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# The Synthesis of Phenyl-substituted Triazole Analogs of Histamine

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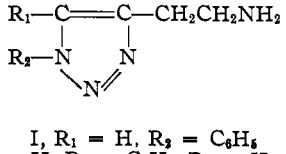
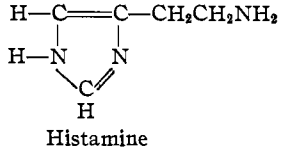
1-Phenyl-, 5-phenyl- and 1,5-diphenyl-1,2,3-triazole-4-ethylamine, phenyl-substituted triazole analogs of histamine, have been synthesized as possible antihistaminics. Each was prepared from the triazolealdehyde by the rhodanine method. 5-Phenyl-1,2,3-triazole-4-carboxaldehyde was synthesized (90%) from hydrazoic acid and phenylpropiolaldehyde. The reaction of phenyl azide with phenylpropiolaldehyde resulted in a mixture from which 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde (40%) and 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde (22%) were isolated. 1-Phenyl-1,2,3-triazole-4-carboxaldehyde (52%) and the isomeric 1-phenyl-1,2,3-triazole-5-carboxaldehyde (23%) were obtained by the addition of phenyl azide to propiolaldehyde diethyl acetal and subsequent hydrolysis.

Based on the antihistaminic activity shown by the triazole analog of histamine, which was previously reported[2] it appeared of interest to extend this investigation to some related compounds. A possible mode of action of antihistaminics is by an antagonism in which a blocking molecule adheres to the cell surface and not only prevents histamine from reaching its site of action but also, by the screening effect of large blocking groups, inactivates adjacent receptors on the cell surface making them likewise unavailable for histamine.[3] This concept suggested that the addition of blocking moieties, such as phenyl groups, to the triazole analog of histamine might result in enhanced antihistaminic activity.

The syntheses of 1-phenyl-, 5-phenyl- and 1,5-diphenyl-1,2,3-triazole-4-ethylamine (I, II and III, respectively), phenyl-substituted triazole analogs of histamine, are described in this communication. In each case the triazole-ethylamine



I, $R_1 = H$, $R_2 = C_6H_5$
II, $R_1 = C_6H_5$, $R_2 = H$
III, $R_1R_2 = C_6H_5$



Histamine

was prepared from the corresponding triazolealdehyde by the rhodanine method[4] following modifications of the procedure described previously.[2] 5-Phenyl-1,2,3-triazole-4-carboxaldehyde was prepared from phenylpropiolaldehyde and hydrazoic acid in 90% yield similarly to the method of Hüttel[5] for 1,2,3-triazole-4-carboxaldehyde. Oxidation to the known carboxylic acid confirmed the structure.

The reaction of phenylpropiolaldehyde with phenyl azide resulted in a mixture of two possible isomeric diphenyltriazoles. The highest yield (90%) was obtained by heating under reflux in dry toluene for 24 hours. Separation of the isomers in pure form afforded the low-melting aldehyde, 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde, in 40% yield and the high-melting isomer, 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde, in 22% yield. It is interesting to note that no examples of the addition of phenyl azide to an unsymmetrical acetylenic compound have been reported previously where both possible isomers were isolated. Analytically pure oximes of both isomers were prepared. The lower-melting aldehyde, obtained by a different route, has been reported[6] as having a melting point eight degrees lower, and that of the oxime, eighteen degrees lower than that of the samples obtained by us. Oxidation of our aldehyde led to the known carboxylic acid in 97% yield. For identification and comparison the isomeric high-melting aldehyde was oxidized to previously unreported 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid. Decarboxylation of this acid gave 1,4-diphenyl-1,2,3-triazole in quantitative yield.

1-Phenyl-1,2,3-triazole-4-carboxaldehyde has been prepared by Hüttel[5] from propiolaldehyde and phenyl azide. In order to avoid the difficult isolation of propiolaldehyde, the corresponding diethyl acetal was allowed to react with phenyl azide. Subsequent hydrolysis of the acetal gave a mixture of isomeric triazolealdehydes from which 1-phenyl-1,2,3-triazole-4-carboxaldehyde was separated in 52% yield and 1-phenyl-1,2,3-triazole-5-carboxaldehyde, in 23% yield. The structure of the latter was confirmed by oxidation to the known carboxylic acid.

