to rearrange with inversion of the crotyl group into O-methylvinylcarbinyl-N-methyl-N-phenylhydroxylamine (XI).

On the basis of this case of rearrangement with inversion, an intramolecular, cyclic mechanism for the reaction is proposed. The rearrangement is related to the Claisen and similar rearrangements in the same way that dyad and triad prototropic systems are related.

New York, N. Y. Received August 14, 1944

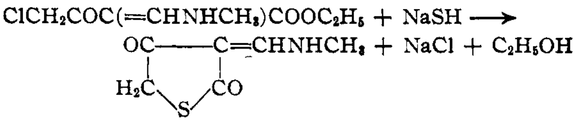
[Contribution from the Research Laboratories of Winthrop Chemical Co., Inc.]

2-Phenylthiolane[1] Derivatives

By A. R. Surrey, H. F. Hammer and C. M. Suter

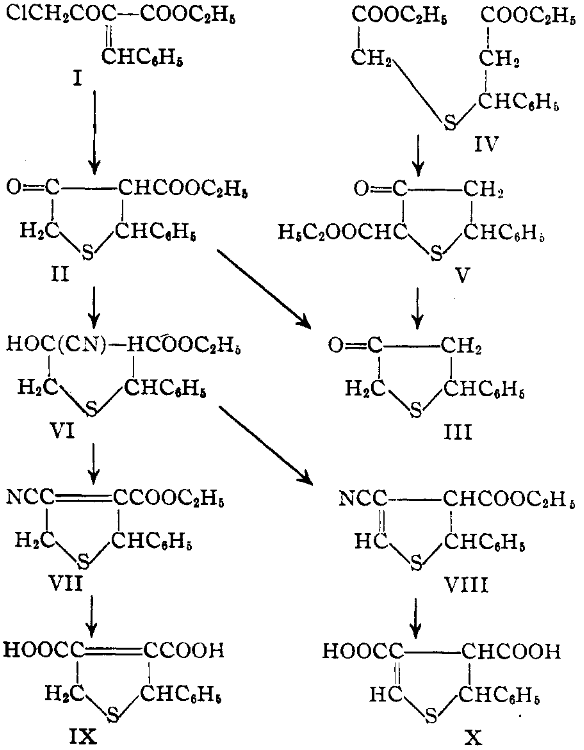
The establishment of the structure for one of the forms of biotin by du Vigneaud and coworkers[2] has increased greatly the interest in compounds of the thiolane series, particularly those substituted in the 2-, 3- and 4-positions. The present paper deals with the synthesis and some reactions of 2-phenylthiolane derivatives which also have substituents in other positions of the heterocyclic nucleus. Several substituted thiolenes (dihydrothiophenes) were also prepared during the course of the investigation.

The reaction of sodium hydrosulfide with ethyl α-methylaminomethylene-γ-chloroacetoacetate has been shown[3] to give methylaminomethylenethiotetronic acid. It seemed possible that ring closure in this type of compound might under the proper conditions be induced to occur through addition of the thiol group across the *alpha* double bond. In accord with this idea it has now been found that when ethyl α-benzylidene-γ-chloroacetoacetate (I) is added to one equivalent of sodium hydrosulfide in absolute alcohol, sodium chloride separates immediately and 3-carbethoxy-2-phenyl-4-thiolanone (II) is formed as the principal product. If the reaction mixture is kept cold during the addition of the chloro ester a considerable amount of another compound is produced.



Although this was not studied extensively, it appears to be the thiolactone, 3-benzylidene-2,4-thiolanedione. The ethyl α-benzylidene-γ-chloroacetoacetate was prepared from benzaldehyde and ethyl γ-chloroacetoacetate either in the presence of hydrogen chloride[4] or piperidine acetate,[5] the latter catalyst giving the best results.

The keto ester, II, undergoes reactions similar to those reported for ethyl 1-cyclopentanone-2-carboxylate.[6] It gives a reddish-brown color with ferric chloride solution and forms a characteristic green copper salt, a 2,4-dinitrophenylhydrazone, m. p. 144–144.5°, an anil, and an anilanilide, m. p. 161–162°.



