[Contribution from the Department of Chemistry, the University of New Mexico]

SOME FURTHER STUDIES OF 2-PHENYL-1,2,3,2*H*-TRIAZOLE DERIVATIVES

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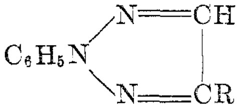
A number of derivatives of 2-phenyl-1,2,3,2*H*-triazole have been reported in previous papers (1, 2) of this series. The preparation of additional compounds belonging to this heterocyclic system is described in this paper.

The readily obtainable 2-phenyl-1,2,3,2*H*-triazole-4-carboxaldehyde (I), which was prepared by the sodium periodate oxidation of phenyl-D-glucosotriazole (2), served as a useful starting material in many of these syntheses. With potassium cyanide and ammonium chloride, I was converted in low yields to 2-phenyl-1,2,3,2*H*-triazol-4-ylaminoacetic acid. When treated with thionyl chloride the oxime of I lost a molecule of water to form 2-phenyl-4-cyano-1,2,3,2*H*-triazole.

2-Phenyl-1,2,3,2*H*-triazol-4-ylcarbinol (II), which was prepared by the reduction of I with formaldehyde (2), was converted to 2-phenyl-1,2,3,2*H*-triazol-4-ylmethyl bromide (III) in the usual way. When III was heated with potassium phthalimide, the expected N-substituted phthalimide was formed. Compound III yielded 2-phenyl-1,2,3,2*H*-triazol-4-ylacetonitrile (IV) when treated with potassium cyanide. Although the nitrogen analysis was slightly less than that calculated for IV, hydrolysis of the latter led to the expected 2-phenyl-1,2,3,2*H*-triazol-4-ylacetic acid. The alcohol (II) was allowed to react with the appropriate acid chlorides to form the following esters: the 4-toluenesulfonate, the 2-phenyl-1,2,3,2*H*-triazole-4-carboxylate, and the 4-nitrobenzoate (V). Compound V was reduced catalytically to the 4-aminobenzoate which, when treated with 2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl chloride (2), yielded the expected N-acyl derivative. The N-(2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl) derivative of 8-amino-6-methoxyquinoline and of 2-(4′-aminophenyl)-1,2,3,2*H*-triazole were prepared similarly.



I R = CHO

II R = CH_2OH

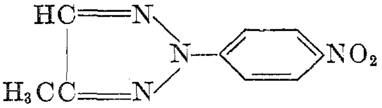
III R = CH_2Br

IV R = CH_2CN

V R = $CH_2OCOC_6H_4NO_2$-4

VI R = CH_3

4-Methyl-2-phenyl-1,2,3,2*H*-triazole (VI) was prepared by heating the phenyl osazone of methylglyoxal with aqueous cupric sulfate. Nitration of VI led to a mononitroderivative. This was presumably 2-(4′-nitrophenyl)-4-methyl-1,2,3,2*H*-triazole (VII), but the position of the nitro group has not been proved.



VII

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Compound VII was reduced catalytically to the corresponding amine (VIII). The hydrochloride, N-acetyl, N-benzoyl, and N-(2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl) derivatives of VIII were prepared.

EXPERIMENTAL

2-Phenyl-1,2,3,2H-triazol-4-ylaminoacetic acid. Potassium cyanide (3 g.) and 2.5 g. of ammonium chloride were dissolved in the least possible amount of water, and 5 g. of the aldehyde (I) was added. Methanol sufficient to dissolve most of the solid material was added, and the mixture was allowed to stand overnight. The methanol was removed by distillation, and the residue was extracted several times with ether. The ether solution was washed thoroughly with water and dried over sodium sulfate. A stream of dry hydrogen chloride gas was passed into the red ether solution, and the ether was decanted from the red precipitate which had formed. The residue was treated with 25 ml. of concentrated hydrochloric acid, and the mixture was allowed to stand overnight. After diluting with an equal volume of water, the mixture was refluxed for 30 minutes, cooled, and filtered. The filtrate was carefully neutralized with dilute aqueous ammonia. The precipitate was filtered, dissolved in concentrated hydrochloric acid, treated with Norit, heated to boiling, and filtered. The filtrate was again carefully neutralized with dilute ammonia. The faintly orange-colored solid, 0.7 g. (11% yield) melted at 169–170°. This experiment was repeated, but the yield was not increased.

