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STUDIES IN TETRAZOLE CHEMISTRY.[1] II. THE SYNTHESIS AND REACTIONS OF 1-PHENYL-5-ACETYLTETRAZOLE[2]

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The preparation of a tetrazole derivative containing the acetyl group as a functional component was first reported by Harvill, Herbst, and Schreiner (1) who converted several 1-substituted-5-haloalkyltetrazoles into the corresponding hydroxyalkyl derivatives through the intermediate acetoxyalkyl compounds. One of these tetrazoles, 1-cyclohexyl-5-(1-hydroxyethyl)tetrazole, was oxidized in aqueous solution with potassium dichromate and sulfuric acid to 1-cyclohexyl-5-acetyltetrazole. However, no further reactions of this compound were reported by the authors.

Harvill also reported the synthesis of 1-phenyl-5-(1-hydroxyethyl)tetrazole in the same manner but did not oxidize this derivative to the ketone.

In this laboratory, 1-phenyl-5-acetyltetrazole (VII) has been prepared by means of the synthetic route shown in Figure I, which contains a variation in the method used by Harvill.

Previous to the publication of Harvill attempts in this laboratory to prepare 1-phenyl-5-(1-hydroxyethyl)tetrazole (VI) from 1-phenyl-5-(1-chloroethyl)-tetrazole through the intermediate acetoxy derivative met with little success and gave at best only very low yields. However, it was found that 1-phenyl-5-(1-chloroethyl)tetrazole reacted readily with sodium methoxide in refluxing methanol to give 1-phenyl-5-(1-methoxyethyl)tetrazole (V). This ether was split by refluxing it with 48% aqueous hydrobromic acid, methyl bromide being evolved and 1-phenyl-5-(1-hydroxyethyl)tetrazole being isolated in good yields. However, 32% aqueous hydrobromic acid had no effect on the methyl ether in the same length of time.

That this ether split in this way is both interesting and significant in that it shows that the methyl carbonium ion is more readily formed than the tetrazole cation even though it is possible to write several stabilizing resonance structures for the latter. In fact, it appears that in this reaction the ketimine structure at the 4,5-position of the tetrazole nucleus not only prevents electron release to substitutents on the 5-carbon atom but may also exert its normal electron-attracting influence to draw electrons from substituents on the 5-position.

Oxidation of 1-phenyl-5-(1-hydroxyethyl)tetrazole in suspension in aqueous acid sodium dichromate solution proceeded exothermically above 70° to give 1-phenyl-5-acetyltetrazole (VII) in yields up to 84%. An over-all yield of 51% of the acetyl derivative was obtained in this series of reactions starting from