When carbethoxymethyl β-carbethoxy-α-phenylethyl sulfide (IV), obtained by the reaction of ethyl thioglycolate with ethyl cinnamate in the presence of piperidine, was cyclized by means of sodium ethoxide in ether at room temperature[7] an isomeric ester, 5-carbethoxy-2-phenyl-4-thiolanone (V) was obtained. Some ethyl cinnamate was also formed during the reaction. This second keto ester, V, gives a bluish color with ferric chloride and no copper salt could be obtained. In addition V gives a 2,4-dinitrophenylhydrazone, m. p. 158–159°, and an

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[1] This is the name given in "Ring Index" by Patterson and Capell. The terms "thiophane" and tetrahydrothiophene have also been used for this ring system.

[2] du Vigneaud, *Science*, **96**, 455 (1942).

[3] Bernary and Ebert, *Ber.*, **56**, 1897 (1923).

[4] Claisen, *Ann.*, **218**, 170 (1883).

[5] Cope and Hofmann, This Journal, **63**, 3456 (1941).

[6] Dieckmann, *Ann.*, **317**, 51 (1901); Linstead and Wang, *J. Chem. Soc.*, 807 (1937).

[7] Bennett and Scorah, *J. Chem. Soc.*, 194 (1927), cyclized bis-(β-carbethoxyethyl) sulfide to the keto ester by a similar procedure.

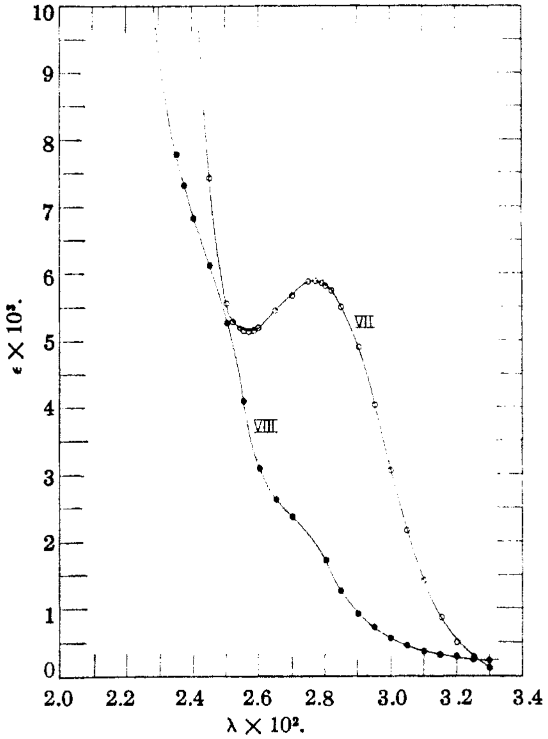

Fig. 1.—Absorption curves of compounds VII and VIII.

anil-anilide, m. p. 153–154°. Mixed melting points of the same derivatives from the keto-esters II and V were depressed. On acid hydrolysis, both keto-esters gave the same ketone, 2-phenyl-4-thiolanone (III). A mixed melting point of their semicarbazones showed no depression. Inasmuch as the only keto-ester that can be formed from I and sodium hydrosulfide is II, there can be little doubt that the structure of the isomer V formed from III with sodium ethoxide must be that indicated.

Woodward and Eastman[8] have recently reported the preparation of two isomeric thiolane keto-esters, 4-carbomethoxy-3-thiolanone[9] and 2-carbomethoxy-3-thiolanone, by the cyclization of carbomethoxymethyl β-carbomethoxyethyl sulfide. The latter keto-ester was prepared at room temperature in ether with sodium methoxide. The structure assigned to this compound appears to be in agreement with our work.

Alkaline hydrolysis of II did not give a dicarboxylic acid but rather cinnamic acid. This is analogous to the rupture of the sulfur–carbon bond in β-keto thioethers[10] to give unsaturated ketones. Oxidation of II with hydrogen peroxide gave both the thiolane oxide and the dioxide. On treatment of II with hydrazine hydrate a small yield of the corresponding pyrazolone derivative was obtained.

