Stirring was continued at room temperature for another 2 hr. Upon standing for several hours at 0°, the solid was collected by filtration and washed with ice cold 50% ethanol. There was obtained 0.77 g. (82.8%) of thiosemicarbazone, m.p. 159°. Recrystallized from 25% ethanol it melted at 160° (reported[8] m.p. 151–152°).

Anal. Calcd. for $C_6H_7N_3S_2$: C, 38.89; H, 3.80; N, 22.68. Found: C, 38.69; H, 3.88; N, 22.55.

The freshly prepared compound was white, but on standing turned yellow.

BELGRADE, YUGOSLAVIA

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF DEPAUL UNIVERSITY AND PURDUE UNIVERSITY]

Synthesis and Isomerization of Substituted 5-Amino-1,2,3-triazoles[1]

EUGENE LIEBER,[2] TAI SIANG CHAO,[3] AND C. N. RAMACHANDRA RAO[4]

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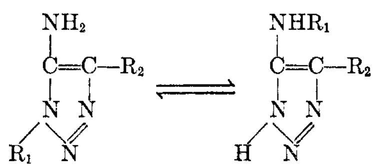
A series of 1,4-disubstituted-5-amino-1,2,3-triazoles were prepared by reactions involving the base-catalyzed condensation of alkyl- and aryl-azides with malonic ester, cyanoacetic ester and phenylacetonitrile. The latter proved advantageous for preparing a series of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles. A mechanism is proposed for the base-catalyzed condensation of azides with phenylacetonitrile which accounts for the resistance of the electropositively substituted azides to form vicinal triazoles. The 1,4-disubstituted-5-amino-1,2,3-triazoles were irreversibly isomerized to a series of 4-phenyl-5-(substituted)anilino-1,2,3-triazoles by refluxing in pyridine-type bases. The comparative rate of irreversible isomerization of a selected group of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles to 4-phenyl-5-(substituted)anilino-1,2,3-triazoles in boiling pyridine was found to depend on the electrical effect of the substituent in the 1-position in a manner comparable to that found for 1-substituted-5-aminotetrazoles. The isomerization of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles to 4-phenyl-5-(substituted)anilino-1,2,3-triazoles, or *vice versa*, at 184–185° in homogeneous melts has been investigated and found to reach an equilibrium. The position of equilibrium shifts to the acidic isomer as the electronegativity of the substituent is increased, yielding an approximately linear relationship between the logarithm of the equilibrium constant and Hammett's σ-value for groups.

The discovery that 1-substituted-5-amino-1,2,3-triazoles undergo a rather facile and apparently reversible isomerization to 5-substituted amino-1,2,3-triazoles:



I II

was made by Dimroth.[5] The examples reported[5] were:

$R_1 = C_6H_5;\ R_2 = CO_2Et$ (1)

$R_1 = C_6H_5;\ R_2 = H$ (2)

$R_1 = C_6H_5;\ R_2 = C_6H_5$ (3)

$R_1 = C_6H_5;\ R_2 = CH_3$ (4)

All except example (1) were carried out under nonequilibrium conditions, *i.e.*, by use of a basic solvent which favors the acidic isomer II, or by allowing the higher melting isomer (usually II) to crystallize out from the melt. Example (1) was run in absolute ethanol and in benzene, in sealed tubes at 150° for 3 hrs. (unfortunately the tubes were cooled under ambient conditions) approaching equilibrium from either pure III or IV:

$$\text{III}\ (R_1 = C_6H_5;\ R_2 = CO_2Et) \rightleftharpoons \text{IV}\ (R_1 = C_6H_5;\ R_2 = CO_2Et)$$

Dimroth's titration data[25] enable an estimation of the positions of equilibrium to be calculated. The results of these calculations are summarized in Table I. It thus appears that the reversible nature of I $\rightleftharpoons$ II has been established, although from limited data, and that the shift in the position of equilibrium with the type of solvent is in the same order as predicted by Henry, Finnegan, and Lieber[6] for substituted 5-aminotetrazoles. However, the magnitude in the shift of the position of equilibrium in a Lewis type of basic solvent appears (Table I) to be abnormally large considering the very weak basic properties of ethanol. The data for the homogeneous melt, while showing perfect coincidence regardless of the direction from which the reaction is initiated, need verification due to the questionable analytical technique[7,25] employed. Further, the limited amount

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

(6) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76,** 88 (1954).

(7) A study of the determination of the weak bases and acids represented by I and II by titration in nonaqueous media has been submitted for publication elsewhere. (*Anal. Chem.*, in press.) Briefly, the determination of the acidic isomer was generally used for estimation of purity and for the determination of the positions of equilibrium. Anhydrous dimethyl formamide was used as solvent, with sodium methoxide as titrant and azoviolet as the visual indicator. The method was tested with the pure isomers of type I giving an average deviation from 100% recovery of ±0.03%.

of data and the lack of kinetic information make any postulations of mechanism untenable. The objective of this investigation was a more exhaustive examination of I ⇌ II to determine whether it is a truly reversible reaction and, if so, to determine the influence of the substituents R_1 and R_2 on the position of equilibrium, the kinetics, and energetics. The present paper is concerned with the synthesis of the necessary I and II type compounds and their thermal isomerization in homogeneous melts. The present investigation differs from that recently reported by Brown, Hammick, and Heritage[25] who studied an apparent acid catalysis for the isomerization in dry ethanol for I(R_1 = *para*-substituted phenyl; R_2 = CO_2Et). A critique of this latter work will be presented in connection with our kinetic and energetics investigation of I ⇌ II (R_1 = substituted phenyl; R_2 = C_6H_5) to be reported elsewhere.[8]

TABLE I

EQUILIBRIUM DATA[a] BY DIMROTH[b]

Starting Triazole	Solvent	% 5-Substituted Aminotriazole at Equilibrium[c]
1-Phenyl-4-carbethoxy-5-amino	Ethanol[d]	76.3
5-Anilino-4-carbethoxy	Ethanol[d]	76.2
1-Phenyl-4-carbethoxy-5-amino	Benzene[d]	56.3
5-Anilino-4-carbethoxy	Benzene[d]	58.2
5-Anilino-4-carbethoxy	Ether[d]	92.7
1,4-Diphenyl-5-amino	None[e]	75
4-Phenyl-5-anilino	None[e]	75

[a] Calculated from titration data. [b] Reference 5. [c] Form II. [d] In sealed tubes at 150° for 3 hours. [e] In homogeneous melt probably above 180° but not stated.

