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

STUDIES IN TETRAZOLE CHEMISTRY. III. SOME REACTIONS OF 1-PHENYL-5-CHLOROMETHYLTETRAZOLE

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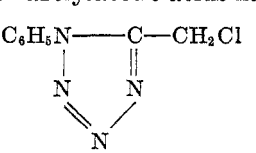
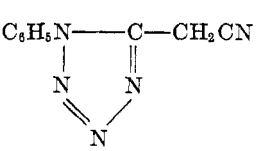
The preparation of 1-phenyl-5-chloromethyltetrazole (I) was first disclosed in a patent (1) issued to Harvill and Herbst covering the preparation of 1-substituted-5-α-halogen alkyltetrazoles. In a more recent publication (2) these authors report the preparation of a wide variety of α-haloalkyltetrazoles and the reaction of these compounds with various reagents to give amino and hydroxy derivatives. They state that the 5-haloalkyltetrazoles react like typical alkyl halides. This observation has been generally substantiated in an investigation of a number of reactions of 1-phenyl-5-chloromethyltetrazole in this laboratory.

Although the structure of 1-phenyl-5-chloromethyltetrazole together with its irritant action on the skin may suggest analogies with compounds of the benzyl chloride type, such a comparison does not appear to be valid. This tetrazole reacts immediately with sodium iodide in acetone solution, precipitation of sodium chloride being essentially complete in less than one minute. In comparison, several minutes reflux of this compound in alcoholic silver nitrate solution gave no evidence of silver chloride precipitation. These results indicate that 1-phenyl-5-chloromethyltetrazole (and possibly the 5-haloalkyltetrazoles in general) is highly reactive in second order nucleophilic substitution reactions (S_N2) but is not prone to react under first order conditions (S_N1). Thus, due to the electron-attracting influence of the ketimine structure at the 4,5 position of the tetrazole ring, the nucleus does not tend to donate electrons to stabilize a conjugated carbonium ion on the α-carbon atom of the 5-substituent. Further support for this effect was found in the observed (3) splitting of 1-phenyl-5-(1-methoxyethyl)tetrazole by the action of 48% hydrobromic acid to give the hydroxy derivative rather than the bromo compound which would be expected if a stable carbonium ion could be formed.

The failure of numerous attempts to prepare 1-phenyl-5-cyanomethyltetrazole (II) from 1-phenyl-5-chloromethyltetrazole (I) as an alternate route to the 1-substituted-5-tetrazolylacetic acids has been mentioned in the first paper of this



I



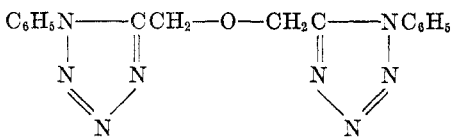
II

series (4). No reaction took place between the chloromethyl derivative and cuprous cyanide in refluxing acetonitrile after 6½ hours, the starting material being quantitatively recovered. Neither did reaction take place in refluxing

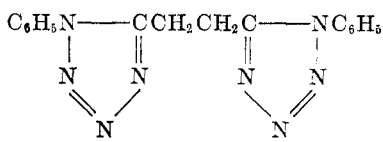
[1] Taken from the Ph.D. Thesis of C. R. Jacobson (1954) and the M.S. Thesis of A. B. Kerr, Jr. (1951).

xylene solution, while in refluxing mesitylene, slow evolution of hydrogen cyanide was observed but no product was isolated that could be identified.

Reaction was observed between 1-phenyl-5-chloromethyltetrazole and potassium cyanide in refluxing absolute methanol or ethanol solutions. After one hour's reflux, and probably in a much shorter period of time, using a 20% excess of potassium cyanide in absolute methanol, 60% of the theoretical yield of precipitated potassium chloride was consistently obtained. Additional reflux gave no more precipitate and caused rapid darkening of the reaction mixture. In every case a viscous brown oil was isolated that could not be purified. Saponification of the crude product in ethanolic potassium hydroxide resulted in considerable tar formation and isolation of low yields of bis-(1-phenyl-5-tetrazolylmethyl) ether (III) and 1,2-bis-(1-phenyl-5-tetrazolyl)ethane (IV). The



III



IV

former compound was apparently formed through hydrolysis of 1-phenyl-5-chloromethyltetrazole in the presence of potassium hydroxide followed by reaction of the resulting alcohol with more of the chloromethyl derivative. Both the structure and mode of formation of this compound are supported by the observation that aqueous potassium hydroxide converted the chloromethyltetrazole into the ether (III) in 53% yield.

The isolation of the disubstituted ethane (IV) from the saponification suggests that potassium cyanide did react with the chloromethyltetrazole to produce the desired nitrile which underwent further reaction with unreacted halogen compound to give 1,2-bis-(1-phenyl-5-tetrazolyl)propionitrile. Saponification would then have formed the acid which apparently decarboxylated upon isolation to give the observed 1,2-bis-(1-phenyl-5-tetrazolyl)ethane.

The inability to obtain higher yields of precipitated potassium chloride in this attempted nitrile synthesis in spite of the observed high reactivity of the chloro compound, also indicates that it was consumed by two or more simultaneous reactions such as those just mentioned. The crude oil isolated from the reaction thus probably consisted of a complex mixture of products.