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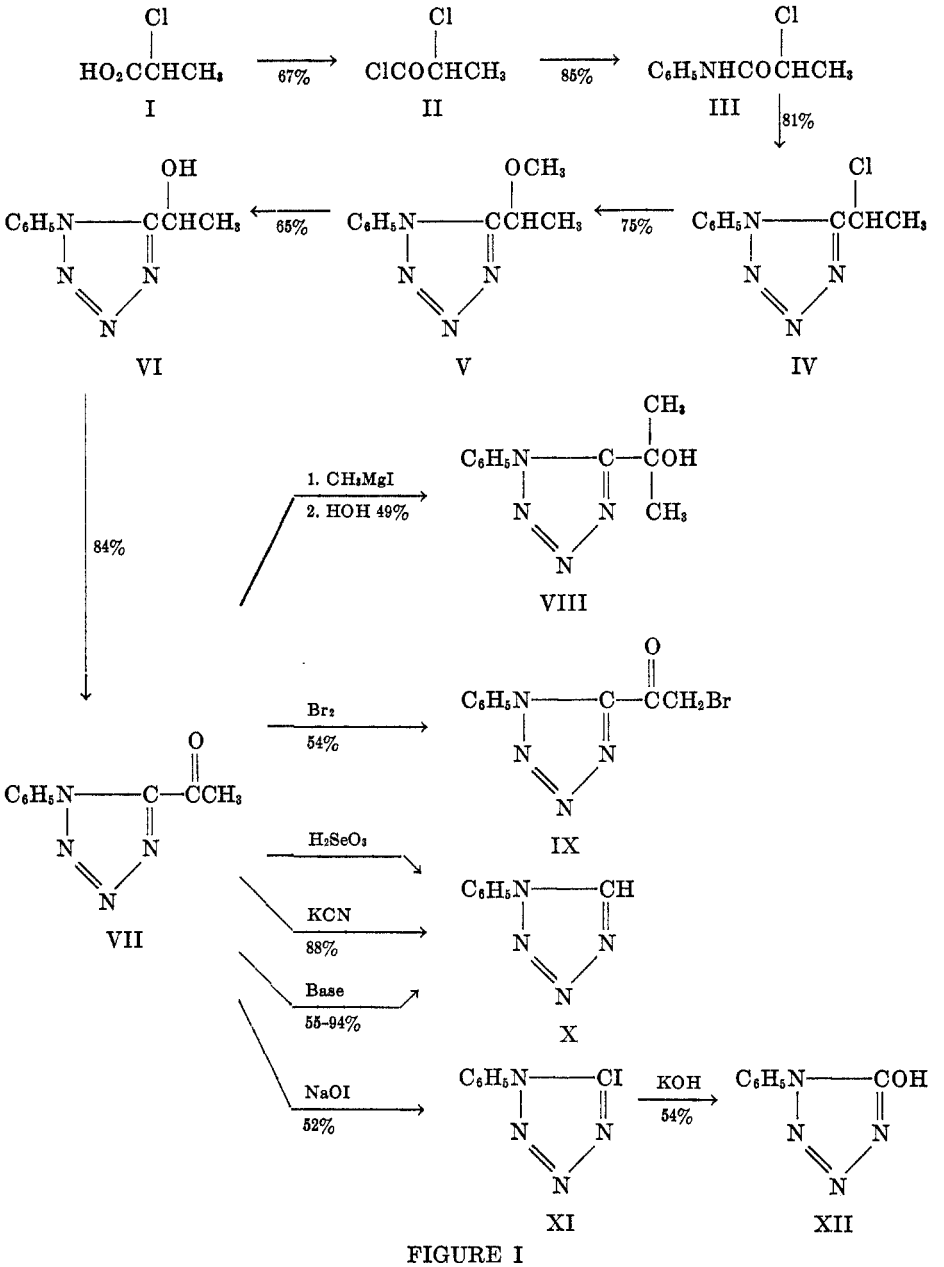
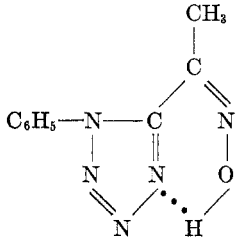


FIGURE I

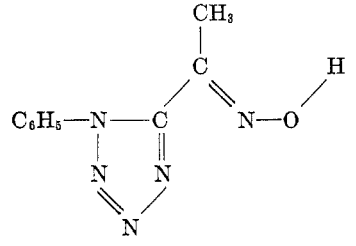
1-phenyl-5-(1-chloroethyl)tetrazole when none of the intermediate products were purified. This can be compared with an over-all yield of 41 % when each of the intermediates was purified and with an over-all yield of less than 20 % in the synthesis of 1-cyclohexyl-5-acetyltetrazole from the hydroxyethyl derivative through the 5-acetoxyethyl intermediate by Harvill.

The usual oxime and 2,4-dinitrophenylhydrazone derivatives have been prepared from 1-phenyl-5-acetyltetrazole but it has not been possible to isolate the bisulfite addition compound. The oxime was prepared in 75% yield by the pyridine method (3a). Only one form was isolated. Attempts to make the oxime undergo the Beckmann rearrangement in the presence of phosphorus pentachloride, phosphorus oxychloride, benzenesulfonyl chloride, and polyphosphoric acid have failed, the starting material being recovered in each case. In connection with this work, one of the possible rearrangement products, 1-phenyl-5-acetaminotetrazole (4), was prepared in 92% yield by refluxing 1-phenyl-5-aminotetrazole in acetic anhydride for 15 minutes.

The failure of this oxime to undergo Beckmann rearrangement indicates that it may be the *syn*-(1-phenyltetrazolyl)methyl ketone (XIII) rather than the *anti* form (XIV). The conjugated, six-membered, chelate structure, in which



XIII



XIV

the *syn* form would probably exist should produce a considerable degree of stabilization of that form and might hinder the formation of the etherified or esterified intermediate known to be required for the rearrangement to occur.

