water (50 ml.) containing a few drops of ammonium hydroxide and added to a boiling solution of hydrated ferrous sulfate (10 g. = 0.0360 mole) in water (25 ml.). Small portions of concentrated ammonium hydroxide were added until the mixture was definitely alkaline. The mixture was filtered hot with suction, and the filtrate acidified and allowed to stand overnight in an icebox. After filtering on a hardened filter, washing with water and drying, the cream colored precipitate weighed 0.7 g. (61% yield). It did not melt up to about 400°.

Anal. Calcd. for $C_{10}H_7O_5N$: C, 54.3; H, 3.19; N, 6.33; neut. equiv., 110.6. Found: C, 54.6, 54.4; H, 3.67, 3.25; N, 6.67, 6.40; neut. equiv., 111.9.

This amino acid burned at a red heat but left no residue. It gave a positive test for an amino group (diazotization and coupling with β-naphthol) but none for a nitro group (reduction with zinc dust and ammonium chloride solution). It was insoluble in cold or hot water, dilute acids, methanol, ethanol, ether, acetone, ethyl acetate or benzene, very slightly soluble in hot glacial acetic acid, but soluble in dilute sodium hydroxide, sodium carbonate, warm sodium bicarbonate, concentrated sulfuric or concentrated hydrochloric acid. Because of its insolubility in water or alcohol the neutralization equivalent was determined by solution in excess standard alkali and back titration with standard acid.

Summary

1. The cyclic hydrazide of 5-aminocoumarone-2,3-dicarboxylic acid has been prepared and characterized.
2. Nitration of coumarone-2,3-dicarboxylic acid has been shown to yield the hitherto unknown 5-nitrocoumarone-2,3-dicarboxylic acid and its structure has been demonstrated.
3. The interpolation of a furan nucleus between the two nuclei of an aminophthalhydrazide has been shown to cause substantial diminution in the oxidative chemiluminescence.

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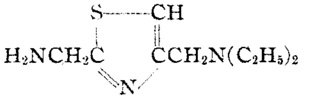
[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, NATIONAL MEDICAL COLLEGE OF SHANGHAI, CHINA]

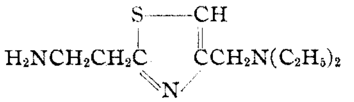
Thiazole Research: Synthesis of 2-Phthalimidomethyl-4-N-diethylamino-methylthiazole

BY YUOH-FONG CHI AND SHI-YUAN TSHIN[1]

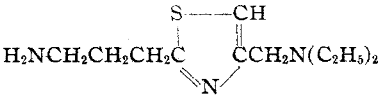
So far as the authors are aware, the diamines containing the thiazole ring, corresponding to the alkylene diamines, are not known. In this paper and in later communications the authors will describe the possible route and technique for the synthesis of the thiazole derivatives represented by formula I, II and III, respectively.



I



II



III

In this paper is described a method of synthesizing 2-phthalimidomethyl-4-N-diethylamino-methylthiazole—a derivative of 2-aminomethyl-4-N-diethylamino-methylthiazole I. This compound was obtained as follows: chloroacetonitrile,[2] which is prepared by heating chloroacetamide with phosphorus pentoxide, condensed with potassium phthalimide at 120–130° to give phthalimido-acetonitrile. Following the technique of Olin and Johnson,[3] an alcoholic solution of the latter is saturated with a stream of dry hydrogen sulfide gas, and phthalimido-acetothioamide is formed. Phthalimido-acetothioamide reacts in a characteristic manner with *sym*-dichloroacetone in an alcoholic solution to form 2-phthalimidomethyl-4-chloro-methylthiazole, which is then treated with diethylamine to give 2-phthalimidomethyl-4-N-diethylamino-methylthiazole. This latter compound is then treated with hydrazine hydrate to remove the phthalyl group, and the free amino compound I liberated. The properties of the free amino compounds will be discussed in a later paper.

So far as the authors are aware, *sym*-dichloroacetone has been used hitherto for thiazole syntheses only by Suter and Johnson,[4] Hinegardner

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[1] The authors desire to express here their appreciation of the help given by Professor Treat B. Johnson of Yale University in organizing this paper for publication.

[2] Scholl, *Ber.*, **29**, 2417 (1896); Steinkopf, *ibid.*, **41**, 2541 (1908); Bisschopinck, *ibid.*, **6**, 731 (1873).

[3] Olin and Johnson, *Rec. trav. chim.*, **50**, 72–76 (1931).

[4] Suter and Johnson, *ibid.*, **49**, 1066 (1930).

and Johnson,[5] and Hooper and Johnson.[6] By interaction with phthalimido-acetothioamide it makes possible the preparation of interesting chlorine compounds containing the halogen in an aliphatic side chain or reactive position, and is useful for fundamental synthesis involving the application of the principle of alkylation. In place of phthalimido-acetothioamide, one may use β-phthalimido-propionthioamide and γ-phthalimido-butyrothioamide; thus, the homologs of 2-phthalimidomethyl-4-chloro-methylthiazole theoretically may be obtained. These compounds also contain the halogen in an aliphatic side chain or reactive position and will be useful for fundamental syntheses. This work will be continued in this Laboratory.

