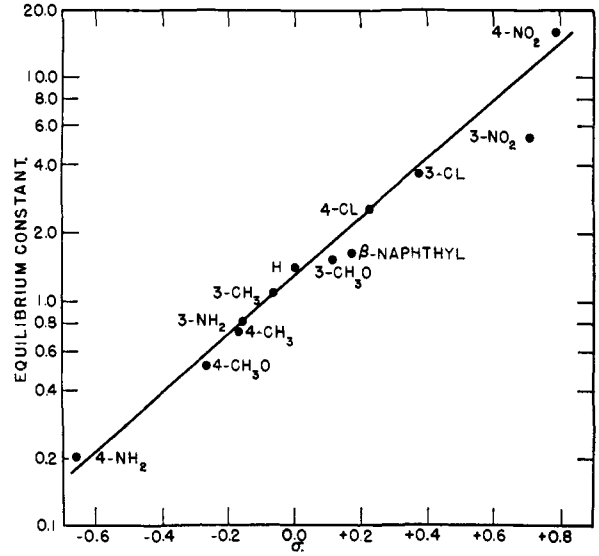


Fig. 3.—Correlation between equilibrium constants and Hammett's σ-values.

Comparison of the equilibrium constants obtained in melts and in ethylene glycol (Table II) indicates that the equilibria are shifted toward the 5-substituted aminotetrazoles in this solvent. This effect is similar to that observed in the isomerization of 1-(2-anisyl)-5-aminotetrazole, in which the acidic isomer is probably favored by internal hydrogen bonding. In this case, the acidic isomers may be stabilized by external hydrogen bonding with the ethylene glycol, a Lewis base.

Insufficient evidence exists to permit evaluation of steric effects in the isomerization of *o*-substituted 1-phenyl-5-aminotetrazoles although, from structural factors, steric hindrance would favor the formation of the 5-arylaminotetrazoles. This has not been observed. For example, 1-(2,6-xylyl)-5-aminotetrazole shows less tendency to isomerize to the 5-arylaminotetrazole than does 1-(2-tolyl)-5-aminotetrazole, although the former is more sterically hindered.

This isomerization of substituted 5-aminotetrazoles is strikingly similar to that observed by Dimroth[7] with certain 1-substituted-5-amino-1,2,3-triazoles. For example, when an ethanolic solution of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole (neutral) is heated at 150° in a sealed tube, an equilibrium mixture is obtained which contains 77% of 4-

(6) E. Lieber, R. A. Henry and W. G. Finnegan, THIS JOURNAL, **75**, 2023 (1953); F. R. Benson, *Chem. Revs.*, **41**, 55 (1947).

(7) O. Dimroth, *Ann.*, **364**, 183 (1909).

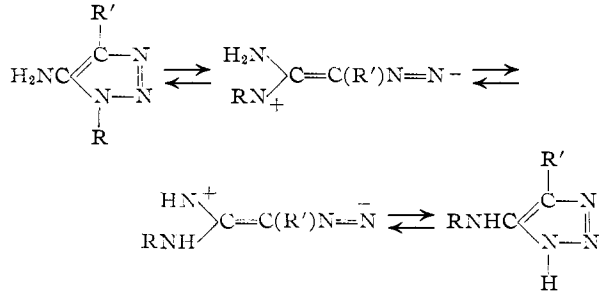
TABLE III

SUBSTITUTED 5-AMINOTETRAZOLE DERIVATIVES RNHC(N—N=N—N)R'