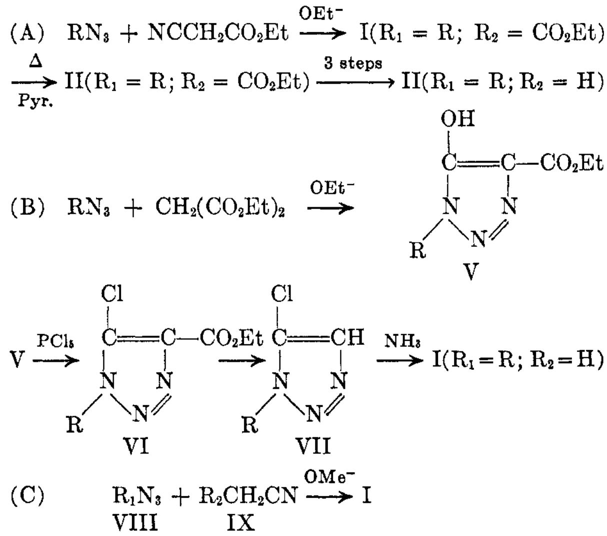
SYNTHESIS OF 1,4-SUBSTITUTED-5-AMINO-1,2,3-TRIAZOLES

From an examination of the literature[5,9–11] three routes were tested for the synthesis of type I compounds summarized in Fig. 1. The most convenient route leading directly to the desired compounds of type I was found to be sequence (C) (Fig. 1, VIII, R_1 = C_6H_5, and substituted aryl; R_2 = C_6H_5). Thus, the initial experiments with phenyl azide and phenylacetonitrile led to practically quantitative yields of pure 1,4-diphenyl-1,2,3-triazole:

$$C_6H_5N_3 + C_6H_5CH_2CN \xrightarrow{OMe^-} I\ (R_1 = R_2 = C_6H_5)$$

The method was first described by Dimroth.[10] The organic azides required for all syntheses are

FIG. 1. SYNTHESIS OF SUBSTITUTED 5-AMINO-1,2,3-TRIAZOLES



listed in Table II. Table III summarizes the 1-substituted-4-phenyl-5-amino-1,2,3-triazoles prepared by the condensation of phenylacetonitrile with the respective azides. The new compounds are so indicated in Table III.

TABLE II

ORGANIC AZIDES, RN_3

R	% Yield,	B.P./Mm.	n_D^{20}	M.P.	Reference
C_2H_5	92	50–50.5/745	1.3997	—	[a]
n-C_6H_{13}	87	85/63	1.4318	—	[b]
$C_6H_5CH_2$	87	78–78.5/12	1.5373	—	[c]
C_6H_5	80[d]	41–42/5	1.5598	—	[e]
4-$CH_3C_6H_4$	80[d]	55–56/4.5	1.5521	—	[f]
3-$CH_3C_6H_4$	88[d]	57.8/5	1.5527	—	[f]
2-$CH_3C_6H_4$	86[d]	61–62/7	1.5568	—	[f]
4-ClC_6H_4	60[d]	65–66/3	—	—	[f]
3-ClC_6H_4[g]	75	49–50/1.2	1.5806	—	[f]
2-ClC_6H_4[g]	67	45/0.85	1.5878	—	[f]
4-BrC_6H_4	73	69/2.1	1.6127	20	[f]
4-$NO_2C_6H_4$	77	—	—	74	[h]
3-$NO_2C_6H_4$	83	—	—	54–55	[h]
2-$NO_2C_6H_4$[i]	80	—	—	51–52	[h]
1-$C_{10}H_8$	34	—	—	12	[j]
2-$C_{10}H_8$	58	—	—	32–33	[j]
4-$CH_3OC_6H_4$	36	—	—	34–35	[k]

[a] E., Oliveri-Mandala, and G. Caronna, *Gazz. chim. ital.*, **71**, 182 (1941). [b] K. Henkel, and F. Weygand, *Ber.*, **76**, 817 (1943). [c] F. Moulin, *Helv. Chim. Acta*, **35**, 167 (1952). [d] Improved yields. [e] R. O. Lindsay, and C. F. H. Allen, *Org. Synthesis*, **22**, 96 (1942). [f] P. V. Dutt, H. R. Whitehead, and A. Wormall, *J. Chem. Soc.*, **119**, 2088 (1921). [g] B.p. and n_D^{20} are in disagreement with H. D. Spauschus, and J. M. Scott, *J. Am. Chem. Soc.*, **73**, 208 (1951). *Anal.* Calcd. for $C_6H_4ClN_3$: C, 46.92; H, 2.62; Cl, 23.09; N, 27.39. Found: for 2-$ClC_6H_4N_3$: C, 47.03; H, 2.61; Cl, 23.00; N, 27.43; for 3-$ClC_6H_4N_3$: C, 46.97; H, 2.69; Cl, 23.01; N, 27.47. [h] E., Noelting, E. Grandmongin, and O. Michel, *Ber.*, **25**, 3338 (1892) by the reaction of N_2H_4 with the diazonium sulfate. [i] New method of preparation. *Anal.* Calcd. for $C_6H_4BrN_3$: C, 36.40; H, 2.02; Br, 40.36. Found: C, 36.33; H, 2.27; Br, 40.51. [j] M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **91**, 1942 (1907). [k] The compound reported as p-anisyl azide by F. Moulin, *Helv. Chim. Acta*, **35**, 167 (1952) is actually p-methoxybenzyl azide.

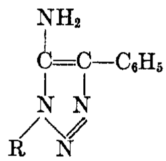
(8) E. Lieber, C. N. R. Rao, and T. S. Chao, *J. Am. Chem. Soc.*, in press.

(9) O. Dimroth and W. Michaelis, *Ann.*, **459**, 44 (1927).

(10) Dimroth, *Ber.*, **35**, 1034 (1902).

(11) F. R. Benson and W. L. Savill, *Chem. Revs.*, **46**, 1 (1950).

