"activated" complexes. To form pentene-1, the pentamethylene diradical must momentarily form a five-membered ring involving one of the beta hydrogen atoms. This ring is slightly more strained than is the five-membered homocyclic ring leading to cyclopentane formation because of the shorter carbon–hydrogen bond distances. However, in the five-membered rings the strain is not large and hence both activated complexes may involve comparable activation energies, as evidenced by comparable yields of pentene-1 and of cyclopentane. In contrast to this, tetramethylene and trimethylene diradicals must form either four- or three-membered rings involving beta hydrogen to rearrange into corresponding olefins. The absence of these olefins among the products suggests that such rings involve much larger strain and hence larger activation energies than homocyclic rings with the same total number of atoms.

These considerations are offered in a preliminary manner and it is hoped that further and more quantitative work will test them adequately.

Summary

Cyclohexanone, cyclopentanone and cyclobutanone have been prepared and their absorption spectra and vapor pressures measured. The ketones have been subjected to photochemical decomposition in a flow system and the products analyzed, runs being made over the temperature range 150–350° and the pressure range 30–200 mm.

It has been found that the ratio of the quantities of gaseous products formed is independent of both the temperature and the pressure. Condensation products were formed only in the case of cyclohexanone and the quantity of these products depends on both temperature and pressure.

The data have been correlated with other data and a consistent hypothesis suggested as to the nature of the intermediates. The primary process is presumed to be absorption of light with the splitting of one bond and the formation of a polymethylene diradical. The previous work of Norrish is shown to be open to experimental criticism and errors in his data are explained.

The photolysis of cyclopentanone suggests a convenient method for the synthesis of cyclobutane.

CAMBRIDGE, MASS. RECEIVED OCTOBER 24, 1941

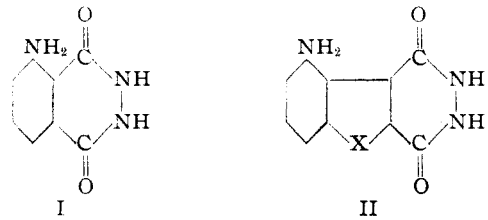
[CONTRIBUTION NO. 255 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of 5-Aminocoumarone-2,3-dicarboxylic Acid Cyclohydrazide. A Heterocyclic Analog of 4-Aminophthalhydrazide

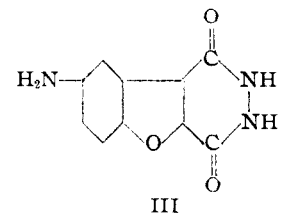
BY ERNEST H. HUNTRESS AND WILLIAM M. HEARON[1,2]

In connection with studies of the influence of structure upon the chemiluminescence observed during the oxidation of "Luminol" (I)[3] more information regarding the effect of interposition of another ring between the carbocyclic nucleus carrying the amino group and the heterocyclic cyclohydrazide ring was desired. The most desirable compounds for this purpose would possess the structure II (X = O, S, or =NH).

Such cyclohydrazides should be readily preparable from appropriately substituted nitro-2,3-di-



I II



III

carboxylic acids of the coumarone, thionaphthene, or indole series. Unfortunately, however, not one of these nitro acids has been reported.

(1) This paper is constructed from part of a dissertation submitted in June, 1940, by Dr. Hearon to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Eastman Kodak Company, Rochester, New York.

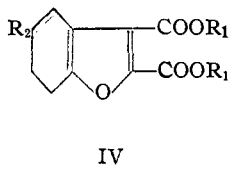
(3) Huntress, Stanley and Parker, *J. Chem. Education*, **11**, 142-145 (1934).

In the coumarone series, however, the ultimate preparation of II (X = O) would require 4-nitrocoumarone-2,3-dicarboxylic acid. At the time of this work, this particular isomer seemed difficult to obtain from available intermediates. On the other hand, in view of the relative accessibility of coumarone-2,3-dicarboxylic acid[4] and the probability that its mononitration would yield mainly 5-nitrocoumarone-2,3-dicarboxylic acid, the synthesis of 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide (III) appeared relatively straightforward.

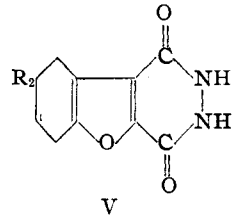
This structure (III) bears to that of 4-aminophthalhydrazide the same relationship that structure II (X = O) bears to 3-aminophthalhydrazide (I). Furthermore, the oxidation of 4-aminophthalhydrazide furnishes a chemiluminescence nearly as great as that from "Luminol" itself. For preliminary examination at least, the influence of the interpolated furan nucleus can be effectively determined from a comparison of structure III with 4-aminophthalhydrazide without the necessity for the preparation of structure II (X = O).

