The results of this study give added evidence, to that already obtained in other ways, that pancreatic amylase either is protein or contains protein as an essential constituent. This is shown to be true of the enzyme as purified by the adsorption method of Willstätter, Waldschmidt-Leitz and Hesse, as well as of that purified by the method of Sherman and Schlesinger.

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SOME REACTIONS OF THIOCARBANILIDE

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Although thiocarbanilide is a very commonly known industrial material its chemical properties have not been studied exhaustively. This paper contributes to the knowledge of its oxidations, nitrations and capacity to form additive compounds.

Various oxidations in acid[1] and neutral[2] solutions have been effected, but hitherto no studies have been attempted in alkaline solution, notwithstanding that thiocarbanilide is soluble in alkalies[3] and such solutions afford ready contact with alkaline oxidizing agents. The primary effect of oxidizing agents is to substitute the sulfur atom by oxygen, thus yielding diphenylurea, a compound lending itself to easy separation and identification. When acid solutions are employed, thiocarbanilide tends[4] to yield aniline, phenyl mustard oil and triphenylguanidine; alkaline oxidizing reagents avoid these by-products.

In the following experiments oxidations were effected by various reagents, most of which gave good yields of diphenylurea, but the sodium peroxide method excels in simplicity of separation and yield of pure product. Some of the reagents separated free sulfur, and others oxidized it to alkali sulfate.

Various other desulfurizing reagents have been employed in contact with thiocarbanilide as, for example, mercuric oxide, lead acetate, etc. The casual view is that double decomposition results in the process; however, closer study indicates that addition reactions are involved. That the addition is not on nitrogen is precluded by the inability of diphenylurea to form corresponding additive compounds. That the addition is on the sulfur atom seems the alternative conclusion; observations that are to be reported on later, however, seem not to substantiate even this con-

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[1] Guareschi, *Gazz. chim. ital.*, **8,** 246 (1878). de Connick, *Compt. rend.*, **128,** 365 (1899).

[2] Hofmann, *Ann.*, **70,** 148 (1849). Herzog, *Z. angew. Chem.*, **33,** 140 (1920). Jacobson, *Ber.*, **19,** 1077 (1885). Vanino and Schinner, *Ber.*, **47,** 699 (1913).

[3] Rathke, *Ber.*, **12,** 772 (1882).

[4] Hofmann, *Jahresber.*, **1858,** 349.

clusion. It is certain that metallic salts add to thiocarbanilide and that these can be decomposed by heat, especially in alkaline solution, to yield diphenylurea and metallic sulfide.

Experimental Part

Oxidation by Sodium Peroxide.—To filtered solutions of two parts of thiocarbanilide, dissolved in sodium hydroxide, were added during vigorous stirring three parts of sodium peroxide, in about half-gram portions. Turbidity resulted with each addition of the peroxide and complete precipitation of diphenylurea was finally promoted by boiling. Filtering and washing gave nearly quantitative yields of needles melting sharply at 235°. Since the alkalinity is progressively increased, pulverized thiocarbanilide suspended in water can be treated directly with peroxide.

TABLE I

OTHER ALKALINE OXIDATIONS

Reagent	*t*	Sulfur	Yield of $(C_6H_5NH)_2CO$, %	Excess of hot reagent
$KMnO_4$	Room	$S + Na_2SO_4$	Good	C_6H_5NC
K_2CrO_4	100°	$S + Na_2SO_4$	70–80	......
$K_2S_2O_8$	Room	S	75	C_6H_5NCS + red dye
CaCl(ClO)	Room	$CaSO_4$	Poor	......
KOBr	Room	K_2SO_4	Good	......
KOI	Room	K_2SO_4	Good	......

From the foregoing it is evident that thiocarbanilide is smoothly oxidized by alkaline oxidants to diphenylurea, the sulfur thereof being precipitated or oxidized to sulfate. Preliminary experiments with other organic compounds containing the C═S linking as, for example, monosubstituted thio-ureas and the mustard oils, indicate that substitution of the sulfur atom by oxygen is a general effect of alkaline oxidants.