Anal. Calc'd for $C_{10}H_{10}N_4O_2$: N, 25.66. Found: N, 25.67.

2-Phenyl-4-cyano-1,2,3,2H-triazole. 2-Phenyl-1,2,3,2*H*-triazole-4-carboxaldoxime (3 g.) (prepared from the aldehyde in the usual way) was dissolved in 25 ml. of hot benzene, and a mixture of 10 ml. of thionyl chloride dissolved in 10 ml. of benzene was added to the boiling solution. The benzene and excess thionyl chloride were removed by evaporation. The residue was recrystallized from an ethanol-water mixture to give 1.9 g. (70% yield) of faintly yellow crystals of the nitrile, m.p. 88–89°.

Anal. Calc'd for $C_9H_6N_4$: N, 32.92. Found: N, 32.82.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl bromide. Sodium bromide dihydrate (14.9 g., 0.107 mole) was dissolved in 9.5 ml. of water, and 15 g. (0.086 mole) of 2-phenyl-1,2,3,2*H*-triazol-4-ylcarbinol was added. Concentrated sulfuric acid (14.6 g., 7.7 ml.) was introduced in small portions with shaking, and the mixture was refluxed gently for 2 hours. After cooling, an equal volume of water was added. The solid material was collected and recrystallized from aqueous ethanol to give 14.1 g. (87% yield) of the slightly yellow bromide, m.p. 37–38°. Upon dilution of the mother liquor with water, 3 g. of the alcohol was recovered.

Anal. Calc'd for $C_9H_8BrN_3$: N, 17.65. Found: N, 17.51.

N-(2-Phenyl-1,2,3,2H-triazol-4-ylmethyl)phthalimide. A mixture of 2.4 g. (0.01 mole) of the bromide and 1.9 g. (0.01 mole) of potassium phthalimide was heated over a small flame until a syrupy mass was obtained. After cooling, the residue was treated with boiling ethanol. The mixture was treated with Norit and filtered. The solid material which separated upon cooling was filtered and recrystallized from ethanol to give 0.5 g. (16% yield) of the light orange-colored imide, m.p. 135–136°.

Anal. Calc'd for $C_{17}H_{12}N_4O_2$: N, 18.47. Found: N, 18.22.

2-Phenyl-1,2,3,2H-triazol-4-ylacetonitrile. Potassium cyanide (3 g., 0.045 mole) was mixed with 2 ml. of water in a flask fitted with a reflux condenser. After most of the salt had dissolved, 9 g. (0.038 mole) of 2-phenyl-1,2,3,2*H*-triazol-4-ylmethyl bromide dissolved in 9 g. of ethanol (warming was necessary to effect solution) was added, and the mixture was refluxed gently for 2 hours. The supernatant liquid was decanted from the warm reaction mixture, and the residue was extracted twice with hot ethanol. The combined extracts (including the original liquid) were treated with Norit and filtered. Upon diluting the hot filtrate with an equal volume of water 5.3 g. (76% yield) of light yellow crystals, m.p. 52–53° were obtained. A small portion of the material, after recrystallization from an ethanol-water mixture with the use of Norit, melted at 53–54°. Another recrystallization failed to raise the melting point.

Anal. Calc'd for $C_{10}H_8N_4$: N, 30.42. Found: N, 29.40.

2-Phenyl-1,2,3,2H-triazol-4-ylacetic acid. The nitrile (1 g.) was refluxed for 1 hour with 20 ml. of 25% aqueous sodium hydroxide. The hot solution was treated with Norit, diluted with water, and filtered. The filtrate was acidified with concentrated hydrochloric acid. The solid product was filtered and upon recrystallization from an ethanol-water mixture gave 0.5 g. (45% yield) of the colorless acid, m.p. 108–109°.

Anal. Calc'd for $C_{10}H_9N_3O_2$: N, 20.67. Found: N, 20.76.

2-Phenyl-1, 2, 3, 2H-triazol-4-ylmethyl-4'-toluenesulfonate. 2-Phenyl-1, 2, 3, 2*H*-triazol-4-ylcarbinol (0.5 g.) and 0.75 g. of 4-toluenesulfonyl chloride were mixed with 10 ml. of 15% aqueous sodium hydroxide. The mixture was shaken and gently warmed. The ester solidified upon cooling. The mixture was diluted with water, and the solid material was recovered by filtration. The crude ester was recrystallized from an ethanol-water mixture giving 0.8 g. (85% yield) of colorless crystals, m.p. 63–64°.

