washed with 10 ml. of cold water, and dried to constant weight in a vacuum desiccator. The product was weighed and, in each instance, the melting point was determined.

The solubility of each of the anthracene derivatives was determined by putting a weighed quantity through the same procedure used in the cyclization, and determining the dissolved portion by difference. The solubilities varied from 195 mg. (20 ml.) for 9-ethylanthracene to 2 mg. (30 ml.) for 9,10-diphenylanthracene.

Preparation of Ketones.—All but three of the ketones employed in this study have been described previously. These three were prepared from *o*-benzylbenzonitrile[9,3] by the action of the following Grignard reagents in the following yields: *p*-fluorophenylmagnesium bromide (77%); *p*-tolylmagnesium bromide (38%); benzylmagnesium chloride (72%). Further details concerning these ketones and the new anthracene derivatives can be found in Table II.

Summary

The rates of cyclization of ten ketones and one aldehyde have been measured at 117.5°. The data suggest that steric factors as well as electronic effects may play an important part in determining the rate of cyclization.

DURHAM, N. C. RECEIVED NOVEMBER 1, 1948

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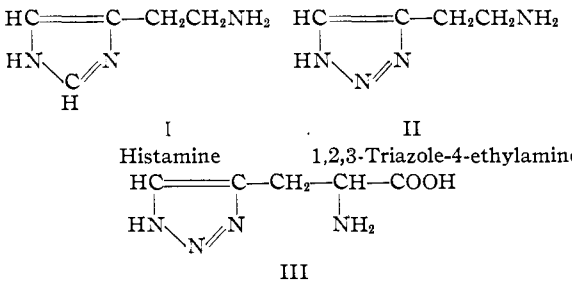
The Synthesis of Triazole Analogs of Histamine and Related Compounds

BY JOHN C. SHEEHAN AND CHARLES A. ROBINSON[1]

The concept of metabolite antagonism[2] has proved to be an especially profitable starting point for the synthesis of biologically active compounds. It is generally believed that close structural similarity is desirable in fashioning molecules as possible metabolite antagonists. Many of the powerful known antagonists differ only slightly in structure; for example, riboflavin and chloroflavin, thiamine and pyrithiamine, and adenine and benzimidazole. For this reason it seemed strange that in the case of antagonists to histamine, compounds with close structural similarity have been generally neglected in the wide search for antihistaminics. Since the triazole ring has been shown to be antagonistic to the imidazole ring in the cases of the triazole analogs of adenine and guanine,[3] the triazole analogs of histamine and histidine were synthesized.



I Histamine

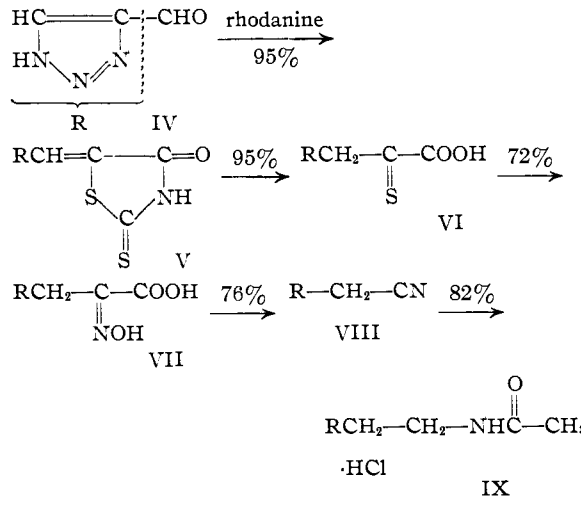
II 1,2,3-Triazole-4-ethylamine

III

α-Amino-1,2,3-triazole-4-propionic acid

The starting compound for the syntheses was 1,2,3-triazole-4-carboxaldehyde (IV), previously prepared by Hüttel[4] from propiolaldehyde and hydrazoic acid. Although the preparation of propiolaldehyde diethyl acetal from acrolein has been reported previously,[5] considerable difficulty was encountered until the modified procedure described in the Experimental Section was used. Extraction of the propiolaldehyde diethyl acetal with chloroform avoids the difficult separation of the azeotrope of this product and ethanol since chloroform does not extract ethanol from the aqueous solution. With this and other improvements a markedly higher over-all yield (50%) was obtained. The diethyl acetal was hydrolyzed and converted into 1,2,3-triazole-4-carboxaldehyde in 50% yield without isolation of the propiolaldehyde.

