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	Calcd. % of M	Found X	Found % 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.

SEATTLE, WASHINGTON

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF JOHNS HOPKINS UNIVERSITY]

SOME AZO DYES CONTAINING ANTIMONY

BY FITZGERALD DUNNING AND E. EMMET REID

RECEIVED AUGUST 23, 1926 PUBLISHED NOVEMBER 5, 1926

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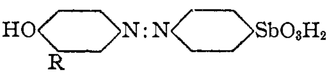
[1] Escomel, *Lancet*, **2,** 355 (1917). Rowntree and Abel, *J. Pharmacol.*, **2,** 109 (1910). Brahmachari, *Indian J. Med. Research*, **10,** 492 (1922) and following.

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

hoping that the value of each specific would be enhanced by their simultaneous presence in the same compound.

To be of value as therapeutic agents, compounds should be stable in the dry form and in solution and reasonably soluble in water. They should also be unaffected by changes in temperature, dampness and light. This paper gives preliminary results of the study of a series of compounds of the type shown. The sodium salts of these compounds have the desired physical properties. Their pharmacological action is now being investigated and will be reported in the near future, together with those of several similar series of compounds. There is no description of the preparation or properties of such compounds in the literature, although a patent mentions the possibility of such compounds.[3]



Results

p-Amino-acetanilide has been diazotized and combined with antimony trioxide to form *p*-acetyl-aminophenylstibinic acid. The preparation gives much trouble on account of excessive foaming. This difficulty has been largely overcome and the yield greatly increased. The substance has been hydrolyzed with sodium hydroxide to stibanilic acid, which has been diazotized and coupled with phenol to give the acid, $HOC_6H_4N{:}N.C_6H_4SbO_3H_2$. Similar couplings have been made with *o*-chlorophenol, *o*-nitrophenol, *o*-aminophenol, *o*-cresol and salicylic acid, to form the corresponding 3-methyl-, 3-chloro-, 3-nitro-, 3-amino- and 3-carboxy-4-hydroxyazobenzene-4′-stibinic acids. The disodium salts are normally formed. These may have either of the two formulas, $HO(R)C_6H_3N{:}NC_6H_4SbO_3Na_2$ or $NaO(R)C_6H_3N{:}NC_6H_4SO_3HNa$. From weighed amounts of the disodium salts in water, the disilver salts are precipitated quantitatively. The sodium salts are all readily soluble in water; the solutions are stable and are unaffected by heat or light. They dye wool a light orange-yellow, showing that they are dyes. Analysis for both antimony and nitrogen proves them to be definite chemical compounds. It is, therefore, apparent that they possess the physical and chemical requisites of therapeutic agents.

Experimental Part

It was necessary to produce stibanilic acid, *p*-aminophenylstibinic acid, in considerable quantity for the succeeding diazotization and coupling. Many methods were tried,[4] but the low yields caused the adoption of the following procedure, which is a complete modification of the method of Schmidt.

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[3] Ger. pat. 254,421 (1912).

[4] (a) Ger. pats. 254,421 (1912); 261,825 (1913); 270,488 (1913). (b) Eng. pat. 16,350 (1912). (c) U. S. pat. 1,260,707 (1918). (d) Schmidt, *Ann.*, **421**, 177 (1920).

A mixture of calculated amounts of *p*-amino-acetanilide and antimony trioxide in just sufficient 15% hydrochloric acid to dissolve the trioxide was diazotized with 15% sodium nitrite solution. The nitrite solution was introduced through a capillary tube reaching to the bottom of the beaker, the contents being stirred by a motor stirrer. A yellow, crystalline molecular compound was formed, a double salt of the type described by May.[5] This was filtered off, suspended in water, cooled to 3–5°, and to it 10% sodium hydroxide solution was added in small portions, the mixture being stirred by a motor stirrer. Unless great care is taken, a stiff foam forms and yields are low. After the vigorous evolution of the nitrogen was over, the solution, containing as impurities inorganic antimony and dark brown by-products, was nearly neutralized, carbon dioxide was passed in and the precipitate that formed was filtered off and discarded. The filtrate was then acidified with dil. acetic acid.

