146.4 g. (77%); $n^{20}D$ 1.4642; d^{25}_4 1.011; $[\alpha]^{26}D$ +25.8° (no solvent).

Anal. Calcd. for $C_{13}H_{23}ClO_2$: C, 63.30; H, 9.39. Found: C, 63.55; H, 9.60.

l-Menthyl Acrylate.—A mixture of 30 g. of *l*-menthyl β-chloropropionate and 66 g. of quinoline was heated for three hours at a bath temperature of 170–180°. Crystalline quinoline hydrochloride separated from the reaction mixture on cooling. One hundred cubic centimeters of benzene was added and the solution was extracted with three 100-cc. portions of water and five 60-cc. portions of 50% sulfuric acid. It was then washed with ten 50-cc. portions of water, in order to remove the last traces of quinoline salts.

The dark oily solution was fractionally distilled through a modified Widmer column and 10.2 g. (39.5%) of product boiling at 64–67° (3 mm.) was obtained. This was redistilled at 78–80° (5 mm.); $n^{20}D$ 1.4628; d^{20}_4 0.927; $[\alpha]^{28}D$ −80.2° (1.002 g. in 10 cc. of dioxane solution).

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.29; H, 10.55. Found: C, 74.53; H, 10.57.

Isolation of Polymers.—The collected washings from all the polarimeter tubes containing 1:1 ethyl acrylate and *l*-monomenthyl maleate were evaporated nearly to dryness and the viscous mixture was dissolved in 50 cc. of methanol. This was poured into 100 cc. of water and the mixture became milky. Polymer droplets adhered to the sides of the beaker and the milky supernatant liquid was poured off. This procedure was repeated and the polymer was then dried overnight at 70°. The result was a clear, light yellow, tacky plastic mass, $[\alpha]^{55}D$ −29.2° (0.0992 g. in 5 cc. of dioxane solution).

Anal. Found: C, 63.15; H, 8.39.

The contents of the two polarimeter tubes used in the experiments described in Fig. 2 (two parts maleate and one part acrylate) were washed into a beaker with dioxane. Water was added and the polymer separated as an oil which stuck to the bottom and sides of the beaker. The milky supernatant liquid was poured off. This procedure was repeated once with dioxane and once with acetone, in which the polymer was soluble. The polymer was then dried overnight at 70°, yielding a clear, amber, brittle resin (0.4 g.); $[\alpha]^{55}D$ −39.5° (0.1030 g. in 5 cc. of dioxane solution).

Anal. Found: C, 64.42, 64.48; H, 8.55, 8.57.

Summary

Some preliminary kinetic studies on mixtures of ethyl acrylate and *l*-monomenthyl maleate and of ethyl maleate and *l*-menthyl acrylate have been recorded. Evidence that *l*-monomenthyl maleate reacts with benzoyl peroxide to give a non-polymeric product has been reported.

URBANA, ILLINOIS RECEIVED MARCH 11, 1942

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY. NO. 882]

The Synthesis of the Three Isomeric *dl*-β-Pyridylalanines

BY CARL NIEMANN, RICHARD N. LEWIS AND JOHN T. HAYS

The knowledge that the known α-amino acids containing heterocyclic ring systems are intimately associated with a number of important biological processes[1] has led us to consider the chemical and physiological properties of α-amino acids containing the pyridine nucleus, a heterocyclic ring system which, to date, has not been found in any naturally occurring α-amino acid,[2] but which is present in other compounds isolated from natural sources.[1,4] In this communication we wish to describe the synthesis of *dl*-β-(2-pyridyl)-alanine, *dl*-β-(3-pyridyl)-alanine, and *dl*-β-(4-pyridyl)-alanine, and to record some of the properties of these amino acids.