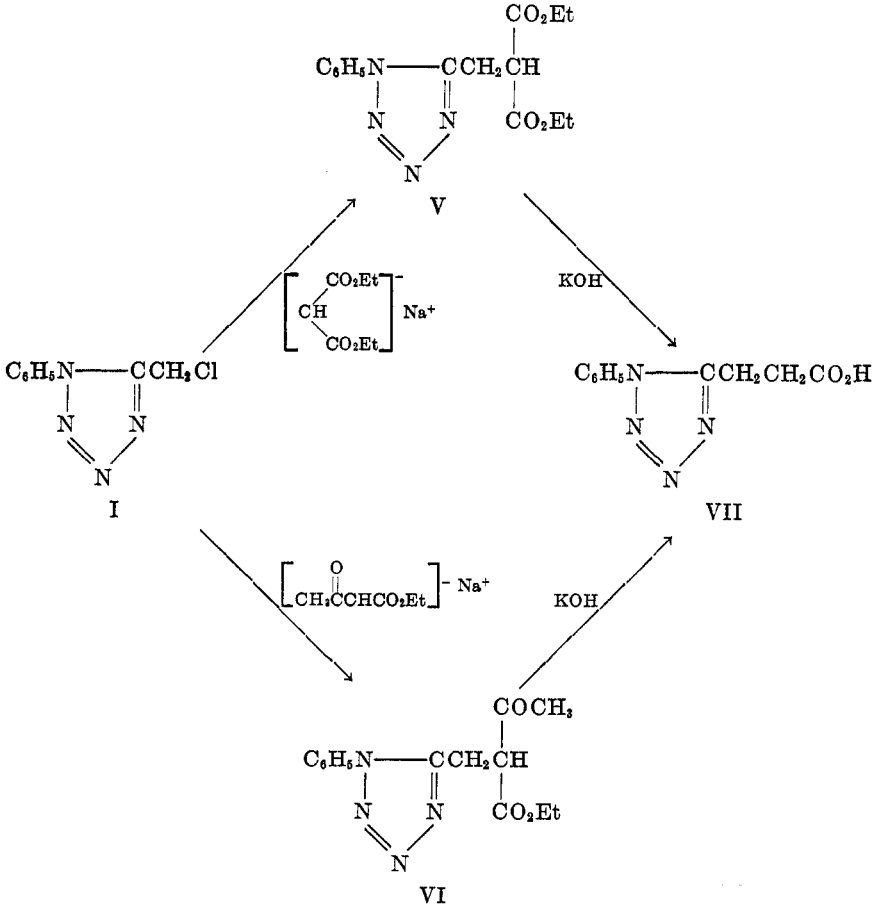
In connection with this work it was desirable to have a sample of 1-phenyl-5-cyanomethyltetrazole in order to be able to recognize its properties. Another possible route to this nitrile was available through dehydration of 1-phenyl-5-tetrazolylacetamide. Although reflux of the amide with thionyl chloride resulted in the formation of a complex resinous product that could not be purified, treatment of the amide with phosphorus pentoxide at 140° caused ready dehydration to produce the nitrile in good yield as colorless needles.

The reaction between 1-phenyl-5-chloromethyltetrazole and the sodio derivatives of active methylene compounds proceeds readily to give the alkylated derivatives. Thus diethyl α-(1-phenyl-5-tetrazolylmethyl)malonate (V) was prepared by reaction of the chloromethyl derivative with sodiomalonic ester, an

83 % yield of crude oil being obtained. The pure malonate was isolated in 35 % yield as a viscous high-boiling oil after two difficult fractionations under reduced pressure. Condensation of the malonate with urea gave a low yield of 5-(1′-phenyl-5′-tetrazolylmethyl)barbituric acid.

Saponification of the crude malonate in alcoholic potassium hydroxide gave a 61 % yield of β-(1-phenyl-5-tetrazolyl)propionic acid (VII) which was first isolated as the monohydrate. Also isolated was a 15 % yield of bis-(1-phenyl-5-tetrazolylmethyl)acetate acid (VIII) resulting from dialkylation of the diethyl malonate.

In a similar way sodioacetoacetic ester was alkylated with 1-phenyl-5-chloromethyltetrazole to give an 82 % yield of a crude oil from which a 35 % yield of pure ethyl α-(1-phenyl-5-tetrazolylmethyl)acetoacetate (VI) was obtained after two fractionations. The pure ester was isolated as a viscous high-boiling oil that slowly formed oily crystals upon standing. The acetoacetate was converted into β-(1-phenyl-5-tetrazolyl)propionic acid (VII) in 41 % yield by saponification in aqueous potassium hydroxide. None of the product of dialkylation (VIII) was isolated in this case.



The propionic acid (VII) is a weaker acid ($pK_a = 5.0$) than the corresponding 1-phenyl-5-tetrazolylacetic acid (4) ($pK_a = 3.1$) as would be expected due to the insulating effect of additional methylene group on the electron attraction of the ketimine structure in the tetrazole nucleus. Similarly, the observation that neither β-(1-phenyl-5-tetrazolyl)propionic acid nor bis-(1-phenyl-5-tetrazolylmethyl)acetic acid undergoes decarboxylation upon melting, as do the tetrazolylacetic acids, suggests that the additional methylene group may prevent intramolecular chelation of the type responsible for the ease of decarboxylation of α-pyridylacetic acids (5) and believed to be responsible for the same effect in the tetrazolylacetic acids.