Nitration of Thiocarbanilide.—In 1877 Losanitch[5] treated thiocarbanilide with nitric acid and obtained yellow needles "melting higher than 200°" which proved to be tetranitro-diphenylurea. Here, simultaneous nitration and desulfurization resulted. Tetranitro-diphenylurea has been prepared by various other methods;[6] of especial importance is the method of Reudler[7] who obtained 90% yields when diphenylurea was nitrated.

The present study is concerned with ascertaining the most favorable conditions for the nitration of thiocarbanilide to tetranitro-diphenylurea, for the nitration of tetranitro-diphenylurea to hexanitro-diphenylurea, and for the nitration of thiocarbanilide to dinitro-thiocarbanilide, the last being a new nitration reaction on thiocarbanilide.

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[5] Losanitch, *Ber.*, **10,** 690 (1877); **11,** 1541 (1878).

[6] (a) Fleischer and Nemes, *Ber.*, **10,** 1295 (1877). (b) Hentschel, *J. prakt. Chem.*, [2] **34,** 426 (1886). (c) Curtius, *ibid.*, [2] **52,** 213 (1895).

[7] Reudler, *Rec. trav. chim.*, **33,** 35 (1914).

Tetranitro-diphenylurea.—The nitration of thiocarbanilide can best be carried out in 3.5 parts of sulfuric acid. Since hot sulfuric acid[8] decomposes thiocarbanilide, the solution must be prepared cold. An efficient mechanical stirrer is set in motion in the solution and 1.4 parts of fuming nitric acid is dropped in at such a rate that the temperature can be controlled at 75–85°. Finally, the mixture is heated on the water-bath until no more red fumes are evolved. The mixture is then slowly poured into 10–15 volumes of cold water while the latter is stirred. After filtering and washing with water, the tetranitro-diphenylurea is separated from dinitro-diphenylurea by extracting with hot alcohol, and from free sulfur by extracting with carbon disulfide. Glassy, lemon-yellow needles melting[9] at 204° are obtained.

Hexanitro-diphenylurea.—This compound has been prepared from tetranitro-diphenylurea, Perkin[10] giving a melting point of 203° and Reudler[7] giving 206–209°. In this study, the tetra compound was suspended in mixtures of the two acids and heated directly on the water-bath, then poured into water and the mixture filtered. Recrystallization from acetonitrile gave needles melting at 209°.

Di-*p*-nitrothiocarbanilide.—Though prepared by another method,[11] this compound has hitherto not been prepared from thiocarbanilide by mild nitration. Powdered thiocarbanilide was added to a freshly prepared solution of the calculated quantity of mercurous nitrate and the mixture was heated on the water-bath. The thiocarbanilide darkened and the clear solution became turbid. The precipitate was separated and extracted with hot alcohol from which yellow crystals melting at 161° were obtained.

Di-*m*-nitrodiphenylurea.—This compound has been prepared by various other methods.[12] It is here prepared by boiling for a number of days 30 g. of *m*-nitroaniline suspended in water containing 15 g. of urea and a little hydrochloric acid. Only 4 g. of dirty green crystals melting at 233° were obtained. Losanitch gave m. p. 233°; Offeret gave m. p. 242°.

Additive Compounds

Though mercuric salts of thiourea[13] and allyl thio-urea[14] are known, no metallic salts of thiocarbanilide and its derivatives have been prepared. With aqueous mercuric chloride, thiocarbanilide gives diphenylurea. When anhydrous solvents such as alcohol, methylethyl ketone or toluene are used, definite additive compounds are formed.

Thiocarbanilide Mercuric Chloride.—This was prepared by adding slowly a cold, alcoholic solution of thiocarbanilide to a cold, alcoholic solution of mercuric chloride, in molecular equivalents. Though the mixture remained clear for some time, fine glassy needles separated and after a day were filtered off and washed with alcohol. The yield is practically quantitative and is not influenced by an excess of mercuric chloride. The crystals melt at 85°.

