

2. 2-Phenylthiazole-2- α -ethanol is oxidized practically quantitatively to the ketone, 4-phenyl-2-acetothiazole, by the action of chromic acid in acetic acid solution.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

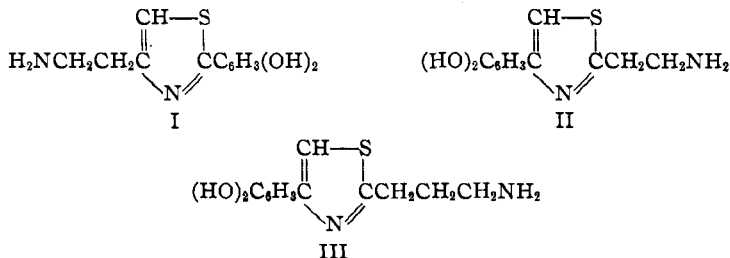
SYNTHESIS OF SOME NEW THIAZOLE AMINES CONTAINING THE CATECHOL GROUP. X

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In the first paper of this series Johnson and Gatewood² reported the use of chloroacetocatechol as a reagent for thiazole syntheses, and described several thiazoles containing the catechol group in position 4 of the thiazole ring. Suter and Johnson³ continued the work and described several thiazoles containing the catechol group in both positions 2 and 4 of the thiazole ring. The next contribution to the chemistry of these catechol derivatives was a paper by Hinegardner and Johnson,⁴ who described a method of preparing the new thiazole amine represented by formula I.



This was found to be a potent substance physiologically, and, therefore, it was decided to synthesize its isomer represented by formula II in which the positions of the aliphatic amine and catechol groups in the thiazole nucleus are reversed. It became very important to determine which one of these two amines would be the most active substance when submitted to a comparative pharmacological study. In this paper is described the synthesis of this new thiazole amine II and also its next higher homolog, or the propyl derivative represented by formula III.

Our method of synthesis involved first the preparation of cyanethyl- and cyanpropylphthalimide, second, their conversion into their corresponding thioamides and third, interaction of these respective thioamides with

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² Johnson and Gatewood, *THIS JOURNAL*, **51**, 1815 (1929); U. S. Patent No. 1,743,083 (1930).

³ Suter and Johnson, *THIS JOURNAL*, **52**, 1685 (1930).

⁴ Hinegardner and Johnson, Paper VI of this series, *ibid.*, **52**, 4141 (1930).

chloroacetocatechol to form the phthalimido derivatives of the bases II and III, respectively. Both of these phthalimide compounds can be obtained easily by our method of synthesis in good yields. They are converted almost quantitatively into the amines II and III, respectively, when heated with hydrazine hydrate according to the technique of Ing and Manske.⁵ A description of the various stages of our two syntheses is given in the experimental part of this paper.

Experimental Part

γ -Phthalimido-butyrothioamide, $C_6H_4(CO)_2NCH_2CH_2CH_2CSNH_2$.— γ -Chlorobutyronitrile was first prepared by the action of potassium cyanide on trimethylene chlorobromide in alcohol solution.⁶ This nitrile was then converted into the phthalimido derivative according to the method of Gabriel⁷ by heating it with the potassium salt of phthalimide at 150°. After crystallizing from alcohol, this melted at 81° and the yield was 80% of the theoretical. This nitrile was then converted into its corresponding thioamide by dissolving in alcoholic ammonium sulfide solution and allowing this to stand for seventy-two hours after saturating with hydrogen sulfide. The thioamide crystallizes from 50% alcohol in plates melting at 181–182°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2S$: N, 11.29; S, 12.91. Found: N, 11.13, 11.26; S, 12.67.

4-(3,4-Dihydroxyphenyl)-2- γ -phthalimidopropyl-thiazole was prepared by the action of the above thioamide on chloroacetocatechol in alcohol solution. It crystallized from 50% acetone solution in the form of yellow, cubical crystals and melted at 114–115° to an oil.

Anal. Calcd. for $C_{20}H_{16}O_4N_2S \cdot H_2O$: H_2O , 4.52; N, 7.03; S, 8.07. Found: H_2O , 4.22; N, 7.13; S, 8.11.

4-(3,4-Dihydroxyphenyl)-2- γ -aminopropyl-thiazole. III.—The sulfate of this base was prepared as follows. Twenty-five grams of the phthalimide derivative was dissolved in hot alcohol, 6 g. of hydrazine hydrate added and the mixture warmed at boiling water-bath temperature until the solvent evaporated. Dilute hydrochloric acid was then added and the mixture heated to boiling, when phthalylhydrazine separated. After filtering and making the solution alkaline, the above thiazole amine separated. After washing with cold water this was then dissolved in 50% alcohol, acidified with sulfuric acid. On cooling, the sulfate separated in the form of needles. On recrystallizing from hot water this deposited in the form of minute colorless needles resembling very much the crystalline appearance of quinine sulfate. A sample of this salt was dried at 107°, when it lost 16.73% of its weight, indicating a hydrate constitution corresponding to the formula $2C_{12}H_{14}O_2N_2S \cdot 2H_2SO_4 \cdot 7H_2O$. This hydrate melted at 120–140° with decomposition when heated in a closed tube. The anhydrous salt melts at 226–228° to a clear liquid.