Overhoff, Boeke and Gorter,[5] starting with (2-pyridyl)-methyl chloride, prepared *dl*-β-(2-pyridyl)-alanine *via* the phthalimidomalonic ester synthesis of Sörensen.[6] The authors also reported that all attempts to prepare the amino acid from β-(2-pyridyl)-α-chloropropionic acid or from picolinaldehyde were unsuccessful. Our experiences have been similar to those described above, but we have found that *dl*-β-(2-pyridyl)-alanine can be prepared in considerably better yield than that reported by Overhoff, Boeke and Gorter[5] by substituting the benzamidomalonic ester synthesis of Redemann and Dunn[7] for the procedure of Sörensen.[6] The failure of picolinaldehyde to condense with hippuric acid[5] or with diketopiperazine in the desired fashion is not due to a lack of reac-

(1) M. Guggenheim, "Die biogenen Amine," S. Karger, Basel, 1940.

(2) It has been suggested[3] that the compound mimosine, obtained from the leaves of *Mimosa pudica*, is a dihydroxypyridylalanine, but this characterization has not been confirmed.

(3) (a) H. Nienburg and K. Tauböck, *Z. physiol. Chem.*, **250**, 80 (1937); (b) J. Renz, *ibid.*, **244**, 153 (1936).

(4) T. A. Henry, "The Plant Alkaloids," 3rd edition, Blakiston's Sons, Philadelphia, Pa., 1939.

(5) J. Overhoff, J. Boeke and A. Gorter, *Rec. trav. chim.*, **55**, 293 (1936).

(6) S. P. L. Sörensen, *Z. physiol. Chem.*, **44**, 448 (1905).

(7) C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

tivity, but rather to side reactions which lead to loss of aldehyde through tar formation. It appears that those aldehydes which undergo condensation with derivatives of glycine, to form azlactones or analogous compounds, in satisfactory yields are aldehydes in which additional stabilization is brought about by the possibility of resonance among excited structures.[8]

A comparison of the various structures that can be written for nicotinaldehyde and for picolinaldehyde[8,9] leads one to the conclusion that nicotinaldehyde has the greater resonance energy and consequently more closely resembles the aromatic aldehydes than does picolinaldehyde. One would therefore expect that nicotinaldehyde could be converted into *dl*-β-(3-pyridyl)-alanine by the Erlenmeyer procedure,[10] or modifications thereof.[11] This expectation was realized when it was found that nicotinaldehyde readily condenses with hippuric acid, diketopiperazine, hydantoin, thiohydantoin, and acetylthiohydantoin. Since the azlactone is not readily purified and the hydantoins are not readily hydrolyzed, the amino acid was prepared from the diketopiperazine-nicotinaldehyde condensation product by the method of Sasaki.[12]

The condensation of (4-pyridyl)-methyl bromide hydrobromide with benzamidomalonic ester[7] was not very satisfactory but hydrolysis of the small amount of condensation product that was obtained gave *dl*-β-(4-pyridyl)-alanine.

During this investigation we attempted to prepare the three isomeric pyridylaldehydes from the corresponding pyridine monocarboxylic acids by the method of McFadyen and Stevens.[13] In the case of nicotinic acid and picolinic acid the method proved to be satisfactory but when applied to isonicotinic acid only traces of isonicotinaldehyde were obtained. McFadyen and Stevens[13] found that *p*-nitrobenzoic acid could not be converted into *p*-nitrobenzaldehyde by their procedure although *m*-nitrobenzaldehyde was readily obtained from *m*-nitrobenzoic acid. Our observation of the difference in the behavior of nicotinic acid and isonicotinic acid in the McFadyen–Stevens reaction provides still another example of the parallel behavior of derivatives of pyridine and nitrobenzene.[9,14] The conversion of picolinic acid to picolinaldehyde by the McFadyen–Stevens reaction cannot be taken as an exception to the above generalization because with picolinic benzenesulfonhydrazide there is an excellent possibility that an intramolecular hydrogen bond is formed between the pyridine nitrogen atom and one of the nitrogen atoms present in the side chain thereby causing a decided structural modification which would preclude any direct comparison of the behavior of the alpha and gamma compounds.