Typical acid derivatives have been prepared from β-(1-phenyl-5-tetrazolyl)propionic acid including the ethyl ester, amide, and ureide.

Several previous attempts have been made (4) to prepare either 1-phenyl-5-tetrazolylcarboxaldehyde or intermediates that would lead to its preparation but none have met with success. Selenious acid oxidation of 1-phenyl-5-methyltetrazole was unsuccessful. Neither did the methyl group of this compound condense with benzaldehyde nor with *p*-nitrosodimethylaniline. In the former case the aldehyde was theoretically available through ozonization of the benzal derivative; in the latter case through hydrolysis of the anil. Two more attempts to prepare 1-phenyl-5-tetrazolylcarboxaldehyde were initiated from 1-phenyl-5-chloromethyltetrazole.

The recently reported oxidation of α-pyridylmethanols to α-pyridylaldehydes (6) by means of lead tetraacetate prompted the attempted application of this oxidation to the tetrazole series. The necessary starting material for this oxidation, 1-phenyl-5-hydroxymethyltetrazole, was readily prepared from 1-phenyl-5-chloromethyltetrazole by application of the method of Harvill, Herbst, and Schreiner (2). Treatment of the chloromethyltetrazole with sodium acetate in glacial acetic acid gave 1-phenyl-5-acetoxymethyltetrazole in 66% yield. This produced a 77% yield of the hydroxymethyl derivative upon hydrolysis in a methanolic solution of hydrochloric acid.

Several lead tetraacetate oxidations of 1-phenyl-5-hydroxymethyltetrazole have been attempted. In each, there were definite indications that oxidation had occurred but only low yields of mixtures of apparently complex products could be isolated. Purification or separation proved impossible. The results of the oxidation suggest that the aldehyde, if it was produced, is extremely reactive.

The other attempt to prepare 1-phenyl-5-tetrazolylcarboxaldehyde was suggested by the work of Fischer and Ernst (7) who synthesized pyrrole aldehydes from the corresponding halomethyl compounds through conversion to the anilinomethyl derivatives followed by permanganate oxidation and hydrolysis of the resulting Schiff base. Thus 1-phenyl-5-chloromethyltetrazole was reacted with aniline, using the method of Harvill and his co-workers (2) for the preparation of 5-N-substituted aminomethyltetrazoles, to give a 52% yield of 1-phenyl-5-anilinomethyltetrazole.

Potassium permanganate oxidation of the anilinomethyl derivative did not proceed as expected to give the Schiff base but instead, resulted in oxidative

cleavage of the anilino group to give a low yield of potassium 1-phenyl-5-tetrazolylcarboxylate. While this salt is very stable, not melting below 250°, the corresponding acid cannot be isolated. An aqueous solution of the salt undergoes immediate decarboxylation upon acidification with formation of 1-phenyltetrazole. This potassium salt readily forms a silver salt that explodes upon rapid heating or striking with a hammer.

The instability of free 1-phenyl-5-tetrazolylcarboxylic acid and probably of 1-substituted-5-tetrazolylcarboxylic acids in general, appears to be of the same order as that of tetrazole-5-carboxylic acid, salts of which are stable but which has never been isolated as the free acid. Decarboxylation of tetrazole-5-carboxylic acid salts by acidification is one method used for the preparation of tetrazole itself (8).