The resulting precipitate, *p*-acetyl-aminophenylstibinic acid, formed a flocculent, yellowish-white mass which was best separated from the liquid by centrifuging. To remove the acetyl group, the method of Schmidt[6] was used.

Stibanilic acid was obtained by this method as an almost white precipitate which was centrifuged, washed and dried. The yield is varied, generally between 35 and 60%. As stibanilic acid decomposes in the dry state, the succeeding diazotizations were carried out as follows.

Diazotizing and Coupling

The moist stibanilic acid was weighed; a portion of this was dried and weighed and the amount of stibanilic acid in the moist mass calculated. This was dissolved in dil. hydrochloric acid, the solution cooled to 0° and diazotized with 10% sodium nitrite solution. Measured quantities of the diazotized solution were poured slowly into cooled sodium hydroxide solutions of various intermediates.

The solutions containing the dyes were allowed to stand for several hours and were then precipitated with concd. hydrochloric acid and centrifuged. The compounds contained phenylstibinic acid and *p*-hydroxyphenylstibinic acid as impurities; therefore, they were washed with concd. hydrochloric acid and centrifuged. This removed the impurity by formation of phenyl- and *p*-hydroxy-phenylstibinic chlorides soluble in hydrochloric acid. The dyes, after thorough washing, were dissolved in aqueous sodium hydroxide, just sufficient to effect solution, the liquids filtered, and precipitated with dil. acetic acid. The dyes were separated from the liquid by centrifuging, washed and dried at 110°. The compounds were then triturated with ether, to remove any excess of intermediate, and dried again at 110°. The dyes dried as hard, black scales which when powdered gave products of various shades of brown. They are all insoluble in water, alcohol. acetone, chloroform, benzene, slightly soluble in phenol and readily soluble in sodium and ammonium hydroxides. They do not melt and are not decomposed at 250°.

The following compounds were made by this method.

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[5] May, *J. Chem. Soc.*, **101**, 1037 (1912).

[6] Schmidt, *Ann.*, **429**, 145 (1922).

I. 4-Hydroxy-azobenzene-4′-stibinic acid, by coupling diazotized stibanilic acid with a sodium hydroxide solution of phenol. The compound was difficult to prepare and was high in antimony content. It was green-brown in color.

Anal. Calcd. for $C_{12}H_{11}O_4N_2Sb$: Sb, 33.01. Found: 34.2.

II. 4-Hydroxy-2-chloro-azobenzene-4′-stibinic acid, from diazotized stibanilic acid and a sodium hydroxide solution of *o*-chlorophenol. The product is red-brown.

Anal. Calcd. for $C_{12}H_{10}O_4N_2ClSb$: N, 6.94; Sb, 30.2. Found: N, 7.0; Sb, 29.7.

III. 4-Hydroxy-3-nitro-azobenzene-4′-stibinic acid. from diazotized stibanilic acid and a sodium hydroxide solution of *o*-nitrophenol. It formed a light brown powder.

Anal. Calcd. for $C_{12}H_{10}O_6NSb$: Sb, 29.4. Found: 29.1.

IV. 4-Hydroxy-amino-azobenzene-4′-stibinic acid, from diazotized stibanilic acid and a sodium hydroxide solution of *o*-aminophenol.

Anal. Calcd. for $C_{12}H_{12}O_4N_3Sb$: Sb, 31.7. Found: 31.2.

V. 4-Hydroxy-3-methyl-azobenzene-4′-stibinic acid. from diazotized stibanilic acid and a sodium hydroxide solution of *o*-cresol. The color was brown.

Anal. Calcd. for $C_{13}H_{13}O_4N_2Sb$: N, 7.31; Sb, 31.8. Found: N, 7.22; Sb, 31.6.

VI. 4-Hydroxy-3-carboxy-azobenzene-4′-stibinic acid, from diazotized stibanilic acid and a sodium hydroxide solution of salicylic acid. The color was a deep red-brown.

Anal. Calcd. for $C_{13}H_{12}O_6N_2Sb$: N, 6.78; Sb. 29.5. Found: N, 6.54; Sb. 29.6.