TABLE III

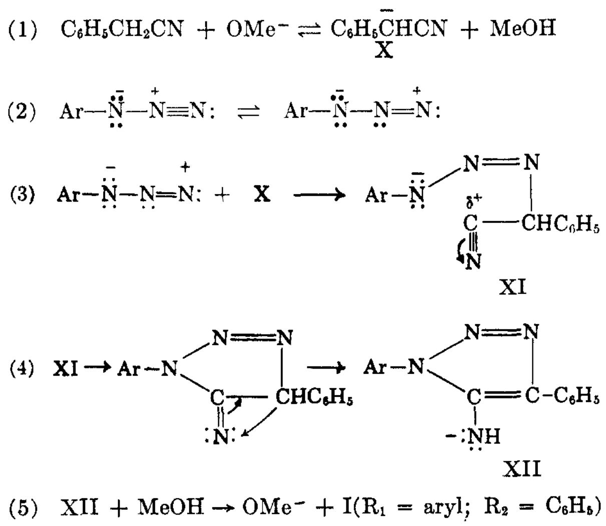


1-SUBSTITUTED-4-PHENYL-5-AMINO-1,2,3-TRIAZOLES

R =	Moles of Azide Used[a]	Procedure[b]	Crystallized from	M.P.	% Yield[c]	Analysis: Calcd. % C	Analysis: Calcd. % H	Analysis: Calcd. % N	Analysis: Found % C	Analysis: Found % H	Analysis: Found % N
C_6H_5[d]	0.3	A	Ethanol[e]	169–170	99	71.16	5.12	23.72	71.24	4.92	23.65
4-$CH_3C_6H_4$	0.1	B	Methanol	175–176	92	71.97	5.64	22.39	71.78	5.85	22.32
3-$CH_3C_6H_4$	0.1	B	Ethyl Acetate	143–144	90	71.97	5.64	22.39	72.08	5.97	22.55
2-$CH_3C_6H_4$	0.11	C	Benzene	116–117	59	71.97	5.64	22.39	71.77	5.80	22.46
4-ClC_6H_4	0.052	A	Benzene	187–188	99	62.11	4.10	20.70	61.90	4.38	20.79
3-ClC_6H_4	0.052	A	Methanol	152	99	62.11	4.10	20.70	61.90	4.38	20.90
2-ClC_6H_4	0.05	C	Toluene	116–117	95	62.11	4.10	20.70	62.05	4.19	20.58
4-$NO_2C_6H_4$[f]	0.28	C, D	Ethyl Acetate	182–183	82	59.78	3.94	24.90	59.83	3.90	25.01
3-$NO_2C_6H_4$[g]	0.1	A	Ethyl Acetate	171–172	51	59.78	3.94	24.90	59.76	4.04	25.20
4-$CH_3OC_6H_4$	0.134	F	Ethyl Acetate	163–164	82	67.65	5.30	21.04	67.52	5.25	21.08
4-BrC_6H_4[h]	0.05	B	Benzene	188–189	71	53.36	3.33	17.78	53.50	3.68	17.83
2-$C_{10}H_7$	0.12	E	Ethyl Acetate	184–185	89	75.50	4.93	19.57	75.73	5.11	19.60
$C_6H_5CH_2$	0.2	G	Benzene[i]	157–158	59[j]	72.31	5.21	22.48	72.19	5.50	22.55

[a] Approximately a 10% excess of phenylacetonitrile and sodium methoxide (dissolved in dry ethanol or methanol) were used. [b] The general procedures are: A. Methoxide was added dropwise to a mixture of azide and nitrile cooled in an ice bath. The mixture was maintained at ice bath temperature overnight and warmed to room temperature (5 hr. to overnight) until precipitation appeared complete. B. If precipitation of the product did not occur, the above procedure was modified by allowing the reactants to warm up to 45–65° for periods until precipitation appeared to be complete. C. Described in Experimental Section. D. Same procedure as A, except that the precipitate obtained was recovered, and the mother liquor refluxed for an additional period. E. The azide, in dry ether, was added last; otherwise the same as A. F. Same procedure as E except that reaction mixture was refluxed at 45–55° for 10 hr., allowing the ether to escape through the hot condenser. G. Same procedure as E except that the reaction mixture was refluxed at 60–65° for 90 hr. [c] Includes work-up of all mother liquors. [d] O. Dimroth[21]; E. Lieber, T. S. Chao and C. N. R. Rao, *Org. Syntheses*, in press. [e] Precipitate washed on the funnel. [f] Dimroth's[9] procedure gave a yield of 54%. [g] The procedure of Dimroth[9] described for R = 4-$NO_2C_6H_4$ gave a yield of 24%. [h] Calcd.: Br, 25.36; Found, 25.20. [i] Product first washed on funnel with dry methanol and ether, respectively, before recrystallizing. [j] Time of reflux has an important bearing on yield, a replicate run for 60 hr. gave a yield of 36%.

FIG. 2. MECHANISM FOR CONDENSATION OF ARYL AZIDES WITH PHENYLACETONITRILE



The mechanism outlined in Fig. 2 is proposed for the condensation reaction between an organic azide with phenylacetonitrile in the presence of a base. Step (1) explains the role of the sodium methoxide and why quantities in slight excess of the stoichiometric in methoxide ion are needed. An experiment using small amounts of triethylamine failed to cause condensation of phenyl azide and phenylacetonitrile. Step (2) indicates why an electron-withdrawing group enhances reaction and an electron-releasing group renders the reaction difficult. Without the help of an electron-withdrawing group at Ar, it would be difficult for the electron-pair to move from the triple bond to the middle nitrogen of the azido-group. The net result of this shift is to move a positive charge farther away from a negative charge. The (3) to (5) steps, inclusive, should be fast since they involve the neutralization of a positive and negative charge. The ring closure step (4) should not be influenced to any great extent by the nature of Ar since the electron shifting occurs away from it. Accordingly, the process is controlled by step (2) which is in turn controlled by the nature of the Ar group. This is in agreement with the experimental results which showed that the formation of I (R_1 = aryl; R_2 = C_6H_5) is favored by negatively substituted aromatic groups in the azide molecule. Thus, while the condensation of nitro-, chloro-, and bromophenyl azides, respectively, with phenylacetonitrile proceeds readily at room temperature, several hours heating was required in the case of tolyl, naphthyl, and anisyl azides, and prolonged heating (70–92 hrs.) was required for benzyl, ethyl, and *n*-hexyl azides. The yields of I (R_1 = aryl; R_2 = C_6H_5) were very high for most aromatic azides, somewhat lower for *p*-anisyl and benzyl azides, and were very low for alkyl azides (Table III).

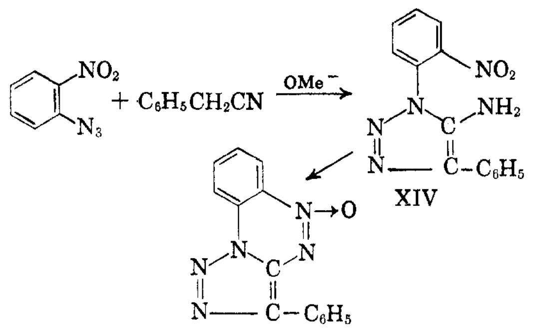
A study was made as to the effect of reaction conditions on the yield and purity of I (R_1 = nitrophenyl; R_2 = C_6H_5) resulting from the condensation of the respective isomeric nitrophenyl azides with phenylacetonitrile. The results indicated that considerable increase in yield was obtained if the reactants were allowed to stir overnight at room temperature before refluxing. Indeed, marked improvement in yield was observed by mixing the nitrophenyl azide and phenylacetonitrile at ice bath temperature and adding the sodium methoxide dropwise. The products so obtained, with the exception of *o*-nitrophenyl azide, discussed below, contained less of the acidic isomer II (R_1 = nitrophenyl; R_2 = C_6H_5) and showed a melting point 6–7° higher than products obtained at higher initial reaction temperatures. The manner in which the three reactants were brought together had only a minor effect on the yield. The importance of controlling the initial condensation temperature for the nitro-aryl azides is illustrated by the increase in yield of 1-*m*-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole from 24 to 51%. The decrease in yield at higher initial condensation temperatures may be due to the instability of the nitrophenyl azides, the instability of the triazoles, or the occurrence of side reactions.

Within a given series of isomeric phenyl azides the ease of condensation with phenylacetonitrile was in the order *para* > *meta* > *ortho*. Considerable difficulties were encountered with *ortho* substituted aryl azides both in the condensation and isolation of product, due to the greater solubility of the latter in methanol and benzene. Intractable oils were usually obtained which were induced to crystallize only after considerable trial and error. It was necessary to determine the optimum reflux time for the *ortho* substituted phenyl azides in order to obtain maximum yield of the triazoles.

