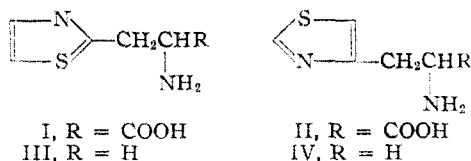


[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORY]

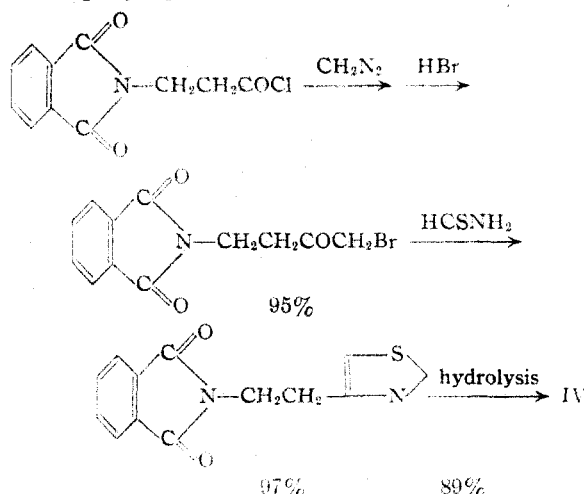
# The Synthesis of Some Analogs of Histamine and Histidine Containing the Thiazole Nucleus

BY REUBEN G. JONES, EDMUND C. KORNFELD AND KEITH C. McLAUGHLIN

For a study of possible relationships between chemical constitution and biological activity, a number of amino acids structurally related to histidine and amines related to histamine have been synthesized,<sup>1</sup> and tested.<sup>2</sup> This paper describes the synthesis of 2-thiazolealanine I, 4-thiazolealanine II, 2- $\beta$ -aminoethylthiazole III, 4- $\beta$ -aminoethylthiazole IV and certain other related aminoalkylthiazoles.



4- $\beta$ -Aminoethylthiazole, IV, has been prepared previously by hydrogenation of 4-thiazoleacetonitrile over a nickel catalyst.<sup>3</sup> We were unable to repeat this hydrogenation, as were also Burger and Ulliot,<sup>4</sup> and therefore an alternative synthesis was devised, which is outlined by the accompanying reactions.

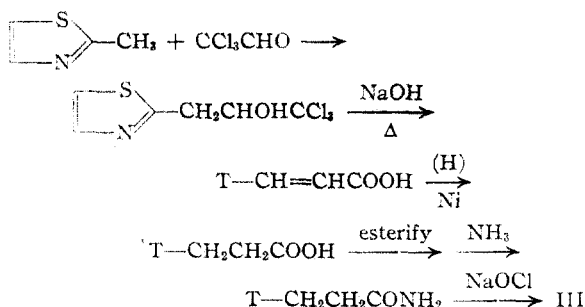


In addition to the amine IV, 2-methyl-4- $\beta$ -aminoethylthiazole<sup>4</sup> and bis-2,4-( $\beta$ -aminoethyl)-thiazole were also prepared by this method using thioacetamide and  $\beta$ -benzoylaminothiopropionamide<sup>5</sup> in place of thioformamide.

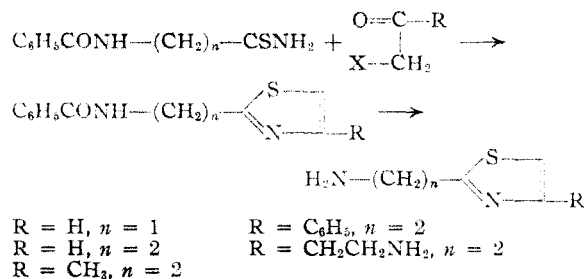
The same general procedure served for the preparation of 4-aminomethylthiazole. In this case phthalimidoacetyl chloride<sup>6</sup> was used as the

starting material in place of  $\beta$ -phthalimido-propionyl chloride<sup>7</sup> in the above series of reactions.