Anal. Calcd. for $C_{12}H_{14}O_2N_2S \cdot H_2SO_4$: N, 8.04; S as sulfate, 9.20; total S, 18.41. Found: N, 8.01; S as sulfate, 9.28; total S, 18.61.

Preparation of 4-(3,4-Dihydroxyphenyl)-2- β -aminoethyl-thiazole. II.— β -Chloropropionitrile was first prepared as follows: 200 g. of thionyl chloride and 100 cc. of chloroform were mixed in a 1-liter two-necked flask to which an Allihn condenser and a

⁵ Ing and Manske, *J. Chem. Soc.*, 128, 2348 (1926).

⁶ Henry, *Bull. soc. chim.*, 45, 341 (1886).

⁷ Gabriel, *Ber.*, 22, 3335 (1889).

dropping funnel were attached. The end of the dropping funnel tube was drawn out to a capillary ending and arranged so as to approach about one inch above the surface of the chloroform-thionyl chloride solution. One hundred and ten grams of ethylenecyanhydrin was then added to the boiling chloroform-thionyl chloride solution at the rate of about 3 cc. per minute and the final reaction mixture refluxed for thirty minutes. The chloropropionitrile was separated by fractional distillation under diminished pressure and different preparations were observed to boil as follows: (a) 84° at 30 mm., (b) 80° at 25 mm., 76° at 20 mm. The yield was 127 g. or 91% of the theoretical. Our product always contained a trace of thionyl chloride which could not be removed easily by distillation. By shaking the chloride with dilute sodium carbonate solution the thionyl chloride is removed easily, giving a pure colorless nitrile.

Phthalimido-propionitrile.—This is prepared by heating the above chloride with the potassium salt of phthalimide at 145°. The phthalimide crystallized from methyl alcohol in plates melting at 147–148°. The yield here is greatly reduced by the formation of acrylic nitrile, which is always produced during the fusion with potassium phthalimide.

Anal. Calcd. for $C_{11}H_8O_2N_2$: N, 14.00. Found: N, 14.12, 14.20.

Phthalimido-propionic-thioamide.—This was prepared by heating the above nitrile with an excess of alcoholic ammonium sulfide in a bomb tube at 90°. It crystallized from a mixture of chloroform and absolute alcohol in the form of rosetts melting at 187–189°. The yield was good.

Anal. Calcd. for $C_{11}H_{10}O_2N_2S$: N, 11.96; S, 13.69. Found: N, 11.72, 11.85; S, 13.54.

4-(3,4-Dihydroxyphenyl)-2- β -phthalimidoethyl-thiazole.—The above thioamide and chloroacetocatechol interacted smoothly in alcohol solution. After warming for thirty minutes at the boiling water-bath temperature this new thiazole separated and was obtained in a crystalline condition after treating the crude reaction product with dilute sodium carbonate solution. It was purified by crystallization from boiling alcohol and separated, on cooling, in the form of needles melting at 203–205°.

Anal. Calcd. for $C_{18}H_{14}O_4N_2S$: N, 7.65; S, 8.75. Found: N, 7.58, 7.53; S, 8.63.

Sulfate of 4-(3,4-Dihydroxyphenyl)-2- β -aminoethyl-thiazole. II.—The above phthalimide compound was dissolved in hot alcohol and the theoretical quantity of hydrazine hydrate added to the solution. On evaporating the solvent, the reaction product was treated with dilute hydrochloric acid and the insoluble phthalylhydrazide separated by filtration. The hot acid filtrate of the thiazole amine was then mixed with a slight excess of dilute sulfuric acid, when the sulfate of the amine separated immediately in the form of colorless needles.

Anal. Calcd. for $C_{11}H_{12}O_2N_2S \cdot H_2SO_4$: N, 8.38; S, as sulfate, 9.59; total S, 19.19; C, 39.52; H, 4.19. Found: N, 8.27; S as sulfate, 9.64; total S, 19.37; C, 39.33; H, 4.05.

Summary

1. In this paper are described methods of synthesizing the two bridged thiazole amines, namely, 4-(3,4-dihydroxyphenylthiazole)-2- β -ethylamine and 4-(3,4-dihydroxyphenylthiazole)2- γ -propylamine.
2. The pharmacological study of both of these amines is now in progress.

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