is about the same as that of Nirvanol, whereas phenyl-*iso*propyl- and phenyl-butyl-hydantoin have no hypnotic effect. These results, together with the observations of Lumière and Perrin[8] working with dialkyl hydantoins, seem to show that the hypnotic reaction is concerned in some way with the number of carbon atoms in a compound as well as with their arrangement. A further study of the relationship of the hypnotic action to the solubilities of these hydantoins indicates that they are exceptions to the general conditions proposed by H. Meyer[9] as being necessary for a narcosis reaction.

Summary

1. Four homologs of 4,4-phenyl-ethyl-hydantoin were prepared by each of the following general methods: (1) the action of alkali cyanate with amino-aceto-nitriles; (2) the action of alkali hypobromites with disubstituted cyano-acetamides.

2. The better yields (those reported in Table I) were obtained with the disubstituted cyano-acetamide method.

3. Melting-point determinations of the mixed products obtained by the two methods showed them to be identical.

4. The solubilities, the melting points and the yields of the several hydantoins are given.

5. Preliminary tests seem to show that there is a wide variation in the narcotic action of the hydantoins.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

ANTIMONYL TARTRATES OF SOME ORGANIC BASES

BY WALTER G. CHRISTIANSEN AND ARTHUR J. NORTON

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In attempting to develop trypanocidally active antimony compounds which might be useful as substitutes for tartar emetic (potassium antimonyl tartrate), some antimonyl tartrates have been studied in which organic radicals replace the potassium atom of tartar emetic. To this end, alkyl antimonyl tartrates and antimonyl tartrates of aliphatic and aromatic amines have been compared with the potassium salt. The use of a series of substitution products of aniline for this purpose makes it possible to vary the nature of the organic base over a wide range without altering the mode of combination between the tartrate and the base. On the other hand, when the alkyl and aniline antimonyl tartrates are employed, different types of compounds, esters and salts, are being compared. The

[8] Lumière and Perrin, *Bull. soc. chim.*, [4] **35-36**, 1022 (1924).

[9] Meyer, *Chem. centr.*, **1899**, II, 64; from *Arch. exptl. Path. Pharm.*, **42**, 109.

alkyl compounds form quite readily when silver antimonyl tartrate is treated with alkyl iodides; the antimonyl tartrates of the amines can be obtained by the action of the sulfate of the amine on barium antimonyl tartrate much more conveniently than by refluxing the bitartrate of the amine with antimony oxide. Similarly, although lithium antimonyl tartrate is very difficult to secure as a pure solid by evaporation of a solution prepared by boiling the bitartrate with antimony oxide, it can be obtained with great ease from lithium sulfate and the barium salt.

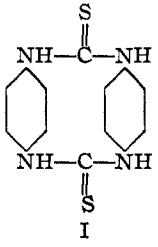
The preparation of an antimonyl tartrate of symmetrical *p*-diamino-diphenylthio-urea cannot be accomplished by any of the usual methods; the sulfate of this amine is very insoluble and reacts extremely slowly with barium antimonyl tartrate; the hydrochloride does not yield readily isolable products when treated with silver antimonyl tartrate; the desired salt cannot be obtained by boiling aqueous tartaric acid with the calculated quantity of the amine and an excess of antimony oxide, and attempts to prepare the bitartrate of this amine by boiling the latter with aqueous tartaric acid lead only to decomposition products of the thio-urea compound (compare below). It has been known for some time that when a suspension of barium antimonyl tartrate in *cold* water is treated dropwise with the calculated quantity of cold, dil. sulfuric acid, the filtrate from the barium sulfate contains antimonyl tartaric acid, and this solution is fairly stable provided it is kept cold. When such a solution is treated with powdered *p*-diamino-diphenylthio-urea, the filtrate from any unchanged amine yields the desired antimonyl tartrate as a slightly pink solid when alcohol is added.

The esters of antimonyl tartaric acid are obtained as amorphous powders, whereas nearly all the salts obtained from the amines are crystalline. The solubilities of these compounds and the hydrogen-ion concentrations of the solutions vary widely, but the solutions behave qualitatively like those of tartar emetic. Toxicologically these substances are very similar to tartar emetic, and none of them is any more active trypanocidally than the potassium salt.