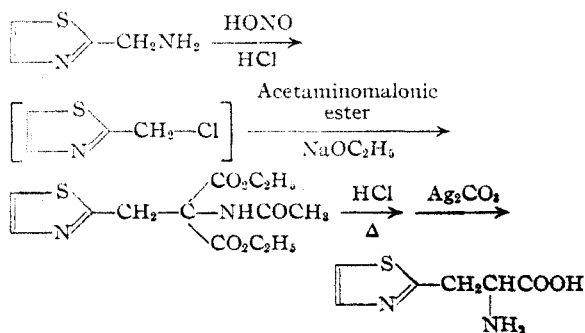
2- $\beta$ -Aminoethylthiazole, III, was prepared through a series of reactions starting from 2-methylthiazole



A more convenient synthesis of III and related 2-aminoalkylthiazoles was the condensation of chloroacetaldehyde and chloro or bromo ketones with appropriately substituted thioamides according to the method of Goldberg and Kelley.<sup>5</sup>



The thiazolealanines, I and II, were prepared by a procedure similar to that of Overhoff, Boeke and Gorter<sup>8</sup> for the synthesis of 2-pyridylalanine. This is illustrated by the following series of reactions for the synthesis of 2-thiazolealanine. 4-



(1) Jones, *THIS JOURNAL*, **71**, 383, 3994 (1949); Jones and McLaughlin, *ibid.*, **71**, 2444 (1949).

(2) Lee and Jones, *J. Pharmacol.*, **95**, 71 (1949).

(3) Erlenmeyer and Müller, *Helv. Chim. Acta*, **28**, 922 (1945).

(4) Burger and Ulliot, *J. Org. Chem.*, **12**, 342 (1947).

(5) Goldberg and Kelly, *J. Chem. Soc.*, 1372 (1947).

(6) Gabriel, *Ber.*, **40**, 2648 (1907).

(7) Gabriel, *ibid.*, **41**, 213 (1908).

(8) Overhoff, Boeke and Gorter, *Rec. trav. chim.*, **55**, 293 (1936); see also, Neimann, Lewis and Hays, *THIS JOURNAL*, **64**, 1678 (1942).

Thiazolealanine was prepared in the same way starting with 4-aminomethylthiazole. The intermediate chloromethylthiazoles were not isolated and purified.

### Experimental

**1-Bromo-4-phthalimido-2-butanone.**— $\beta$ -Phthalimido-propionic acid was prepared in 98% yield by heating phthalic anhydride with  $\beta$ -alanine according to the directions of Gabriel.<sup>9</sup> The acid, 0.5 mole, was mixed with 100 ml. of thionyl chloride and allowed to stand for four hours. The mixture was then warmed for one-half hour, and the resulting clear solution was evaporated under vacuum to remove the excess thionyl chloride. The crystalline residue was taken up in 100 ml. of hot dry benzene, and this solution was diluted with 100 ml. of petroleum ether. The yield of white crystalline acid chloride was 97%, m. p. 107–108° (lit.<sup>7</sup> 107–108°).

A diazomethane solution prepared in one liter of methylene chloride from 90 g. of nitrosomethyl urea was dried for two hours over potassium hydroxide pellets. The solution was placed in a dry 3-l. three-necked flask provided with a stirrer, dropping funnel and thermometer and cooled to 0°. With stirring 60 g. (0.25 mole) of  $\beta$ -phthalimidopropionyl chloride in 400 ml. of benzene (partially in solution) was added from the dropping funnel during one-half hour. The resulting solution was stirred for two hours and then allowed to warm up to 20°. Again the solution was cooled to 0°, and 60 ml. of 48% hydrobromic acid was added dropwise with stirring over a period of fifteen minutes. After stirring at 0 to 15° for one hour the solution was placed in a separatory funnel and shaken with excess aqueous sodium carbonate solution. The solution was dried with magnesium sulfate and evaporated in vacuum leaving a white crystalline residue. This product was recrystallized by dissolving in 200 ml. of hot benzene followed by the addition of 200 ml. of petroleum ether and chilling to 0°. The yield of 1-bromo-4-phthalimido-2-butanone was 70.0 g. (95%); m. p. 119–120°.

*Anal.* Calcd. for  $C_{12}H_{10}BrNO_3$ : N, 4.73. Found: N, 4.72.

**1-Bromo-3-phthalimido-2-propanone.**—This compound was prepared from phthalimidoacetyl chloride<sup>8</sup> in the same way as described above for the bromophthalimidobutanone. The yield was comparable. It melted at 145–146°.