A preliminary determination of the apparent dissociation constants[11] of the three isomeric *dl*-β-pyridylalanines[15] led to results which may be interpreted as follows. Considering first the zwitterionic structures, one would expect that in all of the amino acids the positively charged ammonium nitrogen atom would try to get as close as is structurally possible to the negatively charged pyridine nitrogen atom. In the case of *dl*-β-(2-pyridyl)-alanine this tendency would lead to the formation of a strong intramolecular hydrogen bond between the ammonium nitrogen atom and the pyridine nitrogen atom. It is obvious that this situation makes it difficult to add a proton to the pyridine nitrogen atom or to remove one from the ammonium nitrogen atom. Therefore one would predict that the pyridine nucleus, in all three *dl*-β-pyridylalanines, would be less basic than pyridine, and that the basicity of the pyridine nucleus would increase as the amino acid side chain is shifted progressively from the 2 to the 4 position with the greatest increment accompanying the shift from the 2 to the 3 position. The observed apparent basic dissociation constants ascribable to the pyridine nucleus are generally in accord with these predictions. Similarly the observed apparent acid dissociation constants are compatible with the idea that it is more difficult to remove a proton from the ammonium nitrogen atom in *dl*-β-(2-pyridyl)-alanine than in *dl*-β-(3-pyridyl)-alanine. However, they also show that the amino group is less basic in these amino acids than in the simple monoamino-monocarboxylic acids. The observed values for the second apparent basic dissociation constants

(8) L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1940.

(9) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

(10) (a) E. Erlenmeyer, Jr., *Ann.*, **271**, 137 (1892); (b) *ibid.*, **275**, 1 (1893).

(11) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," C. C. Thomas, Springfield, Ill., 1938.

(12) T. Sasaki, *Ber.*, **54**, 163 (1921).

(13) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

(14) (a) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, New York, 1937, pp. 522–523; (b) C. Naegeli, W. Kündig and H. Brandenburger, *Helv. Chim. Acta*, **22**, 912 (1939).

(15) In the case of *dl*-β-(4-pyridyl)-alanine a complete titration curve was not determined because of the small amount of amino acid available.

of *dl*-β-(2-pyridyl)-alanine and *dl*-β-(3-pyridyl)-alanine make it clear that the carboxyl group is more acidic in the case of the *dl*-β-pyridylalanines than in the case of the simple monoamino-monocarboxylic acids. This increase in acid strength as well as the decrease in basic strength of the amino group can be explained in terms of the inductive effect of the pyridine nucleus. Summing all of the above effects one finds that the values for the isoelectric points of these amino acids (pI = 6.6–6.8) are more acid than one would expect upon casual examination.

Experimental[16]

***dl*-β-(2-Pyridyl)-alanine.**[5]—Sodium nitrite, 4 g., in 6 ml. of water, was added dropwise, with stirring, to a well-cooled solution of 5.4 g. of (2-pyridyl)-methylamine,[17] b. p. 87–89° (2.2 mm.), in 25 ml. of concentrated hydrochloric acid. Forty grams of powdered potassium hydroxide was then added to the cold reaction mixture, the solution quickly filtered, and the filtrate extracted with ether. The ethereal solution was dried, filtered, the solvent removed by evaporation *in vacuo*, and the residue dissolved in 50 ml. of absolute ethanol. This solution was added to a warm solution of 12.1 g. of benzamidomalonic ester[7] and 1.56 g. of sodium in 76 ml. of absolute ethanol and the mixture refluxed for four hours. The ethanol was removed by evaporation *in vacuo*, the residue taken up in dilute aqueous hydrochloric acid, and the excess benzamidomalonic ester removed by extraction with ether. The aqueous phase was made alkaline, extracted with ether, the ethereal phase dried, filtered, and the solvent removed to give 5.6 g. (30%) of oily (2-pyridyl)-methylbenzamidomalonic ester. This condensation product was refluxed for eight hours with 25 ml. of 49% hydrobromic acid. The hydrolysate was diluted with 150 ml. of water, the solution cooled to 25°, and the liberated benzoic acid removed by extraction with ether. The aqueous phase was evaporated to dryness, the residue taken up in water, the solution freed of inorganic ions with the aid of silver carbonate and hydrogen sulfide, and evaporated to dryness. The residue was collected, washed with a mixture of absolute ethanol and isopropyl ether and then recrystallized from a mixture of isopropyl ether and 80% aqueous ethanol to give 1.38 g. (17%) of *dl*-β-(2-pyridyl)-alanine; m. p. 205.5–206°. Overhoff, Boeke and Gorter[5] give 216° as the melting point.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 58.0; H, 6.2; N, 16.8.