The present paper reports the preparation of 5-nitrocoumarone-2,3-dicarboxylic acid and its conversion to 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide.

Nitration of coumarone-2,3-dicarboxylic acid[4] with a mixture of concentrated and fuming nitric acid readily gave 5-nitrocoumarone-2,3-dicarboxylic acid (IV, R_1 = H, R_2 = NO_2). That the principal nitration product is a mononitrodibasic acid is attested by color reactions, combustion analyses, and neutralization equivalent. That



IV



V

the nitro group is actually located in the 5-position is evidenced by the formation of 5-nitrosalicylic acid when the material is oxidized with potassium permanganate. Of the four possible nitrosalicylic acids which could conceivably result from oxidation of a mononitrocoumarone-2,3-dicarboxylic acid, the 3-nitro isomer (m. p. 145°) and its methyl ester methyl ether (m. p. 60°) both have melting points far below those observed for our oxidation product. Although 4-nitrosalicylic acid itself melts at 235° (which value is not far from our product), yet its methyl ester methyl ether (m. p. 88–89°) is quite different from ours. Although 6-nitrosalicylic acid and its methyl ether methyl ester are as yet unreported, the concurrence of our melting points and mixed melting points with those for 5-nitrosalicylic acid and its methyl ether methyl ester constitutes positive evidence for the structure of our degradation product and hence for our 5-nitrocoumarone-2,3-dicarboxylic acid.

Attempts to convert dimethyl 5-nitrocoumarone-2,3-dicarboxylate to the corresponding cyclohydrazide by the method[4a] successfully employed in the parent series were uniformly unsuccessful. The desired product was obtained, however, by nitration of coumarone-2,3-dicarboxylic acid cyclohydrazide[4a] itself. Under conditions which minimize oxidation 5-nitrocoumarone-2,3-dicarboxylic acid cyclohydrazide was obtained in 82% yield. Its structure is evidenced by its identity with the cyclohydrazide obtained by the action of hydrazine hydrate upon 5-nitrocoumarone-2,3-dicarboxylic acid and by its oxidation with concd. nitric and concd. sulfuric acids at 35° to that acid. Since the introduction of the nitro group into the parent hydrazide can thus be effected as easily as by the alternative method of nitrating the acid and then converting it to the hydrazide, we prefer the former route as a method of preparation.

The preparation of dimethyl 5-aminocoumarone-2,3-dicarboxylate from 5-nitrocoumarone-2,3-dicarboxylic acid could conceivably be effected either by reducing first and afterward esterifying or esterifying first and afterward reducing. The second sequence using catalytic reduction proved successful. Although the reduction of 5-nitrocoumarone-2,3-dicarboxylic acid to 5-aminocoumarone-2,3-dicarboxylic acid gave a 61% yield, the methylation of this product proved unsatisfactory. Diazomethane not only esterified the carboxyl groups, but also methylated the amino group, giving a mixture of materials from which the only isolable product appeared to be dimethyl 5-dimethylaminocoumarone-2,3-dicarboxylate (m. p. 65–67°). When the silver salt of the amino acid was heated with methyl iodide either together or mixed with xylene, the original silver salt was recovered unchanged. The action of dimethyl sulfate upon an alkaline solution of the amino acid was also ineffective.

(4) (a) Huntress and Hearon, THIS JOURNAL, 63, 2762 (1941); (b) Koelsch and Whitney, *ibid.*, 63, 1762 (1941).

The desired 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide was obtained both by ferrous sulfate and alkali reduction of the corresponding nitrohydrazide and from dimethyl 5-aminocoumarone-2,3-dicarboxylate on heating with 87% hydrazine hydrate. Since the material showed no melting point, the identity of the product from the two methods was demonstrated by the spectrophotometric identity of the resultant dyestuffs obtained by diazotization and coupling with β-naphthol.

The oxidation of 5-aminocoumarone-2,3-dicarboxylic acid cyclohydrazide under the conditions which Drew and Pearman[5] employed for other cyclohydrazides gave definitely less luminescence than that obtained under identical conditions from 4-aminophthalhydrazide.

Experimental

All melting points given are uncorrected.

