the catalyst was an alkali metal carbonate, passage of acetic acid over the catalyst before the initial arsenic trioxide vapors improved the yield by reducing the sudden evolution of carbon dioxide during the initial phases of the experiment. An asbestos plug just above the arsenic trioxide allowed a relatively constant rate of vaporization of the acetic acid. During the reaction period a slow stream of carbon dioxide was passed through the tube to prevent condensation of vapors in the upper part of the tube. The catalyst was maintained at an almost constant temperature during the course of the reaction. Acetic anhydride, glacial acetic acid and various strengths of aqueous acetic acid were tried, and it was found that the highest yields were obtained with 75% acetic acid. In a typical run 6.8 g. of arsenic trioxide and 31 ml. of 75% acetic acid were passed at 350° over potassium carbonate on no. 10 mesh pumice. Addition of water to the receiver before the experiment was begun often aided in protecting the product. The duration of the run was ten hours.

The yield was determined by conversion of the Cadet's liquid to cacodyl chloride by treatment with hydrochloric acid and ferric chloride by the method of Witten.[5] To the material in the receiver was added 60 ml. of concentrated hydrochloric acid containing 20 g. of ferric chloride, and the mixture was subjected to steam distillation. It was found desirable to maintain an atmosphere of carbon dioxide in the apparatus at the beginning of the distillation. The distillate was collected in a separatory funnel containing concentrated hydrochloric acid. Crude cacodyl chloride, after being washed with hydrochloric acid and dried over calcium chloride, was obtained in a 66% yield based on the arsenic trioxide. From 36 g. of crude product prepared in this manner, 30 g. of cacodyl chloride, b. p. 106–107°, was obtained by fractionation through a 25 × 1.2 cm. column packed with Berl saddles. No higher-boiling and only 1–2 g. of lower-boiling material was obtained.

Catalyst.—The catalyst was prepared by allowing the support, usually pumice, to stand for two hours in a concentrated solution of the catalytic compound. The excess solution was decanted, and the catalyst dried in a vacuum oven. In four runs in which cesium carbonate was employed in place of potassium carbonate the yields varied from 66 to 77%. Lithium acetate, sodium carbonate and soda-lime gave much lower yields. In one run in which potassium carbonate was supported on asbestos in place of pumice the yield was 69%. The same catalysts were used continuously except for occasional regeneration by passing air through the tube at the reaction temperature.

Diethylchloroarsine.—By the use of propionic in place of acetic acid it was possible to prepare a mixture of ethyl cacodyl and ethyl cacodyl oxide. Arsenic trioxide (7.0 g.) and 30 ml. of 75% propionic acid were passed over pumice impregnated with potassium carbonate at 350° during twelve hours. Substantially no arsenic trioxide sublimed through the tube unchanged, and a relatively large amount of material separated at the bottom of the receiver from the excess propionic acid. From this, it appeared that the conversion to the arsenicals was almost as complete as in the case of the preparation of Cadet's liquid.

The product of the above reaction was treated with 60 ml. of concentrated hydrochloric acid containing 20 g. of ferric chloride which deposited the expected heavy oily liquid. When the receiver was opened to permit addition of the ferric chloride solution, the product gave an arsenic trioxide smoke, but not as rapidly as the corresponding product from acetic acid. By steam distillation of the reaction mixture, 1.1 g. of diethylchloroarsine was obtained; yield, 9.3% of the theoretical. The reaction of the product with ferric chloride and concentrated hydrochloric acid apparently gives several products since a large amount of black residue remained in the flask after steam distillation.

Summary

Cadet's liquid has been produced in good yields by passing a mixture of arsenic trioxide and acetic acid over a catalyst at temperatures of 300–400°.

The new method, when applied to propionic acid and arsenic trioxide, gave relatively high yields of a mixture of ethyl cacodyl and ethyl cacodyl oxide.

(5) Witten, report on file at the Edgewood Arsenal.

URBANA, ILLINOIS RECEIVED NOVEMBER 12, 1946

[CONTRIBUTION FROM THE LABORATORY OF E. A. H. FRIEDHEIM]

Organic Antimony Compounds Derived from *s*-Triazine with Therapeutic and Prophylactic Activity in Experimental Trypanosomiasis[1]

BY ERNST A. H. FRIEDHEIM, HENRY J. VOGEL AND ROSE L. BERMAN

It is well known[1a] that free phenylstibonic acids have a pronounced tendency to polymerize, in particular to trimerize, and to form colloidal solutions.

