[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

# 2-PHENYL-2,1,3-TRIAZOLE AND DERIVATIVES

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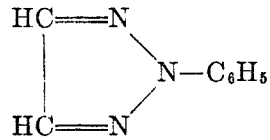
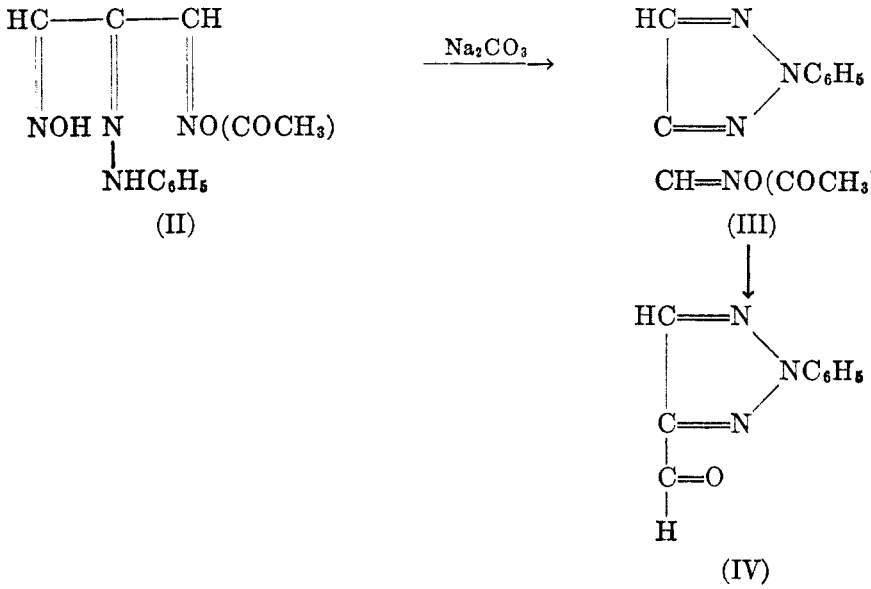
The synthesis of 2-phenyl-2,1,3-triazole (I) was reported by von Pechmann



I

(1) who decarboxylated the silver salt of 2-phenyl-2,1,3-triazole-4-carboxylic acid by heating the latter compound in a retort. The 2-phenyl-2,1,3-triazole-4-carboxylic acid was obtained by heating (II) with 10% aqueous sodium carbonate.



This treatment first resulted in ring closure, forming the acetylated oxime (III), which in turn was hydrolyzed to 2-phenyl-2,1,3-triazole-4-carboxaldehyde (IV). The aldehyde was oxidized readily to the corresponding acid (2).

The yield of (I) was quite low, following the above series of reactions. It has been demonstrated that (I) can be prepared with an over-all yield of about 60% by heating the osazone of glyoxal with aqueous cupric sulfate. This method is an adaptation of that used by Hann and Hudson (3) for the synthesis of substituted osotriazoles from the sugar osazones. Because of the simpler structure of

glyoxal osazone, the 2-phenyl-2,1,3-triazole is obtained directly from its phenylosazone through decomposition with aqueous copper sulfate. The synthesis of (I) is simpler because it does not involve the side chain oxidation with sodium periodate as in the aldehyde preparation.

von Pechmann (1) produced a mononitro derivative (m.p. 183–184°) of (I) by treating it with fuming nitric acid. He gave no indication regarding the orientation of the nitro group. Upon nitration of (I) with a cold sulfuric-nitric acid mixture we obtained two mononitro derivatives. One of these compounds melted at 183–184° and was formed in high yield. The second melted at 126–127° and was obtained in low yield. On the basis of the general rules of orientation one would expect the *p*-isomer to melt higher and to be produced in greater quantity. Therefore, it is believed that the compound which melted at 183–184° is the *p*-isomer and the one which melted at 126–127° is the *o*-isomer. An effort was made to prove unequivocally the structure of the *p*-isomer by subjecting the *p*-nitrophenyl osazone of glyoxal to conditions which might effect a ring closure to form 2-(4′-nitrophenyl)-2,1,3-triazole (V) directly. All attempts to do so resulted in failure. When the *p*-nitrophenylosazone was heated with aqueous cupric sulfate no change was observed even in a sealed tube at 200°. The presence of the nitro group either reduces the reactivity of the osazone, or its inability to react may result from its extremely low solubility in water. When the osazone was heated with acetic anhydride, ring closure also failed.