*Anal.* Calcd. for  $C_{11}H_8BrNO_3$ : N, 4.97. Found: N, 5.12.

**4- $\beta$ -Phthalimidoethylthiazole.**<sup>4</sup>—A suspension of 55 g. (0.185 mole) of 1-bromo-4-phthalimido-2-butanone in a mixture of 200 ml. of absolute alcohol and 100 ml. of ether was cooled in an ice-salt-bath to 0° and with stirring a solution of 29 g. (0.37 mole) of crude freshly prepared<sup>10</sup> thioformamide hydrate<sup>11</sup> in 50 ml. of absolute alcohol was added dropwise. No change appeared to take place. The mixture was stirred and left in the ice-bath overnight during which time the ice melted and the reaction mixture came to room temperature. The mixture which now contained a large quantity of white crystalline solid was filtered, and the filtrate was evaporated in vacuum. To the residue was added the solid which had been filtered together with 100 ml. of ether, and the whole was extracted with 250 ml. of 1 N hydrochloric acid. The aqueous solution was separated and treated with excess ammonium hydroxide to precipitate 46.5 g. (97% yield) of 4- $\beta$ -phthalimidoethylthiazole as a white crystalline solid. A sample recrystallized from aqueous alcohol melted at 101–102°.

*Anal.* Calcd. for  $C_{13}H_{10}N_2O_3S$ : N, 10.85. Found: N, 10.76.

(9) Gabriel, *Ber.*, **38**, 633 (1905).

(10) In this and other related experiments it was found that high yields of thiazole compounds could be obtained only if the thioformamide was freshly prepared. Thioformamide that was allowed to stand for twelve hours or longer before use gave poor results.

(11) Willstätter and Wirth, *Ber.*, **42**, 1911 (1909).

**4- $\beta$ -Aminoethylthiazole Dihydrochloride.**—To a solution of 46 g. (0.18 mole) of the above phthalimide compound in 150 ml. of hot alcohol was added 10 g. (0.20 mole) of 100% hydrazine hydrate. The solution was kept hot for one-half hour, and then to the resulting mixture containing a large quantity of gelatinous solid was added 50 ml. of concentrated hydrochloric acid followed by 200 ml. of water. The mixture was filtered and the solid was washed with an additional 100-ml. portion of water. The combined filtrates were evaporated in vacuum to dryness; the residue was treated with 50 ml. of 12 N sodium hydroxide solution, and the mixture was extracted with four 150-ml. portions of ethyl acetate. Treatment of the dried ethyl acetate solution with hydrogen chloride caused the precipitation of 32 g. (89% yield) of 4- $\beta$ -aminoethylthiazole dihydrochloride. It melted at 206–207° (uncor.), and the melting point remained unchanged after recrystallization from absolute alcohol.

*Anal.* Calcd. for  $C_6H_8N_2S \cdot 2HCl$ : N, 13.93. Found: N, 14.13.

**4-Phthalimidomethylthiazole.**—This was prepared from 1-bromo-3-phthalimido-2-propanone and thioformamide in the same way as described above for the preparation of 4- $\beta$ -phthalimidoethylthiazole. The yield was 75%; m. p. 156–157°.

*Anal.* Calcd. for  $C_{12}H_8N_2O_3S$ : N, 11.48. Found: N, 11.34.

**4-Aminomethylthiazole.**—The phthalimide compound was hydrolyzed and the 4-aminomethylthiazole was isolated in the same manner as described above for 4- $\beta$ -aminoethylthiazole. The free base distilled at 90–93° (12 mm.); yield 64%. The monohydrochloride was obtained by treatment of the base in ether solution with dry hydrogen chloride; m. p. 183–185°.

*Anal.* Calcd. for  $C_4H_8N_2S \cdot HCl$ : Cl, 23.58. Found: Cl, 24.00.

**2-Methyl-4- $\beta$ -phthalimidoethylthiazole.**—To 25 ml. of methanol containing 2 ml. of pyridine was added 7.4 g. (0.025 mole) of 1-bromo-4-phthalimido-2-butanone and 2.0 g. (0.027 mole) of thioacetamide. The solid dissolved with the evolution of a little heat, and then the solution was heated under reflux for two hours. After evaporation of the solution to dryness, the residue was taken up in 60 ml. of 4 N hydrochloric acid, the solution was decolorized with carbon, filtered and made basic with ammonium hydroxide to precipitate 5.3 g. (78% yield) of the desired product; m. p. 99–100°. A sample recrystallized from 50% aqueous alcohol melted at 102–103°.