Further evidence that the isolated oxime is the *syn* compound is provided by an inspection of its infrared spectrum. A strong, broad absorption peak, not present in the ketone, is centered at 3.12μ, the region in which associated O•••H•••X stretching vibrations are normally found. No other absorption peaks occur at shorter wave lengths in the region of unassociated hydroxyl stretching.

The reaction of 1-phenyl-5-acetyltetrazole with methylmagnesium iodide gave the expected 2-(1-phenyl-5-tetrazolyl)-2-propanol (VIII) in moderate yield. Likewise, the action of bromine on this acetyl derivative in dry chloroform solution produced 1-phenyl-5-ω-bromoacetyltetrazole (IX). The reaction with bromine at room temperature was preceded by an induction period of one to two hours' duration, even in the presence of benzoyl peroxide, hydrogen bromide, and ultraviolet light as catalysts. The initiation of hydrogen bromide evolution was accompanied by precipitation of an orange solid that slowly redissolved as the reaction proceeded. No attempt was made to isolate or identify the intermediate.

In refluxing chloroform solution slow evolution of hydrogen bromide began immediately and continued for nine hours to give a 54% yield of the brominated product as compared to a 38% yield from the reaction carried out at room temperature. There was no indication that the product would react with a second

molecule of bromine under the milder conditions. The colorless product was not stable upon prolonged storage, considerable darkening resulting after several months while kept in a tightly closed bottle in the dark.

Attempted reactions of 1-phenyl-5-ω-bromoacetyltetrazole with amines resulted in the isolation of orange to red, high-melting solids that appeared to be of a highly complex nature. The products obtained in low yields could not be satisfactorily purified. Similarly, the action of sodium acetate on the bromo derivative according to the usual procedure for the preparation of phenacyl esters (3b), gave a dark red oil that could not be purified.

The attempted aldol condensation of 1-phenyl-5-acetyltetrazole with benzaldehyde in the presence of 10% sodium hydroxide resulted in the isolation of only 1-phenyltetrazole (X). This led to the discovery that organic bases as well as hydroxide ion readily cause cleavage of the acetyl group from the tetrazole nucleus, even at room temperature. The cleavage is believed to result *via* attack of a nucleophilic reagent on the carbonyl carbon atom of the acetyl group as represented in Figure II. The inherent electron attraction of the C=N function of the tetrazole ring thus weakens the carbon to carbon bond between the ring and the acetyl group allowing the cleavage to occur.

The results of two other reactions on 1-phenyl-5-acetyltetrazole serve to support the postulated mechanism. Addition of concentrated hydrochloric acid to an aqueous alcoholic solution of the acetyltetrazole and potassium cyanide in attempted cyanohydrin formation resulted in isolation of an 88% yield of 1-phenyltetrazole, none of the expected product being obtained. However, when this reaction was repeated in anhydrous media using dry liquid hydrogen cyanide at 0–25°, no reaction was observed after six hours, a quantitative recovery of 1-phenyl-5-acetyltetrazole being made. That the concentrated hydrochloric acid used in the first case did not bring about the acetyl cleavage was demonstrated by allowing 1-phenyl-5-acetyltetrazole to stand in an ethanolic solution of concentrated hydrochloric acid for 24 hours. Recovery of the acetyltetrazole was quantitative.

These results indicate that reaction of the cyanide ion with the carbonyl carbon atom of 1-phenyl-5-acetyltetrazole occurred before acidification in the first mentioned case causing cleavage of the acetyl group according to the pro-

