[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY LEHIGH UNIVERSITY]

STUDIES IN TETRAZOLE CHEMISTRY.[1] I. SIDE CHAIN ACID DERIVATIVES

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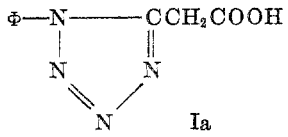
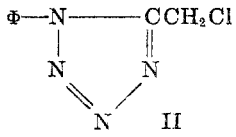
Although investigations in the field of tetrazole chemistry have led to the synthesis of over five hundred known 1,5-disubstituted tetrazoles,[3] the number of different chemical types represented is very small and with few exceptions amino, halogen, hydroxyl, and mercapto groups are the limit of the functional components available for further investigation into the chemistry of this series.

In the course of our study of the tetrazoles we have developed and here report new methods for the synthesis of 1,5-disubstituted tetrazoles containing the carboxyl group as the functional component.

Previous attempts by Kerr (11) in this laboratory to prepare 1-phenyl-5-tetrazolylacetic acid (Ia) from 1-phenyl-5-chloromethyltetrazole (II) have failed. Although II was found to be highly reactive, it did not give a Grignard reagent



Ia



II

upon reaction with magnesium nor was the nitrile obtained by reaction with aqueous or alcoholic potassium cyanide. We have also failed to obtain the nitrile using cuprous cyanide.

Phenyllithium and phenylsodium have been found to be satisfactory reagents for use in synthesizing tetrazole acids containing the carboxyl group on the α-carbon of the substituent in the 5-position. These compounds would be tetrazole relatives of substituted acetic acids and their preparation can be represented by the general formula given in Figure 1.

This synthesis was found to work satisfactorily with four 1,5-disubstituted tetrazoles and with five pentamethylenetetrazoles and appears to be generally applicable. Results of these preparations are given in Table I.

Reaction of the appropriate tetrazole with phenyllithium or phenylsodium proceeded instantaneously near room temperature producing yellow to brown solutions often containing a colored precipitate of the resulting tetrazolyllithium

[1] The authors wish to express their appreciation to E. Bilhuber, Inc. for their support of this work and for the generous supplies of tetrazoles contributed.

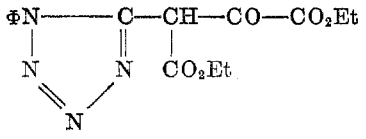
[2] This work is taken in part from the thesis of C. R. Jacobson presented to the Graduate School of Lehigh University in partial fulfillment of the requirements for the degree of Master of Science, June 1952.

[3] An excellent review of the literature on tetrazoles through 1946 is provided by Benson (1). More recently most of the work on the synthesis of 1,5-disubstituted tetrazoles has been reported by Harvill, Herbst and others (2–10).

compound. Carbonation with Dry Ice followed by hydrolysis and acidification gave the desired tetrazole acid.

The acids are colorless crystalline solids that decarboxylate upon melting. They are generally slightly stronger than acetic acid having dissociation constants ranging from 10^{-3} to 4×10^{-5} and neutralization curves very similar to that for acetic acid.

Another new type of tetrazole derivative containing the carboxyl group has been prepared by condensing 1-phenyl-5-methyltetrazole (III) and 1-methyl-5-benzyltetrazole (IV) with diethyl oxalate in refluxing ethanol solutions of sodium ethoxide producing ethyl 1-phenyl-5-tetrazolylpyruvate (V) and ethyl β-phenyl-1-methyl-5-tetrazolylpyruvate (VI), respectively, as shown in Figure 2.



VIII

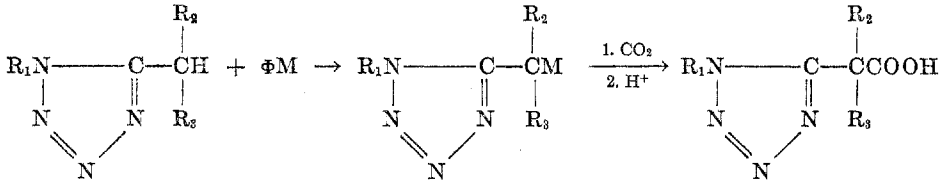


FIGURE 1

The sodio derivative of V was isolated as an extremely stable white, water-insoluble solid. It is formed with particular ease from the pyruvate, dilute bicarbonate being sufficient to precipitate the salt. This pyruvate gives a deep red ferric chloride test and although the bisulfite addition compound has not been isolated the oxime and the 2,4-dinitrophenylhydrazone have been prepared. All attempts to decarbonylate this compound have failed and it has been found sufficiently stable to be distilled at 200–205° at 0.06 mm. pressure.