3,4-Dihydroxy-azobenzene-4′-stibinic acid was made from diazotized stibanilic acid and a sodium hydroxide solution of pyrocatechin. The analyses did not correspond with the predicted formula of the product.

Preparation of Sodium Salts of Dyes

Several sodium salts of these compounds are possible theoretically. In order to ascertain which of these is normally formed, a weighed amount of each acid was titrated with 0.1 *N* sodium hydroxide solution until the acid was completely dissolved. In every case the disodium salt was formed.

A weighed amount of each dye was shaken with insufficient *N* sodium hydroxide to effect complete solution. The liquid was allowed to stand for several hours during repeated shaking. The solution was filtered several times. The filtrate was then evaporated to dryness either on a water-bath or preferably in a vacuum dryer. The disodium salts are obtained in solid form as scales of various shades of brown.

The disilver salts were precipitated quantitatively as dark red, amorphous solids from water solutions containing known amounts of the disodium salts. This affords more evidence that the acids are dibasic.

The colors of the dilute water solutions of the sodium salts of these dyes range from deep orange-brown to yellow-brown. The solutions dye wool light orange-yellow. They are perfectly stable over a period of six months, and are unaffected by heat or light. The salts themselves are insoluble in most organic solvents. In water-alcohol mixtures they are fairly soluble, precipitating on long standing.

The analyses of the sodium salts were as follows.

		Sb	
Compound	Formula	Calcd., %	Found, %
I	$C_{12}H_9O_4N_2SbNa_2$	29.5	31.0
II	$C_{12}H_8O_4N_2ClSbNa_2$	27.2	26.9
III	$C_{12}H_8O_6N_3SbNa_2$	26.6	26.4
IV	$C_{12}H_{10}O_4N_3SbNa_2$	28.3	27.9
V	$C_{13}H_{11}O_4N_2SbNa_2$	28.5	28.0
VI	$C_{13}H_9O_6N_2SbNa_2$	26.6	26.9

The analyses of these compounds occasioned great difficulty and many methods were tried with varying results.[7]

For the estimation of antimony in the acid dyes, a modification of the method of Schmidt was used. After the sample had been digested with 5 g. of sodium bisulfate and 10 cc. of concd. sulfuric acid until colorless, aqueous solutions of sulfur dioxide and tartaric acid were added to reduce pentavalent antimony. The sulfur dioxide was removed by boiling while carbon dioxide was passed in, the solution cooled, neutralized with sodium bicarbonate and titrated with 0.1 *N* iodine solution.

The method of Macallum[7c] works very well for the water-soluble sodium salts.

Summary

Stibanilic acid has been diazotized and coupled with phenol, *o*-chlorophenol, *o*-nitrophenol, *o*-aminophenol, *o*-cresol and salicylic acid to give compounds of the type $HO(R)C_6H_3N{:}NC_6H_4SbO_3H_2$, in which R is H, —Cl, —NO_2, —CH_3, —NH_2 or —COOH. These acids form disodium salts which are stable in water solution.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE LABORATORY OF WIDEN-LORD TANNING COMPANY]

A MAXIMUM REACTIVITY OF THE HIDE PROTEIN IN ITS ISO-ELECTRIC ZONE[1]

BY K. H. GUSTAVSON

RECEIVED AUGUST 31, 1926 PUBLISHED NOVEMBER 5, 1926

The concept of protein as ampholyte and the application of physicochemical laws to protein behavior have marked a great advance in this field and have also made possible quantitative treatment of a number of protein reactions as, for example, the combination of acids and alkalies with gelatin, and tannin with collagen. The ionic protein chemistry postulates the existence of protein cations on the acid side and protein anions on the alkaline side of the iso-electric point of the protein. In the former range only the combination between cations of the protein and anions of the

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[7] (a) Rohmer, *Ber.*, **34**, 1565 (1901). (b) Fargher and Gray, *J. Pharmacol.*, **18**, 356 (1921). (c) Macallum, *J. Soc. Chem. Ind.*, **42**, 468T (1923). (d) Ref. 4 d, p. 244.

[1] Read before the Division of Leather and Gelatin Chemistry, 72nd meeting of the American Chemical Society, September 6–11, 1926, Philadelphia, Pennsylvania.