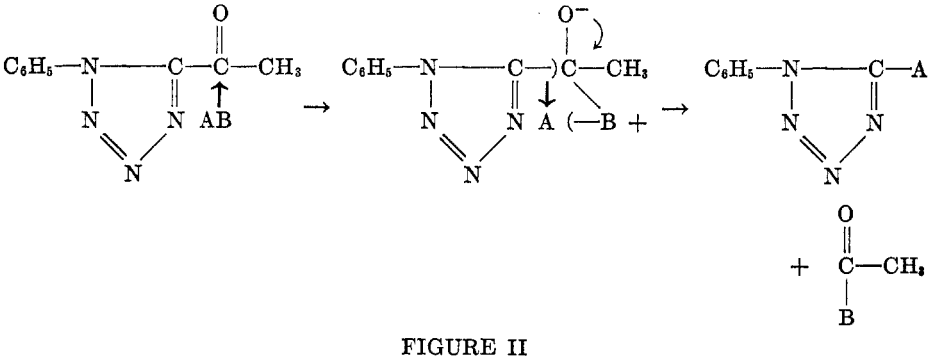


FIGURE II

posed mechanism. The resulting tetrazolyl carbanion would then extract a proton from a solvent molecule to give 1-phenyltetrazole.

From the haloform reaction on 1-phenyl-5-acetyltetrazole using sodium hypoiodite, there was isolated a 52% yield of 1-phenyl-5-iodotetrazole (XI). This result would also be expected on the basis of the mechanism given in Figure II. No iodoform was detected in the reaction mixture. The structure of the iodo derivative was proved by its conversion into the known 1-phenyl-5-hydroxytetrazole (XII) by long heating with 60% potassium hydroxide.

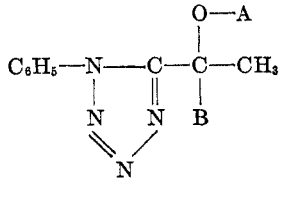
Attempted selenious acid oxidation of 1-phenyl-5-acetyltetrazole in refluxing glacial acetic acid did not give the expected 1-phenyl-5-tetrazolylglyoxal but resulted in isolation of 1-phenyltetrazole. This recalls the preparation of 1-phenyltetrazole by oxidation of 1-phenyl-5-mercaptotetrazole either with hydrogen peroxide in the presence of ammonium hydroxide (5) or with chromium trioxide in refluxing acetic acid (6). The isolation of a nearly quantitative yield of precipitated selenium from the oxidation indicates that the desired glyoxal may have formed and have subsequently undergone decarbonylation to produce the 1-phenyltetrazole.

Four other reactions typical of active methyl groups failed to take place with 1-phenyl-5-acetyltetrazole. Attempts to make it undergo the Mannich reaction with piperidine, morpholine, and diethylamine hydrochlorides under a variety of conditions have given no evidence of condensation, a good recovery of starting materials being obtained in each case. Neither did any reaction occur between this compound and *p*-nitrobenzenediazonium chloride in either acid or basic solution.

Attempts to nitrosate 1-phenyl-5-acetyltetrazole with *n*-butyl nitrite in the presence of both alkoxide and acid failed to produce any of the desired isonitroso derivative, small amounts of the starting material being recovered from the reactions in the presence of base and a large recovery being realized from the reaction in acid solution. It is likely that in the reactions run in the presence of alkoxide ion cleavage of the acetyl radical occurred but no attempts were made to isolate other products.

Another unsuccessful reaction of this type was the attempted condensation of diethyl oxalate with 1-phenyl-5-acetyltetrazole in the presence of sodium ethoxide. Here as in the nitrosation, the basic catalyst may have caused cleavage of the acetyl group.

In general, 1-phenyl-5-acetyltetrazole appears to be stable in the presence of acids but unstable in the presence of bases or nucleophilic reagents unless a stable intermediate or product of the type represented by XV can be formed.



XV

In other words, it is indicated that nucleophilic attack on the acetyl group will result in its being cleaved from the tetrazole ring unless such attack is nucleophilic addition across the carbonyl group. In connection with this, carbanion formation at the methyl group apparently does not occur in the presence of nucleophilic reagents due to their preferential attack on the carbonyl carbon atom accompanied by acetyl cleavage.

EXPERIMENTAL[4]

SYNTHESIS OF 1-PHENYL-5-ACETYLTETRAZOLE

α-Chloropropionyl chloride (II). A mixture of α-chloropropionic acid (325.6 g., 3.0 moles) and phosphorus trichloride (275 g., 2.0 moles) was slowly heated and refluxed during 5½ hours to a bath temperature of 115°, at which time the evolution of hydrogen chloride had almost stopped and a large, solid, puffy, white mass had formed in the reaction flask. Upon distillation of the product from the reaction mixture through a Widmer column, only one fraction boiling continuously from 80–106° was obtained. Distillation was stopped when the residue began to decompose. Fractionation of the distillate through a one-meter Todd column packed with glass helices gave excellent separation, 254.2 g. (67%) of colorless α-chloropropionyl chloride boiling at 111–112° being obtained.