The addition of ninhydrin to an aqueous solution of *dl*-β-(2-pyridyl)-alanine resulted in the formation of a violet color.

Picolinic Benzenesulfonhydrazide.—Benzenesulfonyl chloride (5 ml.) was added, with stirring, to a chilled solution of 4.62 g. of picolinic hydrazide[18] in 35 ml. of pyridine.[13] The clear red solution was allowed to stand for four hours before the pyridine was removed by evaporation *in vacuo*. When the sirupy residue was stirred with a large volume of cold water a solid separated. This was washed with water, a small amount of cold ethanol, and finally with ether to give picolinic benzenesulfonhydrazide, m. p. 202–203.5°, after recrystallization from ethanol. The yield of crude product was practically quantitative.

Anal. Calcd. for $C_{12}H_{11}O_2N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 52.4; H, 4.1; N, 15.1.

Picolinaldehyde.[19]—The procedure of McFadyen and Stevens[13] was modified as follows: 25 g. of picolinic benzenesulfonhydrazide, 24 g. of anhydrous sodium carbonate and 100 ml. of C. P. glycerol were heated to 160° and maintained at that temperature for two minutes. One hundred ml. of water was added to the reaction mixture, the solution saturated with sodium nitrate, filtered, and the filtrate extracted with ether in a continuous extractor for ten hours. The ethereal phase was dried, filtered, and the solvent evaporated to give 1.99 g. (20%) of picolinaldehyde. The liquid aldehyde was converted into the phenylhydrazone hydrochloride; m. p. 194.5–197°. Lénárt[19] gives a melting point of 196° for this compound. All attempts to condense the above picolinaldehyde with diketopiperazine were unsuccessful.

Nicotinic Benzenesulfonhydrazide.—The addition of 230 g. of benzenesulfonyl chloride to a suspension of 169 g. of nicotinic hydrazide[20] in 1.2 liters of technical pyridine gave 328 g. (96%) of nicotinic benzenesulfonhydrazide, m. p. 186–186.5° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{11}O_2N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 51.7; H, 4.2; N, 15.2.

Nicotinaldehyde.[21]—Nicotinic benzenesulfonhydrazide (177 g.) was decomposed, in 25-g. portions, to give 14.3 g. (22.5%) of nicotinaldehyde; b. p. 97–99° (26 mm.). The liquid aldehyde was converted into the phenylhydrazone; m. p. 157.5–158°. Harries and Lénárt[21] give a melting point of 158° for this compound.

5-(3-Pyridylmethyl)-thiohydantoin.—One gram of acetylthiohydantoin,[22] 0.53 g. of dry sodium acetate, both finely powdered, 0.67 g. of nicotinaldehyde, and 5 ml. of acetic anhydride were heated in an oil-bath at 110–115° for thirty minutes. The solid reaction product was extracted with hot water leaving 1.2 g. of a light yellow solid as a residue. This product was refluxed for six hours with 6 ml. of acetic anhydride, 6 ml. of hydriodic acid (d. 1.7) and 1.3 g. of red phosphorus. The hydrolyzate was filtered, the acetic anhydride and hydriodic acid removed by repeated evaporation, following the addition of water, and the residue dissolved in 20 ml. of ethanol. The addition of 6 *N* aqueous ammonium hydroxide to the filtered alcoholic solution precipitated an oil which solidified in contact with methanol. This product was recrystallized from aqueous ethanol to give 0.8 g. (60%) of 5-(3-pyridylmethyl)-thiohydantoin; m. p. 249–252°.