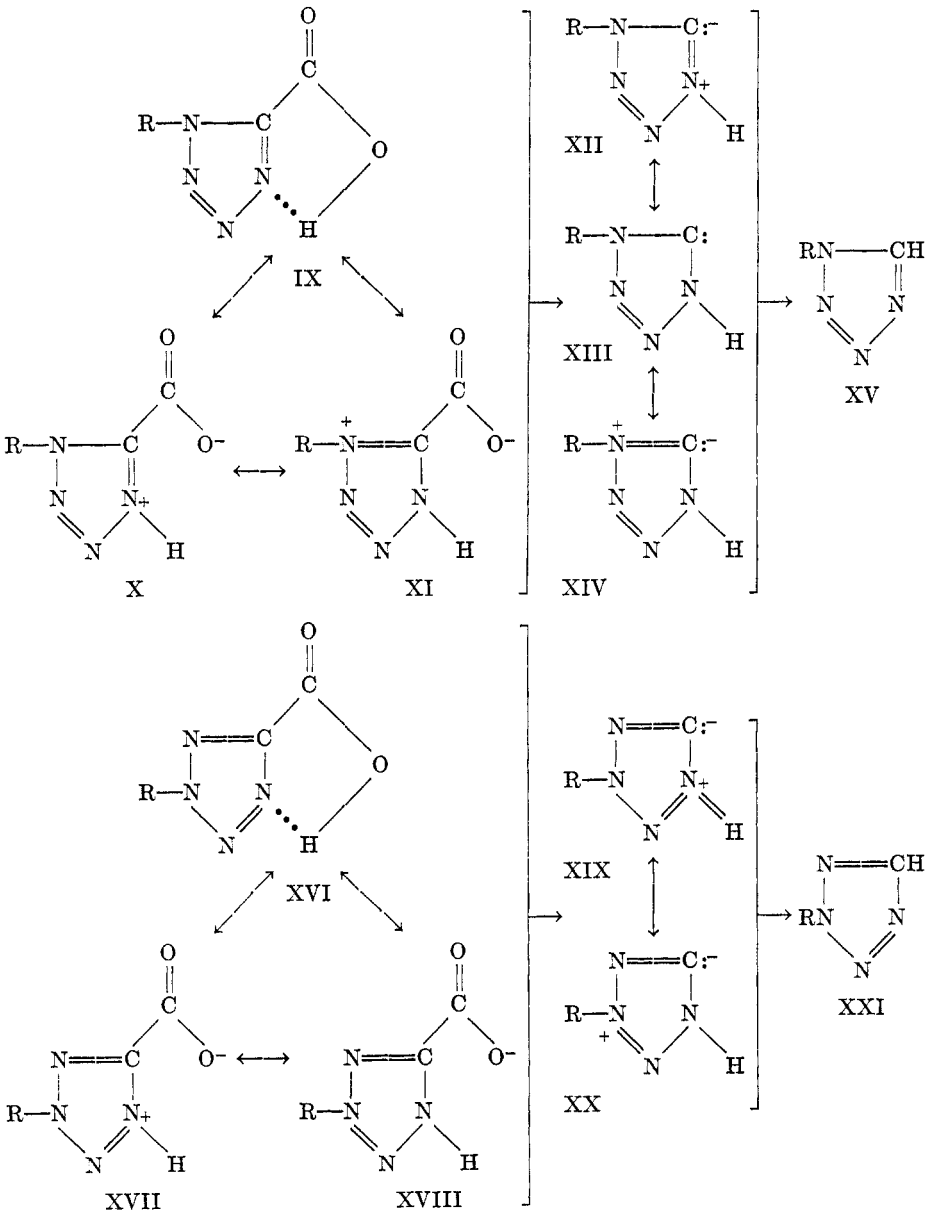
On the other hand, 2-substituted-5-tetrazolylcarboxylic acids are known to possess considerable stability in the free state (8). They have melting points above 100° and generally melt with decarboxylation to give the corresponding 2-substituted tetrazoles.

The great difference in the stability of the 1-substituted- and 2-substituted-5-tetrazolylcarboxylic acids must be attributed to the dissimilar effects that 1- and 2-substitution have on the electronic distribution in the tetrazole nucleus. The difference in the ease of decarboxylation of these isomers should arise from two principal effects: first, the comparative ability of the initial reactants to participate in the promotion of bond rupture through chelation or zwitterion formation; second, the comparative ability of the carbanions formed by loss of carbon dioxide to stabilize themselves.

A detailed examination of the possible structures and mechanisms involved in the decarboxylation of these isomers indicates that the difference in their stability would not readily be anticipated. However, as experimental evidence for the existence of the dissimilar stabilities is now on hand, an attempt to correlate the evidence with theory should be of value.

Based on the structures considered to be involved in the decarboxylation of picolinic acids (9), it is reasonable to assume that the initial reactants involved in the decarboxylation of the 1-substituted-5-tetrazolylcarboxylic acids are of similar structure. This assumption is also supported by the observation that neither the acids in the pyridine series nor potassium 1-phenyl-5-tetrazolylcarboxylate undergoes decarboxylation upon refluxing in alkaline solution. The initial reactant should then be either the chelated structure (IX) or the reasonating zwitterionic forms (X and XI) as shown in Figure 1. Loss of carbon dioxide by the initial reactant would lead to the formation of three possible intermediate structures (XII, XIII, and XIV) capable of equilibrium. The uncharged structure (XIII) containing an open sextet on the nuclear carbon atom can be considered to be the stabilized resonance hybrid resulting from the two ionic forms. If the formation of XIII can occur by direct charge transfer upon loss of carbon dioxide by the initial reactant, then a lower energy route may be available for the decarboxylation than would be possible if the neutral intermediate could not be formed.

FIGURE 1



For the 2-substituted-5-tetrazolylcarboxylic acids, seemingly equivalent structures to those represented for the 1-isomers can be formed for both the initial reactant and the intermediate carbanion, if association of the carboxyl hydrogen atom occurs with the 1-nitrogen atom, forming a five-membered singly unsaturated chelate ring identical with that proposed for the 1-sub-

stituted-5-carboxylic acids. The only apparent difference between the structures involved in the two series is an extension of the (1)N—C=N(4) conjugation in the 1-substituted isomers to an (2)N—N=N—C=N(1) system for the 5-substituted isomers. This change does not reasonably reconcile the apparent difference in stability of the participating structures.

If, however, association of the carboxyl hydrogen atoms of the 2-substituted-5-tetrazolylcarboxylic acids took place with the 4-nitrogen atom of the ring in preference to the 1-nitrogen atom a different situation arises. The reasons for any preference in this case are definitely not clear and involve the use of numerous assumptions concerning the opposing effects operating in the tetrazole nucleus. Association of the carboxyl hydrogen with the 4-nitrogen atom would lead to another similar set of structures (XVI, XVII, and XVIII) representing the the initial reactant in which charge transfer would occur over the system (2)N—N=N(4). The difference in this route of decarboxylation lies in the inability of the initial reactant to form a neutral structure similar to XIII by direct charge transfer upon cleavage of carbon dioxide. Only the ionic structures XIX and XX can result and their formation would require a greater activation energy than the direct formation of a neutral intermediate, as in the 1-substituted isomers, in order to account for the differing ease of decarboxylation.