Compounds I, II and III were examined pharmacologically[7] by blood pressure experiments in anesthetized dogs. I and III were found to possess some antihistaminic activity, but are markedly inferior to pyribenzamine. I and II show anti-acetylcholine action, with I being the most effective although it is very much less active than atropine in this respect.

## Experimental[8]

**5-Phenyl-1,2,3-triazole-4-carboxaldehyde.**—Phenylpropiolaldehyde[9] (26.3 g., 0.202 mole) was added to an equimolar amount of a titrated hydrazoic acid–ether solution prepared by method B of Audrieth and Gibbs.[10] After 2 days at room temperature, the pale yellow crystalline product amounted to 25.9 g. (74%); m.p. 186.5–187.5°. Cautious evaporation of the mother liquors afforded an additional 5.6 g., m.p. 186–187.5°; or a total yield of 31.5 g. (90%). A colorless analytical sample was obtained by

(1) Bristol Laboratories Fellow, 1948–1949. Arnold, Hoffman & Co., Inc., Providence, Rhode Island.

(2) J. C. Sheehan and C. A. Robinson, THIS JOURNAL, **71**, 1436 (1949).

(3) C. C. Pfeiffer, *Science*, **107**, 94 (1948); *Modern Hosp.*, **71**, 88 (1948).

(4) C. Granacher, *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923); P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

(5) R. Hüttel, *Ber.*, **74B**, 1680 (1941).

(6) C. A. Rojahn and H. Trieloff, *Ann.*, **445**, 304 (1925).

(7) The pharmacological testing was kindly carried out by Dr. H. L. Dickison and Mr. J. B. Hoekstra of Bristol Laboratories, Syracuse, N. Y.

(8) All melting points are corrected. We are indebted to Mr. S. M. Nagy and associates for the microanalytical data.

(9) C. F. H. Allen and C. O. Edens, Jr., "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 92.

(10) L. F. Audrieth and C. F. Gibbs, "Inorganic Syntheses," Vol. I, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 77.

recrystallization of a portion of the first crop from ethanol–water (charcoal); m.p. 186.5–187.5°.

*Anal.* Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.41; H, 4.15; N, 24.48.

This compound is soluble in absolute ethanol, in acetone, or in hot water.

For proof of structure, a sample was oxidized to 5-phenyl-1,2,3-triazole-4-carboxylic acid by a procedure similar to that described below for 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid. The recrystallized acid decomposed at 207.5° (reported,[11] 205–206°) and the cooled melt crystallized and remelted at 140–142° (reported melting point of 4-phenyl-1,2,3-triazole,[11] 143–145°).

**5-(5-Phenyl-1,2,3-triazol-4-ylmethylene)-rhodanine.**—Following the general procedure previously described,[2] 10.4 g. (0.060 mole) of 5-phenyl-1,2,3-triazole-4-carboxaldehyde was converted into 14.9 g. (86%) of the rhodanine derivative including a small second crop obtained by neutralization of the filtrate to *p*H 6. Two recrystallizations from methanol–water gave an analytical sample as lemon-yellow needles.

*Anal.* Calcd. for $C_{12}H_8N_4OS_2$: C, 49.98; H, 2.80; N, 19.43. Found: C, 50.35; H, 3.04; N, 19.56.

**Hydrochloride of 5-Phenyl-1,2,3-triazole-4-pyruvic Acid Oxime.**—The crude rhodanine compound (5.77 g., 0.020 mole) was hydrolyzed and the resulting crude, moist thiopyruvic acid was treated with hydroxylamine in the manner described for the unsubstituted compound.[2] In this case, the product was best isolated as the sodium salt by dissolving the reaction mixture, after concentration, in 16 ml. of hot 5% sodium hydroxide solution. The sodium salt crystallized on cooling, weight 3.42 g. Acidification of a suspension of this compound in 11 ml. of warm water with 3.2 ml. of concentrated hydrochloric acid afforded 3.00 g. (53%) of colorless crystalline hydrochloride decomposing at 192°. Recrystallization from absolute ethanol–ether failed to alter the decomposition point.

*Anal.* Calcd. for $C_{11}H_{10}N_4O_3 \cdot HCl$: C, 46.73; H, 3.92; N, 19.82. Found: C, 46.93; H, 4.10; N, 19.51.