R	R'	M.p., °C.[a]	Method[b]	Yield, %[c]	Crystallized from	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H[1]	2-$CH_3OC_6H_4$	172–174[d]	A	62.3	Ethyl acetate	...	...	..	..	...	...
2-$CH_3OC_6H_4$	H	213–214	B	*ca.* 100	95% ethanol	50.25	50.34	4.74	5.10	36.63	37.07[e]
H	3-$CH_3OC_6H_4$	140.5–141.5	A	82.5	95% ethanol	50.25	50.20	4.74	5.07	36.63	36.52
H	4-$CH_3OC_6H_4$	209–210	A	81.8	95% ethanol	50.25	50.28	4.74	4.71	36.63	36.42
4-$CH_3OC_6H_4$	H	200–202	*g*	30.8	40% ethanol	50.25	50.16	4.74	4.86	36.63	36.84[f]
H	2-$CH_3C_6H_4$	191–192	A	87.0	50% ethanol	54.84	54.98	5.18	5.43	39.98	40.23
H	3-$CH_3C_6H_4$	162–163	A	76.2	33% ethanol	54.84	55.12	5.18	5.02	39.98	40.60
3-$CH_3C_6H_4$	H	190.5–191.5	B	*ca.* 100	50% ethanol	54.84	54.98	5.18	4.92	...	...[h]
H	4-$CH_3C_6H_4$	175.5–177[i]	A	78.8	8% ethanol	...	...	..	..	...	...
4-$CH_3C_6H_4$	H	200.5–201	B	*ca.* 100	15% ethanol	...	...	..	..	39.98	39.94[j]
H	2,4-$(CH_3)_2C_6H_3$	199–201[k]	A	88.8	95% ethanol	...	...	..	..	...	...
H	2,6-$(CH_3)_2C_6H_3$	161.5–163.5	A	29.6	Ethyl acetate	57.12	57.27	5.86	5.89	37.02	37.10
H	2-HOC_6H_4	190–191 dec.	A	...	15% ethanol	47.45	47.60	3.98	4.07	39.53	39.15[l]
H	4-HOC_6H_4	241–242 dec.	A	88.2	50% ethanol	47.45	47.81	3.98	3.78	39.53	39.91
H	3-$NH_2C_6H_4$	142–143	*m*	...	Water	47.72	47.91	4.57	4.57	47.71	47.52
H	4-$NH_2C_6H_4$	199.5–201.5	*m,n*	77.4	Water	47.72	47.95	4.57	4.60	...	...
H	2-ClC_6H_4	*ca.* 185–190°	A	28.5	Ethyl acetate	42.98	43.22	3.09	3.09	35.80	36.06
H	3-ClC_6H_4	174–175[p]	A	82.6	95% ethanol	...	...	..	..	...	...
H	4-ClC_6H_4	215–217[q]	A	84.1	95% ethanol	...	...	..	..	...	...
H	3-$NO_2C_6H_4$	170–171[r]	A	69.2	95% ethanol	40.78	41.33	2.93	3.21	40.77	40.47
H	4-$NO_2C_6H_4$	185–187[s]	A	97	95% ethanol	40.78	40.83	2.93	2.97	40.77	40.71
H	3-$CF_3C_6H_4$	176–178	A	38.7	Isopropanol	41.92	42.28	2.64	2.62	...	...
H	2-$C_{10}H_7$	192–194[t]	A	...	95% ethanol	...	...	..	..	...	...
2-$C_{10}H_7$	H	221.5–222	B	100	95% ethanol	62.55	62.58	4.29	4.37	...	...[u]
H	2-$C_6H_5C_6H_4$	175–176	A	98.4	50% ethanol	65.80	65.60	4.67	4.67	29.52	29.05
2-$C_6H_5C_6H_4$	H	211–213	B	*ca.* 100	Acetic acid	65.80	65.58	4.67	4.82	29.52	29.45[v]

[a] The melting points are corrected. [b] Method A, cyclization of a substituted guanylazide; method B, isomerization of the corresponding 1-aryl-5-aminotetrazole. [c] With method A the yields are based on the weight of thiourea used in the synthesis of the guanyl azide. [d] Resolidifies, then remelts 210°. R. Stollé, *et al.*, *J. prakt. Chem.*, **134**, 282 (1932), reported 172°. [e] Equivalent weight, calcd. 191.20, found 194.3. [f] Equivalent weight, calcd. 191.20, found 193.1. [g] Prepared by catalytic debenzylation of 5-(benzyl-4-anisyl)-aminotetrazole over palladium-in-glacial acetic acid. [h] Equivalent weight, calcd. 175.19, found 175.4. [i] J. v. Braun and W. Keller, *Ber.*, **65**, 1677 (1932), reported 176°. [j] Equivalent weight, calcd. 175.19, found 176.3. [k] R. Stollé, ref. *d*, reported 198°. [l] Equivalent weight, calcd. 177.17, found 176.1. [m] Made by the catalytic hydrogenation of the corresponding 1-(nitrophenyl)-5-aminotetrazole in absolute ethanol over Adams platinum oxide. [n] The picrate crystallized from aqueous ethanol as felted needles, m.p. 203–205° dec. [o] If heated slowly, melted at 223–224° dec. If plunged into a hot bath, melted completely in indicated range, then resolidified, and remelted at 223°. [p] R. Stollé, ref. *d*, reported 173° dec. [q] After the compound had partially melted, it would resolidify, and then remelt at 225° dec. R. Stollé, ref. *d*, reported 213° dec. [r] Resolidifies, then remelts 212–214° dec. [s] This compound would only partially melt, then it would resolidify, and remelt at 223–225° dec. [t] Resolidifies, then remelts 220.5–221.5°. R. Stollé, ref. *d*, reported 193°. [u] Equivalent weight, calcd. 211.22, found 214.7. [v] Equivalent weight, calcd. 237.27, found 238.8.