Finally, the dissimilarity in the decarboxylation abilities of these two series of acids may be attributed to a difference in the type of association in the isomers. Although no information relative to the type of association occurring in these compounds is available, if it is assumed that the 2-substituted derivatives undergo intermolecular association rather than that of the intramolecular nature, as assumed previously, then the normally weaker bonding that would result could effectively reduce the tendency toward the formation of an electronic distribution within the nucleus that would favor elimination of carbon dioxide.

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EXPERIMENTAL[2]

1-Phenyl-5-chloromethyltetrazole (I) was prepared in 75% yields by the method of Harvill, *et al.* (1, 2) m.p. 75–76°.

The reaction of 1-phenyl-5-chloromethyltetrazole with potassium cyanide. A solution of 1-phenyl-5-chloromethyltetrazole (7.8 g., 0.04 mole) and potassium cyanide (3.1 g., 0.048 mole) in 200 ml. of absolute methanol (or ethanol) was refluxed for one hour. Filtration of the cooled, light brown solution gave 1.8 g. (60%) of precipitated potassium chloride. Additional reflux (up to four hours) in other runs caused no further precipitation, the reaction mixture rapidly turning dark brown after one hour's reflux. The basic filtrate was slightly acidified (hood) with hydrochloric acid and the solvent was removed under reduced pressure. After refluxing the oily residue for 30 minutes with each of five 100 ml.-portions of ether, the combined extracts were dried and the ether was distilled off leaving a dark brown viscous oil that could not be crystallized or distilled.

Several hours' reflux of the brown oil in 95% ethanolic potassium hydroxide followed by removal of the ethanol under reduced pressure, addition of water, and ether extraction of the dark basic mixture, gave a tan solid after removal of the ether from the dried extract.

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

Recrystallization from dilute ethanol gave 1.2 g. (18%) of colorless crystals of *bis-(1-phenyl-5-tetrazolylmethyl) ether* (III) m.p. 158–159°.

Anal. Calc'd for $C_{16}H_{14}N_8O$: C, 57.5; H, 4.2; N, 33.5.

Found: C, 57.8; H, 4.3; N, 33.3.

The basic solution remaining from the ether extraction was acidified with concentrated hydrochloric acid, a brown oil separating. Upon refluxing this oil with water and cooling, a base-insoluble tan powder was isolated. Recrystallization from ethyl acetate gave small buff needles of *1,2-bis-(1-phenyl-5-tetrazolyl)ethane* (IV), m.p. 204–205°.

Anal. Calc'd for $C_{16}H_{14}N_8$: C, 60.5; H, 4.8; N, 35.2.

Found: C, 60.4; H, 4.4; N, 35.1.

The reaction of 1-phenyl-5-chloromethyltetrazole with aqueous potassium hydroxide. 1-Phenyl-5-chloromethyltetrazole (1.94 g., 0.01 mole) in 50 ml. of 2 *N* potassium hydroxide was refluxed for one hour and the resulting colorless solid was filtered off and recrystallized from ethanol to yield 0.89 g. (53%) of small glistening plates of *bis-(1-phenyl-5-tetrazolylmethyl) ether* (III), m.p. 158–159°. No melting-point depression was observed in a mixture melting-point with the material obtained from the reaction between the chloromethyl derivative and potassium cyanide.

Ethyl 1-phenyl-5-tetrazolylacetate was prepared in 76% yield by Fischer esterification of 1-phenyl-5-tetrazolylacetic acid (4) in saturated absolute ethanolic hydrogen chloride. The ester distilled at 160°/0.1 mm. as a colorless oily liquid.

Anal. Calc'd for $C_{11}H_{12}N_4O_2$: C, 56.9; H, 5.2.

Found: C, 56.8; H, 5.3.

1-Phenyl-5-tetrazolylacetamide was prepared in 90% yield from ethyl 1-phenyl-5-tetrazolylacetate by allowing the ester to stand overnight in concentrated ammonium hydroxide and filtering off the resulting colorless crystals. Recrystallization from water produced needles of m.p. 176–177°.

Anal. Calc'd for $C_9H_9N_5O$: C, 53.1; H, 4.5.

Found: C, 53.3: H, 4.4.

1-Phenyl-5-cyanomethyltetrazole (II). Finely powdered 1-phenyl-5-tetrazolylacetamide (1.0 g., 0.005 mole) and powdered phosphorus pentoxide (1.4 g., 0.005 mole) were thoroughly mixed and heated for 30 minutes in an oil-bath at 140°. The powder turned to a yellow plastic mass that was continually mixed and pressed. Upon cooling, a hard solid formed that was thoroughly ground under 25 ml. of water. Filtration gave 0.75 g. of a crude yellow solid, m.p. 109–111°. Two recrystallizations from water using Norit yielded flat colorless needles of the nitrile, m.p. 111–112°.

Anal. Calc'd for $C_9H_7N_5$: C, 58.4; H, 3.8; N, 37.8.

Found: C, 58.2; H, 4.0; N, 37.6.