**Acetyl Derivative of 5-Phenyl-1,2,3-triazole-4-acetonitrile. A. From the Hydrochloride of the Oximino Acid.**—To a chilled mixture of 0.74 g. of fused sodium acetate in 10.7 ml. of acetic anhydride, 2.32 g. (0.00820 mole) of the hydrochloride of 5-phenyl-1,2,3-triazole-4-pyruvic acid oxime was added. The temperature was allowed to rise slowly until reaction began; a vigorous evolution of carbon dioxide resulted and solution was complete below 40°. The excess acetic anhydride was decomposed by stirring with 33 ml. of water. The product, which separated as nearly colorless crystals, amounted to 1.66 g. (90%) after washing with water; m.p. 118–120°. By recrystallization from 16 ml. of hot isopropyl alcohol a 90% recovery of product melting at 120.5–121.5° was obtained. A second recrystallization from absolute ethanol gave an analytical sample as colorless rods, m.p. 121–121.5°.

*Anal.* Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.77. Found: C, 63.60; H, 4.52; N, 24.68.

The acetylated nitrile is somewhat soluble in cold methanol but very slightly soluble in cold ethanol or isopropyl alcohol. It gives no coloration with ferric chloride solution.

**B. From the Sodium Salt of the Oximino Acid.**—The reaction of 1.27 g. (0.00473 mole) of crude sodium salt of 5-phenyl-1,2,3-triazole-4-pyruvic acid oxime in 6.2 ml. of cold acetic anhydride also proceeded readily and afforded a nearly colorless, crystalline product amounting to 0.880 g. (82%); m.p. 120.5–121.5°.

**5-Phenyl-1,2,3-triazole-4-acetonitrile.**—A suspension of 0.452 g. (0.0020 mole) of recrystallized acetyl derivative of 5-phenyl-1,2,3-triazole-4-acetonitrile in 20 ml. of water was heated under reflux for one-half hour. On cooling, the colorless solution afforded a 92% yield (0.340 g.) of non-acetylated nitrile as colorless rods, m.p. 130–130.5°. An analytical sample melting at 130–130.5° was obtained by recrystallization from water containing 10% ethanol.

*Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.41; H, 4.67; N, 30.82.

This non-acetylated nitrile is soluble in cold ethanol, isopropyl alcohol, ether or in hot water. Acetylation by heating on a steam-bath with acetic anhydride for 15 minutes gave a 94% yield of the acetyl derivative of 5-phenyl-1,2,3-triazole-4-acetonitrile.

**5-Phenyl-1,2,3-triazole-4-ethylamine Dihydrochloride.**—Following the general procedure previously described,[2] 0.870 g. (0.00385 mole) of the acetyl derivative of 5-phenyl-1,2,3-triazole-4-acetonitrile was hydrogenated, and the resulting acetylated amine was hydrolyzed without purification. Concentration of the aqueous solution afforded a quantitative yield (1.00 g.) of crystalline amine dihydrochloride melting with decomposition at 199–200°. Recrystallization from methanol–ether gave a 72% recovery of tiny colorless crystals which melted with decomposition at 212–214°; the decomposition point of this compound varies over a 25° range depending on the rate of heating. An analytical sample melting with decomposition at 214–215° (slow heating) was obtained after further recrystallization from methanol–ether.

*Anal.* Calcd. for $C_{10}H_{12}N_4 \cdot 2HCl$: C, 45.99; H, 5.40; N, 21.46. Found: C, 45.81; H, 5.50; N, 21.60.

**Addition of Phenyl Azide to Phenylpropiolaldehyde.**—A mixture of 6.50 g. (0.050 mole) of phenylpropiolaldehyde,[9] 5.96 g. (0.050 mole) of phenyl azide,[12] and 65 ml. of dry toluene was refluxed gently for 24 hours. Cautious distillation of the solvent under reduced pressure left a solid which was triturated with 100 ml. of petroleum ether. After separating by filtration and drying under reduced pressure, the granular, tan-colored mixture of isomers amounted to 11.2 g. (90%).

**1,5-Diphenyl-1,2,3-triazole-4-carboxaldehyde** was separated by extraction with 700 ml. of boiling ethanol–water (3:7). The extracts on chilling overnight deposited pale yellow needles amounting to 6.65 g. (53%); m.p. 105–108.5°. Recrystallization from absolute ethanol gave a 75% recovery in several crops; m.p. 112–113°. An analytical sample obtained as colorless needles after three recrystallizations from xylene–petroleum ether also melted at 112–113° (reported,[6] 104–105°).

