thermodynamic functions, ΔF_i^0, ΔH_i^0, $\Delta C_{p_i}^0$ and ΔS_i^0 may be evaluated.

4. Equations, valid from 0 to 50° and 0 to $1M$, are given by means of which $[-\log K_{(S=0)}]$, $[-\log K_{(S)}]$, $\gamma_H\gamma_{HCO_3}/\gamma_{CO_2}a_{H_2O}$, $\gamma_H\gamma_{HCO_3}$, γ_{CO_2}, and m_{CO_2} may be calculated. Estimations of the accuracy of these computations in solutions containing both sodium bicarbonate and chloride have been made.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Hypochlorites in Organic Oxidations

BY JOHN WEIJLARD

The shortage of permanganates during the past few years prompted the investigation of the possibility of utilizing hypochlorites as oxidizing agents in the production of important compounds. Accordingly, it was found that in the production of Vitamin C, diacetone-levo-sorbose which generally is oxidized to diacetone-2-keto-levo-gulonic acid by potassium permanganate[1] could be oxidized in the same yields using alkaline hypochlorites. This method is economical and has other advantages such as freedom from oxalic acid formation and greater simplicity of handling.

Oxidations of aromatic amino sulfides and sulfoxides to sulfones in acetic acid solutions are also suitable reactions for hypochlorites. The oxidations of sulfides and sulfoxides to sulfones are generally carried out with nitric acid, chromic acid, and hydrogen peroxide. Phenyl, benzyl and aliphatic sulfides are also oxidized to sulfones by hypochlorites in alkaline solution,[2] but acetylated aminophenyl sulfides or sulfoxides could not be cleanly oxidized to sulfones by this method, probably because chlorimines tend to form under these conditions.[3] In acetic acid solutions, the sulfides and sulfoxides could be oxidized to the sulfones by hypochlorites in high yields and without the formation of chlorinated by-products.

A third type of oxidation to which hypochlorites readily lend themselves entails the cleavage of two heterocyclic rings at the carbon–carbon linkage. Nicotine could thus be oxidized to nicotinic acid in yields high by comparison with other oxidizing agents such as nitric acid, chromates, and permanganates. In the same manner 4-amino-5-(3-pyridyl)-pyrazole[4] was oxidized to nicotinic acid with hypochlorite.

Compounds such as quinoline and quinoxaline were not oxidized to the desired carboxylic acids under the described experimental conditions; the same held true concerning alkyl substituted pyridines.

Experimental

Oxidation of Diacetone-levo-sorbose with Hypochlorite.—Fifty-six grams of chlorine was dissolved in a cold solution of 80 g. of sodium hydroxide in 750 cc. of water. To this freshly prepared hypochlorite solution was added a solution of 50 g. of diacetone-levo-sorbose in 250 cc. of water, followed by 2 g. of nickel chloride in a little water. The mixture was warmed to 50° when a vigorous reaction set in. The temperature was held between 50–60° by occasionally immersing the flask in an ice-bath. After a reaction time of twenty minutes practically all available chlorine was consumed. The catalyst was filtered off and the solution was neutralized with hydrochloric acid, then concentrated *in vacuo* to 350 cc. To the ice cold neutral solution was added 25 cc. of cold concentrated hydrochloric acid, the precipitated diacetone-2-keto-levo-gulonic acid was collected on a filter, washed with ice water, and the yield of anhydrous product estimated to be about 47.5 g. (90%).

Because of the difficulty in drying this acid without partial hydrolysis, a sample for analysis was prepared by dissolving some of the moist product in acetone (saturated solution), adding one volume of ether followed by two volumes of petroleum ether. The precipitated acid was filtered off, washed with petroleum ether and air dried; m. p. 101–102°.

Anal. Calcd. for $C_{12}H_{18}O_7 \cdot H_2O$: C, 49.29; H, 6.90. Found: C, 49.18; H, 6.84.

To further check the yield, the diacetone-2-keto-levo-gulonic acid (47 g.) was directly hydrolyzed and simultaneously rearranged to Vitamin C and isolated as such by known methods[5]; yield, 22.0 g. (73%); m. p. 189.5–190°.

Anal. Calcd. for $C_6H_8O_6$: C, 40.90; H, 4.82. Found: C, 40.87; H, 4.76. No chlorine could be detected.

Oxidation of Sulfides and Sulfoxides to Sulfones with Hypochlorite: *4,4'-Diacetyldiaminodiphenylsulfide.*—Fifty grams of chlorine was dissolved in a cold solution of 75 g. of sodium hydroxide in 1000 cc. of water. To 20 g. of 4,4'-diacetyldiaminodiphenylsulfide dissolved in 500 cc. of hot glacial acetic acid was added in a rapid stream 200 cc. of the prepared hypochlorite solution at 80°, or sufficient hypochlorite solution to produce a slight excess of free chlorine. The reaction mixture was diluted with 2000 cc. of water; the sulfone which precipitated out was collected on a filter, washed with water and dried; yield 22.0 g. of 4,4'-diacetyldiaminodiphenylsulfone (100%); m. p. 289–289.5°.

Anal. Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.80; H, 4.85; N, 8.43. Found: C, 57.72; H, 4.90; N, 8.35. No chlorine could be detected.

4,4'-Diacetyldiaminodiphenylsulfoxide oxidized as above gave 84% yield of sulfone; m. p. 290–290.5°.

Anal. Found: C, 57.50; H, 4.85; N, 8.70.

Oxidation of Nicotine and Nicotine-like Compounds with Hypochlorite: (a) *Nicotine.*—Seventy grams of chlorine was dissolved in a mixture of 600 g. of ice and 400 g. of

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(1) Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 321 (1934); U. S. Patent 2,301,811.