Diethyl α-(1-phenyl-5-tetrazolylmethyl)malonate (V). Sodium (2.3 g., 0.1 g.-atom) was dissolved in 50 ml. of absolute ethanol with the aid of heating on the steam-bath. After removing the heat, diethyl malonate (32.0 g., 0.2 mole) was added to the stirred solution during five minutes, a colorless gel forming. The mixture was cooled and a solution of 1-phenyl-5-chloromethyltetrazole (19.4 g., 0.1 mole) in 100 ml. of warm absolute ethanol was added during ten minutes. The reaction mixture warmed barely to reflux and a cream-colored suspension formed. After stirring and refluxing the suspension on the steam-bath for five hours, the ethanol was removed from the slightly basic mixture under reduced pressure and the oily residue was shaken with 100 ml. of water. Extraction of the aqueous mixture with two 50 ml.-portions of ether followed by distillation of the dried yellow ether extract gave as the first fraction 15.2 g. of recovered diethyl malonate boiling at 58–59°/1.5 mm. There then remained 26.5 g. of high-boiling oil.

Fractionation of a 21.0 g.-sample of this oil yielded 1.7 g. of recovered 1-phenyl-5-chloromethyltetrazole of b.p. 125–127°/0.07 mm. and 11.9 g. of the malonate boiling 197–201°/0.07 mm. The undistillable black residue weighed 7.0 g. Upon refractionation the malonate distilled at 192°/0.05 mm. and was obtained as a pale yellow oil.

Anal. Calc'd for $C_{15}H_{18}N_4O_4$: C, 56.6; H, 5.7; N, 17.6.

Found: C, 56.9; H, 5.8; N, 17.8.

5-(1'-Phenyl-5'-tetrazolylmethyl)barbituric acid. Sodium (0.69 g., 0.03 mole) was dissolved in 150 ml. of absolute ethanol and to the resulting solution was added diethyl α-(1-phenyl-5-tetrazolylmethyl)malonate (9.55 g., 0.03 mole) and urea (1.80 g., 0.03 mole). The solution was stirred and refluxed on the steam-bath for five hours. The resulting colorless sodium salt then was filtered from the cooled solution and was thoroughly washed with absolute ethanol and ether. The dried salt weighed 5.5 g.

The sodium salt was dissolved in 200 ml. of hot water and the cooled solution was acidified with concentrated hydrochloric acid to yield 3.4 g. of the colorless acid that underwent gaseous decomposition at 227°. The product was further purified by dissolving it in 200 ml. of hot water containing just sufficient sodium hydroxide to make the solution basic (*p*H 8) and then acidifying the cooled solution to give 2.3 g. (27%) of colorless acid that decomposed at 229°.

Anal. Calc'd for $C_{12}H_{10}N_6O_3$: C, 50.4; H, 3.5.

Found: C, 50.4; H, 3.5.

β-(1-Phenyl-5-tetrazolyl)propionic acid (VII). The crude product from the preparation of diethyl α-(1-phenyl-5-tetrazolylmethyl)malonate (26.5 g.) was refluxed for several hours with an excess of aqueous-alcoholic potassium hydroxide. After removal of the solvents under reduced pressure, water was added and the basic solution was extracted with ether. Acidification of the aqueous solution caused separation of a yellow oil that solidified upon scratching and cooling. The tan solid was treated with 5% sodium bicarbonate solution and the insoluble portion was rapidly separated by filtration. Recrystallization from 95% ethanol gave 2.9 g. (15% based on 1-phenyl-5-chloromethyltetrazole) of colorless crystals of *bis-(1-phenyl-5-tetrazolylmethyl)acetic acid* (VIII), m.p. 189–190°. This acid dissolved very slowly in 10% sodium bicarbonate solution.

Anal. Calc'd for $C_{18}H_{16}N_8O_2$: C, 57.4; H, 4.7; N, 29.8.

Found: C, 57.1; H, 4.5; N, 29.5.

Acidification of the basic filtrate caused separation of an oil that solidified upon cooling and scratching. The tan solid was recrystallized from water to afford 14.4 g. (61% based on 1-phenyl-5-chloromethyltetrazole) of colorless crystals of *β-(1-phenyl-5-tetrazolyl)propionic acid monohydrate* of m.p. 89–90°.

Anal. Calc'd for $C_{10}H_{12}N_4O_3$: C, 50.9; H, 5.1; Neut. equiv., 236.

Found: C, 50.8; H, 5.4; Neut. equiv., 237.

Dehydration of the monohydrate in the vacuum oven at 93° produced *β-(1-phenyl-5-tetrazolyl)propionic acid* (VII) of m.p. 118–119°, $pK_a = 5.0$.

Anal. Calc'd for $C_{10}H_{10}N_4O_2$: C, 55.5; H, 4.7; Neut. equiv., 218.

Found: C, 55.3; H, 4.7; Neut. equiv., 219.

Ethyl α-(1-phenyl-5-tetrazolylmethyl)acetoacetate (VI). Sodium (2.3 g., 0.1 g.-atom) was dissolved in 50 ml. of absolute ethanol on the steam-bath. After removing the heat, ethyl acetoacetate (26.0 g., 0.2 mole) was added during five minutes and the resulting pale yellow solution was then cooled to room temperature. A solution of 1-phenyl-5-chloromethyltetrazole (19.4 g., 0.1 mole) in 100 ml. of warm absolute ethanol was added during ten minutes giving a clear solution that was stirred and refluxed on the steam-bath for six hours. The strongly basic solution became slightly basic and a colorless suspension formed in the yellow solution.