One important problem in connection with the preparation of I and II is the isolation of a pure isomer instead of a mixture of the two isomeric forms. Based upon the experience with the aminotetrazoles[12] it was believed that the isomerization would not proceed to such an extent as to prevent their recrystallization from solvents of reasonably low boiling points. However, a lowering of melting point and appearance of the acidic isomer was observed on recrystallization from boiling solvents. For example, 1-*p*-chlorophenyl-4-phenyl-5-amino-1,2,3-triazole had a melting point of 187–188° when recrystallized once from benzene. Upon further recrystallization from boiling dry ethanol, the product had a melting point of 185–186° which was found to be due to a 4 per cent conversion into 4-phenyl-5-(*p*-chlorophenyl)amino-1,2,3-triazole. Preliminary experiments indicated that this isomerization is more pronounced in polar than in nonpolar solvents. An experiment was thus designed to determine the effect of the nature of the solvent on the extent of isomerization during recrystallization. 1-*p*-Nitrophenyl-4-phenyl-5-amino-1,2,3-triazole, XIII (R_1 = 4-NO_2–C_6H_4; R_2 = C_6H_5), a compound which shows the highest rate of isomerization (discussed below) was selected for this purpose. A definite amount of XIII, which had been repeatedly washed with methanol but never recrystallized, was stirred individually with a number of solvents at their respective boiling points (except dimethyl formamide which was kept at 82–85°) for a definite period of time. After cooling, the crystals were filtered, washed, dried, and analyzed[7] for content of acidic isomer. The solvents used were benzene, absolute ethanol, ethyl acetate, 60% aqueous dimethyl formamide, and acetone, in order of increasing dielectric constant. It was found that the percentage of acidic isomer in the recrystallized product increases in the same order, while the melting point of the product decreases accordingly (Table VIII). This means that the isomerization into the acidic isomer is enhanced by the use of the more polar solvent. For purpose of purification of the basic isomer (I), benzene is the recommended solvent. If the solubility in this solvent is too low, the use of ethanol or ethyl acetate may be the second best choice. In all cases, however, the heating period must be kept as short as possible and the temperature as low as possible. It was found to be good practice to heat up the solvent first before adding the compound to be recrystallized. This is particularly important in the cases of I where the 1-substituent is a strong electronegative group. Washing with ether was found to be an advantageous means of removing small amounts of II from I due to the fact that the basic isomers are almost insoluble in this solvent, while that of the acidic isomer may be very high. Crude XIII, having a melting point of 171–176° and containing about 4% of the corresponding acidic isomer, on washing with ether gave a product melting at 181–182° and containing only 0.36% of acidic isomer. However, as pointed out previously, low temperature control of the initial condensation is a much more important factor leading to a pure type I where R_1 is a strong electronegative group.

An orange colored product, melting at 219°, was obtained from the condensation of *o*-nitrophenyl azide and phenylacetonitrile. The analysis did not correspond to that calculated for 1-*o*-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole but indicated the loss of a molecule of water. This suggests that the following reaction may have taken place:

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



XIV

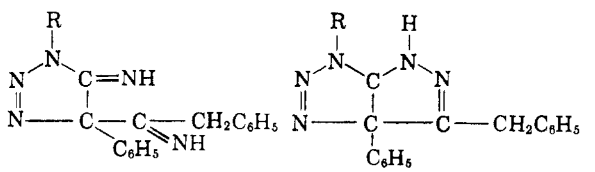
XV

A second less likely possibility is the elimination of water after the isomerization of XIV to II (R_1 = 4-NO_2-C_6H_4; R_2 = C_6H_5). In either event, confirmation for the presence of the *N*-oxide group was obtained by infrared absorption spectroscopy. Further studies on the nature of the condensation product of *o*-nitrophenyl azide and phenylacetonitrile are in progress and will be reported separately.

Considerable difficulty was encountered in the condensation of ethyl- and *n*-hexyl azides with phenylacetonitrile. Two types of products were isolated, XVI (I, R_1 = C_2H_5; R_2 = C_6H_5, m.p. 111–112°) corresponding to the expected triazole and unknown products, XVII (or XVIII) whose analyses corresponds to the reactions:

$$C_2H_5N_3 + 2C_6H_5CH_2CN \xrightarrow{OMe^-} C_{18}H_{19}N_5$$

$$C_6H_{13}N_3 + 2C_6H_5CH_2CN \xrightarrow{OMe^-} C_{22}H_{27}N_5$$



XVII XVIII

This could result from an initial dimerization[14,15] followed by addition of the alkyl azide:

$$2C_6H_5CH_2CN \xrightarrow{OMe^-} C_6H_5CH_2C(:NH)CH(C_6H_5)CN \xrightarrow{RN_3}$$
XIX XVII or XVIII

It will be noted that XVII and XVIII are isomeric. It is not surprising that an initial dimerization will take place in the presence of the less reactive alkyl azides. In the presence of the more reactive aromatic azides, this dimerization is repressed in favor of the formation of I. XVIII is derived from the ring system pyrazolo-(3,4)-v-triazole (number 584 in the Ring Index[13]) and its possible formation from preformed dimer of phenylacetonitrile, 1-cyano-2-imino-1,3-diphenylpropane, XIX, is under study and will be reported separately.

(13) A. M. Patterson and L. T. Capell, *The Ring Index*, Reinhold Publishing Corp., N. Y., 1940.

(14) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1930 (1906).

(15) N. Lee and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1287 (1907).

In addition to the series of 1-substituted-4-phenyl 5-amino-1,2,3-triazoles prepared (Table III), the following were synthesized in order to determine the effect of substituents in the 4-position of I and II, while maintaining R_1 constant as phenyl:

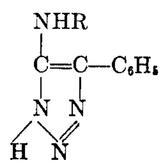
XX: I (R_1 = C_6H_5; R_2 = CO_2Et)
XXI: II (R_1 = C_6H_5; R_2 = CO_2Et)
XXII: II (R_1 = C_6H_5; R_2 = H)
XXIII: I (R_1 = C_6H_5; R_2 = H)

XX [scheme (A), Figure No. 1, R = C_6H_5] has been described by Dimroth.[5] XXI was prepared by irreversible isomerization of XX following the procedure of Dimroth and Pfister.[22] XXII was derived from XXI by saponification, acidification and decarboxylation. The preparation of XXIII involved the three step synthesis of VII (R = C_6H_5) followed by ammonolysis [Figure 1, sequence (B)].