In the case of stibanilates, the polymerization was found to increase the tolerance, but to decrease the trypanocidal activity.[2]

In this paper we have described a new trypanocidal phenylstibonic acid derivative, *i. e.*, sodium *p*-melaminylphenylstibonate (I).[3] In this case, polymerization yields an amorphous sodium salt (II) having, in comparison with the crystalline sodium salt (I), a greatly decreased toxicity, and surprisingly also an enhanced trypanocidal activity. This spells a rise of the therapeutic index (*T. equiperdum* infection of the mouse) from 3 for (I) to 200 for the polymer (II) (Table I).

TABLE I

COMPARATIVE DATA IN MICE: I. P. ACUTE TOXICITY AND TRYPANOCIDAL ACTIVITY (*T. equiperdum*) OF SODIUM *p*-MELAMINYLPHENYLSTIBONATE BEFORE AND AFTER POLYMERIZATION

Compound	Dose max. tol. g./kg. 50%	100%	Dose min. cur. 100% g./kg.	Therapeutic index
Cryst. sodium salt	0.24	0.15	0.05	3
Amorphous polymer	4.0	2.5	.0125	200

(1) Presented on the program of the Division of Medicinal Chemistry at the Chicago meeting of the American Chemical Society, September, 1946.

(1a) Schmidt, *Ann.*, **421**, 159 and 174 (1920).

(2) Fischl and Schlossberger, "Handbuch der Chemotherapie," Leipzig, 1934, p. 589.

(3) *p*-Melaminyl = *p*-(2,4-diamino-*s*-triazinyl-6)-amino.

Polymerization here has a further significant biological effect: After a single oral or parenteral application, the polymerized compound is very slowly eliminated from the organism. Thus, a single dose maintains a sufficient level in the organism to afford over months an efficient protection against infection and multiple re-infections with virulent trypanosomes. In contradistinction, I has no significant prophylactic effect.

This is to our knowledge the first organometallic compound described to have a pronounced prophylactic effect in trypanosomiasis. So far only two organic compounds, both metal free, are known to afford protection against a trypanosoma infection over a considerable length of time: Naphuride (Bayer 205, Germanin, Moranyl) and Pentamidine.

Table II gives results of comparative prophylactic experiments with the polymeric compound (II) and Naphuride. It follows that a single dose

TABLE II

PROPHYLAXIS OF *T. equiperdum* INFECTION IN MICE

Compound	Naphuride	Polymerized sodium melaminyl-phenyl-stibonate		
Dose expressed as				
a. Grams per kilogram	0.012	0.05		
b. Fraction of maximum tolerated dose	1/50	1/50		
c. Multiple of minimum curative dose	8	4		
Prophylactic effect				
a. Time in days between pretreatment and test infection	61	68	105	167
b. Number of test infections	1	1	2	3
c. Number protected mice / Number pretreated mice	0/5	5/5	5/5	1/5

of Naphuride amounting to eight times the minimum curative dose (equal to one-fiftieth of the maximum tolerated dose) does not protect any of five mice after sixty-one days against an infection with *T. equiperdum*, while a single dose of (II), corresponding to only four times the minimum curative dose (equal to one-fiftieth of the maximum tolerated dose) still fully protects five out of five mice after one hundred and five days.

The polymerization is brought about by heating a solution of the crystalline sodium salt (I) in a solvent such as 40% aqueous urea solution. The analytical data show that urea does not enter into the chemical structure of the polymer. Temperature, heating time and *p*H of the reaction mixture are factors influencing the polymerization.

In contrast to the crystalline sodium salt, the polymer shows the following features: Pronounced flow birefringence, increased relative viscosity of aqueous solutions, tendency of aqueous solutions to form thixotropic gels and greatly increased water-solubility.