Proceeding on the assumption that reduced solubility might have caused the failure of the ring closure, the *p*-nitrophenylosazone of glucose was prepared. Because of the hydroxylated side chain this osazone should be more soluble in water than the osazone of glyoxal. The *p*-nitrophenylosazone of glucose was heated with aqueous cupric sulfate but the expected ring closure again failed. Accordingly it is believed that the presence of the nitro group in these osazones markedly reduces their reactivity.

While compounds (I) and (V) have been prepared previously, there was no literature reference found describing any derivatives of (V). Several such derivatives have now been prepared and some of them have been examined for possible medicinal uses.

When (V) was reduced with tin and hydrochloric acid, 2-(4′-aminophenyl)-2,1,3-triazole (VI) was produced in good yield. The hydrochloride, acetyl, and benzoyl derivatives of (VI) were prepared by the usual methods.

When compound (V) was subjected to the usual conditions for the diazotization of an aromatic amine, some diazotization took place, but for some unexplained reason the yields were not very satisfactory. The diazonium salt coupled with beta-naphthol to give a red solid which analyzed correctly for the expected 1-*p*-[2′-(2′,1′,3′-triazolybenzene-azo)]-2-naphthol. When the diazonium salt was treated under the usual conditions of the Bart reaction, 2-(4′-arsonophenyl)-2,1,3-triazole was produced with an over-all yield of 27%. But when the diazonium salt solution was warmed none of the expected 2-(4′-hydroxyphenyl)-2,1,3-triazole was obtained.

When the amino compound (VI) was allowed to react with *p*-acetylamino-

benzenesulfonyl chloride, a good yield of the acetyl derivative of 2-(*p*-sulfanilamido)phenyl-2,1,3-triazole was obtained, which upon hydrolysis gave 2-(*p*-sulfanilamido)phenyl-2,1,3-triazole.

2-Phenyl-2,1,3-triazole was treated with chlorosulfonic acid. The product formed was not purified but was assumed to be *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride. When ammonium hydroxide was added to a portion of this sulfonyl chloride a white solid formed which analyzed correctly for *p*-2-(2,1,3-triazolyl)benzenesulfonamide. Following the usual procedure the sulfonyl chloride was treated with aniline to produce *p*-2-(2,1,3-triazolyl)benzenesulfonanilide.

2-Phenyl-2,1,3-triazole was mixed with acetyl chloride and aluminum chloride hoping to bring about a typical Friedel-Crafts reaction, but under the conditions tried none of the expected reaction took place.

## EXPERIMENTAL

*Synthesis of 2-phenyl-2,1,3-triazole (I).* In a typical experiment a solution was prepared containing 115.6 g. (0.8 mole) of phenylhydrazine hydrochloride, 218 g. of sodium acetate, and 1 liter of water. While stirring this solution at room temperature, 74 g. of 30% glyoxal (0.4 mole) was added portionwise. More water was added as the reaction proceeded so that the mixture could be stirred. After stirring 4 hours, the yellow osazone of glyoxal was filtered. The yield was practically quantitative (95 g.).

The entire yield of the osazone from above was transferred to a 5-liter flask containing 1 liter of water and 250 g. of cupric sulfate pentahydrate. This mixture was heated with stirring at 75–80° for 6.5 hours, after which the reaction product was steam distilled to remove the triazole. The triazole-water mixture was saturated with sodium chloride and extracted with ether. The ether extract was washed with 10% hydrochloric acid to remove aniline. It was then washed with water, dried over sodium sulfate, and distilled. A yield of 33 g. (59%) of the triazole was obtained which boiled at 115–118° at 22 mm.

*Anal.* Calc'd for $C_8H_7N_3$: C, 66.18; H, 4.86; N, 28.94.
Found: C, 66.15; H, 4.72; N, 29.07.