SYNTHESIS OF 4-PHENYL-5-(SUBSTITUTED)AMINO-1,2,3-TRIAZOLES

The required pure isomers of type II were prepared from the purified compounds of type I (Table III) by an irreversible thermal isomerization in the presence of excess base. The compounds so prepared are summarized in Table IV. Pyridine was invariably used except for R = *p*-anisyl and benzyl which were isomerized in boiling 4-picoline. Longer

TABLE IV



4-PHENYL-5-SUBSTITUTED AMINO-1,2,3-TRIAZOLES

R	% Yield[b]	M.P., °C.	Analysis[a] % N calcd.	% N found
C_6H_5[c]	92[d]	167–168	23.72	23.64
4-$CH_3C_6H_4$	100[e]	158–159	22.39	22.45
3-$CH_3C_6H_4$	90[e]	168–169	22.39	22.16
2-$CH_3C_6H_4$[f]	98[g]	98–99	22.39	22.40
4-ClC_6H_4	80[d]	158–159	20.70	20.90
3-ClC_6H_4	96[e]	166–167	20.70	20.77
2-ClC_6H_4	93[g]	134–135	20.70	20.67
4-$NO_2C_6H_4$[c]	83[h]	164–165	24.90	24.85
3-$NO_2C_6H_4$[f]	100[i]	136–137	24.90	24.86
4-$CH_3OC_6H_4$[j]	100[g]	134–135	21.04	21.03
4-BrC_6H_4	90[k]	174–175	17.78	17.58
2-$C_{10}H_7$	89[d]	214–215	19.57	19.57
$C_6H_5CH_2$[l]	—	121–122	22.39	22.28

[a] In addition to the N analysis, freedom from basic isomer was determined by non-aqueous titration. [b] Recrystallized from. [c] Known compounds. [d] Ethanol-water. [e] Benzene. [f] Forms an oil which crystallizes after long standing. [g] Toluene. [h] Ether. [i] Ether-hexane. [j] 4-Picoline used as solvent at 141–142°; crystals washed with CCl_4 to remove brownish contamination. [k] Ethanol. [l] In small quantities by ether extraction of mixed isomers.

refluxing times and completely dry solvent were needed where R was a positively substituted phenyl group. Considerable difficulty was encountered in the isomerization of 1-benzyl-4-phenyl-5-amino-1,2,3-triazole (I, $R_1 = C_6H_5CH_2$; $R_2 = C_6H_5$) into 4-phenyl-5-benzylamino-1,2,3-triazole. Even after 48 hr. refluxing in 4-picoline, the product was found to contain only 24% of the acidic isomer. Its eventual preparation in pure form was achieved by ether extraction of the mixture of isomers.

The same pronounced effect of substituents was noticed in the base-catalyzed irreversible isomerization of I to II. While there was no trouble in obtaining pure acidic isomers in the case of most negatively substituted phenyl compounds of type I, considerable difficulties were encountered for the positively substituted phenyl derivatives. The case of I ($R_1 = C_6H_5CH_2$) was particularly resistant to isomerization in boiling dry pyridine, 8 hr. refluxing producing no change in melting point. A study was made of the comparative rates of irreversible isomerization in an excess of boiling dry pyridine. The data obtained are summarized in Table V which shows that negative groups enhance the rate of isomerization in agreement with similar observations in the 5-aminotetrazole system.[6,12,16]

TABLE V

$$\text{I}(R_1 = R; R_2 = C_6H_5) \xrightarrow[\Delta]{\text{Pyr}} \text{II}(R_1 = R; R_2 = C_6H_5)$$

EFFECT OF 1-SUBSTITUTION ON THE RATE OF IRREVERSIBLE ISOMERIZATION

R	Rate ($C_6H_5CH_2$ = 100)[a,b]
$C_6H_5CH_2$	100
4-$CH_3OC_6H_4$	300
C_6H_5	700
4-$NO_2C_6H_4$	1000

[a] Based on 30-min. reaction time in boiling pyridine. [b] A similar series based on 90-min. reaction time showed the same relative order.

ISOMERIZATIONS IN HOMOGENEOUS MELTS

In order to determine whether the reaction I $\rightleftharpoons$ II represents a true equilibrium reaction, a careful study of the isomerization of pairs of isomers represented by pure I or II in homogeneous systems (undisturbed melts) was carried out at 184–185°. Preliminary experiments with $R_1 = R_2 = C_6H_5$ showed that a reaction time of 15 min. at this temperature was adequate to insure the attainment of equilibrium. The results obtained are summarized in Table VI, for all cases of I and II, respectively, in which $R_2 = C_6H_5$, while Table VII summarizes the results of maintaining $R_1 = C_6H_5$ and varying the R_2 substituent in the 4-position.

Tables VI and VII show that the equilibrium is reached starting with either of the isomeric forms I or II. The position of equilibrium is again dependent on the electrical nature of the substituent in the 1- position in a manner very nearly parallel to the effect observed in the substituted 5-aminotetrazole system[6,16] (Table VI for II, $R_2 = C_6H_5$) and in all probability a similar mechanism[16] is operative.[26] Corroboration for this appears in the plot, Fig. 3, of the logarithm of the equilibrium constant with Hammett's σ value for groups.[17] It will be noted that an approximately linear relationship is obtained. However, complete verification for the similarity in mechanism in the isomerization of the substituted 5-aminotetrazoles and the substituted 5-amino-1,2,3-triazoles must await kinetic information. This latter study will be reported in a separate communication. It is also evident from Table VII that much more information is needed regarding the effects of substituents in the 4- position of I and II on the position of equilibrium. This problem is being currently investigated.

TABLE VI

PROOF OF EQUILIBRIUM IN HOMOGENEOUS MELTS

Starting Vicinal Triazole	5-(Substituted)-aminotriazole in Equilibrium Melt[a] (%)	K[b]
1-Benzyl-5-amino-4-phenyl-	7.6	
5-Benzylamino-4-phenyl-	7.7	0.083
1-(4-Anisyl)-5-amino-4-phenyl-	50.4	
5-(4-Anisyl)amino-4-phenyl-	50.8	1.03
1-(4-Tolyl)-5-amino-4-phenyl-	65.3	
5-(4-Tolyl)amino-4-phenyl-	65.2	1.94
1-(3-Tolyl)-5-amino-4-phenyl-	69.1	
5-(3-Tolyl)amino-4-phenyl-	69.5	2.26
1-Phenyl-5-amino-4-phenyl-	77.0	
5-Anilino-4-phenyl-	77.2	3.37
1-(4-Nitrophenyl)-5-amino-4-phenyl-	94.4	
5-(4-Nitrophenyl)amino-4-phenyl-	94.4	16.9
1-(4-Bromophenyl)-5-amino-4-phenyl-	85.9	
5-(4-Bromophenyl)amino-4-phenyl-	85.8	6.14
1-(4-Chlorophenyl)-5-amino-4-phenyl-	85.1	
5-(4-Chlorophenyl)amino-4-phenyl-	85.2	5.66
1-(3-Chlorophenyl)-5-amino-4-phenyl-	89.7	
5-(3-Chlorophenyl)amino-4-phenyl	89.3	8.50
1-(2-Naphthyl)-5-amino-4-phenyl-	81.3	
5-(2-Naphthyl)amino-4-phenyl-	81.5	4.37
1-(3-Nitrophenyl)-5-amino-4-phenyl-	93.2	
5-(3-Nitrophenyl)amino-4-phenyl-	93.2	13.7

[a] At 184–185° for 15 min. [b] Equilibrium constant calculated as the ratio of II to I.