*Anal.* Calcd. for  $C_{14}H_{12}N_2O_3S$ : N, 10.29. Found: N, 10.22.

**2-Methyl-4- $\beta$ -aminoethylthiazole Dihydrochloride.**—The phthalimido compound was converted to the amine dihydrochloride by the procedure described above for 4- $\beta$ -aminoethylthiazole dihydrochloride. The yield was 72%; m. p. 196–198°.

*Anal.* Calcd. for  $C_6H_{10}N_2S \cdot 2HCl$ : N, 13.02. Found: N, 12.66.

**2- $\beta$ -Benzoylaminoethyl-4- $\beta$ -phthalimidoethylthiazole.**—This was prepared from 1-bromo-4-phthalimido-2-butanone and  $\beta$ -benzoylaminothiopropionamide<sup>8</sup> in the same manner as described above for the preparation of 2-methyl-4- $\beta$ -phthalimidoethylthiazole. The yield was 71%; m. p. 107–107.2° (from 50% aqueous alcohol).

*Anal.* Calcd. for  $C_{22}H_{19}N_3O_3S$ : N, 10.37. Found: N, 10.36.

**Bis-2,4-( $\beta$ -aminoethyl)-thiazole Trihydrochloride.**—A solution of 3.3 g. of 2- $\beta$ -benzoylaminoethyl-4- $\beta$ -phthalimidoethylthiazole in 100 ml. of 12 N hydrochloric acid was heated on the steam-bath for sixty hours. The precipitated benzoic and phthalic acids were removed by filtration, and the filtrate was washed well with ether and evaporated to dryness. The crystalline residue was triturated with absolute alcohol, collected on a filter, and air dried; yield, 2.2 g. (96%). A sample was recrystallized from 95% alcohol and was apparently obtained as a hy-

drate which lost water of hydration at 182–184°. It melted at 182–184°, then resolidified and again melted at 190–192°.

*Anal.* Calcd. for  $C_7H_{13}N_3S \cdot 3HCl \cdot H_2O$ : N, 14.07. Found: N, 14.27.

**3,3,3-Trichloro-1-(2'-thiazole)-2-propanol.**—2-Methylthiazole,<sup>12</sup> 58 g., was mixed with 86.2 g. of chloral and 138 ml. of dry pyridine. The mixture was warmed on a steam-bath for 48 hours after which the pyridine was removed by distillation under vacuum. The residue was stirred with water, and the semisolid product was filtered and washed with water. The crude product was dissolved in ethanol, and the dark solution was treated with two portions of decolorizing carbon. The filtrate from the carbon treatment was then concentrated, whereupon the adduct crystallized, m. p. 118–124°; yield, 32%. A sample for analysis was sublimed at 100° in vacuum (0.5 mm.), m. p. 126–128°.

*Anal.* Calcd. for  $C_6H_6Cl_3NOS$ : N, 5.68. Found: N, 5.84.

**$\beta$ -2-Thiazoleacrylic Acid.**—Chloral-2-methylthiazole, 37.8 g., was dissolved in 150 ml. of boiling ethanol, and to the hot solution was added slowly and with caution a hot solution of 30.6 g. of sodium hydroxide in 25 ml. of water. The dark mixture was refluxed for a few minutes after which the ethanol was distilled in vacuum. Hot water, 100 ml., was added to the residue, and the dark solution was decolorized with carbon, and the filtrate was acidified to about pH 2 with concentrated hydrochloric acid. The product was filtered, washed with water, and dried, m. p. 150–170° dec., yield 53%. A sample for analysis was sublimed at 140° in vacuum (0.5 mm.), m. p. 187–190°.

*Anal.* Calcd. for  $C_6H_6NO_2S$ : N, 9.03. Found: N, 9.15.