In the preparation of ethyl β-phenyl-1-methyl-5-tetrazolylpyruvate (VI) the sodium salt did not precipitate from the anhydrous reaction mixture even upon addition of absolute ether. However, upon treatment with water and acidification of the separated aqueous layer the product was obtained. In contrast to V this pyruvate did not form an insoluble sodium salt upon treatment with either 10% sodium bicarbonate or 10% sodium hydroxide. It gave a green ferric chloride complex and was also resistant to decarbonylation.

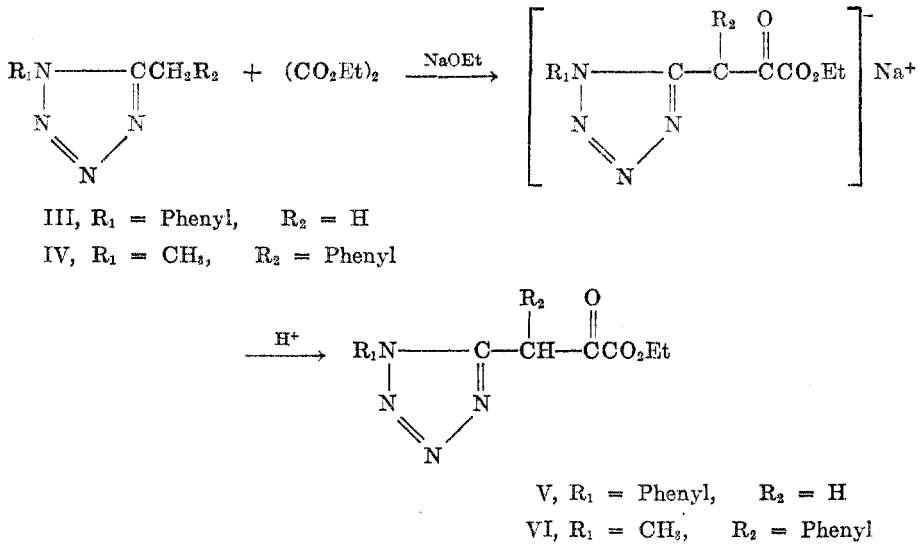
Determination of the enol content of an approximately 0.02 *molar* solution of V and VI in 95% ethanol by the Kurt Meyer method (12) gave values of 93% and 87% enol respectively. The high proportion of enol in these compounds is not surprising in view of the previously mentioned ease of formation of an extremely stable sodium salt of V and suggests that the enol may have the struc-

TABLE I

TETRAZOLE ACIDS

NO.	COMPOUND	YIELD, %	M.P., °C.	pK_a	SOLVENT	FORMULA	ANALYSES					
							Calc'd			Found		
							C	H	Neut. Equiv.	C	H	Neut. Equiv.
Ia	1-Phenyl-5-tetrazolylacetic acid	66	135.0–135.5 d.	3.1	Water (80°)	$C_9H_8N_4O_2$	52.9	4.0	204	53.0	4.0	210
Ib	1-α-Naphthyl-5-tetrazolylacetic acid[d]	low	136 d.	—	20% Ethanol	$C_{13}H_{10}N_4O_2$	61.4	4.0	254	61.2	4.2	258
Ic	α-(1-Cyclohexyl-5-tetrazolyl)isobutyric acid[e]	64[a]	146–147 d.	3.7	Water	$C_{11}H_{18}N_4O_2$	55.4	7.6	238	55.4	7.6	242
Id	1-Methyl-5-α-phenyltetrazolylacetic acid[f]	62	104 d.	4.0	Not recryst.[b]	$C_{10}H_{10}N_4O_2$	55.0	4.6	218	55.0	4.7	224
Ie	Pentamethylenetetrazolyl-6-carboxylic acid[g]	57	147–148 d.	3.4	Nitroethane	$C_7H_{10}N_4O_2$	46.1	5.5	182	45.9	5.5	187
If	6-Methylpentamethylenetetrazolyl-6-carboxylic acid[h]	36[a]	128–130 d.	3.3	Benzene	$C_8H_{12}N_4O_2$	49.0	6.2	196	49.0	6.2	197
Ig	7-Methylpentamethylenetetrazolyl-6-carboxylic acid[h]	57[a]	105–127 d. –127–135[c]	3.0	Toluene	$C_8H_{12}N_4O_2$	49.0	6.2	196	49.0	6.2	199
Ih	8-Methylpentamethylenetetrazolyl-6-carboxylic acid	51[a]	136–138 d.	3.2	Ethyl acetate	$C_8H_{12}N_4O_2$	49.0	6.2	196	49.1	6.4	197
Ii	8-*tert*-Butylpentamethylenetetrazolyl-6-carboxylic acid	75[a]	153–154 d.	4.4	30% Ethanol	$C_{11}H_{18}N_4O_2$	55.4	7.6	238	55.6	7.6	240