α-Chloropropionanilide (III) was prepared in 85% yield by the method of Bishoff and Walden (2), m.p. 89–90°.

1-Phenyl-5-(1-chloroethyl)tetrazole (IV) was prepared in 81% yield by the action of phosphorus pentachloride followed by hydrazoic acid on α-chloropropionanilide according to the directions of Harvill, Herbst, and Schreiner (1). m.p. 94–95°.

1-Phenyl-5-(1-methoxyethyl)tetrazole (V). 1-Phenyl-5-(1-chloroethyl)tetrazole (104.4 g., 0.50 mole), sodium methoxide (40.5 g., 0.75 mole), and absolute methanol (500 ml.) were refluxed together for three hours; a large quantity of sodium chloride was precipitated and the originally colorless solution became pale orange. After filtering the sodium chloride from the cooled reaction mixture all of the methanol was removed under reduced pressure, and the oily residue was treated with 200 ml. of cold water and extracted into 400 ml. of ether. Removal of the ether from the dried solution left 93.5 g. (90%) of crude pale orange 1-phenyl-5-(1-methoxyethyl)tetrazole. Fractionation of this crude product gave 78.0 g. (75%) of a pale yellow liquid boiling at 163–166°/3 mm. Further fractionation gave pale yellow product that distilled at 133–134°/0.1 mm.

Anal. Calc'd for $C_{10}H_{12}N_4O$: C, 58.8; H, 5.9.
Found: C, 58.7; H, 6.1.

1-Phenyl-5-(1-hydroxyethyl)tetrazole (VI). 1-Phenyl-5-(1-methoxyethyl)tetrazole (20.4 g., 0.1 mole) dissolved in 50 ml. of 48% HBr was refluxed for one hour and the cooled dark red solution then was neutralized with 10% sodium hydroxide solution, an orange oil forming that solidified upon cooling and scratching. Recrystallization from xylene using Norit gave 12.4 g. (65%) of pale orange crystals of m.p. 102–104°. After a second and third recrystallization a melting point of 103–104° was obtained.

1-Phenyl-5-acetyltetrazole (VII). Finely pulverized 1-phenyl-5-(1-hydroxyethyl)tetrazole (7.6 g., 0.04 mole) was added to a solution of sodium dichromate (8.0 g., 0.027 mole) dissolved in a mixture of 40 ml. of water and 4 ml. of concentrated sulfuric acid. The suspension was vigorously stirred and heated to 70° where a slightly exothermic reaction started, the red solution rapidly turning dark green. The suspension was stirred at 85–90° for 30 minutes, cooled, and the solid was filtered off and washed with water. The almost colorless product was recrystallized from about 700 ml. of petr. ether (b.p. 90–100°) to give 6.3 g. (84%) of fluffy white crystals. m.p. 126.0–126.5°. Recrystallization could be accomplished from isoamyl alcohol using much less solvent but both the quality of the product and the recovery were much lower.

[4] All melting points taken with Anschutz thermometers.

Anal. Calc'd for $C_9H_8N_4O$: C, 57.4; H, 4.3.
Found: C, 57.4; H, 4.4.

1-Phenyl-5-acetyltetrazole oxime. 1-Phenyl-5-acetyltetrazole (1.0 g., 0.005 mole), hydroxylamine hydrochloride (1.0 g., 0.014 mole), pyridine (5 ml.), and absolute ethanol (5 ml.) were refluxed together for three hours and the solvents were removed under a srteam of air in the hood. After triturating the residue with 5 ml. of cold water, it was filtered off and recrystallized from an ethanol-water mixture. A yield of 0.8 g. of colorless needles of m.p. 182.8–183.4° was obtained.

Anal. Calc'd for $C_9H_9N_5O$: C, 53.2; H, 4.5.
Found: C, 53.2; H, 4.7.

1-Phenyl-5-acetyltetrazole-2,4-dinitrophenylhydrazone shrinks at 216° and melts at 238–240° with gaseous decomposition.