The synthesis of the nitrile (VIII) was accomplished by the rhodanine method,[6] analogous to the excellent procedure of Julian and Sturgis.[7]



R IV

V

VI

VII

VIII

IX

(1) Bristol Laboratories Fellow, 1947–1948.

(2) For reviews of metabolite antagonism, see R. O. Roblin, Jr., *Chem. Rev.*, **38**, 255 (1946), and D. W. Woolley, "Currents in Biochemical Research," edited by D. E. Green, Interscience Publishers, Inc., New York, N. Y., 1946, p. 357.

(3) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(4) R. Hüttel, *Ber.*, **74B**, 1680 (1941). Hüttel represented the triazole aldehyde as a 2,1,3-triazole. In order to show its relationship to histamine more clearly, we have chosen to use the tautomeric 1,2 3-triazole structure as in formula IV.

(5) L. Claisen, *Ber.*, **31**, 1010 (1898); **31**, 1021 (1898); **36**, 3664 (1903); **40**, 3907 (1907); F. Reitzenstein and G. Bönitsch, *J. prakt. Chem.*, **86**, 34 (1912); M. Grard, *Ann. chim.*, **13**, 337 (1930).

(6) C. Granacher, *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923).

(7) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

The rhodanine compound (V), prepared in 95% yield, was hydrolyzed to VI in 95% yield. On treatment with hydroxylamine this crude thioketo acid was converted into the oximino acid (VII) in 72% yield. Only one isomer of the oxime was isolated.

Recrystallization of the oxime gave an 88% recovery of analytically pure product. Decarboxylation and dehydration of VII by heating in acetic anhydride led to the recrystallized nitrile (VIII) in 76% yield regardless of whether crude or recrystallized oxime was used. In this reaction of acetic anhydride on VII, a by-product was detected by its brilliant blue ferric chloride test and was isolated in 1.5% yield by virtue of its water insolubility. Analysis indicates that this by-product is an acetyl derivative of the nitrile (VIII).

The nitrile (VIII) was hydrogenated by the general method of Carothers and Jones,[8] using acetic anhydride as a solvent with platinum oxide catalyst to yield the acetylated amine. The absorption of hydrogen stopped at the theoretical amount, indicating no tendency to hydrogenate the triazole ring under these conditions. The difficult purification of the acetylated amine as the base can be avoided by isolation of the pure hydrochloride (IX) in 82% yield. Hydrolysis of either the base or its hydrochloride (IX) to pure, crystalline 1,2,3-triazole-4-ethylamine dihydrochloride was quantitative. The free base (II) was obtained from the dihydrochloride by treatment with sodium ethoxide in ethanol. The amine dihydrochloride was reconverted into the acetylated amine by the Schotten–Baumann procedure using acetic anhydride, and the product was isolated as the pure hydrochloride (IX) in 76% yield.

N-Isopropyl-1,2,3-triazole-4-ethylamine was prepared in 82% yield from the amine (II) and acetone by a reductive alkylation procedure based on that of Hancock and Cope.[9]

N-Isopropylhistamine was prepared from histamine by the same reductive alkylation procedure. Since the base did not crystallize, it was converted into the pure dihydrochloride in 84% over-all yield. Due to the necessity for complete absence of histamine, the pharmacological sample was tested for primary amine using the sensitive nickel chloride and 5-nitrosalicylaldehyde test.[10] A negative test was obtained, whereas histamine produced a strong test.

A brief, slight blocking action against the arterial blood pressure response (dog) to histamine was observed with 1,2,3-triazole-4-ethylamine; the N-isopropyl derivative had no activity. N-Isopropylhistamine gave a typical histamine response, but it was only about $^1/_{30}$ as active as the parent compound.[11]

(8) W. H. Carothers and G. A. Jones, THIS JOURNAL, **47**, 3051 (1925).

(9) E. M. Hancock and A. C. Cope, "Organic Syntheses," Vol. 26, edited by H. Adkins, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 38.

(10) F. R. Duke, *Ind. Eng. Chem., Anal. Ed.*, **17**, 196 (1945).

(11) The pharmacological testing was done by Dr. Leo Dickinson and Mr. Justin Hoekstra of Bristol Laboratories, Syracuse, N. Y.