EXPERIMENTAL[18,19]

Organic azides. The organic azides used in this research

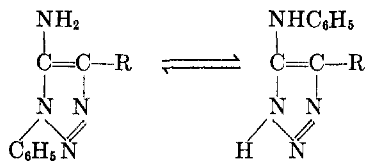
(16) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **77**, 2264 (1955).

(17) Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1940, Chapter VII.

(18) All melting points are taken on a Fisher-Johns Block and are corrected.

(19) Microanalyses by Galbraith Microanalytical Laboratories.

TABLE VII



EQUILIBRIUM MEASUREMENTS IN HOMOGENEOUS MELTS AT 184–185°. EFFECT OF 4-POSITION

R	Starting Vicinal Triazole	5-(Substituted)-aminotriazole (Acidic Form) in Equilibrium Melt (%)
C_6H_5	1-Phenyl-5-amino-	77.0
C_6H_5	5-Anilino-	77.2
H	1-Phenyl-5-amino-	67.1
H	5-Anilino-	67.2
$—CO_2Et$	1-Phenyl-5-amino-	66.4
$—CO_2Et$	5-Anilino-	67.0

and summarized in Table II were made from procedures or adaptations of procedures described in the literature. A new method for the preparation of alkyl azides, which avoids the formation of troublesome azeotropes, is described elsewhere.[20]

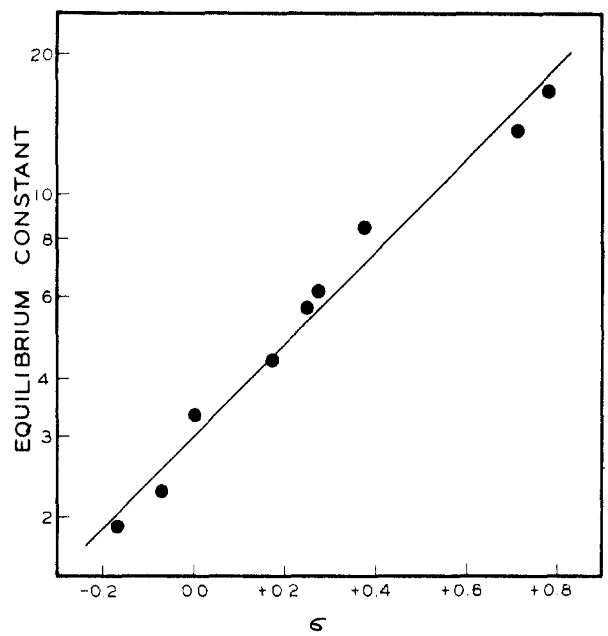


FIG. 3. CORRELATION BETWEEN EQUILIBRIUM CONSTANT AND HAMMETT'S SIGMA VALUE FOR GROUPS

1-Substituted-4-phenyl-5-amino-1,2,3-triazoles. The compounds prepared are summarized in Table III. Those preparations which differ markedly from the general procedures summarized in Table III, or gave particular difficulty in recovery of product, are given below.

1-o-Tolyl-4-phenyl-5-amino-1,2,3-triazole. While the procedure was substantially that of B (Table III), considerable difficulty was experienced in isolating a solid product. This was overcome after some modifications in the procedure. The following was the best procedure. The reaction flask was charged with 12.9 g. (0.11 mole) of phenylacetonitrile and a solution of 8.1 g. (0.15 mole) of sodium methoxide in 100 ml. of methanol. With constant stirring at room temperature, a solution of 13.3 g. (0.1 mole) of *o*-tolyl azide in 10 ml. of methanol was added dropwise over 1 hr. The reaction mixture was stirred at room temperature overnight (no precipitation was observed) and then refluxed for a total of 30 hr. at 65–75°. The reaction mixture, after cooling to room temperature, was filtered from the small amount of sodium methoxide which had precipitated, and the filtrate evaporated under vacuum until free of methanol. The residue was an intractable dark red thick oil. It was diluted with 300 ml. of benzene and filtered to remove the sodium methoxide. The filtrate was then evaporated under vacuum to remove the benzene and the oily residue containing some precipitated solid (later identified as sodium methoxide) was extracted with about 200 ml. of ether. The ether solution was evaporated at room temperature with occasional stirring. When the volume was reduced to about 100 ml. turbidity was observed, and, upon stirring, a rapid crystallization took place. After standing for 2 hr., the light brown, large crystals were filtered and suction dried. Yield, 11.5 g. with an additional 3.2 g. obtained by further concentration of the mother liquor.

1-o-Chlorophenyl-4-phenyl-5-amino-1,2,3-triazole. As in the case of *o*-tolyl azide, considerable difficulty was experienced in isolating a solid product. The inability of conveniently isolating a solid product was the occasion for a study in recovery methods. The difficulties were finally overcome and the yield markedly improved by diluting with benzene and filtering, after which the entire reaction mixture was poured slowly into ice water. A white semisolid was formed, which, after standing under water at room temperature for 8 days, turned into a yellowish-white crystalline solid. This was broken up, filtered, suction and air-dried. From 7.67 g. (0.05 mole) of *o*-chlorophenyl azide was obtained 12 g. of product.

1-p-Nitrophenyl-4-phenyl-5-amino-1,2,3-triazole (XIII). The procedure of Dimroth and Michaelis[9] yields 53.5% of this product (from 0.0277 mole of *p*-nitrophenyl azide). It was best modified by carrying out the initial condensation at 0–3° and stirring overnight, recovering the product and refluxing the filtrate for 4 hrs. for a combined yield of 11.5 g. (81.8%).

In a series of experiments in which the initial and final conditions in the condensation of *p*-nitrophenyl azide (0.05 mole) with phenylacetonitrile were varied, it was found that the purity of the product, *i.e.*, lack of acidic isomer, was favored by low temperature, although this factor very materially reduces the yield. Thus, when the reagents were reacted at room temperature and then refluxed 4 hr. the yield was 57% and the m.p. 175–176° whereas, when the reagents were reacted at 0–3° (1 hour) and then overnight at room temperature, the yield was 20.7% but the m.p. was 181–182° (the pure isomer melts at 182–183°) and the content of acidic isomer by nonaqueous titration[7] was 0.36%. Relatively impure samples of product having a m.p. of 170–175° were readily freed of acidic isomer by washing with dry ether. About 5 g. of material, m.p. 171–172°, in the form of very fine crystals, was placed on a sintered glass funnel and washed with four 50-ml. portions of ether. After suction and air-drying, the melting point was found to be 181–182°. Table VIII summarizes the effect of solvent and temperature on the extent of isomerization that occurs during recrystallization.

Condensation of o-nitrophenyl azide with phenylacetonitrile (XV). A mixture of 100 ml. of dry ether, 16.6 g. (0.10 mole) of *o*-nitrophenyl azide and 11.7 g. (0.10 mole) of phenylacetonitrile was treated dropwise, with constant stirring at 0°, with a solution of 5.4 g. (0.10 mole) of sodium methoxide (in 50 ml. of methanol) over a period of 2 hr. The mixture was stirred at 0–20° (in a melting ice bath) overnight and then at room temperature for 6 hr. The solid product was filtered from the dark colored solution and washed with 200 ml. of ether and 40 ml. of methanol. There was obtained

(20) E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 238 (1957).