After removing the solvent under reduced pressure the residual suspension was shaken with 100 ml. of water and the aqueous mixture was shaken with two 100 ml.-portions of ether. The ether was distilled from the dried extract and then 8.4 g. of unreacted ethyl acetoacetate was distilled over at 72°/12 mm. The remaining yellow viscous oil weighing 23.5 g. was fractionated under reduced pressure with some difficulty due to solidification of the lowest-boiling fraction in the delivery tube.

The first fraction consisted of 1.2 g. of recovered 1-phenyl-5-chloromethyltetrazole boiling at 122–125°/0.06 mm. The acetoacetate distilled over at 189–196°/0.08 mm., 10.7 g. of yellow oil being obtained. The black tarry residue weighed 10.5 g. Upon refractionation the acetoacetate distilled over at 169.5°/0.03 mm. as a viscous yellow oil that slowly solidified to oily crystals after long standing.

Anal. Calc'd for $C_{14}H_{16}N_4O_3$: C, 58.3; H, 5.6.
Found: C, 58.6; H, 5.6.

β-(1-Phenyl-5-tetrazolyl)propionic acid (VII) was isolated as the monohydrate by refluxing the crude oil (23.5 g.) from the preparation of ethyl α-(1-phenyl-5-tetrazolylmethyl)-acetoacetate with an excess of concentrated potassium hydroxide, followed by ether extraction of the basic solution and then acidification with concentrated hydrochloric acid in the cold. The yield of the monohydrate was 9.7 g. (41% based on 1-phenyl-5-chloromethyltetrazole), m.p. 89–90°. The anhydrous acid was obtained as before by heating the monohydrate at 93° in the vacuum oven. Yield, 8.9 g., m.p. 118–119°.

Ethyl β-(1-phenyl-5-tetrazolyl)propionate. The usual Fischer esterification of β-(1-phenyl-5-tetrazolyl)propionic acid (5.0 g., 0.023 mole) in saturated absolute ethanolic hydrogen chloride porduced a viscous yellow oil after standing overnight followed by removal of the solvent under reduced pressure. Distillation of the oil at 201–202°/8 mm. furnished 3.95 g. of pale yellow distillate that crystallized upon standing. Recrystallization from water gave colorless plates of m.p. 83–84°.

Anal. Calc'd for $C_{12}H_{14}N_4O_2$: C, 58.5; H, 5.7; N, 22.8; Sapon. no., 246.
Found: C, 58.4; H, 5.7; N, 22.9; Sapon. no., 252.

β-(1-Phenyl-5-tetrazolyl)propionamide. β-(1-Phenyl-5-tetrazolyl)propionic acid (1.0 g., 0.0046 mole) was refluxed for one hour with an excess of thionyl chloride which was then removed under reduced pressure. Upon treatment of the residue with concentrated ammonium hydroxide a tan solid formed that was recrystallized from water using Norit. The colorless amide had m.p. 155–156°.

Anal. Calc'd for $C_{10}H_{11}N_5O$: C, 55.2; H, 5.1.
Found: C, 54.9; H, 5.1.

β-(1-Phenyl-5-tetrazolyl)proponic acid ureide. The acid chloride, prepared as above with thionyl chloride, was treated with urea (0.33 g., 0.0055 mole) and the mixture was heated to 60° where a vigorous reaction took place. The resulting tan solid was recrystallized from nitrobenzene to give a cream-colored solid of m.p. 206–207°.

Anal. Calc'd for $C_{11}H_{12}N_6O_2$: C, 50.8; H, 5.0.
Found: C, 50.6; H, 4.7.

1-Phenyl-5-acetoxymethyltetrazole. A mixture of 1-phenyl-5-chloromethyltetrazole (25.0 g., 0.13 mole), fused sodium acetate (13.0 g., 0.15 mole) and glacial acetic acid (100 ml.) was stirred and refluxed for five hours. After concentrating the mixture to dryness under reduced pressure, the residue was suspended in 200 ml. of water and the mixture was neutralized with dry sodium bicarbonate. Extraction of the mixture with three 100 ml.-portions of benzene followed by removal of the benzene from the dried extract left an oil that solidified to a tan solid upon scratching. Recrystallization from a benzene-petr. ether (b.p. 60–68°) mixture produced 18.5 g. (66%) of colorless crystals of m.p. 61–64°. Another recrystallization gave a product of m.p. 65.5–67.0°.

Anal. Calc'd for $C_{10}H_{10}N_4O_2$: C, 55.0; H, 4.6.
Found: C, 55.1; H, 4.8.

1-Phenyl-5-hydroxymethyltetrazole. A solution of 1-phenyl-5-acetoxymethyltetrazole (15.0 g., 0.069 mole) in 150 ml. of absolute methanol containing 20 ml. of concentrated hydrochloric acid was refluxed for 3½ hours. Concentration of the solution to dryness under reduced pressure left a colorless oil that solidified to a colorless solid. Recrystallization from water gave 9.3 g. (77%) of colorless crystalline plates of m.p. 99–101.5°. After another recrystallization the product had a m.p. of 99.5–101.5°.