[a] Crude yields. [b] This acid is not stable, decarboxylating rapidly in solution above 60° and slowly in the solid state upon standing for several months. Purification was effected by repcated isolation from the sodium salt. [c] Slowly shrinks and melts and then slowly decarboxylates. [d] The 1-naphthyl-5-methyltetrazole used to prepare this acid was prepared by the method of Harvill, *et al.* (5), m.p. 110–111°. *Anal.* Calc'd for $C_{12}H_{10}N_4$: C, 68.5; H, 4.8. Found: C, 68.4; H, 5.0. [e] Isolated as the monohydrate which lost water at 111° without melting but accompanied by decrepitation. [f] The 1-methyl-5-benzyltetrazole used to prepare this acid was prepared by the method of Harvill, *et al.* (5), m.p. 71.5–72.0°. *Anal.* Calc'd for $C_9H_{10}N_4$: C, 62.0; H, 6.0. Found: C, 61.9; H, 6.0. [g] The numbering system used for the pentamethylenetetrazolecarboxylic acids is that of Harvill (6). [h] That the structures of the pentamethylenetetrazoles from which these acids have been prepared are not unequivocal has previously been discussed (6).

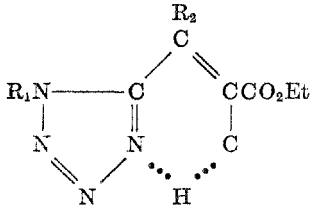


III, R_1 = Phenyl, R_2 = H
IV, R_1 = CH_3, R_2 = Phenyl

V, R_1 = Phenyl, R_2 = H
VI, R_1 = CH_3, R_2 = Phenyl

FIGURE 2

ture represented by VII, which resembles the chelated enol form of β-diketones. Thus, the resonance of VII should stabilize the enol form and lead to the high percentage of enol found in V and VI.



VII

Basic saponification of V in the presence of 10% sodium hydroxide led to its cleavage and the recovery of 1-phenyl-5-methyltetrazole. 1-Phenyl-5-tetrazolylpyruvic acid was obtained by hydrolysis of V in aqueous acetic acid solution in the presence of catalytic amounts of sulfuric acid. This acid underwent gaseous decomposition at its melting point of 172–173° which is far above the decarboxylation temperature (135°) of the 1-phenyl-5-tetrazolylacetic acid that would be produced. It is probable that this decomposition consisted in decarboxylation rather than decarbonylation for no 1-phenyl-5-methyltetrazole was isolated, only tarry products being obtained. Decarboxylation would lead to 1-phenyl-5-tetrazolylacetaldehyde which at the existing temperature (173°) would probably polymerize.

The sodium salt of V condensed with ethyl chlorocarbonate to yield ethyl α-ethoxalyl-1-phenyl-5-tetrazolylacetate (VIII). This product underwent slow gaseous decomposition only above 215° (m.p. 100–101°) to give tarry products.

It did not form an insoluble sodio derivative but gave a red ferric chloride complex.

The enol content of this compound in a 0.02 *molar* solution in 95% ethanol was too small to be detected by the Kurt Meyer method (12).