(2) Wood, Lowry and Faragher, *Ind. Eng. Chem.*, **16**, 1116 (1924); Wood and Graves, THIS JOURNAL, **50**, 1226 (1928); Birch and Norris, *J. Chem. Soc.*, 1934 (1925).

(3) Willstätter and Mayer, *Ber.*, **37**, 1494 (1904).

(4) Gough and King, *J. Chem. Soc.*, 2968 (1931).

(5) U. S. Patents 2,189,830, 2,190,167.

25% sodium hydroxide solution. Ten grams of nicotine base was dissolved in the hypochlorite solution followed by 0.25 g. of nickel sulfate in a little water. The mixture was heated to 50° and held at 50–55° until the available chlorine was practically exhausted (about three hours). The catalyst was filtered off, the solution was acidulated with sulfuric acid and heated to boiling to expel the carbon dioxide, then neutralized. An excess of copper sulfate solution was added and the copper nicotinate was filtered off. The nicotinic acid was isolated from the copper salt by the usual methods; yield, 4.54 g. (60%). After one recrystallization from water, about 90% pure acid was obtained; m. p. 235–236°.

Anal. Calcd. for $C_6H_5O_2N$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.81; H, 4.43; N, 11.32. No chlorine could be detected.

(*b*) *4-Amino-5-(3-pyridyl)-pyrazole.*—Ten grams of 4-amino-5-(3-pyridyl)-pyrazole dihydrochloride was dissolved in 125 cc. of 10% sodium hydroxide. A solution of 17.5 g. of sodium hydroxide and 13.5 g. of chlorine in 250 cc. of water was added, then 0.1 g. of nickel chloride as catalyst. The experiment was carried out as under (a). The yield of crude nicotinic acid was 2.9 g. (55%). This acid was of a poor quality yielding only about 65% pure acid on recrystallization from water.

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Summary

Hypochlorites have been found to be efficient and economical oxidizing agents in the oxidation of aromatic sulfides to sulfones, nicotine and nicotine-like compounds to nicotinic acid, and diacetone sorbose to diacetone-2-keto-levo-gulonic acid in the Vitamin C synthesis.

RAHWAY, NEW JERSEY RECEIVED MARCH 17, 1945

NOTES

The Antibacterial Principle of *Allium sativum*. III. Its Precursor and "Essential Oil of Garlic"[1]

BY CHESTER J. CAVALLITO, JOHN HAYS BAILEY AND JOHANNES S. BUCK

In prior communications[1] a new type of antibacterial principle in garlic has been described and a tentative structure assigned. This substance (I) is relatively stable in aqueous solutions of 0.2% and less and is very unstable in the pure state. Nevertheless, it is present in whole garlic to the extent of 0.3–0.4% and appears to be stable therein over long periods of time. We have carried out the following experiments to arrive at an explanation of this behavior.

Whole garlic cloves and powdered Dry Ice were ground thoroughly under acetone in a mortar. The solid was filtered off, washed several times with acetone and dried at 70°. The acetone extracts upon evaporation yielded only minute quantities of residue and no sulfides, indicating the absence of free sulfides in the plant. The white garlic powder obtained constituted 30% of the weight of the whole garlic and contained all of the potential active principle. The powder had practically no odor, but upon addition of small quantities of water, the typical odor was detected and the antibacterial principle could be extracted and isolated. This demonstrates that neither I nor the allyl sulfides found in "Essential Oil of Garlic" are present as such in whole garlic.

Dry garlic powder, prepared as described, lost no potential activity when heated for three days at 85°. Heating to reflux in absolute ethanol, acetone or chloroform for one hour produced no inactivation. When the powder was heated to reflux for thirty minutes with a small volume of 95% ethanol, no activity could be demonstrated by addition of water to the insoluble residue or to the small amount of material extracted by the alcohol. When, however, a small quantity (1 mg. per cc.) of fresh garlic powder was added to the alcohol-insoluble fraction in water (20 mg. per cc.), the activity of the treated sample was shown to be equal to that of the original untreated powder (32 mm. diameter zone of inhibition *vs. S. aureus* by the Oxford cup method). The 95% ethanol treatment had inactivated the enzyme required for cleavage of the precursor and addition of a small quantity of fresh enzyme brought about the usual cleavage. The enzymatically catalyzed cleavage of the precursor proceeded at *p*H values of between 3 and 9. This shows that whole garlic contains the active principle in the form of a thermostable precursor (II) which is very rapidly broken down to yield I when the garlic cells are crushed. This conversion takes place only in the presence of an enzyme III and water. The precursor and enzyme are apparently present in different cells of the plant.

It has been possible to obtain crude preparations of II and III from garlic in such a manner as to prevent the formation of I. The absence of free I or of the allyl sulfides in such material indicates that the sequence of events in the usual preparation of "Essential Oil of Garlic" is: Precursor II + Enzyme III $\xrightarrow{H_2O}$ $C_3H_5—SO—S—C_3H_5$, which upon steam distillation yields $C_3H_5—S—S—C_3H_5$ and small quantities of other sulfides.

The closely related *Allium cipa* or onion does not contain I or II, but some varieties do contain an enzyme similar in action to III and will yield I from garlic precursor II. The red onion is more effective than the yellow in this respect, whereas the white varieties tested do not contain III.

It is of interest to note that garlic preparations in which the enzyme III has been destroyed do not possess the characteristic odor or flavor of garlic.

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(1) This is a continuation of previously published articles entitled "Allicin, the Antibacterial Principle of *Allium sativum*. I. Isolation, Physical Properties and Antibacterial Action" (THIS JOURNAL, **66**, 1950 (1944)) and "II. Determination of the Chemical Structure" (*ibid.*, **66**, 1952 (1944)). The name "allicin" has now been dropped in view of its possible confusion with certain well-established medicinal products.