Anal. Calc'd for $C_{16}H_{15}N_3O_3S$: N, 12.76. Found: N, 12.75.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl-2'-phenyl-1',2',3',2H'-triazol-4-carboxylate. A mixture of 2 g. of 2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl chloride, 1.5 g. of 2-phenyl-1,2,3,2*H*-triazol-4-ylcarbinol, and 5 ml. of pyridine was warmed until all of the solid material had dissolved. The mixture was diluted with ice and water and the crude ester was filtered and recrystallized from ethanol giving 2.2 g. (74% yield) of colorless crystals, m.p. 123–124°.

Anal. Calc'd for $C_{18}H_{14}N_6O_2$: N, 24.32. Found: N, 24.31.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl-4'-nitrobenzoate. The carbinol (II, 3 g.) and 4 g. of 4-nitrobenzoyl chloride were dissolved in 5 ml. of pyridine by warming over a small flame. The mixture solidified upon cooling, and 25 ml. of water was added. Several grams of solid sodium carbonate were added in order to dissolve any excess of the acid chloride. The solid material was filtered and dried. The crude ester was finely pulverized with a mortar and pestle and then was stirred with 20 ml. of 10% Na_2CO_3. The solid material was again filtered, washed with water, and dried. The ester was finally recrystallized from an *n*-propanol-benzene mixture to give 5 g. (90% yield) of the colorless ester, m.p. 160–161°.

Anal. Calc'd for $C_{16}H_{12}N_4O_4$: N, 17.27. Found: N, 17.12.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl-4'-aminobenzoate. The 4'-nitrobenzoate (4.2 g.) was suspended in 75 ml. of ethanol, and 0.1 g. of Adams' platinum oxide catalyst was added. Hydrogen was introduced under 43 lbs. pressure. The hydrogen pressure dropped to 39 lbs. (with some warming) during the first hour of shaking. There was no further loss in pressure upon shaking for two hours longer. An evil-smelling solid remained undissolved. The mixture was heated to boiling, the solid material dissolved, and the catalyst was removed. The colorless crystals which separated from the filtrate upon cooling weighed 2.9 g. (89% yield), m.p. 134–135°.

Anal. Calc'd for $C_{16}H_{14}N_4O_2$: N, 19.03. Found: N, 19.92.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl N-(2'-phenyl-1',2',3',2H'-triazole-4'-carboxylyl)-4''-aminobenzoate. The preceding aminobenzoate (2 g.) and 2 g. of 2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl chloride were mixed with 5 ml. of pyridine. The mixture was warmed over a small flame, until a clear dark solution formed. The hot mixture was allowed to stand for ten minutes. Cracked ice and water were added, and the mixture was acidified with concentrated hydrochloric acid. The solid material was filtered and dried. After grinding thoroughly with a mortar and pestle, the crude ester was washed by stirring with 25 ml. of 10% sodium carbonate. The solid material was again collected, washed with water, and dried. The product was finally recrystallized from *n*-butanol producing 2.6 g. (82% yield) of faintly yellow crystals, m.p. 168–169°.

Anal. Calc'd for $C_{25}H_{19}N_7O_3$: N, 21.05. Found: N, 21.08.

N-(2-Phenyl-1, 2, 3, 2H-triazole-4-carboxylyl)-8'-amino-6'-methoxyquinoline. 2-Phenyl-1,2,3,2*H*-triazole-4-carboxylyl chloride (2 g.) and 1.5 g. of 6-methoxy-8-aminoquinoline were mixed with 5 ml. of pyridine. The mixture was warmed until all of the solid material dissolved forming a dark red solution. The mixture solidified upon cooling. Water was added, and the solid material was filtered, dried, and recrystallized from *n*-propanol, thus yielding 2.3 g. (77% yield) of colorless crystals, m.p. 182–183°.

Anal. Calc'd for $C_{19}H_{15}N_5O_2$: N, 20.27. Found: N, 20.71.

