was removed by filtration and the filtrate distilled. The latter proved to be unaltered butyl bromide.

Action of Grignard Reagent on Acetal.—To a Grignard solution made from 50 g. of ethyl bromide was added gradually at 5–10° an ethereal solution of dipropargyl methylene ether. Ethane was evolved steadily and was collected and tested. After 24 hours outdoors, two layers formed in the liquid. To this mixture was then added 50 g. of butyl bromide, and the whole heated for 3 hours under a reflux condenser; dry toluene was then added and the ether removed. The heating was continued for 1 hour longer. No magnesium bromide separated. The reaction mixture was then treated with dil. sulfuric acid, and the upper layer dried and distilled. After removal of the solvent, no oil was obtained. The residue, which was insoluble in solvents, could not be resolved into any individual product.

This experiment was repeated several times under various conditions, but so far unsuccessfully.

Summary

1. Dipropargyl methylene ether was prepared from the acetal of β-dibromohydrin.

2. It was found that the silver derivative of dipropargyl methylene ether did not react with alkyl halides under the conditions indicated.

3. Dipropargyl methylene ether reacts with ethylmagnesium bromide but the resulting reaction product did not aid in the synthesis of the higher homologs of propargyl alcohol.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

OBSERVATIONS ON THE PROPERTIES OF ARSPHENAMINE[1]

BY WALTER G. CHRISTIANSEN

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The Relation of Arsphenamine to Some Methyl Ketones

In connection with an investigation of the ease of solution of arsphenamine in water, samples were precipitated from methyl alcohol solution by acetone instead of ether. Analytical data on material precipitated in this way confirm the conclusion of Fargher and Pyman[2] that the product contains 1 molecule of acetone in addition to the usual 2 molecules of water.

Calc. for $C_{12}H_{14}O_2N_2Cl_2As_2.2H_2O.(CH_3)_2CO$: As, 28.2; Cl, 13.3. Found: As, 28.1; Cl, 13.1.

Prolonged drying in a vacuum removes the 2 molecules of water but the acetone remains unchanged;[2] when the material is dried to constant

[1] This is the twelfth of a series of studies on the properties contributing to the toxicity of arsphenamine being made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work is under the general direction of Dr. Reid Hunt.

[2] Fargher and Pyman, *J. Chem. Soc.*, **117**, 372 (1920).

weight at about 98° in a slow stream of dry carbon dioxide the loss is that calculated for 2 molecules of water and the dried product gives a strong qualitative test for acetone.

Calc. for 2 H_2O: H_2O, 6.7. Loss at 98°: 6.1.

Moreover, when arsphenamine containing a molecule of acetone is dissolved in absolute methyl alcohol and reprecipitated with ether, the dried product still gives a very positive test for acetone. Since neither drying or reprecipitation from acetone-free solvents removes the acetone, the latter must be bound very firmly to the arsphenamine molecule and is not retained mechanically. In view of this strong union, one would expect that if a small amount (0.5 cc.) of acetone be added to a methyl alcohol solution of arsphenamine (1 g. in 8 cc. of methyl alcohol) before the latter is poured into ether, the product, after it is washed and dried, would contain acetone; this has been found to be true. In similar experiments using methylethyl, methyl-*n*-propyl, methyl-*n*-butyl, and methyl-*iso*butyl ketone, instead of acetone, the products always give positive tests for methyl ketone.

From the work described above it is evident that arsphenamine possesses a strong affinity for methyl ketones. The tests for ketones were made by testing with alkali and iodine the first portions of the distillate of a 5% aqueous solution of the arsphenamine.

The Conversion of Arsphenamine Into a Polyarsenide

The reduction of a mixture of 2 different aryl arsonic acids or the digestion of a mixture of 2 symmetrical aryl arseno compounds always results in the formation of 1 unsymmetrical arseno compound. Also, when an arsonic acid is reduced in the presence of an inorganic arsenical, an organic polyarsenide, such as Ar_2As_4, is formed instead of a mixture of ArAs=AsAr and metallic arsenic. It has now been found that an arseno compound in the presence of nascent arsenic changes to a polyarsenide.