Experimental

p-Melaminylphenylstibonic Acid.—The preparation follows essentially the procedure described by one of us for the synthesis of *p*-melaminylphenylarsonic acid.[4] A solution of 204 g. (1.1 moles) of freshly distilled cyanuryl chloride in 900 ml. of acetone is poured with mechanical stirring, into 2000 ml. of water, 2000 g. of chipped ice and 10 ml. of 2-ethylhexyl alcohol contained in a 22-liter flask. To the resulting milky suspension is added slowly, with stirring and external cooling, a solution of 308 g. (1 mole) sodium stibanilate and 69 g. (0.5 mole) of anhydrous potassium carbonate in 3600 ml. of water. The temperature of the reaction mixture is maintained at −3 to −5° and the *p*H at 7 by addition of concentrated aqueous potassium carbonate solution. When the test for primary aromatic amine has become negative in the resulting thick white paste, 5000 ml. of ice-cold 28% aqueous ammonia are added and the reaction mixture is saturated at 25° with gaseous ammonia. The temperature is then raised to 95° as rapidly as the violent evolution of ammonia will permit, *i. e.*, within two to two and one-half hours. Activated charcoal (20 g.) are added to the resulting milky suspension. The mixture is cooled to 10° and filtered. The clear, slightly yellowish filtrate is cooled to 0° and saturated with carbon dioxide, whereupon *p*-melaminylphenylstibonic acid precipitates. The almost white precipitate is filtered, washed free from ammonium salts with ice–water saturated with carbon dioxide and dried *in vacuo;* yield 149 g. (40%).

The stibonic acid is a white amorphous powder, insoluble in cold, sparingly soluble in hot water; insoluble in ethanol, ether and chloroform; decomposes with charring above 250°.

Anal. Calcd. for $C_9H_{11}O_3N_6Sb$: Sb, 32.6; N, 22.5; N/Sb, 6.0. Found: Sb, 32.7; N, 22.8; N/Sb, 6.06.

Sodium p-Melaminylphenylstibonate.—*p*-Melaminylphenylstibonic acid (100 g.) is dissolved in 4000 ml. of water containing 12 g. of sodium hydroxide. The slightly turbid solution is treated with charcoal and filtered; 320 g. of sodium hydroxide are added gradually, with stirring and cooling, to the clear filtrate while the temperature is maintained below 35°. On standing at 5°, sodium *p*-melaminylphenylstibonate forms a crystalline precipitate, which is filtered, washed with 2 *N* sodium hydroxide, ethanol and ether. When dried at a pressure of 25 mm. at 25° over sulfuric acid, the product has a moisture content corresponding to an octahydrate.

The yield, calculated on the basis of anhydrous material, was 95 g. (90%); white needles or platelets from hot water; sparingly soluble in cold water. Insoluble in ethanol and acetone; precipitated from aqueous solutions by carbonic, acetic and hydrochloric acids.

Anal. Calcd. for $C_9H_{10}O_3N_6SbNa$: Sb, 30.8; N, 21.2; N/Sb, 6.0. Found: Sb, 30.9; N, 20.9; N/Sb, 5.9.

Polymerization of Sodium p-Melaminylphenylstibonate.—Crystalline sodium *p*-melaminylphenylstibonate (80 g., calculated on the basis of anhydrous material) is dissolved with warming in a solution of 110 g. of urea in 190 ml. of water. The *p*H of the reaction mixture is adjusted with carbon dioxide to 8.5 (Hydrion paper). The solution is filtered, heated at 56° for forty-five minutes, and 1500 ml. of 95% ethanol are added with stirring. The polymerized sodium *p*-melaminylphenylstibonate precipitates, is filtered, washed with ethanol and ether and dried *in vacuo;* yield 70 g. (88%). Amorphous, white powder, readily soluble in cold water, very soluble in aqueous urea solutions, soluble in propylene glycol. Insoluble in ethanol and ether. It is precipitated from its aqueous solutions by carbonic, acetic and phosphoric acids in the form of gelatinous paste.

Anal. Calcd. for $C_9H_{10}O_3N_6SbNa$: Sb, 30.8; N, 21.2; N/Sb, 6.0. Calcd. for $C_9H_{11}O_3N_6Sb$: Sb, 32.6; N, 22.5; N/Sb, 6.0. Found: Sb, 32.1; N, 21.6; N/Sb, 5.9.

The analysis shows that the N/Sb ratio is not changed by the polymerization; the per cent. value for nitrogen

(4) Freidheim, THIS JOURNAL, **66**, 1775 (1944).

and antimony are intermediate between those calculated for the monomeric monosodium salt and free acid.

The viscosity of aqueous solutions increases with time, up to the formation of stiff, thixotropic gels. For example, a 3% solution of the polymer in 4% urea solution, showed four hours after preparation a relative viscosity of 1.8, the solvent at the same temperature being taken as unity. The relative viscosity of a solution of the crystalline stibonate of equal antimony content was less than 1.05.