**$\beta$ -2-Thiazolepropionic Acid.**—Crude  $\beta$ -2-thiazoleacrylic acid, 11.8 g., was dissolved in a solution of 80 ml. of water containing 3.5 g. of sodium hydroxide and hydrogenated at three atmospheres pressure using a few grams of Raney nickel catalyst. The theoretical volume of hydrogen was taken up in eight hours. The solution was filtered, and the  $\beta$ -2-thiazolepropionic acid was precipitated by acidification of the filtrate with 7 ml. of concentrated hydrochloric acid; yield, 62%, m. p. 128–131°. A sample for analysis was sublimed in vacuum, m. p. 129–132°.

*Anal.* Calcd. for  $C_6H_7NO_2S$ : N, 8.91. Found: N, 8.42.

**$\beta$ -2-Thiazolepropionamide.**—The crude  $\beta$ -2-thiazolepropionic acid was converted to the methyl ester by means of excess diazomethane in ether-methanol solution. The crude methyl ester so obtained was allowed to stand in methanolic ammonia solution for four days, after which the solution was evaporated to dryness in vacuum. The crude  $\beta$ -2-thiazolepropionamide was recrystallized from ethyl acetate, m. p. 106–109°; yield, 53%.

*Anal.* Calcd. for  $C_6H_7N_2OS$ : N, 17.94. Found: N, 17.64.

**2- $\beta$ -Aminoethylthiazole Dihydrochloride.**—Chlorine, 1.5 g., was bubbled into a solution of 3.9 g. of sodium hydroxide in 30 ml. of ice and water. Powdered  $\beta$ -2-thiazolepropionamide, 3 g. was added, and the suspension was stirred until the amide dissolved. The solution was allowed to warm up to room temperature in the course of about one hour, after which it was warmed on a steam-bath for one hour. The solution was cooled and extracted with 200 ml. of ethyl acetate in eight portions. The extracts were dried over sodium sulfate, after which the product was precipitated as the dihydrochloride by addition of a solution of hydrogen chloride in ether. The solvents were decanted from the oily product, and methanol and ether were added. The crystalline 2- $\beta$ -aminoethylthiazole dihydrochloride was recrystallized from methanol-ether using a little decolorizing carbon, m. p. 153–158°; yield, 69%.

*Anal.* Calcd. for  $C_6H_9N_2S \cdot 2HCl$ : N, 13.93. Found: N, 13.70.

**2- $\beta$ -Aminoethylthiazole Dihydrochloride from  $\beta$ -Benzamidothiopropanamide.**—Anhydrous oxalic acid, 10 g., and 17 g. of chlorodiethylacetal were heated under reflux for two hours at a bath temperature of 130°.  $\beta$ -Benzamidothiopropanamide,<sup>5</sup> 20.7 g., was added, and heating was continued for one-half hour at 125°. The dark solution was then poured into 125 ml. of *N* hydrochloric acid. The resulting mixture was extracted once with ether, and the aqueous layer was decolorized with carbon and then neutralized with ammonium hydroxide. The crude 2- $\beta$ -benzoylaminoethylthiazole which precipitated was separated from the aqueous solution by decantation. It was then heated under reflux with 125 ml. of 5 *N* hydrochloric acid for four hours. The solution was cooled, and the benzoic acid was removed by filtration. The filtrate was evaporated to dryness under vacuum. A little 12 *N* sodium hydroxide was added to the residue, and the 2- $\beta$ -aminoethylthiazole was extracted with three 20-ml. portions of ether. The extracts were dried over potassium carbonate, and the dihydrochloride was precipitated with hydrogen chloride gas. The product was recrystallized from methanol-acetone; yield, 30%, m. p. 154–158°, mixed m. p. with 2- $\beta$ -aminoethylthiazole dihydrochloride prepared above 154–158°.

**2-Aminomethylthiazole.**—This was prepared from benzoylaminothioacetamide<sup>7</sup> and chloroacetal in the same way as just described for 2- $\beta$ -aminoethylthiazole. The yield was 31%, and the product was isolated as the free base, b. p. 93–95° (14 mm.).

*Anal.* Calcd. for  $C_4H_6N_2S$ : N, 24.54. Found: N, 23.70.

**4-Methyl-2- $\beta$ -aminoethylthiazole Dihydrochloride.**—The free base was prepared from chloroacetone and  $\beta$ -benzoylaminothiopropanamide by the method of Goldberg and Kelly.<sup>5</sup> The dihydrochloride was precipitated from an ethereal solution with dry hydrogen chloride and was recrystallized from methanol-acetone, m. p. 157–160°.