*Anal.* Calcd. for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.04; H, 4.45; N, 17.27, 17.15.

Further recrystallizations from ethanol or from cyclohexane failed to alter the melting point. This aldehyde is readily soluble in cold acetone, in ether, or in hot ethanol, but is sparingly soluble in hot water.

**The oxime** of 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde was obtained as colorless needles in 71% yield after recrystallization from dilute ethanol; m.p. 194–195° (reported,[6] 176°).

*Anal.* Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58. Found: C, 68.45; H, 4.69.

The identity of the aldehyde of melting point 112–113° was confirmed by oxidation to 1,5-diphenyl-1,2,3-triazole-4-carboxylic acid. In analogy to the preparation of 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid described below, a 97% yield was obtained (m.p. 183° dec.) which, after recrystallization from methanol–water, decomposed at 184° with evolution of gas (reported,[13] 183°). The decomposed melt crystallized on cooling and remelted at 112.5–113.5° (reported for 1,5-diphenyl-1,2,3-triazole,[14] 113–114°).

**1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde** was obtained from the dried residue (3.00 g., m.p. 166–170°) remaining after extraction of the low-melting isomer. After stirring this material with 14 ml. of 95% ethanol at room temperature for 5 minutes, the tan-colored insoluble fraction was removed by filtration and washed with ethanol; yield 2.68 g. (22%); m.p. 170–171.5°. An analytical sample prepared by two recrystallizations from hot absolute ethanol (charcoal) was obtained as tiny, colorless rods melting at 171–172°.

*Anal.* Calcd. for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.64; H, 4.73; N, 17.03.

This high-melting isomer is soluble in hot acetone, moderately soluble in ether, sparingly soluble in hot ethanol and insoluble in hot water.

**The oxime** of 1,4-diphenyl-1,2,3-triazole-5-carboxalde-

(11) E. Oliveri-Mandala and A. Coppola, *Gazz. chim. ital.*, **40**, II, 438–440 (1910).

(12) R. O. Lindsay and C. F. H. Allen, "Organic Syntheses," Vol. 22, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 96.

(13) A. Michael, F. Luehn and H. H. Higbee, *Am. Chem. J.*, **20**, 394 (1898).

(14) O. Dimroth, *Ber.*, **35**, 4048 (1902).

hyde was obtained as colorless needles after three recrystallizations from methanol–water; m.p. 160.5–161.5°.

*Anal.* Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.20; H, 4.49; N, 21.38.

**1,4-Diphenyl-1,2,3-triazole-5-carboxylic Acid.**—To a solution of 1.25 g. (0.0050 mole) of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde (m.p. 171–172°) in 200 ml. of ethanol was added 1.85 g. of silver nitrate in 7 ml. of water followed by 44 ml. of 0.5 *N* NaOH solution added dropwise with stirring. After stirring the mixture overnight and removing the insoluble material by filtration, the solution was concentrated to a small volume. The alkaline solution was extracted with ether to remove non-acidic impurities and then acidified with dilute hydrochloric acid. The precipitated product amounted to 1.19 g. (90%); m.p. 175.5° with evolution of gas. Recrystallization from methanol–water at room temperature gave a 78% recovery (0.93 g.) as tiny, colorless rods, m.p. 177° with evolution of gas. A second recrystallization raised the decomposition point to 177.5°; the decomposed melt crystallized and remelted at 185–185.5°.

*Anal.* Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84; neut. equiv., 265.26. Found: C, 67.78; H, 4.48; N, 15.87; neut. equiv., 266.

1,4-Diphenyl-1,2,3-triazole-5-carboxylic acid is easily soluble in cold acetone or in hot methanol or ethanol but insoluble in water.

**1,4-Diphenyl-1,2,3-triazole.**—A sample of recrystallized 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid (0.398 g., 0.00150 mole) was heated at 190° until the evolution of carbon dioxide was complete. The melt crystallized to give a quantitative yield (0.335 g.) of nearly colorless product, m.p. 185–185.5°. Recrystallization from hot acetone failed to alter the melting point. An analytical sample was obtained as colorless needles by recrystallization from hot benzene; m.p. 185–185.5°.

*Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.13; H, 5.27; N, 19.14.

1,4-Diphenyl-1,2,3-triazole is soluble in hot benzene, less soluble in hot acetone, and very sparingly soluble in hot methanol, ethanol, ether or ligroin.