A solution of 0.2 g. of arsphenamine in 3.2 cc. of water is treated with 2.4 cc. of 50% hypophosphorous acid, 0.4 cc. of hydrochloric acid (d., 1.19) and 3.2 cc. of an aqueous solution of sodium arsenite (1 g. of $NaAsO_2$ in 16 cc. of solution). The pale yellow solution, in a stoppered cylinder, is allowedto st and at room temperature in the dark; it becomes orange colored, and then red; turbidity sets in and finally a precipitate forms. When the material stands long enough, the solution becomes colorless and the orange-colored precipitate becomes covered by a black layer of metallic arsenic. Before this stage is reached, the mixture of orange-colored solid and solution is poured into 2 volumes of 1 to 1 cold hydrochloric acid and the solid is washed with acid and dried in a vacuum over sodium hydroxide. From 1.3 g. of arsphenamine, 1.7 g. of a red polyarsenide of arsphenamine is obtained.

Analysis. Calc. for $C_{12}H_{14}O_2N_2Cl_2As_4$: As, 50.9. Found: 52.5.

When a mixture of 3-amino-4-hydroxyphenyl-arsenious oxide and sodium arsenite in aqueous solution containing hydrochloric acid, is reduced with hypophosphorous acid and the polyarsenide isolated as described above, a red solid is obtained which contained 53.7% of arsenic and dissolves in water to give a red solution.

The rate of polyarsenide formation as determined by the color change and appearance of turbidity varies greatly depending upon the method of preparation of the arsphenamine. The following methods are arranged in the order in which resulting arsphenamine undergoes polyarsenide formation with decreasing speed: (1) reduction of 3-nitro- or 3-amino-4-hydroxyphenylarsonic acid with pure hydrosulfite; (2) reduction of the nitro acid to toxic arsphenamine with commercial hydrosulfite; (3) reduction of the amino acid or the nitro acid to relatively non-toxic arsphenamine with commercial hydrosulfite; (4) reduction of the amino acid with hypophosphorous acid followed by precipitation with hydrochloric acid.

When a sample which gives the polyarsenide reaction quite rapidly is allowed to stand in aqueous solution with a small amount of hydrochloric acid, the viscosity of the solution increases and the rate at which it is converted into a polyarsenide decreases. Also, when a specimen of arsphenamine base which gives a polyarsenide fairly rapidly is converted into the dihydrochloride the latter gives a polyarsenide less rapidly than the original base. It seems that the rate at which this reaction takes place is closely connected with the degree of polymerization[3] of the arsphenamine.

The Precipitation of Dilute Aqueous Solutions of Arsphenamine with Hydrochloric Acid

During the investigation of the reduction of 3-nitro-4-hydroxyphenylarsonic acid to arsphenamine base with commercial hydrosulfite, it was shown that the conditions under which the nitro group is reduced exert a great influence on the toxicity of the product; and two sets of conditions were developed, one of which favored the formation of toxic products whereas the other enabled one to obtain products of low toxicity. In both procedures the quantities of reagents are identical. Mr. George, of this Laboratory, has examined the action of precipitants on dilute aqueous solutions of a number of samples of arsphenamine and finds that the amount of hydrochloric acid required to precipitate a solution of a specimen prepared under the conditions most favorable to the development of low toxicity is nearly twice as great as that required for the toxic specimen prepared under the other procedure.

Two-tenths cc. of a 2% solution of alkalinized arsphenamine, that is, one containing the disodium salt of arsphenamine, is diluted with 1 cc. of water in a 7 cc. test-tube which is then placed in a water-bath at 37°. Hydrochloric acid (1:1) is added from a small buret until a permanent precipitate is secured. All specimens prepared under the most favorable conditions require 1.95 cc. of acid and those prepared under the least favorable conditions require only 1.12 cc.

When marked changes are made in the preparation of the arsphenamine, such as changes in the acidity of the reduction mixture, the hydrochloric

[3] Sherndal, *J. Lab. Clin. Med.*, 7, No. 12 (1922).

acid titration fluctuates greatly from the values given above. Since the amount of hydrochloric acid is constant only when every detail of the preparation of the arsphenamine is exactly duplicated each time, this titration is a rapid way to detect variations in the routine preparation of this material, and specimens giving a low precipitation value should be carefully examined toxicologically.