*Anal.* Calcd. for  $C_6H_{12}Cl_2N_2S$ : Cl, 32.96. Found: Cl, 32.28.

**4-Phenyl-2- $\beta$ -aminoethylthiazole Hydrochloride.**— $\beta$ -Benzoylaminothiopropanamide<sup>5</sup> and phenacyl bromide were condensed, and the crude 4-phenyl-2- $\beta$ -benzoylaminoethylthiazole was hydrolyzed without purification. The monohydrochloride of 4-phenyl-2- $\beta$ -aminoethylthiazole was precipitated from an ethereal solution of the free base by means of excess dry hydrogen chloride. It was recrystallized from ethanol-acetone, m. p. 217–218°; yield, 76%.

*Anal.* Calcd. for  $C_{11}H_{12}N_2S \cdot HCl$ : Cl, 14.73; N, 11.64. Found: Cl, 14.89; N, 11.36.

**4-Thiazolealanine.**—A solution of 5.7 g. (0.05 mole) of 4-aminomethylthiazole in 25 ml. of concentrated hydrochloric acid was cooled to about –10°, and 6.9 g. (0.10 mole) of sodium nitrite dissolved in 10 ml. of water was added very slowly with stirring. The mixture was removed from the cooling bath and allowed to stand at room temperature for one-half hour. It was again cooled to –30° in a Dry Ice-bath, and 40 g. of powdered potassium hydroxide was added in small portions with stirring. The resulting mixture was extracted with three 75 ml. portions of ether, and the ether solution was dried over magnesium sulfate at –10°. The solution was evaporated in vacuum to a volume of about 25 ml., diluted with 50 ml. of absolute alcohol. This was added to a solution made by dissolving 1.5 g. (0.65 g. atom) of sodium in 70 ml. of absolute alcohol and adding 17 g. (0.78 mole) of acetaminomalonic ester. After standing at room temperature for two hours the mixture was heated under reflux for one hour, and evaporated in vacuum to remove most of the alcohol. To the residue was added 80 ml. of ice-cold 6 *N* hydrochloric acid, and the resulting solution was washed with four 75-ml. portions of ethyl acetate. The aqueous solution was neutralized with excess sodium

carbonate, and extracted with four 75-ml. portions of ethyl acetate. The extract was dried and evaporated in vacuum to a sirup which crystallized after cooling and standing. The yield was 5.5 g. (35% based on 4-amino-methylthiazole) of ethyl  $\alpha$ -acetamino- $\alpha$ -carboxy- $\beta$ -(4-thiazole)-propionate. A sample was recrystallized from an ether-petroleum ether mixture; m. p. 103–104°.

*Anal.* Calcd. for  $C_{13}H_{15}N_2O_6S$ : C, 49.67; H, 5.77; N, 8.91. Found: C, 49.84; H, 5.88; N, 8.91.

The above crude product, 5 g., in 25 ml. of concentrated hydrochloric acid was heated on the steam-bath for four hours, and then the solution was evaporated in a vacuum. The residual sirup was taken up in 100 ml. of water, and the solution was freed of chloride ion with silver carbonate in the usual way. Evaporation of the aqueous solution until crystallization began, and then addition of absolute alcohol gave 1.3 g. of finely divided, white crystalline, 4-thiazolealanine (47% yield or 16.8% over-all yield); m. p. 227–230°. It was readily soluble in water, very sparingly soluble in absolute alcohol. A sample recrystallized from a large volume of 95% alcohol melted at 237–238° (dec.) uncor.

*Anal.* Calcd. for  $C_6H_8N_2O_2S$ : C, 41.85; H, 4.68; N, 16.27. Found: C, 42.01; H, 5.35; N, 16.23.

**2-Thiazolealanine.**—This was prepared starting from 2-aminomethylthiazole in the same manner as described for

the preparation of the 4-isomer. The intermediate ethyl  $\alpha$ -acetamino- $\alpha$ -carboxy- $\beta$ -(2-thiazole)-propionate was not isolated in a crystalline form but was hydrolyzed directly. The over-all yield was 28.5%; m. p. 197–198° (dec.) uncor.