In earlier experiments the triazole was extracted with ether (instead of steam distillation) after heating the osazone with aqueous copper sulfate. The procedure proved to be very unsatisfactory and was discontinued.

*Nitration of 2-phenyl-2,1,3-triazole.* To 420 ml. of concentrated sulfuric acid was added slowly with cooling 200 g. of 2-phenyl-2,1,3-triazole. Keeping the temperature below 20°, 210 ml. of concentrated nitric acid was added dropwise with stirring. After the nitric acid had been introduced, the mixture was allowed to stand at room temperature one hour and was then poured into 3,000 ml. of cold water. The solid which formed was filtered and dried. This solid was washed thoroughly with ethanol and the washings combined. The solid which remained undissolved melted at 182–184°; yield, 215 g. (82%). A portion was purified for analysis by crystallizing from ethanol.

*Anal.* Calc'd for $C_8H_6N_4O_2$: N, 29.45. Found: N, 29.53.

The ethanol extract was partially evaporated and, upon cooling, some more of the solid melting at 183° was recovered. The filtrate from this was evaporated and after many crystallizations another solid melting at 126–127° was produced. It is believed to be 2-(2′-nitrophenyl)-2,1,3-triazole.

*Anal.* Calc'd for $C_8H_6N_4O_2$: N, 29.45. Found: N, 29.53.

*Reduction of 2-(4'-nitrophenyl)-2,1,3-triazole to 2-(4'-aminophenyl)-2,1,3-triazole.* To 215 g. (1.65 moles) of 2-(4'-nitrophenyl)-2,1,3-triazole was added 344 g. of granulated tin in a 5-liter flask fitted with a condenser. To this mixture was added 1000 ml. of concentrated hydrochloric acid portionwise with gentle heating until the reaction was complete. The mixture was then poured into water. Sodium hydroxide was added in excess and the mixture extracted with benzene. The benzene extract was dried over solid potassium hydroxide and distilled. It boiled at 165° at 2 mm. and solidified upon standing; yield 151.5 g. (84%).

*Anal.* Calc'd for $C_8H_8N_4$: N, 34.98. Found: N, 34.99.

*Conversion of 2-(4'-aminophenyl)-2,1,3-triazole to its hydrochloride.* A small sample of the amine was dissolved in anhydrous ether and treated with dry hydrogen chloride. A white precipitate formed at once which was filtered and washed with dry ether. It was then crystallized twice from 98% ethanol.

It melted at 199° with previous softening. The melting point was not sharp.

*Anal.* Calc'd for $C_8H_9ClN_4$: Cl, 18.03. Found: Cl, 17.97.

*Preparation of 2-(4'-acetylaminophenyl)-2,1,3-triazole.* To 2 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added 5 g. of acetic anhydride. The mixture was warmed over steam 30 minutes. Water was added and the white solid which formed was filtered, washed with water, and crystallized twice from ethanol; yield 1.5 g., melting point 189–190°.

*Anal.* Calc'd for $C_{10}H_{10}N_4O$: N, 27.69. Found: N, 27.99.

*Preparation of 2-(4'-benzoylaminophenyl)-2,1,3-triazole.* To 1 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added 5 ml. of water and 3 g. of benzoyl chloride. To this mixture was added 15 ml. of 20% aqueous sodium hydroxide solution in small portions and with vigorous shaking. A white solid formed which was filtered, washed with water, and crystallized twice from ethanol; yield 1.3 g., melting point 193–194°.

*Anal.* Calc'd for $C_{15}H_{12}N_4O$: N, 21.20. Found: N, 21.59.