DL-α-Amino-1,2,3-triazole-4-propionic acid (III) was prepared by two independent routes. The catalytic hydrogenation of the oximino acid (VII) was extremely slow and the yield of the amino acid was small (17%). As an unambiguous method, the synthesis was also accomplished through the azlactone.

From 1,2,3-triazole-4-carboxaldehyde (IV), the crude azlactone was obtained (52%) as a mixture of a ring-acetylated azlactone and a small amount of the non-acetylated form which was separated through its insolubility in chloroform. The latter compound was readily converted into the former by acetylation. Purified samples of both forms gave α-benzamido-1,2,3-triazole-4-acrylic acid dihydrate on hydrolysis (86–88%). The yield of the acrylic acid dihydrate from the crude mixture of azlactones was 85%. α-Benzamido-1,2,3-triazole-4-propionic acid was obtained in 61% yield by hydrogenation of the acrylic acid in glacial acetic acid using platinum oxide. Hydrolysis of this benzamido acid gave analytically pure DL-α-amino-1,2,3-triazole-4-propionic acid (III) in 51% yield; this compound had the same decomposition point and the same properties as the product from the hydrogenation of VII.

Experimental[12]

Propiolaldehyde Diethyl Acetal.—α,β-Dibromopropionaldehyde diethyl acetal was prepared in 79% yield from acrolein following essentially the procedure of Grard[5] except that the crude α,β-dibromopropionaldehyde was used without distillation while the diethyl acetal was distilled at 108–110° (10 mm.) before the next step.

To a solution of 35 g. (0.625 mole) of potassium hydroxide pellets in 240 ml. of absolute ethanol was added in a thin stream with good stirring 72.5 g. (0.250 mole) of α,β-dibromopropionaldehyde diethyl acetal, allowing the temperature to rise to 50–55°. After cooling to 10°, the potassium bromide was removed by filtration and washed well with 40 ml. of absolute ethanol. The dried potassium bromide amounted to 30 g. (100% of theory for one molecular equivalent). The combined filtrate and washes was refluxed for two and one-half hours. After cooling to 20°, the pale yellow solution containing crystallized potassium bromide was poured into 2 l. of water and extracted three times with 235 ml. of chloroform. The extracts were washed twice with 20 ml. of water and dried over anhydrous magnesium sulfate.

After removal of chloroform by distillation through a short Vigreux column at atmospheric pressure, the residue was fractionated using an eighteen-inch Fenske column. The fraction distilling at 138–139.5° amounted to 20.3 g. (63%) and remained colorless on storing at 5°. Grard[5] reported a boiling point of 137–141°.

1,2,3-Triazole-4-carboxaldehyde (IV).[13]—A mixture of 32.7 g. (0.255 mole) of propiolaldehyde diethyl acetal and 50 ml. of 0.2 *N* sulfuric acid containing 100 mg. of hydroquinone was heated on a steam-bath under a reflux condenser with frequent shaking. The two-phase mixture gradually became homogeneous. Reflux was continued until the solution remained homogeneous on cooling to 15°; a total of forty-five minutes heating was required. After cooling, 16 g. of ammonium sulfate was added and the red oil was separated. The aqueous layer was extracted with 40 ml. of ether and the combined oil

(12) All melting points are corrected.

(13) Due to a marked tendency for polymerization of the propiolaldehyde, sufficient time must be available to complete this step without interruption.

and extracts was dried over anhydrous sodium sulfate for thirty minutes.

After removing the desiccant the propiolaldehyde–ether–ethanol mixture was distilled until the vapor reached 75°. Additional product remaining in the high-boiling residue was removed by twice adding anhydrous ether and again distilling to 80°. The total distillate was immediately added to 0.19 mole of a titrated hydrazoic acid–ether solution prepared by method B of Audrieth and Gibbs.[14] Heat of reaction caused gentle reflux, after which the solution was allowed to stand at room temperature overnight. The solvent and excess hydrazoic acid were removed by cautious distillation, leaving a colorless crystalline product which amounted to 12.5 g. (50%) after thorough drying; m. p. 141–142°. Hüttel[4] reported a melting point of 141–142° for this compound.