Anal. Calc'd for $C_{15}H_{12}N_8O_4$: C, 48.9; H, 3.3.
Found: C, 49.0; H, 3.5.

Attempted Beckmann rearrangement of 1-phenyl-5-acetyltetrazole oxime. A. Use of phosphorus oxychloride. 1-Phenyl-5-acetyltetrazole oxime (0.5 g.) dissolved in 10 ml. of phosphorus oxychloride was allowed to stand at room temperature for 24 hours, no change occurring in the clear solution. After refluxing for 30 minutes the solution darkened and the phosphorus oxychloride was removed under reduced pressure leaving an orange oil that solidified upon standing. The solid was titurated with cold water and then recrystallized from boiling water giving recovered 1-phenyl-5-acetyltetrazole oxime.

B. Use of phosphorus pentachloride in phosphorus oxychloride. A solution of 1-phenyl-5-acetyltetrazole oxime (0.5 g.) and phosphorus pentachloride (0.5 g.) in 10 ml. of phosphorus oxychloride was refluxed for two hours the solution becoming very dark. Upon working up the reaction mixture in the same way as above, only tarry material and a small quantity of recovered oxime could be isolated.

C. Use of benzenesulfonyl chloride. A solution of 1-phenyl-5-acetyltetrazole oxime (0.5 g.) and benzenesulfonyl chloride (2.0 ml.) in 10 ml. of benzene was refluxed for nine hours becoming dark colored. Upon cooling, the tan crystals that separated were filtered off and identified as the starting material.

D. Use of polyphosphoric acid. A suspension of the oxime (1.0 g.) in 30 g. of polyphosphoric acid was heated at 130° for 15 minutes and then was poured over 150 g. of ice. Recrystallization of the solid from water gave only recovered oxime.

REACTIONS OF 1-PHENYL-5-ACETYLTETRAZOLE

With methylmagnesium iodide. Addition of a solution of 1-phenyl-5-acetyltetrazole (5.65 g., 0.03 mole) dissolved in a mixture of 150 ml. of dry benzene and 150 ml. of absolute ether during 30 minutes to a solution of methylmagnesium iodide (6.67 g., 0.05 mole) in 80 ml. of absolute ether caused the solution to warm. Upon cooling the reaction mixture after addition was completed, a white precipitate formed.

Hydrolysis of the reaction product by addition of 50 ml. of 25% sulfuric acid during 10 minutes caused the precipitate to disappear and the resulting orange ether-benzene layer was separated from the aqueous layer, washed with sodium bicarbonate solution until neutral, then with water, and finally dried.

Removal of the ether and benzene under reduced pressure left 4.1 g. (67%) of a red-brown oil that solidified to a brown solid upon scratching. Two recrystallizations from water gave 3.0 g. (49%) of colorless crystals of *2-(1-phenyl-5-tetrazolyl)-2-propanol* (VIII), m.p. 94.5–95.5°. Recrystallization from petr. ether (b.p. 90–100°) gave long, fine, colorless needles of m.p. 95–96°.

Anal. Calc'd for $C_{10}H_{12}N_4O$: C, 58.8; H, 5.9.
Found: C, 59.0; H, 5.9.

Bromination. A solution of 1-phenyl-5-acetyltetrazole (9.4 g., 0.05 mole), bromine (8.0 g., 0.05 mole), and a trace (approx. 10 mg.) of benzoyl peroxide in 75 ml. of dry chloro-

form was heated to reflux, slow evolution of hydrogen bromide beginning almost immediately. After nine hours' reflux the solution had become light orange and evolution of hydrogen bromide had ceased. The solution was concentrated to dryness under reduced pressure and the residual oily orange solid was recrystallized twice from petr. ether (b.p. 90–100°) to give 7.2 g. (54%) of flat colorless needles of *1-phenyl-5-ω-bromoacetyltetrazole* (IX). m.p. 98–100°. Further recrystallization gave product of m.p. 101.5–102.0°.

Anal. Calc'd for $C_9H_7BrN_4O$: C, 40.5; H, 2.6.

Found: C, 40.5; H, 2.7.