*Synthesis of 2-(4'-arsonophenyl)-2,1,3-triazole.* This synthesis was effected using the well known Bart procedure. In a typical run a solution of 20 g. (0.125 mole) of 2-(4'-aminophenyl)-2,1,3-triazole in 335 ml. of water containing 30 ml. (0.35 mole) of concentrated hydrochloric acid was diazotized at 0–5° by dropwise addition of 8.7 g. (0.125 mole) of sodium nitrite in 75 ml. of water. The mixture was stirred about 15 minutes after the addition was completed. To this diazonium salt solution was added a solution containing 22.3 g. of sodium hydroxide, 25 g. of arsenic trioxide, and 5.5 g. of cupric sulfate in 175 ml. of water. Nitrogen was evolved readily. This mixture was stirred 4 hours at 0°, and finally heated to 65°. It was then nearly neutralized with hydrochloric acid, and after adding decolorizing charcoal was filtered. To the filtrate was added hydrochloric acid until just acid to Congo Red. A light yellow solid formed which was crystallized twice from dilute acetic acid. The solid was nearly white. It did not melt when heated to 285°; yield of pure product 9.3 g. (27%).

*Anal.* Calc'd for $C_8H_8AsN_3O_3$: As, 27.84. Found: As, 27.56.

One attempt was made to reduce this compound to the corresponding arsine oxide using sulfur dioxide. The substance produced did not give a suitable analysis.

*Attempted synthesis of 2-(4'-hydroxyphenyl)-2,1,3-triazole.* Five different experiments were conducted in an attempt to prepare 2-(4'-hydroxyphenyl)-2,1,3-triazole. This compound might be of interest as an antiseptic. The basis of the attempted synthesis was to diazotize 2-(4'-aminophenyl)-2,1,3-triazole and to warm the diazonium salt as in the classical procedure for the replacement of the amino group with hydroxyl. Regardless of the conditions tried all these experiments resulted in failure.

*Synthesis of 1-p-[2'-(2',1',3'-triazolylbenzene-azo)]-2-naphthol.* To about 1 g. of 2-(4'-aminophenyl)-2,1,3-triazole was added hydrochloric acid and sodium nitrite under the usual conditions for diazotization. The diazonium salt solution was poured into a potassium hydroxide solution of beta-naphthol. A red precipitate formed which was washed thoroughly with water. The solid was placed in 60 ml. of 10% hydrochloric acid and allowed to stand 24 hours. The solid was filtered, washed thoroughly with water, and finally with ethanol. Since it was not very soluble in ethanol, it was not crystallized, but dried for analysis.

*Anal.* Calc'd for $C_{18}H_{13}N_5O$: N, 22.06. Found: N, 22.21.

*Preparation of acetyl 2-(p-sulfanilamido)phenyl-2,1,3-triazole.* A mixture of 11.7 g. (0.05 mole) of *p*-acetylaminobenzenesulfonyl chloride, 8 g. of 2-(4'-aminophenyl)-2,1,3-triazole, 100 ml. of water, and 10 ml. of pyridine was warmed just below the boiling point for 5 minutes. An oil first formed which gradually crystallized. This was crystallized from ethanol; yield 17 g. (95%), melting point 209–210°.

*Anal.* Calc'd for $C_{16}H_{15}N_5O_3S$: N, 19.59. Found N, 20.57.

*Preparation of 2-(p-sulfanilamido)phenyl-2,1,3-triazole.* The 17 g. of the acetyl derivative from the preceding experiment was hydrolyzed by refluxing 3 hours in 7% hydrochloric acid solution. Refluxing was continued until all the product had dissolved. The solution was neutralized with sodium bicarbonate and the white solid which formed was crystallized from ethanol; yield 9.6 g. (64%), melting point 212–214°.

*Anal.* Calc'd for $C_{14}H_{13}N_5O_2S$: N, 23.49. Found: N, 22.82.

*Preparation of p-2-(2,1,3-triazolyl)benzenesulfonamide.* To 14.5 g. (0.10 mole) of 2-phenyl-2,1,3-triazole which was cooled to 0° was added 32 ml. of chlorosulfonic acid. The reaction was not so vigorous as observed with acetanilide. The mixture was warmed over steam 30 minutes, cooled, and poured slowly into ice-water. A white solid was formed which melted at 152–153°. It was assumed to be *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride and was used without further purification; yield 7 g. (40%). Four grams of the 2-phenyl-2,1,3-triazole was recovered. Better yields may be obtained by longer heating of the reaction mixture.