N-(2-Phenyl-1,2,3,2H-triazole-4-carboxylyl)-2'-(4''-aminophenyl)-1',2',3',2H'-triazole. 2-(4'-Aminophenyl)-1,2,3,2*H*-triazole (2 g.) and 2.5 g. of 2-phenyl-1,2,3,2*H*-triazole-4-carboxylyl chloride were mixed with 5 ml. of pyridine. After the initial reaction was over, the mixture was warmed over a small flame, until a clear dark solution formed. The product was isolated and purified in the same manner as that for the compound described immediately above to give 2.6 g. (63% yield) of faintly yellow crystals, m.p. 178–179°.

Anal. Calc'd for $C_{17}H_{13}N_7O$: N, 29.58. Found: N, 29.75.

4-Methyl-2-phenyl-1,2,3,2H-triazole. Methylglyoxal (1 mole, 240 g. of 30.7%) was added to a mixture of 289.2 g. (2 moles) of phenylhydrazine hydrochloride, 2 l. of water, and 544 g. (4 moles) of sodium acetate. After 5.5-hours stirring, the solid material was collected and washed with water. The phenylosazone was then mixed with 450 g. of copper sulfate in 2 l. of water. After refluxing for four hours, the mixture was steam-distilled over a period of six hours. The distillate was saturated with sodium chloride, and the triazole extracted with benzene. The benzene solution was washed with 10% hydrochloric acid followed by water and then dried over sodium sulfate. After evaporation of the benzene, the triazole was distilled, 45.6 g. (35% yield) of the colorless liquid being collected at 122–125° at 37 mm.

Anal. Calc'd for $C_9H_9N_3$: C, 67.92; H, 5.68; N, 26.40.
Found: C, 67.72; H, 5.26; N, 26.16.

4-Methyl-2-(4'-nitrophenyl)-1,2,3,2H-triazole. Conc'd nitric acid (28.5 g.) was added with stirring to a well-cooled mixture of 25 g. of 4-methyl-2-phenyl-1,2,3,2*H*-triazole and 46 ml. of concentrated sulfuric acid. The mixture was kept below 20° during the addition of the nitric acid and then was allowed to stand at room temperature for one hour. The mixture was poured into ice and water, and the solid material was collected. The crude product was washed by decantation with water followed by a similar treatment with ethanol. After two recrystallizations from ethanol, 14.1 g. (47% yield) of faintly yellow crystals, m.p. 134–135°, were obtained.

Anal. Calc'd for $C_9H_8N_4O_2$: N, 27.44. Found: N, 27.50.

4-Methyl-2-(4'-aminophenyl)-1,2,3,2H-triazole (VIII). The preceding nitro compound (14.5 g.) was dissolved in 150 ml. of ethanol, and 0.1 g. of Adam's platinum oxide catalyst was added (the nitro compound was only slightly soluble in cold ethanol). The mixture was shaken for 6 hours under approximately 40 pounds hydrogen pressure. The catalyst was filtered, and the ethanol was removed by distillation. The residue was distilled at 3 mm. to give 10.5 g. (85% yield) of the colorless amine, b.p. 170°. The amine solidified on standing, m.p. 61–62°.

Anal. Calc'd for $C_9H_{10}N_4$: N, 32.17. Found: N, 31.84.

The hydrochloride of 4-methyl-2-(4'-aminophenyl)-1,2,3,2H-triazole. A few drops of concentrated hydrochloric acid was added to a small quantity of the amine, and the salt formed immediately. The mixture was heated to boiling, and water sufficient to dissolve the hydrochloride was added. The crystals which formed when the solution cooled were collected and washed with a small quantity of cold ethanol (the salt was somewhat soluble in the latter). The colorless crystals melted at 200–201°, subliming below the melting point.

Anal. Calc'd for $C_9H_{11}ClN_4$: N, 26.59. Found: N, 26.46.

2-(4'-N-Acetylaminophenyl)-4-methyl-1,2,3,2H-triazole. A small quantity of 4-methyl-2-(4'-aminophenyl)-1,2,3,2*H*-triazole was treated with an excess of acetic anhydride. The reaction was spontaneous as indicated by warming. The solution was heated to boiling for several minutes; then several small pieces of ice were added. The solid material was filtered and washed with water. This crude product was recrystallized from an ethanol-water mixture to give colorless crystals melting at 156–157°. The yield was good but the exact percentage is not known.

Anal. Calc'd for $C_{11}H_{12}N_4O$: N, 25.92. Found: N, 25.87.

2-(4'-N-Benzoylaminophenyl)-4-methyl-1,2,3,2H-triazole. 4-Methyl-2-(4'-aminophenyl)-