Anal. Calc'd for $C_8N_5N_4O$: C, 54.5; H, 4.6; N, 31.8.
Found: C, 54.6; H, 4.7; N, 31.7.

Attempted lead tetraacetate oxidation of 1-phenyl-5-hydroxymethyltetrazole. A mixture of 1-phenyl-5-hydroxymethyltetrazole (7.0 g., 0.04 mole), lead tetraacetate (17.6 g., 0.04 mole) and 400 ml. of dry benzene was stirred and refluxed for seven hours, the originally dark brown mixture becoming cream-colored. A small quantity of a light colored precipitate re-

mained. The excess lead tetraacetate was decomposed by the addition of several drops of ethylene glycol (until potassium iodide-starch paper did not turn blue). After filtering the cooled solution, the precipitate was washed twice with 25-ml. portions of benzene and the combined benzene solutions were washed with dilute potassium carbonate solution. Removal of the solvents from the dried benzene solution left 3.7 g. of a tan oily solid. Ethyl acetate was found to be the only useful solvent for recrystallization. After numerous recrystallizations with considerable loss, a colorless, curdy solid of m.p. 111–114° was obtained. This product was not identified.

1-Phenyl-5-anilinomethyltetrazole. A stirred solution of 1-phenyl-5-chloromethyltetrazole (9.73 g., 0.05 mole) and aniline (14.0 g., 0.15 mole) in 60 ml. of dry benzene was refluxed for eight hours (four hours' reflux in another run gave about the same yield of pure product); a fine white precipitate slowly forming. Fifty ml. of water was added to the mixture which then was made strongly basic with sodium hydroxide and steam-distilled to remove the benzene and unreacted aniline. The remaining oil was extracted from the aqueous solution with two 100 ml.-portions of ether and the ether extracts were dried. Addition of about 300 ml. of petr. ether (b.p. 60–68°) to the dry ether solution precipitated 8.8 g. of crude tan product that was recrystallized from an ether-petr. ether (b.p. 60–68°) mixture to give 6.5 g. (52%) of colorless needles of 1-phenyl-5-anilinomethyltetrazole. m.p. 78–79°.

Anal. Calc'd for $C_{14}H_{13}N_5$: C, 66.9; H, 5.2; N, 27.9.

Found: C, 66.7; H, 5.3; N, 28.2.

Potassium permanganate oxidation of 1-phenyl-5-anilinomethyltetrazole. A solution of potassium permanganate (23.7 g., 0.15 mole) in a mixture of acetone (250 ml.) and water (250 ml.) was added during one hour to a stirred solution of 1-phenyl-5-anilinomethyltetrazole (14.0 g., 0.056 mole) dissolved in a mixture of acetone (75 ml.) and water (25 ml.). The solution warmed spontaneously to 42° with precipitation of manganese dioxide, after which it was stirred for two hours until the temperature had again fallen to 28°. The manganese dioxide was filtered off and washed successively with two 100 ml.-portions of acetone and two 100 ml.-portions of water.

Concentration of the combined filtrates under reduced pressure left a dark oil from which a cream-colored solid (7.9 g.) precipitated upon addition of acetone. Extraction of the solid with two 50 ml.-portions of hot 95% ethanol left 2.5 g. of inorganic matter. The hot extract was diluted with about 300 ml. of chloroform causing precipitation of 2.4 g. of potassium 1-phenyl-5-tetrazolylcarboxylate. Further recrystallization from an ethanol-chloroform mixture afforded very fine colorless needles. A small additional quantity of the salt was recovered from the original acetone solution. The salt did not melt below 250° and was very water soluble.

Addition of hydrochloric acid to a water solution of the salt caused gaseous evolution and the precipitation of 1-phenyltetrazole which was identified by melting point (64–65°) and mixture melting-point after recrystallization from carbon tetrachloride.

A 5% solution of silver nitrate added to an aqueous solution of the salt gave a fine colorless precipitate of the corresponding silver salt. The silver salt rapidly turned grey when dried and exploded on impact or rapid heating.

Anal. Calc'd for $C_8H_5KN_4O_2$: N, 24.6. Found: N, 24.7.

SUMMARY

The high reactivity of 1-phenyl-5-chloromethyltetrazole is observed only in S_N2 reactions and not under S_N1 conditions.

Although this chloromethyltetrazole reacted with potassium cyanide none of the desired nitrile could be isolated. The nitrile was prepared by dehydration of 1-phenyl-5-tetrazolylacetamide.

The reaction of sodiomalonic ester and sodioacetoacetic ester with 1-phenyl-5-

chloromethyltetrazole has produced the corresponding malonate and acetoacetate. Saponification of both these compounds has lead to the isolation of β-(1-phenyl-5-tetrazolyl)propionic acid.

In one of two attempts to prepare 1-phenyl-5-tetrazolylcarboxaldehyde from the chloromethyl derivative, potassium 1-phenyl-5-tetrazolylcarboxylate has been isolated and characterized. A discussion of the relative ease of decarboxylation of 1-substituted- and 2-substituted-5-tetrazolylcarboxylic acids is presented.

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