To 6 g. of the sulfonyl chloride produced above was added excess concentrated ammonium hydroxide. The mixture was warmed 15 minutes, water was added, and the white solid filtered. The solid was crystallized from ethanol. It melted at 245–247°; yield 4.5 g. (83%).

*Anal.* Calc'd for $C_8H_8N_4O_2S$: N, 24.94. Found: N, 24.66.

*Preparation of p-2-(2,1,3-triazolyl)benzenesulfonanilide.* To 2.4 g. (0.01 mole) of *p*-2-(2,1,3-triazolyl)benzenesulfonyl chloride was added 0.93 g. of aniline, 20 ml. of water, and a little pyridine. This mixture was warmed below the boiling point 10 minutes. Upon cooling, a solid formed which was crystallized from 95% ethanol; yield 1.7 g. (57%), melting point 163°.

*Anal.* Calc'd for $C_{14}H_{12}N_4O_2S$: N, 18.65. Found: N, 18.77.

*Attempted preparation of 2-(4'-acetylphenyl)-2,1,3-triazole.* A mixture was prepared containing 14.5 g. (0.1 mole) of 2-phenyl-2,1,3-triazole, 50 ml. of carbon disulfide, and 16 g. (0.12 mole) of anhydrous aluminum chloride. To this mixture was added 7.8 g. (0.10 mole) of acetyl chloride. Not much hydrogen chloride was evolved. The mixture was refluxed 30 minutes after addition was complete. The product was poured into ice-water containing hydrochloric acid, extracted with ether, the ether extract dried and distilled. Thirteen grams of the original 2-phenyl-2,1,3-triazole was recovered. In a similar experiment the refluxing was continued for 3 hours instead of 30 minutes but this resulted in

recovery of the original triazole with none of the expected compound. Nitrobenzene was substituted for carbon disulfide as a solvent but the results were still unfavorable.

## PHARMACOLOGICAL STUDIES

A few of the compounds described above have been examined and a summary of the results follow.

2-(4′-Arsonophenyl)-2,1,3-triazole in aqueous solutions was administered orally and i. p. to mice infected with *T. equiperdum*, *T. gambiense* "V", and *Spirochaeta movyi* but no therapeutic activity was indicated in any instance. *In vitro* the arsonic acid was active on the above organisms in dilutions of 1:10,000 to 1:20,000 in egg slope medium and 1:20,000 to 1:50,000 in liquid liver medium.

2-(*p*-Sulfanilamido)phenyl-2,1,3-triazole was found to be ineffective in the treatment of mice infected with tetanus toxemia, or influenza virus, or rabic virus. It was slightly effective in the treatment of mice infected with *Streptococcus hemolyticus*.

TABLE I

ACTIVITY OF *p*-2-(2,1,3-TRIAZOLYL)BENZENESULFONANILIDE

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No | bactericidal | action | at | 1-1,000 | | against | *Staph. aureus*-209 |
| No | bactericidal | action | at | 1-1,000 | | " | *B. typhosus*-221 |
| Bacteriostatic | | action | at | 1-1,000 | but not at 1-5,000 | " | *Staph. aureus*-209 |
| " | | action | at | 1-1,000 | " " " 1-5,000 | " | *B. typhosus*-221 |
| No | fungicidal | action | at | 1-1,000 | | " | *T. interdigitale* |
| No | " | " | " | 1-1,000 | | " | *T. rubrum* |
| No | " | " | " | 1-1,000 | | " | *C. albicans* |
| Fungistatic | | " | " | 1-1,000 | " " " 1-5,000 | " | *T. interdigitale* |
| " | | " | " | 1-1,000 | " " " 1-5,000 | " | *T. rubrum* |
| No | " | " | " | 1-1,000 | | " | *C. albicans* |

Streptococcus hemolyticus, or tetanus toxemia, or influenza virus, or rabic virus.

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## SUMMARY

1. A good method for the synthesis of 2-phenyl-2,1,3-triazole has been presented.

2. Eleven derivatives of this triazole have been prepared.

3. No therapeutic value has been suggested for any of the compounds with which pharmacological studies have been made.

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