Attempted aldol condensation. A mixture of 1-phenyl-5-acetyltetrazole (5.65 g., 0.03 mole), benzaldehyde (3.18 g., 0.03 mole), 95% ethanol (40 ml.), and 10% sodium hydroxide solution (10 ml.) was shaken at room temperature for six hours. After removal of the ethanol and unreacted benzaldehyde by steam-distillation, the aqueous residue was extracted with benzene from which was isolated 4.1 g. of solid that melted at 64.5–65.5° after two recrystallizations from petr. ether (b.p. 60–68°). The product was identified as 1-phenyltetrazole (X) by analysis and mixture melting point.

Reaction with piperidine. A mixture of 1-phenyl-5-acetyltetrazole (3.76 g., 0.02 mole), 95% ethanol (50 ml.), and piperidine (0.5 ml.) was shaken at room temperature for 48 hours. Removal of the solvents followed by recrystallization of the residue from carbon tetrachloride and then petr. ether gave 1.6 g. of colorless crystals of m.p. 63–65°. The product was identified as 1-phenyltetrazole by mixture melting point.

Attempted cyanohydrin formation. Concentrated hydrochloric acid (5.0 g., 4.2 ml. of 37% HCl, 0.05 mole) was added during 30 minutes to 1-phenyl-5-acetyltetrazole (7.5 g., 0.05 mole) and potassium cyanide (3.3 g., 0.05 mole) dissolved in a mixture of 375 ml. of absolute methanol and 25 ml. of water while the solution was stirred and kept at 10–15° in a cold water-bath. After standing for 24 hours below 20°, the precipitated potassium chloride was filtered off and the filtrate was concentrated in dryness in vacuo. The solid residue (5.1 g.) was found to be 1-phenyltetrazole after recrystallization from carbon tetrachloride. m.p. 64–65°.

When this reaction was repeated by adding liquid hydrogen cyanide (0.54 g., 0.02 mole) to a solution of 1-phenyl-5-acetyltetrazole (3.8 g., 0.02 mole) in 50 ml. of absolute ether no reaction occurred at 0–25° during six hours, as shown by quantitive recovery of the acetyltetrazole upon evaporation of the solvent.

Attempted oxidation with selenious acid. A solution of 1-phenyl-5-acetyltetrazole (1.9 g., 0.01 mole) and selenious acid (1.3 g., 0.01 mole) in 15 ml. of glacial acetic acid to which five drops of water had been added was refluxed until no further precipitation of selenium was observed (5¼ hours). A total of 0.75 g. (95% of theoretical) of black precipitated selenium was filtered from the reaction mixture. After removal of the acetic acid *in vacuo* the resulting red oil was taken up in ether, shaken with dilute sulfurous acid followed by 10% sodium bicarbonate, and finally water. Removal of the ether from the dried solution left an orange oil that quickly solidified. Recrystallization from petr. ether (b.p. 60–68°) gave colorless crystals of 1-phenyltetrazole of m.p. 64–65°.

Attempted haloform reaction. To a stirred solution of 1-phenyl-5-acetyltetrazole (3.76 g., 0.02 mole) in 100 ml. of dioxane was added 50 ml. of 10% sodium hydroxide solution, immediately followed by the slow addition of an iodine-potassium iodide solution [prepared from iodine (100 g.), potassium iodide (200 g.), and water (800 ml.)]. When the iodine color remained after about five minutes stirring, the solution was warmed to 60° and the addition of the iodine-potassium iodide solution was continued until the iodine color was not discharged after 15 minutes stirring. Approximately 100 ml. of the iodine-potassium iodide solution was required and the addition required about two hours.

The addition of 10 ml. of 10% sodium hydroxide then removed the red color leaving a yellow solution that was cooled and diluted with 300 ml. of cold water. A tan precipitate separated that was filtered off and dried. Yield, 2.8 g. (52%). Two recrystallizations from 95% ethanol gave 1.4 g. of almost colorless crystals of 1-phenyl-5-iodotetrazole (XI).

Upon slow heating the product began to darken at 134° and underwent vigorous gaseous decomposition at 138°. Stolle and Henke-Stark (5) report a m.p. of 140° (dec.). The product exploded with evolution of iodine vapors upon rapid heating or striking with a hammer.

Anal. Calc'd for $C_7H_5IN_4$: C, 30.9; H, 1.9.