The keto-ester II reacts with hydrogen cyanide to give 3-carbethoxy-4-cyano-4-hydroxy-2-phenylthiolane (VI). Depending upon the conditions used, the cyanohydrin VI, on treatment with thionyl chloride and pyridine, gives two isomeric dihydrothiophene derivatives. At low temperatures the main product, melting at 77–78.5°, appears to be 3-carbethoxy-4-cyano-2-phenyl-4-thiolene (VIII). When the reaction was carried out at room temperature the main product was 3-carbethoxy-4-cyano-2-phenyl-3-thiolene (VII), melting at 115–116°. The structures were assigned mainly on the basis of their absorption spectra[11] (Fig. 1). Compound VII seemed to show a higher degree of conjugated unsaturation. Alkaline hydrolysis of the two cyano esters gave two dibasic acids, 3-thiolene-3,4-dicarboxylic acid (IX) and the 4-thiolene-3,4-dicarboxylic acid (X).[12]

Experimental

Ethyl α-Benzylidene-γ-chloroacetoacetate (I).—A mixture of 55 g. (0.33 mole) of ethyl γ-chloroacetoacetate and 36 g. (0.34 mole) of benzaldehyde was cooled to 0°, saturated with dry hydrogen chloride and allowed to stand at room temperature for five days. The mixture was cooled in ice and the water which separated was decanted from the viscous oil. The oil was heated on a steam-bath under reduced pressure with a stream of carbon dioxide bubbling through it. When the mixture became clear the oil was distilled to give 12 g. of unreacted ethyl γ-chloroacetoacetate, and 37 g. (44%) of product boiling at 165–175° (3.5 mm.). On redistillation most of the product came over at 165–166° (2 mm.).

Anal. Calcd. for $C_{13}H_{13}O_3Cl$: C, 61.78; H, 5.15; Cl, 14.02. Found: C, 61.47; H, 4.81; Cl, 14.36.

A mixture of 51.3 g. (0.312 mole) of ethyl γ-chloroacetoacetate, 36.1 g. (0.340 mole) of benzaldehyde, 1.1 g. of piperidine, 3.8 g. of acetic acid and 30 cc. of benzene was refluxed until no more water was collected in a water separator connected to the apparatus. After two to three hours the calculated amount of water was collected. The reaction mixture was cooled to room temperature and taken up in about 200 cc. of ether, washed three times with 60-cc. portions of water and dried over sodium sulfate. After removing the ether 45.8 g. of product (58%) was collected at 149–151° (0.5 mm.).

3-Carbethoxy-2-phenyl-4-thiolanone (II).—A solution of 45.8 g. of ethyl α-benzylidene-γ-chloroacetoacetate in 125 cc. of absolute alcohol was added with stirring over a period of ten to fifteen minutes to 117.5 cc. of 2 *N* sodium ethylate which had been saturated with hydrogen sulfide. The temperature rose to about 40°. After stirring for several hours the sodium chloride which separated was filtered off and the filtrate evaporated under reduced pressure. Ice and acetic acid were added to the residue and then extracted with ether. The combined ether extractions were extracted with several portions of 5% potassium hydroxide. Each extraction was immediately acidified

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[8] Woodward and Eastman, This Journal, 66, 849 (1944).

[9] The corresponding ethyl ester has been prepared in a similar manner by Buchman and Cohen, *ibid.*, 66, 846 (1944), and Karrer and Schmid, *Helv. Chim. Acta*, 27, 116 (1944).

[10] Nicolet, This Journal, 53, 3066 (1931).

[11] The absorption spectra of alcoholic solutions of VII and VIII were determined on a Beckman Quartz Spectrophotometer by J. R. McCormick.

$$\epsilon = \frac{1}{cl}\log_{10}\left(\frac{I_0}{I}\right)$$

where I_0 and I are the intensities of light incident upon and emerging from the absorption cell, respectively; where c is the concentration in moles/liter and where l is the thickness of the cell in cm. λ = wave length in millimicrons.

[12] Of the two isomeric cyclopentenedicarboxylic acids reported by Birendra Lal Nandi, *C. A.*, 28, 4389 (1934), the higher melting one has, as in our series, the greater degree of conjugated unsaturation.

with acetic acid to give a light tan colored solid. The combined solids were filtered, washed with water and dried, yield, 30.5 g. (67%) m. p. 71–72°. A sample was purified by recrystallization from methyl alcohol, m. p. 76–77°. It gave a reddish-brown color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{14}O_3S$: C, 62.4; H, 5.6; S, 12.8. Found: C, 62.3; H, 5.1; S, 12.5.

Copper Salt.—To a solution of 0.25 g. of II in 5 cc. of alcohol was added a slight excess of an aqueous solution of copper sulfate. When the calculated amount of dilute ammonium hydroxide was added the green copper salt separated. It was recrystallized from alcohol; m. p. 166°.