TABLE VIII

EFFECT OF SOLVENT AND TEMPERATURE ON ISOMERIZATION OF 1-p-NITROPHENYL-4-PHENYL-5-AMINO-1,2,3-TRIAZOLE

	Conditions[a]			Recovered	
Solvent	Temp., °C.	Triazole used, g.	Solvent used, ml.	M.P.	Isomer[b]
Benzene	80	0.6	600	177–178	2.55
Abs. ethanol	78	0.8	300	175–176	2.58
Ethyl acetate	77	0.5	100	175–176	3.90
DMF[c]	82–85	1.0	20	172.5–173.5	4.45
Acetone	56	1.0	20	173–174	5.74
(Before recrystallization)				177–178	0.31

[a] The triazole was maintained at the specific temperatures for 5 min., filtered, and allowed to crystallize. [b] Per cent acidic isomer by nonaqueous titration.[7] [c] Dimethyl formamide, 60% aqueous solution.

7.8 g. of orange colored needle-like crystals, m.p. 220–222°, dec.; after four recrystallizations from ethyl acetate, m.p. 218–219° (dec.).

Anal. Calcd. for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.61. Found: C, 64.14; H, 3.66; N, 26.80.

Condensation of ethyl azide with phenylacetonitrile. 1-Ethyl-4-phenyl-5-amino-1,2,3-triazole (XVI, XVII, and XVIII). A solution of sodium ethoxide in 100 ml. of ethanol was prepared under a stream of dry nitrogen from 5.06 g. (0.22 mole) of sodium. After cooling the flask to room temperature and immersing it in an ice bath, 25.7 g. (0.22 mole) of phenylacetonitrile and 13.8 g. (0.194 mole) of ethyl azide were added. A Dry-Ice trap was connected to the top of the reflux condenser to prevent any loss of ethyl azide. The reaction mixture was allowed to warm up to room temperature and then heated slowly to 60° and maintained there for 70 hr. The reaction mixture was then cooled to −17°. The crystals which separated out were filtered and washed with 50 ml. of methanol. After suction and air-drying, 14.8 g. of small white crystals, m.p. 147–148°, was obtained. Upon evaporation of the mother liquor, a second crop of 8 g., a third one of 6.6 g., and a fourth of 1.5 g. were obtained.

The first crop of product on successive recrystallization from hot benzene gave fine white needles of constant m.p. of 151–152°. It was identified as XVII (or XVIII) by analysis ($R = C_2H_5$).

Anal. Calcd. for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.94. Found: C, 70.60; H, 6.20; N, 22.97.

The second, third and fourth crops of crystals were combined and recrystallized successively from boiling benzene to a constant m.p. of 111–112°. The compound was identified as XVI ($R = C_2H_5$).

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43. Found: C, 64.57; H, 6.49.

Condensation of n-hexyl azide with phenylacetonitrile (XVII or XVIII, $R = C_6H_{13}$). The reaction mixture comprised 14 g. (0.12 mole) of phenylacetonitrile, 8.65 g. (0.16 mole) of sodium methoxide (in 70 ml. of methanol) and 14 g. (0.11 mole) of *n*-hexyl azide (in 30 ml. of methanol) added last. The reaction was maintained at room temperature overnight and then refluxed at 62–65° for 73 hrs. Upon vacuum evaporation to about 50 ml., 2.3 g. of yellowish solid precipitated which was washed with ethanol and ether and recrystallized from toluene to white shiny crystals, m.p. 196–197°.

Anal. Calcd. for $C_{22}H_{27}N_5$: C, 73.09; H, 7.53; N, 19.38. Found: C, 72.41; H, 7.54; N, 20.31.

The mother liquor was decomposed by ice water, yielding an oily layer extractable by benzene. Removal of the benzene gave an oil from which no crystallization could be induced.

Ethyl 1-phenyl-5-amino-1,2,3-triazole-4-carboxylate (XX). This was prepared by the method of Dimroth[5] from 0.42 mole of phenyl azide and 0.44 mole of ethyl cyanoacetate. Yield, 67 g. (69%), m.p. 126°.[5]

Ethyl 5-anilino-1,2,3-triazole-4-carboxylate (XXI). This was prepared by irreversible isomerization of XX following the procedure of Dimroth and Pfister.[22] From 5 g. of XX, yield 4 g. (80%), fine feltlike needles, m.p. 129–130°.[23]

5-Anilino-1,2,3-triazole (XXII). By saponification of 6 g. of XXI with alcoholic KOH, isolation and acidification gave 4 g. (77%) of *5-anilino-1,2,3-triazole-4-carboxylic acid.* After drying it was decarboxylated at 152–154° and recrystallized from hot water. Yield, 2.8 g. (90% based on the carboxylic acid), m.p. 139°.[5]

1-Phenyl-4-chloro-1,2,3-triazole (XXVI). From 0.3 mole of methyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate[24] and PCl_5 was obtained 41 g. (57%) of *methyl 1-phenyl-5-chloro-1,2,3-triazole-4-carboxylate*, m.p. 87°[24] (XXIV). From 0.1 mole of XXIV by saponification and acidification was obtained 15.6 g. (70%) of *1-phenyl-5-chloro-1,2,3-triazole-4-carboxylic acid* (XXV), m.p. 134°. Without purification, 0.7 mole of XXV on thermal decarboxylation gave 10.8 g. (84%) of XXVI, m.p. 47–48°.

1-Phenyl-5-amino-1,2,3-triazole (XXIII). By ammonolysis of 1.8 g. (0.01 mole) of XXVI in ethanolic ammonia in a sealed tube at room temperature for five weeks. Yield, 0.5 g. (31%), m.p. 110–111°.[5]

4-Phenyl-5-substituted-amino-1,2,3-triazoles. Table IV. Except where noted the preparation of *4-phenyl-5-(p-tolyl)-amino-1,2,3-triazole* was typical.

Five g. (0.02 mole) of *1-p-tolyl-4-phenyl-5-amino-1,2,3-triazole* was dissolved in 20 ml. of dry pyridine. The solution was refluxed at 113–115° for 48 hr. After cooling, it was filtered into 500 ml. of ice water. A white semisolid was formed which, after standing 1 hr., with occasional stirring and scratching, crystallized. It was filtered, washed twice with water, and suctioned and air-dried. Yield, 5 g. Recrystallized from 100 ml. of hot benzene into fine, white needles. A nonaqueous titration showed the absence of basic isomer.[7]

4-Phenyl-5-(m-nitrophenyl)amino-1,2,3-triazole. Seven g. (0.025 mole) of *1-m-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole* was mixed with 30 ml. of dry pyridine. The compound dissolved on warming the pyridine to reflux, which was maintained for 12 hr. After cooling, it was filtered into 500 ml. of ice water, whereupon a brownish colored oil separated. The latter did not crystallize after standing several hours with occasional stirring and scratching. However, after several days at room temperature, solidification was achieved. It was filtered and washed with three 40-ml. portions of water. After suction and air-drying, the yield was 7 g. The compound is very soluble in ether, benzene, and methanol and insoluble in cyclohexane. Recrystallization from aqueous methanol yielded irregular crystals, m.p. 134–136°. It is best recrystallized by dissolving in ether, diluting with 2 volumes of petroleum ether, and evaporating slowly to produce deep yellow crystals.