5-(1,2,3-Triazolyl-4-methylene)-rhodanine (V).—To a hot solution of 23.3 g. (0.240 mole) of 1,2,3-triazole-4-carboxaldehyde and 32.0 g. (0.240 mole) of rhodanine in 210 ml. of glacial acetic acid, 59.8 g. of freshly fused sodium acetate was added. With frequent shaking, the mixture was refluxed for twenty minutes during which time a bright yellow product separated. After cooling and slurrying with 700 ml. of water, the product was removed by filtration and washed well with water, then with acetone until the filtrate was clear, and finally with ether. The dried product weighed 48.5 g. (95%) and did not melt below 300°. This compound is insoluble in all common organic solvents. An analytical sample was prepared by solution in 0.2 *N* ammonium hydroxide followed by acidification to give yellow needles.

Anal. Calcd. for $C_6H_4N_4OS_2$: C, 33.95; H, 1.90; N, 26.40. Found: C, 33.69; H, 2.09; N, 26.48.

1,2,3-Triazole-4-thiopyruvic Acid (VI).—A solution of 48.5 g. (0.228 mole) of the crude triazole–rhodanine compound (V) in 238 ml. of 15% sodium hydroxide solution was heated on a steam-bath at 88–92° for twenty minutes with occasional shaking. The chilled solution was added in a thin stream with rapid stirring to an excess of 2.5 *N* hydrochloric acid (368 ml.), maintaining the temperature below 10°. After being stirred for one-half hour in an ice-bath, the cream-colored product was collected, washed with ice-water, and carefully dried at slightly above room temperature. The yield of material decomposing at 157° with gas evolution was 37.1 g. (95%). This product was non-crystalline and has not been further purified. With ferric chloride it gave a brilliant green coloration.

1,2,3-Triazole-4-pyruvic Acid Oxime (VII).—Hydroxylamine was prepared by dissolving 20.8 g. (0.30 mole) of hydroxylamine hydrochloride in 18.4 ml. of warm water and adding sodium ethoxide solution prepared from 6.88 g. (0.30 mole) of sodium in 200 ml. of ethanol. The sodium chloride was removed by filtration and washed with 22 ml. of ethanol. To this solution 17.1 g. (0.10 mole) of the crude thioketo acid (VI) was added and the solution was refluxed gently for twenty minutes; at the end of this time the evolution of hydrogen sulfide had ceased. After removing the solvent under reduced pressure, the residual thick sirup was dissolved in 86 ml. of 5% sodium hydroxide solution, filtered and acidified to *p*H 1 with 2.5 *N* hydrochloric acid; on scratching an immediate crystallization began. After allowing several hours for crystallization, the pale yellow crystals were removed by filtration, washed with ice-water, and dried at 55°. The product decomposing at 168° with gas evolution amounted to 12.2 g. (72%).

Recrystallization of a sample of this material from twelve volumes of hot water gave glistening pale yellow flakes in 88% recovery, m. p. 169° with decomposition.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.30; H, 3.56; N, 32.93. Found: C, 35.41; H, 3.76; N, 32.82.

This compound is slightly soluble in ethanol and nearly insoluble in acetone, ether, benzene or cold water.

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

1,2,3-Triazole-4-acetonitrile (VIII).—A suspension of 5.1 g. (0.030 mole) of the crude oximino acid (VII) (finely powdered) in 30 ml. of acetic anhydride was heated to 80–85° in an oil-bath; a vigorous evolution of gas ensued and the heat of reaction occasionally necessitated removing the flask from the bath. After thirty minutes at 80–85°, the material had completely dissolved and gas evolution ceased. The pale orange solution was concentrated under reduced pressure in a 60° bath until no more acetic anhydride distilled. With stirring and cooling to 20°, 2.5 *N* sodium hydroxide solution was added until all the residual acetic anhydride had decomposed; the *p*H was adjusted to 6.

The nitrile was extracted to completion with ether, adjusting the *p*H to 6 as necessary between extractions. The nitrile is incompletely extracted from more basic or more acidic solutions. Removal of ether from the dried extracts left a colorless crystalline mass which was dried to constant weight under reduced pressure, giving a crude yield of 3.1 g. (96%); m. p. 78–85°. The crude product, recrystallized from absolute ethanol–chloroform, gave a recovery of colorless crystals of 2.47 g. (80%) or a yield of 76% including second crops; all crops melted between 89 and 91°. An analytical sample recrystallized from hot benzene was obtained as beautiful colorless needles melting at 91–91.5°.