When a small quantity of *sym-p*-diamino-diphenylthio-urea[1] is recrystallized from water, a pure, crystalline product is obtained that dissolves readily in dil. hydrochloric acid. However, when a large amount of the crude amine is used, the product contains some white, amorphous material which is insoluble in hydrochloric acid. This is due to the fact that *p*-diamino-diphenylthio-urea gradually decomposes in hot aqueous solution; when a small quantity is recrystallized, the hot aqueous filtrate cools quite rapidly and very little decomposition occurs. It is advisable, therefore, to add the crude material to boiling water containing some vegetable carbon, filter the solution rapidly through a hot funnel into a cold flask and cool the filtrate as rapidly as possible. The decomposition

[1] Bolser and Hartshorn, THIS JOURNAL, **45**, 2349 (1923).

of *p*-diamino-diphenylthio-urea in boiling water is accompanied by the evolution of hydrogen sulfide and the separation of a white precipitate which appears to be identical with the *p*-diphenylene-dithio-urea (I) ob-



I

tained by refluxing *p*-phenylenediamine or *p*-diamino-diphenylthio-urea in alcoholic solution with carbon disulfide[1] or by boiling a solution of *p*-diamino-diphenylthio-urea in glacial acetic acid.

A dihydrochloride of *p*-diamino-diphenylthio-urea can be obtained as a slightly cream-colored solid by pouring a solution of the amine in dil. hydrochloric acid into a large volume of acetone.

Experimental Part

General Method of Preparing Amine Antimonyl Tartrates.—The calculated quantity of powdered barium antimonyl tartrate is added to a solution of 10 g. of an amine sulfate[2] in 200–300 cc. of water, and the system is stirred mechanically at 50–80° for several hours. The barium sulfate is removed by filtering the warm solution through a mat of carbon on a Büchner funnel, and the filtrate is evaporated to crystallization. Whenever the product does not separate from the concentrated solution, it is precipitated by the addition of alcohol. In each case the tolerated dose is determined by injecting a 2% solution of the compound intravenously, using white rats. The following substances were prepared in this way.

Benzylamine Antimonyl Tartrate, $C_6H_5CH_2NH_3[C_4H_4O_6(SbO)]\cdot{}^1/_2H_2O$.—Yield, first crop, 17 g.; second crop, 2 g. Tolerated dose: 20 mg. per kg.

Anal. Calcd.: H_2O, 2.2; Sb, 30.2. Found: H_2O, 2.4; Sb, 30.5.

Phenylhydrazine Antimonyl Tartrate, $C_6H_5NHNH_3[C_4H_4O_6(SbO)]$.—A solution of the crude product in 125 cc. of water is treated with an equal volume of alcohol, and the filtered solution is evaporated to about 25 cc.; yield, 16 g. of light yellow crystals; tol. dose, 20 mg. per kg.

Anal. Calcd.: Sb, 30.8. Found: 30.6.

***p*-Amino-acetophenone Antimonyl Tartrate,** $CH_3CO\langle\bigcirc\rangle NH_3[C_4H_4O_6(SbO)]\cdot H_2O$.—This substance was obtained as slightly pink, stout crystals; yield, first crop, 13.5 g.; 2nd crop, 2 g.; tol. dose, 30 mg. per kg.

[2] The majority of the amine sulfates precipitate when sulfuric acid is added to an alcoholic solution of the amine. In the case of *m*-aminobenzoic acid the alcoholic solution must be poured into ether to precipitate the sulfate.

Anal. Calcd.: H_2O, 4.09. Found: 4.48. Calcd. for the anhyd.: Sb, 28.9. Found: 28.4.

m-Carboxyaniline Antimonyl Tartrate,  $NH_3[C_4H_4O_6(SbO)]H_2O$.—This was obtained as slightly purple, needle-like crystals; yield, first crop, 17 g.; second crop, 4 g.; tol. dose: 20 mg. per kg.

Anal. Calcd.: Sb, 27.5. Found: 27.4.

Dehydration at 110° removes one-half a molecule of water of constitution in addition to the water of crystallization.

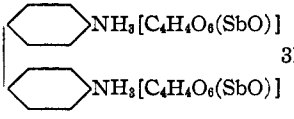
Anal. Calcd. loss for 1.5 H_2O: 6.1. Found: 5.6, 5.6.

Calcd. for $C_{11}H_{12}O_9NSb$ minus 0.5 H_2O: Sb, 29.4. Found: 29.2.

The solution for injection is prepared by dissolving 0.2 g. of the substance in 8 cc. of water and 0.3 cc. of a 10% solution of sodium bicarbonate and diluting to 10 cc.

***p*-Amino-acetanilide Antimonyl Tartrate,** CH_3CONH  $NH_3[C_4H_4O_6(SbO)]$-H_2O.—A light brown powder; yield, 12 g.; tol. dose, 30 mg. per kg.

Anal. Calcd.: Sb, 26.8; H_2O, 3.96. Found: Sb, 26.7; H_2O, 3.7.