5-Nitrocoumarone-2,3-dicarboxylic Acid (IV, R_1 = H, R_2 = NO_2).—Coumarone-2,3-dicarboxylic acid (5 g.), stirred to a thin paste with 15 ml. of concentrated nitric acid (d. 1.42), was treated with 15 ml. of fuming nitric acid (d. 1.5), with stirring and warming at 100° until solution was complete. After one minute the solution was cooled, poured into four volumes of ice water and allowed to stand for an hour. The precipitated product was filtered, washed with 20 ml. of cold 5% nitric acid and dried at 100° until no test for nitrate was given by diphenylamine-sulfuric acid reagent. The yield was 4.6 g. (75% theoretical); m. p. 282–284°.

Anal. Calcd. for $C_{10}H_6O_7N$: N, 5.58; neut. equiv., 125.6. Found: N, 5.68, 5.44; neut. equiv., 127.

The product was a fine white powder soluble in water, methanol, ethanol, and acetone; slightly soluble in ethyl acetate, cold glacial acetic acid, or benzene; insoluble in ether, chloroform, ligroin, or petroleum ether.

This material gave a positive test for nitro group by the tests of Mulliken,[6] Hearon and Gustavson,[7] and by that of Janovsky,[8] the latter indicating also that only one nitro group was present.

Although the α,β relationship of the two carboxyl groups is beyond doubt, yet the compound failed to give an anhydride and even after refluxing three hours with excess acetic anhydride was recovered (70%) in unchanged condition.

Evidence for the Position of the Nitro Group.—On oxidation of 0.5 g. of the acid dissolved in 10% sodium hydroxide solution (2 ml.) plus 20 ml. of water with potassium permanganate (1 g.) at 100° for one hour, acidification gave 16% of the theoretical amount of 5-nitrosalicylic acid, m. p. 224–226° (recorded[9] 228°). This material did not depress the melting point of an authentic sample and gave, on methylation with diazomethane, methyl 2-methoxy-5-nitrobenzoate, crystals from methanol, m. p. 97–98° (recorded[10] 99–100°), which did not depress the melting point of material similarly prepared from authentic 5-nitrosalicylic acid.

Dimethyl 5-Nitrocoumarone-2,3-dicarboxylate (IV, R_1 = CH_3, R_2 = NO_2).—The acid (1.6 g.), finely powdered and suspended in ether (20 ml.), was treated with excess ethereal diazomethane until evolution of nitrogen ceased and the mixture acquired a permanent yellow color. Since both the original acid and the resultant ester were insoluble in ether, a solid phase was present throughout. After evaporation of the solvent and recrystallization from hot methanol the desired ester was obtained (84% yield) as white needles, m. p. 150–151°.

Anal. Calcd. for $C_{12}H_9O_7N$: C, 51.6; H, 3.25; N, 5.02. Found: C, 51.6, 51.4; H, 3.23, 3.25; N, 5.06, 5.25.

The product was insoluble ine ither cold or hot water, in dilute aqueous sodium carbonate or dilute sodium hydroxide. It was readily soluble in hot methanol, ethanol, acetone, ethyl acetate or glacial acetic acid; slightly soluble in cold methanol, ethanol, or ether.

Attempts to determine the saponification equivalent of this compound by means of heating with excess standard alcoholic potassium hydroxide and back titration with standard hydrochloric acid always yielded low results, *e. g.*, 128, 129; calcd. 139.5.

This nitro ester was also obtained from dimethyl coumarone-2,3-dicarboxylate by nitration at −10 to −15° with fuming nitric acid (d. 1.50).

5-Nitrocoumarone-2,3-dicarboxylic Acid Cyclohydrazide (V, R_2 = NO_2)

A. From Coumarone-2,3-dicarboxylic Acid Cyclohydrazide by Nitration.—Coumarone-2,3-dicarboxylic acid cyclohydrazide (1.0 g.) cooled in solid carbon dioxide was treated with fuming nitric acid (20 ml. of d. 1.50) which had previously been cooled to −15°. Keeping the temperature below −10°, the mixture was stirred until solution had occurred (about ten minutes). The liquid was then poured into four volumes ice water, and the precipitate filtered, washed with water and dried. The weight of pale tan product melting at 332–333° uncor. was 1.0 g. representing 82% theoretical yield. Even better yields (90%) were obtained by dissolving the cyclohydrazide (1.0 g.) in concentrated sulfuric acid (10 ml.) at room temperature, cooling in dry-ice to a viscous sirup and then adding concentrated nitric acid (10 ml.) previously cooled to −20°, m. p. 335–336°.