Anal. Calcd. for $C_4H_4N_4$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.79; H, 3.85; N, 52.09.

1,2,3-Triazole-4-acetonitrile is readily soluble in water, ethanol, acetone or ether.

A by-product was isolated from the aqueous mother liquors by adjusting the *p*H to 5 and extracting with ether. The product obtained by evaporating the ether was washed well with cold water to remove traces of the nitrile (VIII) and then dried at 65°. The pale yellow product weighed 0.065 g.; m. p. 212° with evolution of gas. Two recrystallizations from hot water gave a good recovery of tiny, nearly colorless crystals decomposing at 214°.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32; mol. wt., 150.14. Found: C, 48.00; H, 4.28; N, 37.67; mol. wt., 144 (Rast).

This acetylated by-product produces a brilliant blue coloration with ferric chloride solution.

N-Acetyl-1,2,3-triazole-4-ethylamine Hydrochloride (IX).—A solution of 1.95 g. (0.0180 mole) of the recrystallized nitrile (VIII) in 25 ml. of acetic anhydride was shaken under hydrogen with 0.30 g. of platinum oxide. After nine hours the theoretical amount of hydrogen had been taken up and no more was absorbed on further shaking. After removing the catalyst by filtration, the solution was treated with just sufficient water to decompose the excess acetic anhydride. The pale yellow solution was concentrated to an oil under reduced pressure, and the residue was twice dissolved in absolute ethanol and reconcentrated to dryness.

The hydrochloride was formed by dissolving the oil in 10 ml. of absolute ethanol and adding 6 *N* ethanolic hydrogen chloride in slight excess. On the addition of 40 ml. of absolute ether to the clear solution a colorless product crystallized. The yield of dried material melting with decomposition at 166–166.5° was 2.80 g. (82%). An analytical sample recrystallized from ethanol–acetone was obtained as tiny colorless crystals; m. p. 166–166.5° with decomposition.

Anal. Calcd. for $C_6H_{11}N_4OCl$: C, 37.79; H, 5.82; N, 29.39. Found: C, 37.90; H, 5.87; N, 29.58.

N-Acetyl-1,2,3-triazole-4-ethylamine.—The nitrile (VIII) (0.54 g., 0.0050 mole) was hydrogenated as described above in the preparation of the hydrochloride (IX). The oil obtained after concentration of the acetic anhydride was dissolved in 5 ml. of water and extracted with 15 ml. of *n*-butanol. The extracts were treated with charcoal and concentrated to a colorless oil under reduced pressure. After dissolving in ethyl acetate and again concentrating, the oil crystallized giving a slightly sticky product. This was dissolved in 35 ml. of hot ethyl ace-

tate and filtered to remove an oily residue; on concentration, 0.63 g. (82%) of crystalline product melting at 65–76° was obtained.

A sample of this crude material was purified by sublimation at 0.002 mm. and 125° (m. p. 76–82°) followed by two recrystallizations from ethyl acetate–ether to give a pure crystalline product melting at 81–82°.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.48; H, 6.53; N, 36.34.

This compound is soluble in water, absolute ethanol, acetone and in hot ethyl acetate; it is nearly insoluble in ether or benzene.

1,2,3-Triazole-4-ethylamine Dihydrochloride.—Hydrolysis of 2.29 g. (0.0120 mole) of the recrystallized N-acetylamine hydrochloride (IX) was accomplished by reflux with 119 ml. of 2.5 *N* hydrochloric acid for three hours. The colorless solution was concentrated under reduced pressure giving a mass of rosettes. After drying to constant weight, the yield was quantitative (2.22 g.); m. p. 181–182° with decomposition. Recrystallization from absolute methanol–ether gave a 92% recovery (2.03 g.); m. p. 185–186° with decomposition. A second recrystallization failed to alter the melting point.

Hydrolysis of the N-acetylamine base (m. p. 65–76°), in a similar manner, gave a quantitative yield of the dihydrochloride. In this case the product was twice recrystallized from 97% ethanol–acetone giving colorless rosettes, m. p. 179–180° with decomposition.

Anal. Calcd. for $C_4H_{10}N_4Cl_2$: C, 25.95; H, 5.45; N, 30.27. Found: C, 25.81; H, 5.47; N, 30.50.