carbethoxy-5-anilino-1,2,3-triazole (acidic). There is a quantitative conversion to the acidic form in the presence of pyridine or sodium ethylate. An equilibrium is also reached between 1,4-diphenyl-5-amino-1,2,3-triazole and 4-phenyl-5-anilino-1,2,3-triazole. The mechanism of the isomerization in the 1,2,3-triazole series is probably similar to the one operative with the tetrazole compounds; in this case the proposed transitory intermediate would be a substituted α-diazoacetamidine.[8]



This isomerization should also be subject to the same inductive effects although Dimroth did not report enough examples from which one could draw a definite conclusion. No further studies on this particular isomerization appear to have been made.

(8) The hydrolysis of 1-phenyl-5-amino- or 5-anilino-1,2,3-triazole (ref. 6) gives products which are consistent with this proposed intermediate.

Experimental

Materials.—1-Substituted 5-aminotetrazoles were synthesized by the previously described method[2]; generally the intermediate S-methyl isothioureas and substituted aminoguanidines were not isolated or purified between steps. 5-Arylaminotetrazoles were prepared by the isomerization of 1-aryl-5-aminotetrazoles at temperatures which permitted solidification of the higher melting, acidic form. New compounds prepared by either of these procedures are listed in Table III. 5-Methyl-, ethyl-, benzyl- and cyclohexylaminotetrazoles were also prepared by procedures given in the previous publication.[2] The remaining 5-alkylaminotetrazoles were synthesized by the hydrogenation of azomethines derived from 5-aminotetrazole salts, and will be described in a forthcoming paper. The ethylene glycol (Eimer and Amend, C.P.) was used without purification.

Procedure.—Solvent-free or melt isomerizations were made by heating an accurately weighed sample (0.2–0.9 g.) of purified, substituted aminotetrazole in a thin-walled test-tube for 10–15 minutes after immersion in a silicone oil-bath, preheated to 188–191° or 199–201°. The sample was then removed and rapidly plunged into an ice–water-bath to freeze the equilibrium. The chilled sample was dissolved in 100 ml. of neutral 95% ethanol and titrated to the phenolphthalein end-point with standard alkali. If the samples were intensely colored, they were dissolved in 100 ml. of 50% ethanol and titrated potentiometrically. The percentage 5-substituted aminotetrazole in the equilibrium mixture

was then calculated from this titer, the equivalent weight and the normality of the standard alkali. Four- to fivefold variations in the sample weights did not change the value obtained for the percentage of 5-substituted aminotetrazole in the equilibrium mixture. This seems to indicate that the equilibrium is not appreciably shifted during freezing of the melt. Every effort was made to avoid disturbing the sample during the heating period. If the melt solidified or if the sample isomerized without melting, the results were not included.

Isomerizations in ethylene glycol were effected by adding an accurately weighed sample of the tetrazole (0.2–0.9 g.) to 10 ml. of ethylene glycol in a 25-ml. flask with an air condenser. The flask was immersed for 15 minutes in a silicone oil-bath preheated to 200–202°; the solution reached the boiling point of ethylene glycol (192–194°) in about 5 minutes. The flask was then removed and rapidly plunged into an ice–water-bath to freeze the equilibrium. The samples were titrated as before and the titer corrected for the slight acidity of the ethylene glycol.

An attempt also was made to study the isomerization in tetrahydronaphthalene at 200°. Three tetrazoles, differing widely in their extent of isomerization, all showed 26–28% acid form in the equilibrium mixture. In contrast to the normal behavior experienced in ethylene glycol solution, these solutions became very darkly colored. The reason for this peculiar result has not been determined.

Approximately 0.011 *N* solutions of 5-substituted aminotetrazoles in 50% aqueous ethanol were titrated potentiometrically with standard alkali at 27°. The *p*H at the half-neutralization point was taken as the pK_a.

1-(4-Anisyl)-2-aminoguanidine Hydroiodide.—This compound was made in essentially quantitative yield by the hydrazinolysis of S-methyl-4-anisylisothiourea hydroiodide in absolute ethanol. After recrystallization from absolute ethanol, it melted at 150–151°.