Anal. Calcd. for $C_{26}H_{12}O_6S_2Cu$: Cu, 11.32. Found: Cu, 11.46.

Anil-anilide.—The method corresponds to that employed by Linstead and Wang[6] for the ethyl cyclopentanonecarboxylate. To a mixture of 5 g. of II, 10 cc. of xylene and 2 drops of pyridine at 130–140° was added dropwise, over a period of three hours, a mixture of 1.86 g. of aniline, 7 cc. of xylene and one drop of pyridine. The mixture was kept at 130–140° for two additional hours and the solvent was removed under reduced pressure. The residue was shaken with 4 per cent. sodium hydroxide. The gummy residue was warmed with alcohol and the crystalline solid which separated was filtered off and recrystallized from a large volume of alcohol, m. p. 161–162°.

Anal. Calcd. for $C_{23}H_{20}N_2OS$: N, 7.53. Found: N, 7.77.

2,4-Dinitrophenylhydrazone.—A mixture of 0.85 g. of dinitrophenylhydrazine and 1 g. of II in 50 cc. of alcohol was brought to reflux and 1 cc. of concentrated hydrochloric acid added. Refluxing was continued for five minutes and the solution was allowed to cool. The solid which separated was filtered off and recrystallized from alcohol, m. p. 144–145.5°.

Anal. Calcd. for $C_{19}H_{18}N_4O_6S$: N, 13.02. Found: N, 13.08.

Anil.—One gram of II, 0.375 g. of aniline and one drop of glacial acetic acid was allowed to stand for ten days in a desiccator over potassium hydroxide. On stirring solidification occurred. The solid was recrystallized several times from alcohol, m. p. 84–85°.

Anal. Calcd. for $C_{19}H_{19}NO_2S$: N, 4.31. Found: N, 4.45.

3-Carbethoxy-4-cyano-4-hydroxy-2-phenylthiolane (VI).—Concentrated hydrochloric acid (51.6 cc.) was added over a period of forty-five minutes to a well-stirred mixture of 30 g. of II in 300 cc. of alcohol and 30 g. of sodium cyanide in 75 cc. of water. The temperature of the reaction mixture was kept at about 20°. After stirring for one hour longer at 20°, the reaction mixture was cooled to 5° and the solid which had separated from solution was filtered off and washed with water. An additional amount of product was obtained from the filtrate. After recrystallization from a 50% mixture of benzene and Skellysolve C the product melted at 120–121°; yield, 24.5 g. A sample recrystallized for analysis melted at 123.5–124.5°.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: N, 5.09. Found: N, 4.86, 4.98.

3-Carbethoxy-4-cyano-2-phenyl-3-thiolene (VII).—Thionyl chloride (6.5 cc.) was added dropwise with stirring and ice cooling, to a solution of 10 g. of the cyanohydrin (VI) in 50 cc. of pyridine. After stirring for one hour the reaction mixture was allowed to stand at room temperature overnight and then poured into ice water. The mixture was made acid to congo red with hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, 10% sodium hydroxide, water, and then dried over sodium sulfate. Evaporation of the ether gave 5 g. of a solid melting at 113–116°. A sample recrystallized from Skellysolve C melted at 115–116°.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: N, 5.41. Found: N, 5.46.

3-Carbethoxy-4-cyano-2-phenyl-4-thiolene (VIII).—The procedure was essentially the same as for the 2,6-dihydro derivative except that the reaction mixture was stirred for two hours with cooling and then allowed to stand in the refrigerator overnight. The product obtained after removal of the ether was recrystallized from Skellysolve C to give 6 g. of product melting at 77–78.5°.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: N, 5.41. Found: N, 5.60.

2-Phenyl-3-thiolene-3,4-dicarboxylic Acid (IX).—The nitrile ester VII (2.6 g.) was refluxed in 23.6 cc. of 22% sodium hydroxide for seven hours. The solution was filtered with charcoal, cooled in ice and acidified with concentrated hydrochloric acid. The white solid which separated was filtered off and then recrystallized from acetic acid, yield 2.3 g., m. p. 242–244° dec.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.6; H, 4.0; neutral equivalent, 125. Found: C, 57.7; H, 3.6; neutral equivalent, 124.