Experimental Part

Chloroacetonitrile.—The following is a description of a modified procedure used by the authors for the preparation of this compound. Ninety-three and one-half grams of chloro-acetamide was mixed thoroughly with 158 g. of phosphorus pentoxide, and the mixture heated in an oil-bath at 120–150° for three hours. The crude nitrile was isolated by distilling the reaction mixture under a diminished pressure of 200 mm., which was gradually reduced to 11 mm. during the distillation. The resulting product was purified by distillation at atmospheric pressure, and boiled at 123–124°. The yield was 53.6 g. or 71% of the theoretical.

Phthalimido-acetonitrile, $C_6H_4(CO)_2NCH_2CN$.—The above chloronitrile was converted into the phthalimido derivative by heating it with potassium phthalimide at 120–130°. A mixture of 3.7 g. of potassium phthalimide and 1.5 g. of chloro-acetonitrile was heated at 120–130° until it was completely liquefied. After cooling, a second portion of 3.7 g. of potassium phthalimide and a second portion of 1.5 g. of chloro-acetonitrile were then added, and the process of heating at 120–130° was repeated. This process of adding the reacting components was repeated for five to ten times. The whole reaction mixture was then heated in an oil-bath at 120–130° for three hours. After crystallizing from absolute alcohol, phthalimido-acetonitrile separated in shining leaflets, melting at 118–120°. The yield was 77% of the theoretical. It crystallized from boiling water.

Anal. Calcd. for $C_{10}H_6O_2N_2$: N, 15.06. Found: N, 14.76, 14.88, 14.66.

Phthalimido-acetothioamide, $C_6H_4(CO)_2NCH_2CSNH_2$.—Eighteen grams of phthalimidoacetonitrile was dissolved in 200 cc. of absolute alcohol, containing 1.4 g. of triethanolamine. This solution was warmed on a water-bath and a current of dry hydrogen sulfide was passed through it for forty-eight hours. The solution was cooled, filtered, and the thioamide dried. It was purified by crystallization from boiling water and separated in golden needles, sintering at 155° and melting at 168–170°. The yield was 59% of the theoretical.

Anal. Calcd. for $C_{10}H_8O_2N_2S$: N, 12.73; S, 14.56. Found: N, 12.82, 12.35; S, 14.29, 14.39.

2-Phthalimido-methyl-4-chloromethyl-thiazole, C_6H_4-$(CO)_2NCH_2T$[7]CH_2Cl.—One and one-tenth grams of phthalimido-acetothioamide was heated with 0.64 g. of *sym*-dichloroacetone in 12 cc. of absolute alcohol on a water-bath for one hour. After being cooled for forty-five to sixty minutes, there was deposited a resin-like impurity on the walls of the vessel. The clear solution was then decanted and left to cool overnight in an icebox when 0.45 g. of crude 2-phthalimidomethyl-4-chloromethylthiazole separated out in the form of rhombic crystals. For purification it was recrystallized from absolute alcohol, and melted at 133–134.5°. The yield was 32% of the theoretical.

Anal. Calcd. for $C_{13}H_9O_2N_2SCl$: N, 9.58; Cl, 12.12; S, 10.96. Found: N, 9.43, 9.38; Cl, 11.83, 11.39; S, 10.81, 10.33.

2-Phthalimidomethyl-4-N-diethyl-amino-methylthiazole, $C_6H_4(CO)_2NCH_2TCH_2N(C_2N_5)_2$.—Two and six-tenths grams of 2-phthalimidomethyl-4-chloromethylthiazole was heated with 2.1 cc. of diethylamine in 40 cc. of absolute alcohol on a water-bath for six hours. After removing the solvent by distillation there was left a residue which was extracted thoroughly with ether. On concentration of the ethereal solution by evaporating off ether in a vacuum desiccator, there separated out 1.4 g. of crude 2-phthalimidomethyl-4-N-diethylaminomethylthiazole. It was purified by recrystallization from ether and melted at 92–93.5°. The yield was 46% of the theoretical.

Anal. Calcd. for $C_{17}H_{19}O_2N_3S$: S, 9.74. Found: S, 9.70.

Summary

1. Phthalimido-acetonitrile is obtained by heating chloroacetonitrile with potassium phthalimide at 120–130°.

2. Phthalimido-acetonitrile reacts with hydrogen sulfide in absolute alcohol in the presence of triethanolamine to form phthalimido-acetothioamide.

3. Phthalimido-acetothioamide interacts with *sym*-dichloroacetone in an alcoholic solution to form 2-phthalimidomethyl-4-chloromethylthiazole.

4. 2 - Phthalimidomethyl - 4 - N - diethylamino-methylthiazole is formed by the action of diethylamine upon 2-phthalimidomethyl-4-chloromethylthiazole in alcoholic solution.

SHANGHAI, CHINA

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[5] Hinegardner and Johnson, THIS JOURNAL, **52**, 3724–3727 (1930); **52**, 4139–4144 (1930); **52**, 4141–4144 (1930).

[6] Hooper and Johnson, *ibid.*, **56**, 470–471 (1934).

[7] T = Thiazole nucleus