It appears that the melting point of this compound depends on the solvent from which it crystallizes; the higher melting product (185–186°) from methanol–ether on crystallizing again from water gave the lower melting point (181–182°).

1,2,3-Triazole-4-ethylamine (II).—A solution of 1.50 g. (0.00810 mole) of 1,2,3-triazole-4-ethylamine dihydrochloride (m. p. 181–182° dec.) in 36 ml. of warm 97% aqueous ethanol was added to a solution of sodium ethoxide prepared from 0.373 g. (0.0162 mole) of sodium in 12 ml. of absolute ethanol. After fifteen minutes at 20°, the crystallized sodium chloride was removed by filtration and washed with absolute ethanol. The colorless filtrate was concentrated under reduced pressure to a crystalline solid weighing 0.96 g. (105%). This crude material was freed from sodium chloride by dissolving in 25 ml. of hot absolute ethanol, removing the inorganic salts by filtration, and evaporating the solvent under reduced pressure. The yield of crystalline, halogen-free product was quantitative (0.91 g.); m. p. 154–155.5°. This product can be further purified by recrystallization from hot absolute ethanol.

An analytical sample was prepared by sublimation of a portion at 0.05 mm. and 100°; m. p. 157.5–159°.

Anal. Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 42.50; H, 7.07; N, 50.40.

1,2,3-Triazole-4-ethylamine is soluble in water and in hot absolute ethanol; it is nearly insoluble in ether, acetone, ethyl acetate or chloroform.

N-Isopropyl-1,2,3-triazole-4-ethylamine.—In a micro-hydrogenator, 100 mg. of platinum oxide in 5 ml. of absolute ethanol was pre-reduced. Then, 0.628 g. (0.0056 mole) of the crude amine (II) (m. p. 154–155.5°) in 7 ml. of absolute ethanol, 0.52 ml. (0.0071 mole) of acetone, and one drop of water to effect complete solution were added, and the solution was stirred under hydrogen at atmospheric pressure. The rate of hydrogenation dropped sharply when the theoretical amount of hydrogen had been absorbed (3.8 hours). After removal of the catalyst, the filtrate was concentrated to a colorless crystalline solid weighing 0.84 g. (97%); m. p. 136–138°.

Recrystallization from seven volumes of hot absolute ethanol gave a 72% recovery of crystals melting at 142.5–144°. A second recrystallization from methyl ethyl ketone gave beautiful, colorless crystals; m. p. 143–144°.

Anal. Calcd. for $C_7H_{14}N_4$: C, 54.52; H, 9.15; N, 36.33. Found: C, 54.58; H, 9.28; N 35.81.

Second crops from the recrystallizations increased the recovery of pure product to 0.707 g. (82%).

This compound is soluble in water, slightly soluble in cold absolute ethanol and soluble in hot acetone; it is nearly insoluble in ether or benzene.

N-Isopropyl-4-imidazoleëthylamine Dihydrochloride.—In a micro-hydrogenator, 50 mg. of platinum oxide in 5 ml. of absolute ethanol was pre-reduced. To this, 0.222 g. (0.0020 mole) of histamine (Eastman Kodak Co., Synthetic) in 5 ml. of absolute ethanol and 0.25 ml. (0.0034 mole) of acetone were added, and the solution was stirred under hydrogen at atmospheric pressure. The rate of hydrogenation dropped sharply when the theoretical amount of hydrogen had been absorbed (four hours). After removing the catalyst, the colorless filtrate was concentrated to an oil weighing 0.33 g. (108%).

This free base did not crystallize even after evaporative distillation of a sample at 0.001 mm. and 70° and refrigeration for several weeks. The remainder of the crude base (0.20 g. containing 0.00121 mole) was converted into the dihydrochloride by dissolving in 5 ml. of acetone and adding 6 *N* ethanolic hydrogen chloride in slight excess. After collecting the crystals and drying in a desiccator, the colorless product weighed 0.26 g. (95%); m. p. 185–193°. Recrystallization of 0.25 g. of the crude dihydrochloride from absolute ethanol–ethyl acetate gave a 62% recovery of product melting at 197–198°. From the mother liquors a second crop melting at 195–196° gave a total recovery of 0.220 g. (83% over-all yield).