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[8] Fleischer, *Ber.*, **9**, 994 (1876).

[9] Losanitch gave m. p. 200°; Rendler gave m. p. 218°.

[10] Perkin, *J. Chem. Soc.*, **63**, 1063 (1893).

[11] Brückner [(a) *Ber.*, **6**, 1103 (1873)] gives m. p. 160–161°.

[12] Brückner, Ref. 11 a; *Bull. soc. chim.*, **7**, 1236 (1874). Losanitch, *Ber.*, **10**, 691 (1877); **16**, 50 (1883). Ref. 6 c, Ref. 11 b, p. 229. Manuelli, *Gazz. chim. ital.*, **29**, 131 (1899). Vittenet, *Chem. Centr.*, [3] **21**, 151 (1899). Offret, *ibid.*, [3] **21**, 788 (1899). Richter, *Dissertation.*

[13] Maly, *Ber.*, **9**, 172 (1875). Claus, *Ber.*, **9**, 226 (1875).

[14] Will, *Ann.*, **52**, 11 (1844).

Anal. Calcd. for $(C_6H_5NH)_2CS.HgCl_2$. Cl, 14.14, S, 6.40. Found: Cl, 13.85; S, 6.46.

The salts in Table II were prepared by dissolving molecular equivalents in methylethyl ketone and then adding toluene.

TABLE II

THIOCARBANILIDE AND OTHER METALLIC HALIDES

Composition $T = C_{13}H_{12}N_2S$	Color	Crystal form	M. p., °C.	Calcd. X	% of M	Found X	% of M	Desulfurized in NH_3ROH
$T_2.CuBr_2$	White	Prisms	187	...	9.06	...	9.12	+
$T_2.CdBr_2$	Yellow	Rhomboids	140	21.93	...	21.53	...	+
$T_2.HgI_2$	White	Rhomboids	183	...	...	...	...	+
$T_2.ZnCl_2$	White	Prisms	172	11.96	11.03	12.12	10.86	+
$T_2.AuCl_3$	White	Prisms	194	...	25.93	...	25.88	+
$T_2.SnCl_4$	White	Prisms	260	...	12.56	...	12.35	+
$T.AsBr_3$	White	Prisms	250+	44.15	...	44.18	...	−
$T.AsI_3$	Yellow	Prisms	250+	55.67	...	55.20	...	−
$T.HgI_2$	Yellow	Prisms	139	37.18	...	37.30	...	+

Summary and Conclusions

1. Thiocarbanilide has been oxidized in alkaline solution to diphenylurea by seven different reagents. The reaction is especially easy and practically quantitative with sodium peroxide.
2. Thiocarbanilide is also oxidized to diphenylurea by nitric acid, nitration then yielding either dinitro- or tetranitro-diphenylurea.
3. The best nitration conditions for the formation of tetranitro-diphenylurea and hexanitro-diphenylurea from thiocarbanilide are given.
4. A number of complex salts of thiocarbanilide with metallic halides have been prepared.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF JOHNS HOPKINS UNIVERSITY]

SOME AZO DYES CONTAINING ANTIMONY

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Introductory

It has long been recognized that antimony in organic combination has definite trypanocidal activity. Various types of antimony compounds have been prepared in the hope that this activity would be manifested.[1] It has been known, furthermore, that some azo dyes, for example, Trypan Red, possess this same trypanosidal activity.[2] These facts have led the authors to attempt the preparation of azo dyes containing antimony,

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[1] Escomel, *Lancet*, **2,** 355 (1917). Rowntree and Abel, *J. Pharmacol.*, **2,** 109 (1910). Brahmachari, *Indian J. Med. Research*, **10,** 492 (1922) and following.

[2] *Arch. Internal Med.*, **2,** 98 (1909).