**5-(1,5-Diphenyl-1,2,3-triazol-4-ylmethylene)-rhodanine.**—The rhodanine derivative was prepared from 6.23 g. (0.0250 mole) of 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde (m.p. 112–113°) in 93% yield (8.48 g.) following the usual procedure.[2] In this case it was found advantageous to carry out the reaction at steam-bath temperature rather than at reflux. Recrystallization from a large volume of hot benzene gave an analytical sample as tiny, yellow rods, m.p. 283–284°.

*Anal.* Calcd. for $C_{18}H_{12}N_4OS_2$: C, 59.32; H, 3.32; N, 15.37. Found: C, 59.52; H, 3.46; N, 15.44.

**1,5-Diphenyl-1,2,3-triazole-4-pyruvic Acid Oxime.**—Hydrolysis of 8.48 g. (0.0233 mole) of crude rhodanine derivative in the customary manner[2] afforded 7.84 g. of colorless thiopyruvic acid after drying under reduced pressure at room temperature. This crude intermediate was allowed to react with hydroxylamine in the usual manner.[2] The gummy mass which separated on acidification was entirely converted into tiny colorless crystals by stirring at room temperature for several days. After drying in a vacuum desiccator, the crude yield was 7.44 g. (99%).

This product was purified only with great difficulty. Digestion of 2.0 g. of crude product in 25 ml. of ethyl acetate at room temperature followed by separation of the insoluble fraction and re-digestion afforded 0.78 g. of material decomposing at 149°. An analytical sample decomposing at 155.5° was obtained as colorless needles after four recrystallizations from boiling absolute ethanol (13% over-all recovery).

*Anal.* Calcd. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.28; H, 4.35; N, 17.48.

**1,5-Diphenyl-1,2,3-triazole-4-acetonitrile.**—Addition of 3.22 g. (0.010 mole) of the crude pyruvic acid oxime to a mixture of 0.82 g. of fused sodium acetate in 10 ml. of acetic anhydride gave a vigorous reaction at 20–25°. After removing most of the solvent under reduced pressure, dilute sodium hydroxide was added to *p*H 9; and the resulting gummy mass was taken up in ether, washed with 0.1 *N* sodium hydroxide solution, and dried. Evaporation of the ether left a yellow crystalline solid weighing 1.55 g. (60%); m.p. 117.5–119.5°.

An analytical sample was obtained as colorless rods by successive recrystallization from benzene–petroleum ether, from hot benzene and from ether–petroleum ether; m.p. 119.5–120.5.

*Anal.* Calcd. for $C_{16}H_{12}N_4$: C, 73.82; H, 4.65; N, 21.53. Found: C, 73.79; H, 4.71; N, 21.61.

This nitrile is readily soluble in ethanol, less soluble in benzene or ether, and insoluble in petroleum ether.

**1,5-Diphenyl-1,2,3-triazole-4-ethylamine.**—The nitrile (1.30 g., 0.00500 mole) was hydrogenated by the general procedure,[2] and the resulting acetylated amine was hydrolyzed directly by heating under reflux for 8 hours with 2.5 *N* hydrochloric acid containing 10% glacial acetic acid. Attempted isolation in the customary manner afforded a hydrochloride of indefinite composition. For isolation as the base, an aqueous solution of the oil obtained by concentration was shaken with ether to remove non-basic material and then, after rendering strongly alkaline, was extracted with ether. Evaporation of the extracts left an oil which crystallized on scratching (0.84 g., 64%). An 84% recovery as colorless needles melting at 106–107° was obtained by recrystallization from 60 ml. of boiling ligroin.

A sample was prepared for analysis by sublimation at 0.01 mm. and 100° followed by recrystallization from ligroin; m.p. 106.5–107.5°.

*Anal.* Calcd. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.72, 73.10; H, 6.16, 6.29; N, 21.22.

**Addition of Phenyl Azide to Propiolaldehyde Diethyl Acetal.**—A mixture of 6.40 g. (0.0500 mole) of propiolaldehyde diethyl acetal,[2] 6.25 g. (0.0525 mole) of phenyl azide,[12] and 65 ml. of dry toluene was refluxed gently for 48 hours. The solvent was removed by cautious distillation under reduced pressure followed by addition of water and reconcentration. Hydrolysis of the acetal was accomplished by reflux with a mixture of 70 ml. of 1 *N* $H_2SO_4$ and 30 ml. of ethanol for 30 minutes. After charcoal treatment, the addition of 200 ml. of water to the yellow solution afforded **1-phenyl-1,2,3-triazole-4-carboxaldehyde** as cream-colored needles amounting to 4.50 g. (52%); m.p. 98–98.5°. Recrystallization from boiling ligroin gave an 85% recovery as colorless needles, m.p. 98.5–99.5° (reported,[6] 99–100°).