The precipitation of arsphenamine from aqueous solutions with hydrochloric acid is a salting-out process and involves the coagulation of the finely divided arsphenamine particles in the original solution. Since the less toxic specimens require more acid than the relatively toxic ones, the arsphenamine is in a more finely divided state in the less toxic solutions. This difference in the state of division may account for some of the unfavorable results encountered in the more toxic material.

The Importance of the Quantity of Hydrochloric Acid Used in Converting Arsphenamine Base into the Hydrochloride

In the common method of converting arsphenamine base into the hydrochloride the base is dissolved in methyl alcoholic hydrochloric acid and this solution is mixed with a large amount of ether to precipitate the arsphenamine. The quantity of hydrochloric acid used in this process has considerable bearing on the physical properties of the resulting arsphenamine. If only 1 molecule of acid per molecule of base is used, the alcohol solution is dark colored; in extreme cases, as when the nitro acid has been reduced improperly, the color may be reddish-brown. As more acid is added, the color changes gradually to a clear yellow. The dark colored solution of the monohydrochloride, poured into ether, gives a gummy and dark colored precipitate; part of the solid remains suspended in the ether and cannot be filtered out easily. When more methyl alcoholic hydrochloric acid is added to the ether suspension, the precipitate coagulates and settles at once. When a solution of the base in methyl alcohol containing 2 or a fraction more molecules of hydrochloric acid is poured into ether, the yellow precipitate coagulates at once and the supernatant liquor is perfectly clear. In order to secure the desired yellow color and to obtain a precipitate that can be manipulated easily it is advisable to use a slight excess of acid over that necessary to form the dihydrochloride.

The amount of acid used in preparing the hydrochloride has very little bearing upon the toxicity and sulfur content of the product. It has been noted, however, that material made with less than 2 molecules of acid produces death more quickly than material prepared with an excess of acid, when administered in fatal doses to rats.

I wish to thank Dr. Reid Hunt for his interest in this work, and Mr. Arthur Norton for preparing the higher methyl ketones.

Summary

Arsphenamine forms additive compounds with methyl ketones in which the ketone is bound very firmly. Neither drying at room temperature or at 98°, nor reprecipitation from ketone-free methyl alcohol with ether removes the ketone. When an aqueous solution of arsphenamine and sodium arsenite is treated with hydrochloric and hypophosphorous acids, the yellow color gradually changes to red and a polyarsenide of arsphenamine is formed. The rate at which this reaction takes place depends upon the method used in preparing the arsphenamine and seems to be related to the physical properties of the latter. The quantity of 1 to 1 hydrochloric acid necessary to precipitate a dil. aqueous solution of arsphenamine is constant when one method of preparation is strictly followed, but slight variations in certain steps in the synthesis cause fluctuations in the amount of acid required. Therefore, this titration has been found useful in determining the closeness with which the routine method of preparation has been followed. The physical properties of arsphenamine are affected materially by the amount of hydrochloric acid used in converting the base into the hydrochloride; it is advantageous to use a slight excess over the two molecules needed to secure the dihydrochloride.

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5,5-DIARYLBARBITURIC ACIDS

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Considering the great importance of veronal (diethylbarbituric acid) and luminal (phenylethylbarbituric acid) as therapeutic agents, and the large number of homologs that have been prepared by substituting other alkyl groups, it is surprising that no attempts to prepare 5,5-diarylbarbituric acids are on record. Luminal, in which one of the ethyl groups of veronal has been replaced by phenyl, is said to be 2.5 times as powerful in its physiological action as veronal, and is widely used in the treatment of epilepsy. The introduction of a second phenyl group might be expected to increase the physiological activity still further, provided the resulting derivatives possessed certain essential physical properties. The isomeric 1,3-diphenylbarbituric acid has been prepared by Whiteley[1] from malonyl chloride and carbanilide. No statement is made regarding its physiological properties, but from analogy with other N-substituted barbituric acids, we should hardly expect this substance to be of medicinal value.

The substitution of one or more aryl groups on the 5-carbon atom of

[1] Whiteley, *J. Chem. Soc.*, **91**, 1330 (1907).