Anal. Calcd. for $C_9H_9ON_3S$ (207.2): C, 52.2; H, 4.4; N, 20.3. Found: C, 52.3; H, 4.7; N, 20.3.

(16) Microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

(17) H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **63**, 492 (1941).

(18) H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912).

(19) G. Lénárt, *Ber.*, **47**, 808 (1914).

(20) T. Curtius and E. Mohr, *ibid.*, **31**, 2493 (1898).

(21) C. Harries and G. H. Lénárt, *Ann.*, **410**, 115 (1915).

(22) T. B. Johnson and B. H. Nicolet, THIS JOURNAL, **33**, 1973 (1911).

Dinicotinaldiketopiperazine.—Nine grams of diketopiperazine, 27 g. of fused sodium acetate, 14.3 g. of nicotinaldehyde, and 25 ml. of acetic anhydride were heated in an oil-bath at 120–125° for five hours.[12] The solid reaction product was digested with hot water, the digest cooled, filtered, and the residue digested with hot ethanol to give 9.7 g. (50%) of crude dinicotinaldiketopiperazine. After two recrystallizations from pyridine the condensation product was obtained in the form of fine yellow needles; m. p. >300°.

Anal. Calcd. for $C_{16}H_{12}O_2N_4$ (292.3): C, 65.8; H, 4.1; N, 19.2. Found: C, 66.0; H, 4.3; N, 19.3.

***dl*-β-(3-Pyridyl)-alanine.**—A mixture of 9.7 g. of dinicotinaldiketopiperazine, 6.7 g. of red phosphorus, 67 ml. of hydriodic acid (d. 1.7), and 67 ml. of acetic anhydride was refluxed for six hours. The reaction product was filtered and the volatile acids removed by repeated evaporation, following the addition of water. The residue remaining after the final evaporation was dissolved in water and the solution freed of inorganic ions with the aid of silver carbonate and hydrogen sulfide. The solution was then evaporated to dryness and the solid residue collected with the aid of ethanol to give 7.6 g. (69%) of crude *dl*-β-(3-pyridyl)-alanine; m. p. 258–260°. The crude amino acid was recrystallized from 80% aqueous ethanol to give *dl*-β-(3-pyridyl)-alanine; pearly flakes; m. p. 262–263°.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 57.6; H, 6.2; N, 16.9.

dl-β-(3-Pyridyl)-alanine has a very sweet taste, gives a violet color when treated with ninhydrin, and forms a dipicrate, needles, m. p. 187–189°, after recrystallization from a dilute aqueous solution of picric acid.

Anal. Calcd. for $C_{20}H_{16}O_{16}N_8$ (624.4): C, 38.5; H, 2.6; N, 18.0. Found: C, 38.5; H, 2.7; N, 18.1.

Isonicotinic Benzenesulfonhydrazide.—A suspension of 13 g. of isonicotinic hydrazide,[22] m. p. 170.5–171.5°,[23] in 90 ml. of pyridine was treated with 18 g. of benzenesulfonyl chloride and the reaction mixture worked up as previously described to give 24.5 g. (93%) of isonicotinic benzenesulfonhydrazide; m. p. 193–194° after recrystallization from water.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$ (277.3): C, 52.0; H, 4.0; N, 15.2. Found: C, 52.2; H, 4.2; N, 15.3.

All attempts to prepare isonicotinaldehyde by decomposing the above sulfonhydrazide in the presence of glycerol and sodium carbonate, as described previously, failed in that only traces of the aldehyde were formed.

(4-Pyridyl)-carbinol Hydrochloride.[24]—A solution of 3.8 g. of (4-pyridyl)-methylamine,[17] b. p. 99–101° (24 mm.), was treated with silver nitrite according to the directions of Graf.[24] The crude carbinol hydrochloride was recrystallized from absolute ethanol to give 2.5 g. of (4-pyridyl)-carbinol hydrochloride; m. p. 167–172°.

Anal. Calcd. for C_6H_8ONCl (145.6): N, 9.6. Found: N, 9.5.