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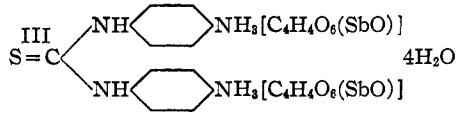

III

Benzidine Antimonyl Tartrate, II.—Using 600 cc. of water as the reaction medium, a yield of 20 g. of white, needle-like crystals was obtained; tol. dose, 30 mg. per kg.

Anal. Calcd.: Sb, 30.0; H_2O, 6.7. Found: Sb, 30.5; H_2O, 6.8.

Hexamethylene Antimonyl Tartrate.—Yield, 19.5 g.; tol. dose, 20 mg. per kg.

Anal. Found: Sb, 39.3, 39.6; H_2O, 2.5.

The composition of this substance was not determined.

***sym-p*-Diamino-diphenylthio-urea Antimonyl Tartrate, III.**—A suspension of 7.6 g. of finely powdered barium antimonyl tartrate trihydrate in 250 cc. of cold water in an efficient cooling bath is stirred mechanically and treated dropwise with a cold solution of 0.5 cc. of concd. sulfuric acid in 10 cc. of water; the temperature falls from 0° to —3°. The stirring is continued for one-half hour after the acid has been added; vegetable carbon is added and the solution filtered through a mat of carbon on a cold funnel into a flask packed in ice. The colorless, clear solution of antimonyl tartaric acid is transferred to a beaker which is packed in ice and water; the solution is strongly acid to Congo Red, and the temperature which rises slightly (to +2°) during the filtration falls at once to —1°. Powdered *sym-p*-diamino-diphenylthio-urea (2.32 g.) is added to the solution which is being stirred and the temperature rises at once to +1°. The stirring is continued at 0° for one-half hour; the solution is no longer acid to Congo Red. The temperature is allowed to rise gradually ($2^1/_2$ hours) to 13°, and the solution is then warmed to 30° during 15 minutes and maintained at this temperature for an additional 15 minutes; the stirring is continued throughout the process.

After the reaction mixture has stood in the ice box overnight, the small residue of unchanged urea base is removed by filtration, and the filtrate is evaporated in a current of warm air (solution temperature 25°) to about 250 cc. The solution is clarified by filtration and poured into 1.25 liters of alcohol. After six hours in the ice box the curdy precipitate is collected on a filter, washed with alcohol and air-dried. The *sym-p*-diamino-diphenylthio-urea antimonyl tartrate (2.2 g.) is a slightly pink powder which is soluble in water; it sinters at 295–300° but does not melt at 310°; it is tolerated in doses of 30 mg. per kg.

Anal. Calcd. for $C_{21}H_{24}O_{14}N_4SSb_2.4H_2O$: H_2O, 7.97. Found: 7.51.
Calcd. for $C_{21}H_{24}O_{14}N_4SSb_2$: N, 6.75; S, 3.85. Found: N, 6.29, 6.31; S, 3.58.

***iso*Propyl Antimonyl Tartrate,** $(CH_3)_2CH[C_4H_4O_6(SbO)].1.5H_2O$.—Ten g. of silver antimonyl tartrate which has been dried at 105° is refluxed for six hours with a solution of 6.5 g. of redistilled *iso*propyl iodide in 50 cc. of dry *iso*propyl alcohol. The insoluble material is a mixture of silver iodide and *iso*propyl antimonyl tartrate; it is collected on a filter and washed with *iso*propyl alcohol and ether. The yellow, dry mixture is extracted at room temperature with four 25 cc. portions of water; each extract is separated from the insoluble matter by centrifuging and is clarified by treatment with vegetable carbon. The first extract is kept separate from the others and evaporated to a sirup at room temperature in a vacuum desiccator over sodium hydroxide; the sirup is triturated with a small amount of alcohol, and the mass is evaporated to dryness at room temperature in a vacuum desiccator. The *iso*propyl antimonyl tartrate is a white powder which is very soluble in water; the yield is 3.1 g.—an additional 1.2 g. can be obtained from the other extracts. An aqueous solution of this compound is slightly acid to Congo Red, but it can be neutralized with sodium bicarbonate without precipitating antimony oxide. The solution of this substance used for toxicological determinations is prepared by dissolving 0.1 g. of the powder in 4 cc. of water and 0.27 cc. of saturated aqueous sodium bicarbonate solution and diluting the mixture to 5 cc. with water; the tolerated dose is 20 mg. per kg.

Anal. Calcd. for $C_7H_{11}O_7Sb.1.5H_2O$: H_2O, 7.61. Found: 7.04.
Calcd. for $C_7H_{11}O_7Sb$: Sb, 36.9. Found: 36.6.