Found: C, 30.6; H, 1.9.

1-Phenyl-5-hydroxytetrazole (XII). A suspension of 1-phenyl-5-iodotetrazole (1.1 g., 0.004 mole) in 20 ml. of 60% aqueous potassium hydroxide solution was heated at 100° for ten hours. The suspension then was diluted with sufficient water to dissolve all of the solid and the filtered solution was acidified in the cold with concentrated hydrochloric acid. The precipitated 1-phenyl-5-hydroxytetrazole (0.45 g.) was recrystallized from dilute ethanol to give 0.35 g. (54%) of tan crystals of m.p. 188.5–189.0° (dec.). Stolle and Henke-Stark (5) report m.p. 187° (dec.).

Attempted Mannich reaction. A. Use of dimethylamine hydrochloride. A mixture of 1-phenyl-5-acetyltetrazole (4.7 g., 0.025 mole), paraformaldehyde (1.0 g., 0.01 mole), dimethylamine hydrochloride (2.5 g., 0.03 mole), and 20 ml. of 95% ethanol containing 3 drops of concentrated hydrochloric acid was refluxed for 7½ hours on a steam-bath. From the reaction mixture there was recovered 3.7 g. (79%) of pure 1-phenyl-5-acetyltetrazole.

B. Use of morpholine hydrochloride. The reaction run as described above in refluxing isoamyl alcohol gave only recovered 1-phenyl-5-acetyltetrazole.

C. Use of piperidine hydrochloride. The reaction was run according to the conditions of Fry (7), the starting material being recovered.

Attempted nitrosation. A. In 20 ml. of absolute ethanol about half saturated with hydrogen chloride was suspended 1-phenyl-5-acetyltetrazole (1.9 g. 0.01 mole). Addition of butyl nitrite (1.0 g., 0.01 mole) caused slow evolution of a gas accompanied by slow solution of the tetrazole. The reaction mixture was warmed to 35° to speed up the reaction until all of the tetrazole had dissolved and then after cooling to 0° an additional 1.0 g. (0.01 mole) of butyl nitrite was added and the solution was kept at 0° with no further gaseous evolution for five days. Oily tan crystals (1.4 g.) which had formed in the solution were filtered off and after several recrystallizations from petr. ether (b.p. 90–100°) were identified as 1-phenyl-5-acetyltetrazole.

B. To an ice-cold solution of sodium ethoxide (0.68 g., 0.01 mole) in 20 ml. of absolute ethanol was added *n*-butyl nitrite (1.0 g., 0.01 mole) and 1-phenyl-5-acetyltetrazole (1.9 g., 0.01 mole) and the solution was kept at 0° for five days. After an additional 15 days standing at room temperature a red-brown precipitate had formed and it was filtered off and dissolved in dilute acetic acid. Through ether extraction of the acid solution a small amount of a red oil was isolated. It did not give a positive test for the presence of the isonitroso group. From the original ethanolic filtrate a small amount of 1-phenyl-5-acetyltetrazole was recovered.

Attempted condensation with diethyl oxalate. To a cold stirred solution of sodium ethoxide (2.04 g., 0.03 mole) in 20 ml. of absolute ethanol was added during 10 minutes a solution of 1-phenyl-5-acetyltetrazole (5.6 g., 0.03 mole) in diethyl oxalate (54.0 g., 50 ml., 0.37 mole). After 15 minutes stirring, the solution had become orange but no precipitate had formed. The solution was heated to 85° for 15 minutes becoming almost black and then was cooled to room temperature. Upon working up the reaction mixture in the usual way, no sodium salt could be isolated. A black tarry residue remained after acidification and ether extraction followed by removal of the ether.

SUMMARY

The synthesis of 1-phenyl-5-acetyltetrazole from 1-phenyl-5-(1-chloroethyl)-tetrazole has been achieved in good yield through the corresponding methoxy- and hydroxy-ethyl derivatives.

The results of various reactions on 1-phenyl-5-acetyltetrazole indicate that it is not a typical methyl ketone due to the influence of the ketimine structure

of the tetrazole nucleus. Nucleophilic reagents cause rapid cleavage of the acetyl group unless nucleophilic addition across the carbonyl group produces a stable product.

BETHLEHEM, PENNA.

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