(4-Pyridyl)-methyl Bromide Hydrobromide.[25]—(4-Pyridyl)-carbinol hydrochloride (1.8 g.) was refluxed with 15 ml. of 49% hydrobromic acid, the solution evaporated to dryness, and the residue washed with absolute ethanol to give 2.8 g. of crude (4-pyridyl)-methyl bromide hydrobromide; m. p. 145–150°. The compound had a very irritating action on the skin.

Anal. Calcd. for $C_6H_7NBr_2$ (253.0): N, 5.5. Found: N, 5.8.

***dl*-β-(4-Pyridyl)-alanine.**—(4-Pyridyl)-methyl bromide hydrobromide (2.8 g.) was refluxed with a solution of sodiobenzamidomalonic ester[7] prepared by adding 0.54 g. of sodium to 5 g. of benzamidomalonic ester dissolved in 50 ml. of toluene. The reaction mixture was filtered, the filtrate extracted with 4 *N* hydrochloric acid, a slight excess of aqueous potassium hydroxide added to the aqueous phase, and the latter extracted with ether. The ethereal solution was dried, filtered, the solvent removed from the filtrate, and the residue recrystallized from aqueous ethanol to give 0.24 g. of condensation product; m. p. 106–107°.[26] The condensation product (0.24 g.) was hydrolyzed as previously described to give 0.11 g. of *dl*-β-(4-pyridyl)-alanine, m. p. 235–236°, after recrystallization from a mixture of isopropyl ether and 80% aqueous ethanol.

Anal. Calcd. for $C_8H_{10}O_2N_2$ (166.2): C, 57.8; H, 6.1; N, 16.9. Found: C, 56.9; H, 6.2; N, 17.0.

The addition of ninhydrin to an aqueous solution of *dl*-β-(4-pyridyl)-alanine resulted in the formation of a red color.

Preliminary Titration Data.—Samples of the amino acids dissolved in 10 ml. of water were titrated at 23° with 0.1 *N* hydrochloric acid and sodium hydroxide. The *p*H measurements were made with a Beckman Laboratory Model *p*H Meter equipped with external shielded electrodes. In the titration of *dl*-β-(2-pyridyl)-alanine and *dl*-β-(3-pyridyl)-alanine the mean volumetric error was less than 0.1% but in the titration of *dl*-β-(4-pyridyl)-

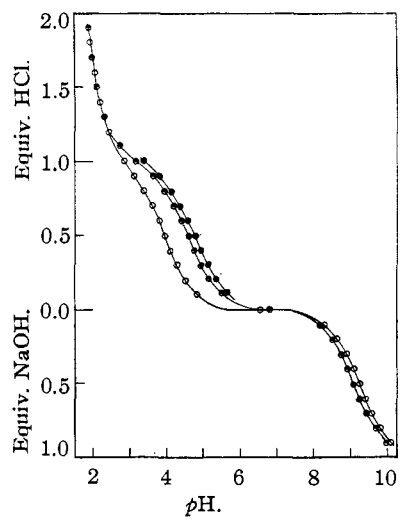


Fig. 1.—○, *dl*-β-(2-Pyridyl)-alanine, volume of solution containing 63.2 mg. of the amino acid after 1.5 equiv. of acid had been added = 17.0 ml.; ◐, *dl*-β-(3-pyridyl)-alanine, volume of solution containing 165.5 mg. of the amino acid after 1.5 equiv. of acid had been added = 27.0 ml.; ●, *dl*-β-(4-pyridyl)-alanine.

(23) Meyer and Mally[18] give a m. p. of 163°.

(24) R. Graf, *J. prakt. Chem.*, **146**, 88 (1936).

(25) All attempts to obtain (4-pyridyl)-methyl chloride directly from (4-pyridyl)-methylamine by treating the latter compound with nitrous acid in the presence of hydrochloric acid were unsuccessful.

(26) A similar yield and a comparable product was obtained when the condensation was carried out in absolute ethanol.

alanine, this error was of the order of 1%. The *p*H measurements were reproducible to within 0.02 of a *p*H unit and in the case of the base titration correction was made for the presence of sodium ion. The titration curves are given in Fig. 1 and the apparent dissociation constants, K_A, K_{B_1}, and K_{B_2}, in Table I.