Attempts to obtain satisfying analytical data on this compound were disappointing. Attempts to obtain a neutralization equivalent by solution in standard alkali followed by back titration with acid gave low values. (This same behavior was observed in the saponification of dimethyl 5-nitrocoumarone-2,3-dicarboxylate.) In attempts at combustion the compound was so refractory that results were erratic.

Acetyl Derivative.—Satisfactory analyses were obtained, however, on the corresponding monoacetyl derivative. This was prepared from the nitrohydrazide by dissolving

(5) Drew and Pearman, *J. Chem. Soc.*, 588 (1937).

(6) Mulliken, "Identification of Pure Organic Compounds," Vol. II, 1916, p. 32.

(7) Hearon and Gustavson, *Ind. Eng. Chem., Anal. Ed.*, **9**, 352–353 (1937).

(8) Janovsky, *Ber.*, **24**, 971–972 (1891).

(9) Beilstein, Vol. X, p. 117.

(10) Simonsen and Rau, *J. Chem. Soc.*, **111**, 229 (1917).

0.2 g. in 50 ml. of warm 10% sodium hydroxide, diluting with 50 ml. of water, and treating with excess acetic anhydride at 4°. It was necessary to avoid any preliminary precipitation of the moderately soluble sodium salt of the hydrazide, and best results were obtained when the solution was supersaturated. The grainy yellow acetate was found to melt at 241–243°.

Anal. Calcd. for $C_{12}H_7O_6N_3$ (monoacetyl): C, 49.8; H, 2.42; for $C_{14}H_9O_7N_3$ (diacetyl): C, 50.8; H, 2.72. Found: C, 49.7, 49.5; H, 2.90, 2.81.

The parent hydrazide was insoluble in cold water and in the usual organic solvents, very sparingly soluble in hot water, somewhat more soluble in hot glacial acetic acid. It was readily soluble in aqueous sodium hydroxide, carbonate or even bicarbonate, yielding an orange-red solution from which a moderately soluble red sodium salt precipitated in gelatinous form on cooling. Because of its sparing solubility in organic solvents, purification was most easily effected by reprecipitation from alkaline solution.

The compound gave a positive test for one nitro group by Janovsky's reaction,[8] and its aqueous solution was colored orange by ferric chloride. When mixed with a sample of the corresponding product from 5-nitrocoumarone-2,3-dicarboxylic acid (see below) of m. p. 331–332°, the mixture melted at 329–330°. Since a mixture of this product (m. p. 332–333°) with the unnitrated parent hydrazide (m. p. 316–318°) was depressed to 300–306°, the nitro hydrazides from the two methods were concluded to be identical.

The nitrated hydrazide of coumarone-2,3-dicarboxylic acid (0.020 g.) dissolved in concd. sulfuric acid (1 ml.), and treated at 0° with concd. nitric acid (1 ml.) immediately evolved heat and gas. After being poured into water and cooled a small precipitate of 5-nitrocoumarone-2,3-dicarboxylic acid, m. p. 282–284°, was obtained. This product did not depress the melting point of an authentic sample of the latter material.

Use of Mixed Acids.—Coumarone-2,3-dicarboxylic acid cyclohydrazide (1.0 g.) was dissolved at room temperature in concentrated sulfuric acid (10 ml.), and the solution cooled in solid carbon dioxide. To the resultant viscous sirup was added concentrated nitric acid (10 ml.) previously cooled to −20°. The mixture was stirred and kept in the freezing bath, but the heat of reaction raised the temperature to +5° and a little gas was evolved. When the temperature had again dropped to −5°, the mixture was poured into ice water (50 ml.) and the resultant white precipitate filtered, washed and dried. The yield was 1.1 g. (90% theoretical) melting at 335–336°. Since this product contained only one nitro group by Janovsky's test, and since it failed to depress the melting point of the material obtained by less vigorous nitration, it is concluded that they are identical.