*Anal.* Calcd. for  $C_6H_8N_2O_2S$ : C, 41.85; H, 4.68. Found: C, 41.47; H, 4.35.

**Acknowledgment.**—The authors express their thanks to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here.

### Summary

The preparations of the following alkylamino-thiazole compounds are described: 2-amino-methylthiazole, 4-aminomethylthiazole, 2- $\beta$ -aminoethylthiazole, 4- $\beta$ -aminoethylthiazole, 2-methyl-4- $\beta$ -aminoethylthiazole, 4-phenyl-2- $\beta$ -aminoethylthiazole, and bis-2,4-( $\beta$ -aminoethyl)-thiazole.

The preparations of 2-thiazolealanine and 4-thiazolealanine are described.

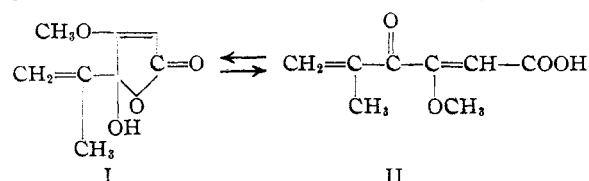
INDIANAPOLIS, INDIANA RECEIVED FEBRUARY 23, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

## The Structure of Penicillic Acid

BY JARED H. FORD, AGATHA R. JOHNSON AND J. W. HINMAN

In 1936, Birkinshaw, Oxford and Raistrick<sup>1</sup> proposed the following structure for the antibiotic penicillic acid, in which the lactol form (I) was in



equilibrium with the keto acid form (II). Recently, Munday<sup>2</sup> has reported infrared spectra which, according to his interpretation, indicated the presence of both of the tautomeric forms in the solid state. Furthermore, it was stated that the crystals of the keto acid form (II) were converted to the lactol form (I) by mulling with Nujol in accordance with a widely used method<sup>3</sup> for obtaining random orientation of the crystals in the absorption cells. In the present investigation, it has been found that the infrared absorption spectrum of Munday's "keto acid" is identical with that of the monohydrate<sup>1</sup> of penicillic acid (see Fig. 1). Thus it appears that the reported "tautomerism" was probably the conversion of the monohydrate to anhydrous penicillic acid (I).

We have found that penicillic acid and its monohydrate give identical infrared spectra in

(1) Birkinshaw, Oxford and Raistrick, *Biochem. J.*, **30**, 394 (1936).

(2) Munday, *Nature*, **163**, 443 (1949).

(3) Barnes, Gore, Williams, Linsley and Petersen, *Ind. Eng. Chem., Anal. Ed.*, **19**, 620 (1947).

chloroform solution. These spectra show hydroxyl absorption at 3335  $\text{cm}^{-1}$ ,  $\gamma$ -lactol carbonyl at 1757  $\text{cm}^{-1}$ , carbon-carbon unsaturation at 1645  $\text{cm}^{-1}$ , and lack of the absorption which is characteristic of conjugated ester and ketone (near 1720  $\text{cm}^{-1}$  and 1685  $\text{cm}^{-1}$ , respectively). Munday<sup>2</sup> failed to report the hydroxyl region of the spectrum which we have found to be critical in distinguishing lactols from the corresponding open chain keto acids.

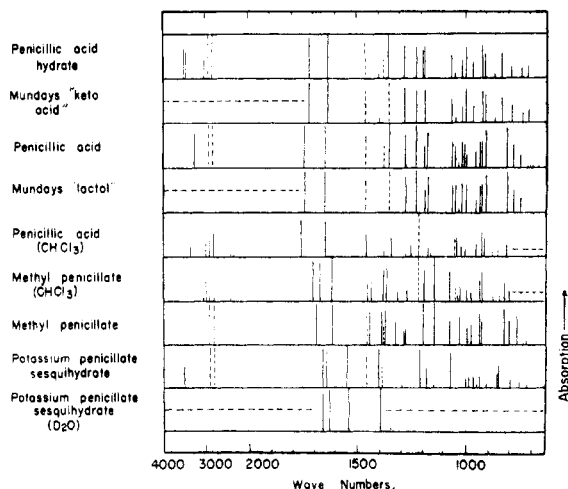


Fig. 1.

The cyclic structure has previously been assigned to penicillic acid and also to its methyl es-