The isomeric **1-phenyl-1,2,3-triazole-5-carboxaldehyde** was obtained from the aqueous ethanolic mother liquors by concentration to a volume of 25 ml. The crude crystalline product which separated (2.58 g.) was recrystallized from 165 ml. of boiling ligroin and yielded 1.98 g. (23%) of colorless needles, m.p. 73–74°.

An analytical sample was obtained by recrystallization from cyclohexane to a constant melting point of 76.5–77°.

*Anal.* Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.55; H, 4.12; N, 24.25, 24.54.

1-Phenyl-1,2,3-triazole-5-carboxaldehyde is soluble in cold benzene, acetone, ethanol or chloroform; less soluble in hot water; and sparingly soluble in hot petroleum ether.

The identity of this triazolealdehyde was confirmed by oxidation to 1-phenyl-1,2,3-triazole-5-carboxylic acid by a procedure similar to that described above for 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid. The crude product obtained in 90% yield (m.p. 174° with decomposition), after recrystallization from aqueous ethanol, decomposed at 175.5° (reported,[15] 176°) and the cooled melt crystallized and remelted at 54.5–55° (reported melting point of 1-phenyl-1,2,3-triazole,[15] 56°).

**5-(1-Phenyl-1,2,3-triazol-4-ylmethylene)-rhodanine.**—From 4.33 g. (0.0250 mole) of recrystallized 1-phenyl-1,2,3-triazole-4-carboxaldehyde, 6.47 g. (90%) of the rhodanine derivative was obtained in the usual manner[2] except that the reaction was carried out at steam-bath temperature. Purification by washing with boiling acetone, then with ether, afforded an analytical sample as lemon-yellow needles.

*Anal.* Calcd. for $C_{12}H_8N_4OS_2$: C, 49.98; H, 2.80; N, 19.43. Found: C, 50.09; H, 3.07; N, 19.47.

**1-Phenyl-1,2,3-triazole-4-pyruvic Acid Oxime.**—Treatment of 6.47 g. (0.0224 mole) of the crude rhodanine derivative with alkali in the usual manner[2] led to 5.53 g. (100%) of the colorless thiopyruvic acid after drying under vacuum at room temperature. After refluxing this crude

(15) O. Dimroth, *Ber.*, **35**, 1034 (1902).

intermediate with an ethanolic solution of hydroxylamine in the customary manner, a mass of colorless rods separated from the reaction mixture and were removed by filtration; weight 5.31 g. Solution of this salt in 5% sodium hydroxide solution followed by acidification with hydrochloric acid led to the crystalline oximino acid which amounted to 4.53 g. (82%); m.p. 167° with evolution of gas.

An analytical sample was obtained as colorless clusters of needles by recrystallization from hot water followed by a wash of the dried crystals with boiling benzene; m.p. 166° with evolution of gas.

*Anal.* Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 54.04, 54.21; H, 4.10, 4.17; N, 23.06, 22.84.

**1-Phenyl-1,2,3-triazole-4-acetonitrile.**—The oximino acid (4.06 g., 0.0165 mole) was added to a chilled mixture of 1.35 g. of fused sodium acetate in 16.5 ml. of acetic anhydride. On allowing the temperature to rise, a vigorous reaction took place below 45°. After most of the solvent had been removed by concentration under reduced pressure, treatment with dilute sodium hydroxide solution to *p*H 8 gave 2.94 g. (97%) of colorless needles, m.p. 95.5–96.5°.

Recrystallization from a mixture of benzene and petroleum ether afforded an analytical sample melting at 95–96°.

*Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.49; H, 4.82; N, 30.70.

This nitrile is soluble in ethanol, acetone, benzene, and in hot water.