An analytical sample was prepared by a second recrystallization of the first crop; m. p. 197.5–199°.

Anal. Calcd. for $C_8H_{17}N_3Cl_2$: C, 42.48; H, 7.58; N, 18.58. Found: C, 42.58; H, 7.74; N, 18.81.

Condensation of 1,2,3-Triazole-4-carboxaldehyde with Hippuric Acid.—A mixture of 4.30 g. (0.024 mole) of hippuric acid, 8.6 ml. of acetic anhydride and one drop of triethylamine was heated rapidly with stirring in a vessel protected from moisture until there was complete solution (110°). To the orange-colored solution cooled to 60°, 1.94 g. (0.020 mole) of 1,2,3-triazole-4-carboxaldehyde and 3.0 ml. of glacial acetic acid were added, and the solution was heated at 60 ± 3° in an oil-bath for two hours. Lemon-yellow needles began to crystallize after thirty-five minutes of heating. After allowing fifteen hours at room temperature for crystallization, the needles were collected, washed with 5 ml. of glacial acetic acid, and dried at 70°. The product amounted to 2.93 g. (52%); m. p. 161–164°.

This crude mixture was washed with boiling water to remove excess hippuric acid and the dried product (2.40 g.) was slurried with 20 ml. of chloroform and the insoluble, non-acetylated azlactone was removed by filtration. The addition of ether to the filtrate gave lemon-yellow crystals (1.63 g.); m. p. 181–182.5°. Further recrystallizations from chloroform–ether gave an analytical sample of the ring-acetylated azlactone of α-benzamido-1,2,3-triazole-4-acrylic acid; m. p. 181.5–182.5°.

Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.42; H, 3.65; N, 20.16.

The chloroform-insoluble fraction from the purification of the ring-acetylated azlactone amounted to 0.250 g. and decomposed at 219°. After three recrystallizations from methanol–water, an analytical sample of the azlactone of α-benzamido-1,2,3-triazole-4-acrylic acid was obtained as pale yellow needles decomposing at 223°.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.95; H, 3.59; N, 23.34.

α-Benzamido-1,2,3-triazole-4-acrylic Acid.—A suspension of 3.0 g. of the crude mixture of azlactones in 250 ml. of 0.25 *N* sodium hydroxide solution was rapidly heated to boiling. After boiling for a few seconds, the clear solution, cooled in ice, was made strongly acid with 50 ml. of 2.5 *N* hydrochloric acid. Crystallization as tiny cubes began on scratching. After one hour at 0–5° the cream-colored product was removed by filtration, washed with cold water, and dried in a desiccator over Drierite. The product, obtained as the dihydrate, weighed 2.66 g. (85%);

m. p. 187° with decomposition (capillary inserted at 110°). Two recrystallizations from hot water gave colorless crystals which were dried in a desiccator over Drierite; m. p. 189° with decomposition (capillary inserted at 110°).

Anal. Calcd. for $C_{12}H_{10}N_4O_3 \cdot 2H_2O$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.01; H, 5.00; N, 19.39.

On drying at 75–85° the dihydrate loses two molecules of water. The dihydrate is soluble in acetone, ethanol or hot water.

DL-α-Benzamido-1,2,3-triazole-4-propionic Acid.—In a micro-hydrogenator, 200 mg. of platinum oxide in 7 ml. of glacial acetic acid was pre-reduced. Then, 0.553 g. (0.00188 mole) of crude α-benzamido-1,2,3-triazole-4-acrylic acid dihydrate and 5 ml. of glacial acetic acid were added, and the solution was stirred under hydrogen at atmospheric pressure. During the hydrogenation an addition of 100 mg. of platinum oxide was made to maintain the rate. When the theoretical amount of hydrogen had been absorbed, the reaction was stopped and the catalyst removed. Concentration of the filtrate under reduced pressure gave an oil which crystallized on adding water. The gray product which was removed by filtration and dried at 65° weighed 0.390 g. (79%); m. p. 206–208° with decomposition.

The crude product (0.39 g.) was recrystallized from 18 ml. of hot water, yielding 0.30 g. (61%) of colorless crystals; m. p. 217.5–218.5° with decomposition. An analytical sample was prepared by a second recrystallization from hot water; m. p. 219–220° with decomposition.