A 2% aqueous solution of the polymer shows strong flow birefringence when observed between crossed nicols. An analogous solution of the crystalline sodium salt is optically inactive.

Comparison of Prophylactic Effect of Polymerized Sodium *p*-Melaminylphenylstibonate and Naphuride in the T. equiperdum Infection of the Mouse.—(See Table II.) Mice were treated with a single i. p. dose of the drug and after an interval of two months injected with a suspension of virulent *T. equiperdum*. Daily blood examinations were then carried out. Animals found to be negative after thirty-seven days were then re-infected, controlled by daily blood examinations for two months, and then submitted to a third test infection. The test infection killed untreated control animals within three to five days.

Summary

1. A crystalline sodium salt of *p*-melaminylphenylstibonic acid has been prepared. It cures the experimental *T. equiperdum* infection of the mouse with a therapeutic index of 3, but has no appreciable prophylactic effect.

2. The crystalline *p*-melaminylphenylstibonate has been polymerized. In comparison with the crystalline stibonate, the polymer has a 4-fold increased trypanocidal activity and a 17-fold decreased toxicity, corresponding to a therapeutic index of 200 in the *T. equiperdum* infection of the mouse.

3. In the *T. equiperdum* infection of the mouse, the polymerized product has a very pronounced prophylactic effect. The duration of this effect is significantly longer than with comparable doses of Naphuride.

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[CONTRIBUTION FROM THE DEPARTAMENTO DE QUÍMICA DA FACULDADE DE FILOSOFIA, CIÊNCIAS E LETRAS DA UNIVERSIDADE DE SÃO PAULO]

Some Steroid Mercaptols

BY HEINRICH HAUPTMANN

There appears to have been no attempt to prepare steroid mercaptols since Mylius[1] let thiophenol react with dehydrocholic acid (3,7,12-triketocholanic acid). As previously reported[2] we began an investigation of these substances, first studying the behavior of 4-cholesten-3-one with different mercaptans. While in this case we observed no reaction with thiophenol and could not isolate any crystallized product except diphenyl disulfide, we were able to prepare a mercaptol by the reaction of 4-cholesten-3-one and benzylmercaptan in the presence of anhydrous zinc chloride and sodium sulfate. 4-Cholesten-3-one dibenzylmercaptol melts at 126.5–127°, $[\alpha]^{27}D + 128 \pm 1°$. It crystallizes so well that it can be used for the identification of 4-cholesten-3-one. With tetranitromethane it turns brown. When refluxed with Raney nickel[3] in dioxane and water it is transformed into 4-cholestene which we identified by its m. p. of 79–80°, specific rotation $[\alpha]^{27}D$ 64.6 ± 1°, and its dibromide with the m. p. 115.5–116.5°. That means that there is no addition of the mercaptan to the conjugated double bonds. This observation is surprising in view of the studies by Posner,[4] Ruhemann[5] and Nicolet[6] of the behavior of α,β-unsaturated ketones with mercaptans, as well as the papers of Diels and Abderhalden,[7] Ruzicka[8] and Grasshoff[9] on 4-cholesten-3-one as an α,β-unsaturated ketone. We attempted to bring the double bond to reaction using piperidine as a catalyst, instead of zinc chloride and sodium sulfate. According to Ruhemann[5] this greatly favors the addition of mercaptan to the double bond instead of the condensation to mercaptol. We were unable, however, to isolate any reaction product containing sulfur, except dibenzyl disulfide. In addition to small quantities of unchanged 4-cholesten-3-one, we obtained a few milligrams of a sulfur-free substance, m. p. 146–150°, which with tetranitromethane gave a strong brown color. We believed that *allo*- and *epi-allo*-cholesterol might have been formed by reduction, possibly mixed with other secondary reaction products. According to Schoenheimer and Evans[10] those two substances form a molecular compound of the m. p. 141°. The lack of reaction with trichloroacetic acid, which according to these investigators[10] is characteristic of these unsaturated steroid alcohols or their dehydration products, seems to exclude the presence of both the *allo*-cholesterols. We must postpone clarification of this question until we have greater quantities of this sulfur-free substance.

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(2) H. Hauptmann, *Anais assoc. quim. Brasil*, **3**, 231 (1944); *C. A.*, **40**, 569 (1946).

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(6) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(7) O. Diels and E. Abderhalden, *Ber.*, **37**, 3099 (1904).

(8) L. Ruzicka, *Helv. Chim. Acta*, **17**, 1414 (1934).

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