**1-Phenyl-1,2,3-triazole-4-ethylamine Dihydrochloride.**—Hydrogenation of the nitrile (2.76 g., 0.0150 mole) and subsequent hydrolysis of the product was carried out in the usual manner.[2] A quantitative yield (3.90 g.) of crystalline amine dihydrochloride was obtained by concentration of the aqueous solution; m.p. beginning at about 182° with slow evolution of gas. Recrystallization from methanol–ether gave a 73% recovery (2.86 g.) as colorless rods, m.p. 198° with slow evolution of gas; the melting point of this compound is difficult to reproduce as it varies over a 20° range depending on the rate of heating. A second recrystallization afforded an analytical sample with the same melting point when taken simultaneously.

*Anal.* Calcd. for $C_{10}H_{12}N_4 \cdot 2HCl$: C, 45.99; H, 5.40; N, 21.46. Found:[16] C, 46.27; H, 5.33; N, 21.62.

(16) Values corrected for 0.25% ash.

CAMBRIDGE 39, MASSACHUSETTS
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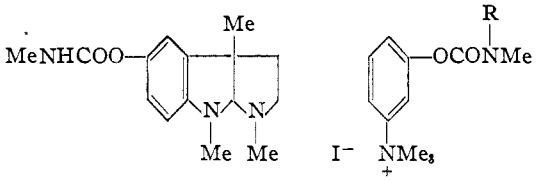
[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

# Some Derivatives of 3-Pyridol with Parasympathomimetic Properties[1]

BY H. M. WUEST AND E. H. SAKAL

The discovery by Stedman and his co-workers[2] that quaternary salts of the N-methylurethans of 3-dialkylaminophenols had physostigmine-like parasympathomimetic activity, opened the way to further synthetic work in the field by other investigators.



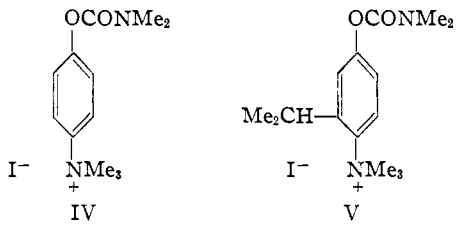
I



II, R = H
III, R = Me

Stedman's "meta" compound (II) was as unstable as physostigmine (I) in aqueous solution. This led Aeschlimann and Reinert[3] to produce a more stable derivative, such as III which, though somewhat less toxic than II, retained a high order of activity. Later, Stevens and Beutel[4] showed that the introduction of nuclear alkyl groups considerably increased the toxicity in mice of the comparatively inactive 4-dimethylaminophenol derivatives higher toxicity being due, presumably, to increased parasympathomimetic activity. Thus V was five hundred times more toxic than IV.

Recently, Haworth, Lamberton and Woodcock[5] applied the idea of nuclear alkylation to the 3-dimethylaminophenol series, synthesizing such compounds as the 4-methyl and the 2-methyl-5-isopropyl derivatives of II. Both these derivatives were found to be four times as toxic to mice as II.

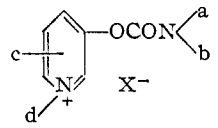


IV



V

The investigation described in the present communication was started with the object of preparing some derivatives of hydroxypyridines with parasympathomimetic activity of possible therapeutic usefulness. 3-Pyridol was selected as the key starting material and a number of derivatives were synthesized, using the general structure VI as a point of departure.



VI

Only two compounds related to this general class have been previously reported. In 1941 Stevens and Beutel[4] listed the dimethylcarbamate of 3-pyridol hydrochloride with its analysis, melting point and $LD_{50}$ in mice (120 mg./kg.) in a table featuring the hydrochlorides and methiodides of some substituted carbamic esters of dimethylaminophenol derivatives. The conspicuous absence, in the table, of the dimethylcarbamate of 3-pyridol methiodide attests the stubborn resistance to crystallization of a number of pyridinium salts of this type. More recently Haworth, Lamberton and Wood-

(1) Presented before the Division of Medicinal Chemistry at the 115th Meeting of the American Chemical Society, San Francisco, Calif., March 27–April 1, 1949.

(2) Stedman and co-workers, *Biochem. J.*, **20**, 719 (1926); *ibid.*, **21**, 1902 (1927); *ibid.*, **25**, 1147 (1931); *ibid.*, **26**, 1214 (1932); *Proc. Roy. Soc. (London)*, **121B**, 142 (1936).

(3) Aeschlimann and Reinert, *J. Pharmacol.*, **43**, 413 (1931).

(4) Stevens and Beutel, THIS JOURNAL, **63**, 308 (1941).

(5) Haworth, Lamberton ann Woodcock, *J. Chem. Soc.*, 182 (1947).