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.12; H, 4.88; N, 21.24.

This compound is soluble in absolute ethanol and insoluble in ether or acetone.

DL-α-Amino-1,2,3-triazole-4-propionic Acid (III). A. Hydrolysis of the Benzoyl Compound.—Hydrolysis of 0.78 g. (0.0030 mole) of α-benzamido-1,2,3-triazole-4-propionic acid was accomplished by reflux for six hours with 20 ml. of 2.5 *N* hydrochloric acid. After ether extraction and charcoal treatment, the aqueous solution was concentrated under reduced pressure to a colorless oil which was twice dissolved in water and reconcentrated to dryness (wt. 0.56 g., 97%). Aniline was added to a warm solution of the oil in 10 ml. of absolute ethanol until the *p*H was 4–5. After twelve hours at room temperature, the crystalline amino acid was collected, washed with absolute ethanol and ether, giving 0.29 g. (62%) of product decomposing with gas evolution at 260°.

The crude product on recrystallization from water–ethanol gave 0.24 g. (51%) of tiny, colorless crystals decomposing at 266°. A second recrystallization failed to alter the decomposition point.

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.36; H, 5.38; N, 35.71.

This compound is moderately soluble in cold water and soluble in hot; it is insoluble in absolute ethanol or ether.

B. Hydrogenation of VII.—After pre-treatment of 0.460 g. (0.0027 mole) of recrystallized oximino acid (VII) in absolute ethanol with Raney nickel catalyst, 0.0028 mole of ethanolic hydrogen chloride was added and the solution was stirred with 200 mg. of platinum oxide in a micro-hydrogenator under hydrogen at atmospheric pressure. After seven days the theoretical amount of hydrogen had been absorbed. The solution, from which the catalyst had been removed, was concentrated to dryness under reduced pressure, dissolved in water, filtered, and again concentrated to a brittle, tan solid weighing 0.55 g. After recrystallization from ethanol–ethyl acetate and water–acetone, the crystalline hydrochloride amounted to 0.14 g. and decomposed at 219°.

Without further purification, 0.040 g. of the hydrochloride was treated with the calculated amount of dilute ammonium hydroxide and the solution concentrated to dryness under reduced pressure. Solution of the residue in hot water and the addition of two volumes of ethanol produced colorless crystals. After washing with aqueous ethanol (1:1) and drying at 65°, the amino acid decomposed at 266° and weighed 0.020 g. (17% from VII).

Summary

1,2,3-Triazole-4-ethylamine and DL-α-amino-1,2,3-triazole-4-propionic acid, the triazole analogs of histamine and histidine, as well as N-isopropyl-1,2,3-triazole-4-ethylamine and N-isopropylhistamine have been synthesized for pharmacological study.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. VIII. The Synthesis of an Amino Alcohol Derived from 2,4-Quinazolinedione-5-carboxylic Acid[1]

BY C. H. WANG AND BERT E. CHRISTENSEN

Methods for the synthesis of 2,4-dimethylquinazoline derivatives with an acetyl-substituent in the 7- and 8-positions have recently been described.[2,3] The 5-isomer, however, could not be synthesized by these procedures due to the difficulties encountered in the attempted preparation of the necessary intermediate 3-acetamino-1,2-diacetylbenzene or 3-acetamino-2-acetylbenzoic acid required for the cyclization.[4]

Since it would be useful to this Laboratory to have a quinazoline compound with an amino alcohol substituent in the 5-position, the possibility of utilizing the easily prepared 2,4-quinazolinedione-5-carboxylic acid (I) as the starting material (see Fig. 1) was studied. This intermediate was converted to the acyl chloride (II), which upon treatment with diazomethane formed the diazoketone and at the same time was simultaneously methylated in the 1,3-positions to yield 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III). This diazoketone upon treatment with dry hydrogen bromide gas was converted to the bromomethyl ketone (IV); however, one of the methyl substituents (either 1 or 3) was lost in the process.

The bromoacetyl derivative (IV) readily combined with morpholine to yield an aminoketone

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(2) Christensen, Graham and Griffith, THIS JOURNAL, **67**, 2001 (1945).

(3) Isensee and Christensen, *ibid.*, **70**, 4061 (1948).

(4) Wang, Isensee, Griffith and Christensen, *ibid.*, **69**, 1909 (1947).