TABLE I

APPARENT DISSOCIATION CONSTANTS

Amino acid	$K_{B_1} \times 10^{-10}$	$K_{B_2} \times 10^{-13}$	$K_A \times 10^{-10}$
dl-β-(2-Pyridyl)-alanine	0.89 ± 0.05	2 ± 1	6 ± 1
dl-β-(3-Pyridyl)-alanine	3.7 ± .5	5 ± 1	8 ± 1
dl-β-(4-Pyridyl)-alanine	6 ± 1		

Summary

1. The three isomeric *dl*-β-pyridylalanines have been synthesized and their apparent acid and basic dissociation constants determined. The effect of structure on acid and base strength is discussed.

2. Picolinaldehyde and nicotinaldehyde have been synthesized by the McFadyen–Stevens reaction and the applicability of this reaction to the pyridine series is discussed.

PASADENA, CALIFORNIA RECEIVED APRIL 21, 1942

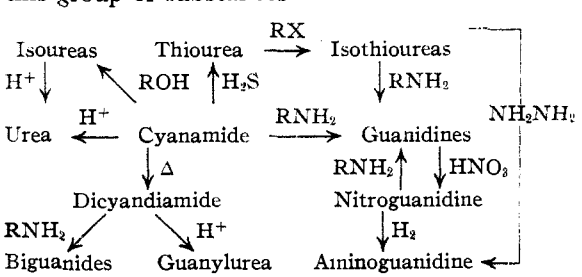
[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. V. Sulfanilylcyanamide and Related Compounds[1]

BY PHILIP S. WINNEK, GEORGE W. ANDERSON, HARRY W. MARSON, H. ELDRIDGE FAITH AND RICHARD O. ROBLIN, JR.

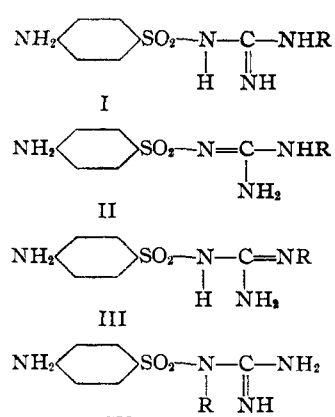
Shortly after sulfanilylguanidine was described in a preceding paper of this series,[2] Marshall and co-workers[3] reported the compound independently. On the basis of a comprehensive bacteriological and pharmacological study, they suggested its use for the treatment of intestinal infections.

Guanidine is one of a large group of compounds which may be prepared from cyanamide. Because of the somewhat unusual characteristics of sulfaguanidine, it appeared to be of interest to investigate the sulfanilyl derivatives of cyanamide and a number of related compounds including a series of substituted guanidines. The following diagram illustrates some of the inter-relationships among this group of substances



Many of the same relationships have been found to exist among the sulfanilyl derivatives of these compounds (Table I). Thus, in addition to the more obvious method, sulfanilylguanidines were prepared from the sulfanilyl derivatives of cyanamide, nitroguanidine and isothioureas. Similarly, sulfanilylcyanamide was converted to the urea or isourea compounds. *p*-Nitrobenzenesulfonyl chloride and isoureas also led to the formation of sulfanilylisoureas, which in turn could be hydrolyzed to the urea derivative.[4] Other similar reactions such as the conversion of sulfanilyldicyandiamide to guanylurea and biguanide derivatives were also investigated.

Because of the alkali insolubility of many of the substituted sulfanilylguanidines (Table I), it was not possible to establish their structure directly when they were prepared through acetylsulfanilyl chloride and the substituted guanidines. For example, the sulfanilylalkylguanidines might have any of the following structures



(1) Presented in part before the Division of Medicinal Chemistry, Memphis meeting of the American Chemical Society, April 22, 1942.

(2) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

(3) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

(4) *Cf.* Cox and Raymond, THIS JOURNAL, **63**, 300 (1941).