***n*-Butyl Antimonyl Tartrate,** $C_4H_9[C_4H_4O_6(SbO)]$.—This substance is prepared in a manner analogous to that used for the *iso*propyl compound using 7.1 g. of *n*-butyl iodide and 50 cc. of *n*-butyl alcohol; yield, 4 g. The product is a white solid that dissolves very readily in water, and the solution is acid to Congo Red. The solution used in determining the toxicity of this compound is neutralized with bicarbonate prior to injection; the tolerated dose is 20 mg. per kg. In drying a sample of this material for analysis it appears as though some water of constitution were removed because the value found for the antimony content is slightly high.

Anal. Calcd. for $C_8H_{13}O_7Sb$: Sb, 35.5. Found: 37.1, 37.2.
Calcd. for $C_8H_{13}O_7Sb$ minus $0.5H_2O$: Sb, 36.5.

Decomposition of *sym*-*p*-Diamino-diphenylthio-urea in Water Solution.—Three g. of *p*-diamino-diphenylthio-urea is added to 800 cc. of boiling water, and the clear solution is refluxed. After one-half hour a white precipitate has started to separate and hydrogen sulfide is being evolved; at the end of five hours a considerable quantity of precipitate is present and hydrogen sulfide can still be detected. The contents of the flask are left at room temperature overnight; during this time the colorless, aqueous liquid becomes slightly reddish-brown. The insoluble matter is collected on a filter, washed with water and dried in the air; 1.3 g. of a white powder is obtained which decomposes at 289° without melting and which is insoluble in water, acids and alkalies. In order to remove any undecomposed *p*-diamino-diphenylthio-urea which might have separated when the system remained at room temperature overnight, the dry powder is triturated with 10 cc. of water and 1 cc. of hydrochloric acid, the mixture centrifuged, and the solid washed with water and air-dried. The material still weighs 1.3 g. and decomposes at 289–290° without melting; it appears to be *p*-diphenylene-dithio-urea.[1]

Anal. Calcd. for $C_{14}H_{12}N_4S_2$: N, 18.66. Found: 18.87, 18.64, 18.85.

When the aqueous mother liquor from the decomposition product described above is left in the ice box, stout, needle-like crystals gradually separate; they are collected on a filter, washed with water and air-dried. This material (0.15 g.) is undecomposed

p-diamino-diphenylthio-urea; it was identified by its qualitative reactions and by the mixed-melting-point method.

sym-p-**Diamino-diphenylthio-urea Dihydrochloride.**—A clarified solution of 30 g. of *p*-diamino-diphenylthio-urea in 270 cc. of water and 30 cc. of hydrochloric acid is poured into 7.5 liters of acetone; the voluminous precipitate is collected on a filter, washed with acetone and air-dried; yield, 37 g. The dihydrochloride is a slightly cream-colored powder that melts with decomposition and is very readily soluble in water.

Anal. Calcd. for $C_{13}H_{16}N_4SCl_2$: S, 9.67. Found: 9.47, 9.78.

The authors wish to thank Miss Hendry of the Department of Physiological Chemistry for making the nitrogen determinations reported in this paper. The expenses necessary for the pursuance of this investigation have been met from a fund for research in the Department of Tropical Medicine, given by a citizen of Boston.

Summary

1. Antimonyl tartrates of a number of organic bases have been studied but none of them is superior to tartar emetic (potassium antimonyl tartrate) toxicologically or trypanocidally.

2. When an aqueous solution of *sym-p*-diamino-diphenylthio-urea is refluxed, decomposition occurs whereby *p*-diphenylene-dithio-urea is formed.

BOSTON 17, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

UNSATURATED 1,4-DIKETONES
I. HALOGEN DERIVATIVES OF DIBENZOYL-ETHYLENE AND RELATED SUBSTANCES

BY JAMES B. CONANT AND ROBERT E. LUTZ

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The recently developed synthesis of dibenzoyl-ethylene from fumaryl chloride and benzene by the Friedel-Crafts reaction[1] makes readily accessible unsaturated 1,4-diketones of the general type, ArCOCH=CHCOAr. Such compounds are of interest because they contain the doubly conjugated system which is also characteristic of *para* quinones and because from them may be prepared substituted diaryl ethanes which readily pass into furanes and pyrroles. This paper deals primarily with the addition of chlorine and bromine to dibenzoyl-ethylene and the transformation of the resulting dihalogen compounds into a variety of substances; later papers will consider other addition reactions of unsaturated 1,4-diketones and the synthesis of certain substituted furanes and pyrroles.

Both the *cis* and *trans* forms of dibenzoyl-ethylene combine rapidly with bromine and chlorine; both isomers yield the same dibromide,[2] but

[1] Conant and Lutz, THIS JOURNAL, **45**, 1303 (1923). Oddy, *ibid.*, **45**, 2156 (1923).

[2] Paal and Schulze, *Ber.*, **33**, 3800 (1900); **35**, 168 (1902).