Anal. Calcd. for $C_8H_{14}N_4OI$: C, 31.08; H, 4.56. Found: C, 31.22; H, 4.23.

1-(2-Tolyl)-2-aminoguanidine hydroiodide was prepared by a method similar to that just described; m.p. 153–154° after recrystallization from absolute ethanol–diethyl ether.

Anal. Calcd. for $C_8H_{14}N_4I$: C, 32.78; H, 4.81. Found: C, 33.01; H, 4.50.

Benzal 1-(2,4-Xylyl)-2-aminoguanidine picrate was prepared by reaction of equivalent quantities of benzaldehyde and 1-(2,4-xylyl)-2-aminoguanidine hydroiodide in hot aqueous alcohol solution and adding an equivalent quantity of ammonium picrate; m.p. 190–192° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{22}H_{21}O_7N_7$: C, 53.33; H, 4.27. Found: C, 53.93; H, 4.28.

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CHINA LAKE, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

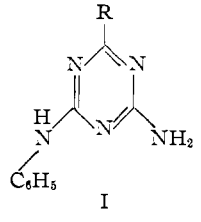
Monomer Synthesis.[1] Triazines. The Reaction of Phenylbiguanide with Ethyl Oxalate and Ethyl Formate

BY C. G. OVERBERGER AND SEYMOUR L. SHAPIRO[2]

RECEIVED JULY 31, 1953

The reaction of phenylbiguanide with formic acid, formamide, dimethylformamide and ethyl formate has been investigated and shown to give I (R = H), the use of ethyl formate being the preferred procedure. Reaction of phenylbiguanide with ethyl oxalate gave a compound of inconclusive structure $C_{10}H_9N_5O_2$ which readily was converted to triazine derivatives, I (R = COOH) and its hydrates, $COOCH_3$, $COOC_2H_5$, COO-*n*-C_3H_7, $CONH-NH_2$. Reactions of I (R = $COOCH_3$ and $COOC_2H_5$) are also described. Decarboxylation of I (R = COOH) to give I (R = H) was effected thermally and with acids. The reaction of chloral with phenylbiguanide was also investigated. A complex reaction mixture was obtained from which I (R = H) and the formic acid salt of phenylbiguanide were characterized.

The preparation of triazine derivatives of type I (R = H, COOH) was required in order to aid in the proof of structure of several intermediates useful in the synthesis of vinyl triazines. Reaction of esters with biguanide to give triazines has been explored in some detail.[3] Compound I (R = H) recently has been reported by several investigators[4] prepared by the reaction of phenylbiguanide and formic acid. We have repeated this synthesis and in addition synthesized I (R = H) using ethyl formate, formamide and dimethylformamide. N-Phenylformoguanamine (I, R = H) forms readily in 67% yield with ethyl formate at room temperature in methanol whereas the procedure of Papini using formic acid required reflux temperatures and a longer time for cyclization to obtain a similar yield. A discrepancy in the melting point of the picrate of I (R = H) with the previously reported value[4a] was noted. A side product in the ethyl formate reaction was the phenylbiguanide salt of formic acid confirmed by independent synthesis of the salt, the formic acid probably arising from hydrolysis of the ester upon liberation of water on aromatization to the triazine. The oxalate, hydrochloride, picrate and phenylurea derivatives of I (R = H) were prepared and characterized. A crystalline well defined monobromide also was obtained and proved to be the *p*-bromophenyl derivative, identical with a known sample prepared from *p*-bromophenylbiguanide and ethyl formate. A recent patent[5] has reported the *p*-bromo derivative al-



I

(1) This is the sixth in a series of papers concerned with the preparation of vinyl monomers. For the fifth paper, see C. G. Overberger, C. Frazier, J. Mandelman and H. F. Smith, THIS JOURNAL, **75**, 3326 (1953).

(2) This paper comprises a portion of a thesis presented by Seymour L. Shapiro in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(3) J. T. Thurston, U. S. Patent 2,461,943 (1949) and similar patents.

(4) (a) P. Papini and A. Folena, *Gazz. chim. ital.*, **80**, 837 (1950); (b) O. Clauder and G. Bulcsu, *Magyar Kém Folyoirat*, **57**, 68 (1951).

(5) Richter, Gedeon, Vegyesseti Gyar Rt. (Hungarian Corp.), Brit. Patent 676,024 (July 23, 1952); *C. A.*, **47**, 3887 (1953).