2-Phenyl-4-thiolene-3,4-dicarboxylic Acid (X).—One gram of the cyano ester (VIII) was refluxed for sixteen hours in 40 cc. of 50% alcohol solution containing 3 g. of potassium hydroxide, cooled and acidified with hydrochloric acid. The solid was filtered off and recrystallized from dilute acetic acid and then dried in a pistol dryer. The product melted at 187–188°.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.6; H, 4.0; neutral equivalent, 125. Found: C, 57.5; H, 4.0; neutral equivalent, 123, 124.

2-Phenyl-4-thiolanone (III).—Ten grams of the keto ester II was refluxed for six and one-half hours in 125 cc. of 3 *N* sulfuric acid. The solid which separated on cooling was filtered off and dried: yield 6 g., m. p. 53–55°. A sample recrystallized from Skellysolve C melted at 55–56°. It did not give a color test with ferric chloride solution.

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.42; H, 5.62. Found: C, 67.79; H, 5.35.

2,4-Dinitrophenylhydrazone, m. p. 131–132°.

Anal. Calcd. for $C_{16}H_{14}N_4O_4S$: N, 15.6. Found: N, 15.5.

Semicarbazone, m. p. 199–200°.

Anal. Calcd. for $C_{11}H_{13}N_3OS$: N, 17.9. Found: N, 17.8.

3-Carbethoxy-2-phenyl-4-thiolanone Oxide.—Five cc. of 27% hydrogen peroxide was added to a solution of 1 g. of the keto ester II in 15 cc. of glacial acetic acid, allowed to stand for one hour and then poured into ice water. The product was filtered off and recrystallized twice from alcohol, m. p. 139–140°. It gives a cherry-red color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{14}O_4S$: C, 58.6; H, 5.3. Found: C, 58.6; H, 5.1.

3-Carbethoxy-2-phenyl-4-thiolanone Dioxide.—Twenty-five cc. of 27% hydrogen peroxide was added to a solution of 5 g. of the keto ester II in 75 cc. of glacial acetic acid and allowed to stand for eighteen hours. The solution was poured into ice-water and the solid filtered off. After several recrystallizations from alcohol the product melted at 119–121°.

Anal. Calcd. for $C_{13}H_{14}O_5S$: C, 55.3; H, 4.9. Found: C, 54.9; H, 4.5.

Pyrazolone Derivative of II.—A mixture of 5 g. of the keto ester II and 1.5 g. of 85% hydrazine hydrate in 25 cc. of absolute alcohol was refluxed for seven hours and then allowed to stand overnight. The small amount of solid which separated was filtered off. On cooling the filtrate an additional amount of solid was obtained which after recrystallization from alcohol melted with decomposition at about 220°. On evaporation of the original filtrate a small amount of material was collected which after recrystallization from alcohol melted at 225–228° dec.

Anal. Calcd. for $C_{11}H_{10}N_2OS$: N, 12.87. Found: N, 12.82.

Hydrolysis of II with Sodium Hydroxide.—One gram of the keto ester II was stirred for several hours in 5% sodium hydroxide and then allowed to stand for three days. On acidification a solid separated which on recrystallization from Skellysolve B melted at 133°. A mixed melting point with a sample of cinnamic acid showed no depression.

Anal. Calcd. for $C_9H_8O_2$: C, 73.0; H, 5.4; neutral equivalent, 148. Found: C, 73.1; H, 5.1; neutral equivalent, 150.

Carbethoxymethyl-β-carbethoxy-α-phenylethyl Sulfide (IV).—A mixture of 11.7 g. (0.67 mole) of ethyl cinnamate, 8 g. (0.67 mole) of ethyl thioglycolate and five drops of piperidine was heated on the steam-bath for four and one-half hours and then distilled. Five grams of a forerun consisting of unreacted materials and 13.5 g. (69%) of product boiling at 163–165° at 2 mm. were collected.

Anal. Calcd. for $C_{15}H_{20}O_4S$: C, 60.8; H, 6.8. Found: C, 61.0; H, 7.2.

5-Carbethoxy-2-phenyl-3-thiolanone (V).—A solution of 34.5 g. of IV in 120 cc. of dry ether was added with stirring and cooling with an ice-salt mixture, to a suspension of 18.7 g. of sodium ethylate in 30 cc. of ether. Stirring and cooling were continued for six hours. After standing at room temperature overnight the reaction mixture was poured into ice water containing about 25 g. of acetic acid and extracted with ether. The ether was extracted with 5% potassium hydroxide and the alkaline extracts acidified with acetic acid. The oil which separated was taken up in ether and the ether was dried with sodium sulfate. Distillation of the product gave 10 g. of a light yellow oil boiling at 158–160° at 1 mm. It gives a bluish color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{14}O_3S$: C, 62.4; H, 5.6. Found: C, 62.7; H, 5.3.