All other attempted reactions that are typical of active methyl compounds have failed with 1-phenyl-5-methyltetrazole. No reaction has been observed with *p*-nitrosodimethylaniline after 48 hours reflux in ethanolic solution in the presence of anhydrous sodium carbonate nor with diazotized sulfanilic acid in neutral or basic solution. Treatment with benzaldehyde at 200° in a sealed tube in the presence of zinc chloride and with selenious acid in ethanolic and acetic acid solutions for long periods has also resulted in almost quantitative recovery of the starting material. Neither 1-phenyl-5-methyltetrazole nor 1-methyl-5-benzyltetrazole reacted with diethyl carbonate in the presence of sodium ethoxide after long reflux.

This observed lack of reactivity of the 5-methyl group of 1-phenyl-5-methyltetrazole toward electrophylic reagents suggests that the methyl ketimine structure of the molecule is not operating as such to lower the electron density of the 5-carbon atom and thus activate the attached methyl group as is observed in the case of 2-picoline, 2-methylquinoline, and similar heterocyclic compounds.

The reasons for this are thought to arise from the peculiar nature of the tetrazole nucleus which is extremely stable in spite of containing a four nitrogen atom chain and which is reported to have a high resonance energy (13) and a large dipole moment (14) and yet shows little or no absorption in the ultraviolet region (15). The results of further investigation of the effect of the tetrazole nucleus on substituents in the 1- and 5-positions will be reported in forthcoming papers.

EXPERIMENTAL[4, 5]

Tetrazole acids. The following general procedure has been found applicable for the preparation of all the tetrazole acids listed in Table I. Phenyllithium is prepared by adding a solution of bromobenzene (7.9 g., 0.05 mole) in 20 ml. of absolute ether to a suspension of lithium filings (0.7 g., 0.10 mole) in 30 ml. of absolute ether under an atmosphere of nitrogen during 20 minutes followed by stirring for 20 minutes. A solution of the substituted tetrazole (0.04 mole) in 100 ml. of absolute ether (more ether or a 50–50 mixture of dry benzene and absolute ether may be used, if necessary, to dissolve the tetrazole) is added to the pale brown phenyllithium solution during 20 minutes followed by stirring for 20 minutes under nitrogen. The yellow to brown solution which may contain a fine precipitate is rapidly poured over about 200 g. of powdered Dry Ice with stirring and the resulting white to cream-colored suspension is allowed to stand until all of the Dry Ice has evaporated. Cold water (approx. 75–100 ml.) is added with stirring until the suspended solid has dissolved in the aqueous layer which is separated and acidified with concentrated hydrochloric acid to below *p*H 2. The product may separate either as a solid or as an oil which may or may not solidify. In the case of an oil or an oily solid it is best to extract the acid solution with ether, extract the ether solution with the minimum amount of a saturated sodium bicarbonate solution,

[4] All melting-points taken with Anschutz thermometers.

[5] Many tetrazoles used in these experiments were obtained from E. Bilhuber, Inc. Those not so obtained were prepared from N-substituted amides through formation of the amide chloride, reaction with hydrazoic acid, and cyclization by the method of Harvill, *et al.* (5).

and again acidify in the cold. The product is obtained as a solid or an oil that will solidify upon standing and can be recrystallized from an appropriate solvent.

The use of an equivalent quantity of phenylsodium in place of the phenyllithium in the above syntheses has been found to be entirely satisfactory.

Ethyl 1-phenyl-5-tetrazolylpyruvate (V). To a hot, gelatinous mass of sodium ethoxide prepared from sodium (2.3 g., 0.11 mole) and the minimum quantity of absolute ethanol to dissolve all of the sodium upon refluxing there was added a solution of 1-phenyl-5-methyltetrazole (8.0 g., 0.05 mole) in diethyl oxalate (73.1 g., 0.5 mole). After 10 minutes reflux with stirring a fine white precipitate formed and during 10 minutes additional reflux the mixture became thick and carbon monoxide was slowly evolved.[6] The cooled mixture was filtered and washed with absolute ethanol and absolute ether leaving the almost white pasty sodio derivative of the pyruvate. The solid was suspended in 500 ml. of ether and upon shaking with 3 *N* hydrochloric acid it dissolved; removal of the solvent from the dried ether solution left 9.1 g. of colorless to pink crystals. Two recrystallizations from a mixture of benzene and petroleum ether (b.p. 60–68°) gave 8.4 g. (65%) of almost white needles, m.p. 87–89°.