B. From 5-Nitrocoumarone-2,3-dicarboxylic Acid.—A sample of 5-nitrocoumarone-2,3-dicarboxylic acid (1.0 g. = 0.004 mole) was dissolved in a solution of 87% hydrazine hydrate (0.23 g. = 0.04 mole) in water (20 ml.). After evaporation to dryness, the powdered solid was heated at 160–170° for three hours, then at 195 ± 5° for five hours more, both times in a gentle air stream. The brown solid was boiled with water (30 ml.) to remove any unchanged reactants, filtered off, dissolved in aqueous sodium carbonate, treated with decolorizing carbon and filtered. This latter purification was twice repeated. On acidification of the deep red filtrate a pale tan colored precipitate of 5-nitrocoumarone-2,3-dicarboxylic acid cyclohydrazide was obtained.

This material melted at 331–332°, gave a positive nitro group test, an orange color with ferric chloride, and did not reduce ammoniacal silver nitrate. The melting point of a mixture with the cyclohydrazide prepared by nitration was not depressed.

5-Aminocoumarone-2,3-dicarboxylic Acid Cyclohydrazide ($V, R_2 = NH_2$)

5-Nitrocoumarone-2,3-dicarboxylic acid cyclohydrazide (1.2 g. = 0.005 mole) dissolved in 50 ml. dilute ammonium hydroxide was added to a boiling solution of hydrated ferrous sulfate (9.5 g. = 0.034 mole) in water (30 ml.). After making the solution definitely ammoniacal with further small additions of concentrated ammonium hydroxide, the ferric hydroxide was removed by hot filtration, the filtrate cooled and barely acidified. After standing overnight in a refrigerator, the resultant yellowish-brown precipitate was filtered, washed and dried. This proved to contain a trace of iron which was therefore removed by reprecipitating from ammoniacal solution as before. The yellow needles thus obtained weighed 0.42 g. (40% theory), and decomposed without true fusion from about 330°.

Anal. Calcd. for $C_{10}H_7O_5N_3$: C, 55.3; H, 3.25; N, 19.35; neut. equiv., 217.2; NH_2, 7.37. Found: C, 51.1, 51.0; H, 4.2, 4.9; N, 19.2; neut. equiv., 218; NH_2, 7.31.

The product gave no test for a nitro group, but on diazotization and coupling with alkaline β-naphthol gave a red-orange color. It did not reduce ammoniacal silver nitrate. It was insoluble in water (either cold or hot), alcohol, ether, acetone, ethyl acetate or benzene; slightly soluble in hot glacial acetic acid; and soluble both in warm dilute alkalies, bicarbonates or dilute acids.

Dimethyl 5-Aminocoumarone-2,3-dicarboxylate ($IV, R_1 = CH_3, R_2 = NH_2$).—The nitro ester (1.9 g. = 0.0068 mole), dissolved in warm glacial acetic acid (100 g.) containing 20 mg. Adams catalyst, was reduced with hydrogen at ordinary pressure. This absorbed 520 ml. of hydrogen at 25° and 760 mm. pressure in forty-five minutes (theoretical 500 ml.). After filtration from the catalyst and concentration to 20 ml. under reduced pressure, the solution was diluted to 50 ml. with water and made slightly basic with concentrated ammonium hydroxide. From the cold solution a heavy yellow precipitate separated; weight 1.7 g. (100%). After recrystallization from hot methanol the yield was 1.5 g. (88%) of fine yellow needles, m. p. 137–138°.

Anal. Calcd. for $C_{12}H_{11}O_6N$: C, 57.8; H, 4.45; sap. equiv., 124.6; NH_2, 6.43. Found: C, 57.6, 57.6; H, 4.49, 4.13; sap. equiv. 123.1; NH_2, 6.47.

The compound was insoluble in cold water, cold dilute aqueous sodium hydroxide or sodium carbonate; it was slightly soluble in hot water or benzene; and soluble in dilute acids, methanol, ethanol, ethyl acetate, acetone, or glacial acetic acid.

5-Aminocoumarone-2,3-dicarboxylic Acid ($IV, R_1 = H, R_2 = NH_2$).—A sample of 5-nitrocoumarone-2,3-dicarboxylic acid (1.3 g. = 0.0059 mole) was dissolved in

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.

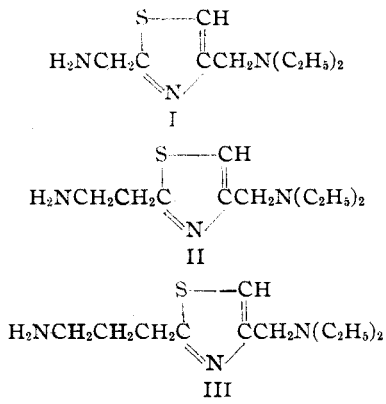
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 23, 1941

[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.



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

(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).