4-Phenyl-5-benzylamino-1,2,3-triazole. Commercial 4-picoline was dried over NaOH pellets and fractionally distilled over the same reagent. The middle fraction, b.p. 143–145° was used. Eight and one-half g. (0.034 mole) of 1-benzyl-4-phenyl-5-amino-1,2,3-triazole was dissolved in 30 ml. of purified 4-picoline, refluxed for 108 hours at 131–132° and cooled to room temperature. No crystals separated. The solution was poured into ice water and the white precipitate, after standing 3 hr., was filtered, washed with water and air-dried. Yield 6.7 g., m.p. 130–132°. Acidimetric titration in nonaqueous solvent[7] showed the presence of 23% of the desired product, indicating that the isomerization was still far from complete even under the drastic conditions used.

About 6 g. of the above mixture was placed in a sintered

(21) O. Dimroth, *Ber.*, **35**, 4058 (1902).

(22) O. Dimroth and K. Pfister, *Ber.*, **43**, 2736 (1910).

(23) O. Dimroth, *Ann.*, **364**, 203 (1909).

(24) O. Dimroth, *Ann.*, **335**, 1 (1904).

glass funnel and extracted with ten 20-ml. portions of dry ether. The ether was removed by evaporation at room temperature. Yield, 1.5 g., white crystals. Nonaqueous titration showed it to be free of the basic isomer.

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.97; H, 5.64; N, 22.39. Found: C, 71.80; H, 5.51; N, 22.28.

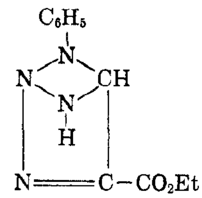
Relative rates of irreversible isomerization (I to II). *Table V.* One g. of each compound in 8 ml. of dry pyridine was refluxed 0.5 hr. on a preheated sand bath. The reaction mixture was poured into 150 ml. of ice water. The product was filtered, washed several times with water and thoroughly dried. The acidic isomer content was determined by titration in nonaqueous solvent.[7]

Equilibrium measurements in homogeneous melts, Table VI. Known quantities of I and II, respectively, were taken in sample tubes with standard inner joints which could be fitted to the two side necks of a 500 ml. 3-necked flask. A reflux condenser and a thermometer well were fitted to the central neck of the flask. Boiling *trans*-decalin gave a temperature of 184–185°. The samples were maintained at this temperature in the molten condition for a known period of time, after which they were chilled to ice temperature and then estimated for type II isomer by nonaqueous techniques.[7,25]

Acknowledgment. A grant-in-aid in support of this investigation from the Office of Naval Research is gratefully acknowledged.

(25) Dimroth, *Ann.*, **377**, 211 (1910) and Brown, Hammick, and Heritage, *J. Chem. Soc.*, 3820 (1953) used alcoholic potassium hydroxide as titrant and phenolphthalein as visible indicator. The accuracy of this work is questionable. For example, the titration of 4-phenyl-5-anilino- and 4-phenyl-5-(*m*-chlorophenyl)amino-1,2,3-triazoles, respectively, in dry ethanol as solvent, sodium methoxide in dry methanol as the titrant and phenolphthalein as visible indicator, gave consistently only 85 to 87 per cent recoveries. Furthermore, it was found necessary to standardize on the shade of the pink (or the red) of the indicator endpoint, otherwise the recovery values were found to lie anywhere between 68 to 98% recoveries (only the stronger 4-substituted-5-(substituted)amino-1,2,3-triazoles gave the higher recovery values. Details of this study are reported elsewhere.[7]

(26) Attention is directed to the polemic between Dutt [*J. Chem. Soc.*, 265 (1923); 2476 (1924)] and Dimroth[5] regarding the structure of II ($R_1 = C_6H_5$; $R_2 = CO_2Et$). Dutt considered the structure to be as indicated at end of this footnote. Attempts to answer this on chemical grounds were made by Dimroth and Michaelis.[9] However, it can be stated that the arguments on either side were not entirely convincing. Dutt's hypothesis of a bicyclic intermediate does not definitely account for the influence of R_1 in I and II on either the position of equilibrium or the relative rate of isomerization.[8] The high degree of ring strain required by this type of intermediate would make its formation very unlikely. W. L. Garbrecht, and R. M., Herbst, *J. Org. Chem.*, **18**, 1269 (1953) have suggested a similar bicyclic intermediate to account for the isomerization of substituted 5-aminotetrazoles[6,16] which is open to the same objections.



CHICAGO 14, ILL.

[CONTRIBUTION FROM ORGANIC CHEMICALS DEPARTMENT RESEARCH DIVISION, JACKSON LABORATORY, E. I. DU PONT DE NEMOURS & CO., INC.]

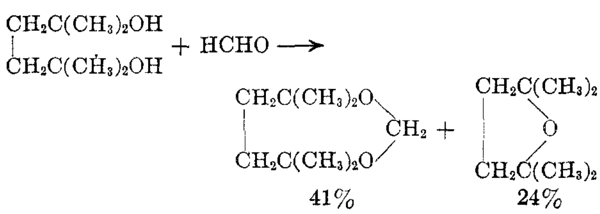
Seven-Membered Cyclic Acetals

DEXTER B. PATTISON

Received December 13, 1956

The general method for the synthesis of 1,3-dioxepane has been extended to eight novel seven-membered cyclic acetals, including 1,3-dioxep-5-ene. The method has been improved.

This paper describes the preparation and properties of various seven-membered cyclic acetals derived from aldehydes and dihydric alcohols containing four carbon atoms between hydroxyl groups. There are two competing reactions which can occur, either ring closure to the desired seven-membered acetal or dehydration of the glycol to a tetrahydrofuran derivative. This is illustrated below in the equation for the synthesis of 4,4,7,7-tetramethyl-1,3-dioxepane.



41% 24%

Substituents on the alpha carbon atoms and to a much lesser extent on the beta position of the diol favor the formation of the tetrahydrofuran derivative and lower the yield of the 1,3-dioxepane. On the other hand, with a double bond beta to the hydroxyl groups of the diol only a trace of dihydrofuran could be isolated.

The reaction of *cis*-2-butenediol-1,4 with formaldehyde to give 1,3-dioxep-5-ene[1] and the reaction of *cis*-2-butenediol-1,4 with various aldehydes to give substituted 1,3-dioxep-5-enes[2] has been described in recent papers. The double bond in 1,3-dioxep-5-ene appears to have normal double bond activity. 1,3-Dioxep-5-ene adds bro-

(1) W. Reppe, *et al.*, *Ann.*, **596**, 1 (1956).

(2) W. Brannock and G. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).