Anal. Calc'd for $C_{12}H_{12}N_4O_3$: C, 55.4; H, 4.7.
Found: C, 55.7; H, 4.8.

The *2,4-dinitrophenylhydrazone* of the pyruvate has m.p. 176.5–177.5°.

Ethyl 1-phenyl-5-tetrazolylpyruvate oxime has m.p. 116–117°.

Anal. Calc'd for $C_{12}H_{13}N_5O_3$: C, 52.4; H, 4.8.
Found: C, 52.5; H, 4.8.

1-Phenyl-5-tetrazolylpyruvic acid. A solution of ethyl 1-phenyl-5-tetrazolylpyruvate (7.8 g., 0.03 mole) in 50 ml. of glacial acetic acid was refluxed together with 10 ml. of water and 5 drops of concentrated sulfuric acid for eight hours. The solvent was removed *in vacuo* and the residual oil was partially neutralized with 10% sodium bicarbonate solution. After extraction of the mixture with ether the extract was extracted with 10% sodium bicarbonate solution and the basic solution was acidified with concentrated hydrochloric acid, a gummy brown precipitate forming. The solid was taken into ether and upon removal of the ether from the dried solution a yellow solid remained that was ground under a small quantity of chloroform, filtered, and recrystallized from a mixture of nitroethane, benzene, and petroleum ether (b.p. 90–100°) .Thus 1.4 g. (20%) of colorless platy crystals of 1-phenyl-5-tetrazolylpyruvic acid were obtained, m.p. 172–173°.

Anal. Calc'd for $C_{10}H_8N_4O_3$: Neut. equiv., 232; C, 51.7; H, 3.5.
Found: Neut. equiv., 229; C, 51.8; H, 3.6.

Ethyl β-phenyl-1-methyl-5-tetrazolylpyruvate (VI). A solution of 1-methyl-5-benzyltetrazole (3.5 g., 0.02 mole) in diethyl oxalate (29.2 g., 0.2 mole) was added to an ethanolic solution of sodium ethoxide prepared from sodium (0.9 g., 0.04 mole) and 15 ml. of absolute ethanol. The stirred solution was heated at 70–75° for two hours during which period it turned red but no precipitate formed. After addition of 100 ml. of ether and 100 ml. of water the mixture was shaken and the aqueous layer was separated and acidified to *p*H 2 with concentrated hydrochloric acid, and an oil separated. Extraction with ether followed by removal of the ether from the dried extract left 4.3 g. (78%) of tan crystals of VI. Recrystallization from an ethanol-water mixture or carbon tetrachloride gave white crystals of m.p. 104–105°.

Anal. Calc'd for $C_{13}H_{14}N_4O_3$: C, 56.9; H, 5.2.
Found: C, 57.0; H, 5.4.

Ethyl α-ethoxalyl-1-phenyl-5-tetrazolylacetate (VIII). The sodio derivative of ethyl 1-phenyl-5-tetrazolylpyruvate (2.6 g., 0.01 mole) was suspended in a mixture of ethyl chlorocarbonate (1.14 g., 0.01 mole) and 50 ml. of dry toluene and the suspension was refluxed for six hours during which two more 1.14 g.-portions of ethyl chlorocarbonate were added. The solution was filtered from the precipitated sodium chloride and the solvent was removed

[6] Due to slow decomposition of the diethyl oxalate.

under reduced pressure. Recrystallization of the tan residue from petroleum ether (b.p. 90–100°) gave 1.1 g. (36%) of pale yellow needles of m.p. 95–99°. Two more recrystallizations gave colorless needles, m.p. 100–101°.

Anal. Calc'd for $C_{15}H_{16}N_4O_5$: C, 54.2; H, 4.9.
Found: C, 54.4; H, 4.9.

SUMMARY

A method has been developed for the synthesis of substituted tetrazolylacetic acids and a series of these acids has been prepared by metalation of various tetrazoles with phenyllithium or phenylsodium followed by carbonation with Dry Ice and hydrolysis. They are generally slightly stronger than acetic acid.

The preparation, properties and some reactions of two tetrazolylpyruvates is described.

A qualitative investigation of the reactivity of the 5-methyl group of 1-phenyl-5-methyltetrazole has been made and the results are briefly discussed.

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