2,4-Dinitrophenylhydrazone, m. p. 158–159°.

Anal. Calcd. for $C_{19}H_{18}N_4O_6S$: N, 13.02. Found: N, 13.02.

Anil-anilide, m. p. 153–154°.

Anal. Calcd. for $C_{23}H_{20}N_2OS$: N, 7.53. Found: N, 7.57.

Hydrolysis of V.—One and one-half grams of V was refluxed for four hours in 20 cc. of 15% sulfuric acid. The oil which separated on cooling was taken up in ether, the ether dried and evaporated. The residual oil (0.8 g.) was shaken with 10% sodium carbonate solution and again taken up in ether. After removing the ether the residue was recrystallized from Skellysolve A to give a product melting at 54°. It gave a semicarbazone melting at 199–200°. A mixed melting point with the semicarbazone prepared from III showed no depression.

Summary

A method is described for the preparation of 3-carbethoxy-2-phenyl-4-thiolanone from ethyl γ-chloroacetoacetate.

A series of reactions leading from this thiolane keto-ester to two isomeric thiolenedicarboxylic acids is described.

An isomeric keto-ester, 5-carbethoxy-2-phenyl-4-thiolanone, was prepared by ring closure of carbethoxymethyl β-carbethoxy-α-phenylethyl sulfide with sodium ethoxide.

RENSSELAER, NEW YORK RECEIVED JULY 17, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

The Catalytic Action of Cupric Ion on the Oxidation of Ascorbic Acid in Pyridine Solution

BY G. N. TYSON, JR.,[1a] AND JACK W. WILEY[1b]

The catalytic action of cupric ion on the oxidation of *l*-ascorbic acid has been noted and discussed for some years.[2] By the use of magnetic susceptibility measurements, it has been found possible to determine the function of cupric ion in the oxidation of ascorbic acid, when the reaction is carried out in pyridine solution.

Experimental

Synthesis.—In the following syntheses J. T. Baker and Co., C. P. cupric chloride was used as the source of the cupric and cuprous ion. The cuprous chloride was specially prepared by reduction of cupric chloride, using the Proust method as modified by Wohler.[3] The *l*-ascorbic acid and pyridine were obtained from Eastman Kodak Company, and the pyridine was carefully distilled, using only the fraction that boiled within 0.2 degree of the proper corrected temperature.

The reaction flask found most convenient to use was constructed from a 200-ml. Pyrex florence flask which had two 25-ml. florence flasks opening into the neck of the larger flask. The entire system could then be connected by means of Pyrex glass tubing and carefully ground stopcock to a Cenco vacuum pump, and reasonable elimination of oxygen obtained by evacuation to incipient boiling of the solvent for some minutes to sweep out the air in the system. The pyridine–copper salt solution was placed in the large flask, and the quantitatively weighed dry ascorbic acid in the small side flask. Removal of oxygen was then effected by evacuation and boiling of the pyridine solution at room temperature, and the dissolving of the dry ascorbic acid by the pyridine–metal salt solution could be done in the virtual absence of oxygen by tipping and shaking the sealed system.

The equipment also allowed for the introduction of measured amounts of air into the evacuated flasks for oxidation. The compositions of the various solutions are shown in Table I.

Magnetic Measurements.—The magnetic susceptibility measurements were made on the solutions using the Gouy method, at a temperature of 22°. The susceptibilities due to the metal ion are shown in Table I. In the column listing the Bohr magnetons, the calculations have been made assuming complete quenching of the orbital contribution to the magnetic moment. In the conversion of the experimental data into Bohr magnetons, a correction has been made for the diamagnetism of the non-metal portion of the molecule.

Discussion

Cupric ion in pyridine solution (I) exhibits the expected paramagnetism due to one unpaired electron, as shown in Table I. It is a reasonable

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(1) Present addresses, (a) Pacific Coast Borax Company, Pasadena, Calif.; (b) Du Pont Chemical Company, El Monte, Calif.

(2) For very recent work in this field, see Weissberger and LuValle, THIS JOURNAL, **66**, 700 (1944).

(3) Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., New York, N. Y., 1923, Vol. III, p. 158.