[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

THE REACTIONS OF THE ARSINES. PRELIMINARY PAPER. CONDENSATION OF PRIMARY ARSINES WITH ALDEHYDES.[1]

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The discovery of arsphenamine greatly stimulated research on organic arsenic compounds. The aim in these investigations has been not only to discover some substance with a higher therapeutic value but, more particularly, some substance of greater stability than arsphenamine. A large number of arsenic compounds have been prepared, but it is noticeable that most of them contain the arseno or arsenic acid groupings, namely, the same groupings which occur in those substances of proved therapeutic value, such as arsphenamine, sodium cacodylate and arrhenal. Comparatively little has been done, however, in attempts to obtain arsenic linked in new ways in organic compounds to determine whether the resulting substances might not be equal or superior therapeutically to those arsenic compounds already found valuable. The research, of which this is a preliminary report, had such an object in view.

A study of the condensation reactions of phenyl arsine with various organic reagents has been undertaken. The experiments have led to such interesting results that a number of investigations have been started to compare carefully the reactions of primary and secondary arsines and arsine itself with the corresponding nitrogen compounds. Experiments have also shown that the phosphines and stibines react similarly, so that a thorough study of these fields is to be taken up.

The previous work on the reactions of the arsines has been very limited. It has been shown that halogens and alkyl halides react with primary and secondary arsines[2] to give respectively arsine halides and arsonium halides. More recently a number of patents[3] have described the condensation of primary aryl arsines with aryl arsenious oxides or chlorides, with aryl stibinous oxides or chlorides, with arsenic, antimony or bismuth trichlorides or tribromides. A more complete review and discussion of these reactions will be given in a future communication.

The present paper deals with the condensation of aldehydes with phenylarsine. Addition products are formed between 2 molecules of aldehyde and one molecule of arsine. The probable structure of the compounds produced is represented by the formula in the following equation

[1] This work was done under a grant from the U. S. Interdepartmental Social Hygiene Board, Washington, D. C., Dr. T. A. Storey, Secretary.

[2] *Ber.*, 34, 3598 (1901); *Am. Chem. J.*, 33, 101 (1905); 35, 1 (1906); 40, 88 (1907).

D. R. P., 254,187; *Frdl.* 11, 1068 (1912–14); 275,216; 251,571; 254,187; *D. R. P.*, 251,104; 253,226; 270,254; 269,699; 269,700; 269,743; 269,744; 269,745.

$RCHO + RAsH_2 \longrightarrow (RCHOH)_2AsR$. When the aldehyde and arsine are mixed, no apparent reaction takes place until a few drops of hydrochloric acid are added as a catalyzer. Considerable heat is then generated and within a few minutes the reaction is complete. During this procedure, care must be used in handling the arsines as they are easily oxidized by the oxygen of the air to arsenobenzene and phenylarsinic acid. The condensation must be carried out in an atmosphere of carbon dioxide or nitrogen.

Up to the present time, benzaldehyde and butyraldehyde have been condensed with phenylarsine. It seems probable that this reaction may be extended to any aromatic or aliphatic arsines and aldehydes. The compounds may be looked upon as corresponding somewhat to aldehyde ammonias except that only one hydrogen atom on the nitrogen atom reacts, whereas both hydrogen atoms on the arsenic atom take part in the change. The compounds, however, in their chemical reactions do not resemble aldehyde ammonias. They are perfectly stable in cold water, 10% sodium hydroxide solution or dil. hydrochloric acid. Even after boiling them 5 minutes with these reagents, no decomposition takes place except with hydrochloric acid, and only a slight change occurs in this case. Other reactions of these substances will be discussed in a later paper.

Whereas the compounds already made are not soluble in water, it is hoped to obtain certain derivatives in this series which will be soluble in water and capable of therapeutic testing.

Experimental.

Phenylarsinic Acid.—This substance is prepared in 150–200 g. lots by a modification of Bart's reaction which was employed in Germany during the war.[1] It consists in the action of benzene diazonium chloride on sodium arsenite at 15° in the absence of free alkali and in the presence of a copper salt. The yields of pure, recrystallized acid are 40–50%, calculated from the aniline.

Phenylarsine.[2]—For the preparation of this primary arsine, phenylarsinic acid in 50 g. lots is reduced with amalgamated zinc dust and hydrochloric acid. The yields obtained are 40–70%.

Di-α-hydroxy-*n*-butyl phenylarsine (Phenylarsine and *n*-butyraldehyde).—A 250-cc. Erlenmeyer flask is fitted with a 3-hole rubber stopper. A tube through which carbon dioxide may be passed into the flask is placed in one hole, an exit tube and a 100 cc. separatory funnel in the other holes. The air in the apparatus is completely replaced by carbon dioxide, then 20 g. of phenylarsine is poured in through the funnel. This is followed by 5 or 6 drops of conc. hydrochloric acid, and, finally,

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[1] *D. R. P.*, 254,092; *Frdl.* 11, 1030 (1913); *J. Ind. Eng. Chem.*, 11, 825 (1919).

[2] *Ber.*, 34, 3598 (1901); *Am. Chem. J.*, 35, 1 (1906).

20 g. of *n*-butyraldehyde is added in small portions. The reaction takes place immediately; enough heat is evolved to cause the mixture to boil. Carbon dioxide is passed in until the reaction mixture is completely cold (30 to 40 minutes). The product is shaken out with 50 cc. of dil. sodium carbonate solution to remove phenylarsinic acid formed by the oxidation of phenylarsine during the manipulations, and then distilled under diminished pressure.

The fraction boiling $226-230°_{28 \text{ mm.}}$ is collected and redistilled. Thus 18 g. of product boiling at $228°_{26 \text{ mm.}}$ is obtained. Although it boils very constant, the cold distillate is slightly turbid, probably due to a trace of phenylarsinic acid not removed by the sodium carbonate. It has the following constants: d_{30}, 1.114; $[n]^{30}$, 1.686.

The compound was analyzed for arsenic by a combination of methods. It was first burned by the method reported by Palmer[1] in a current of oxygen in a tube packed with zinc oxide, the product then dissolved in conc. hydrochloric acid and precipitated with hydrogen sulfide. From this point, the procedure was the same as reported by Little.[2]

Subs., 0.1966, 0.2380: CO_2, 0.4120, 0.5027; H_2O, 0.1371, 0.1602.

Subs., 0.2206: 17.6 cc. iodine (1 cc. sol. = 0.0031 g. arsenic).

Calc. for $C_{14}H_{23}O_2As$: C, 56.36; H, 7.71; As, 25.17. Found: C, 56.47, 57.22; H, 7.29, 7.53; As, 24.74.

This substance is a slightly volatile oil, readily soluble in organic solvents, but practically insoluble in water. It is a stable substance which remains undecomposed in cold water, 10% sodium hydroxide solution and dil. hydrochloric acid. Even when boiled with these reagents, the substance seems to be stable to all except the dilute acid.

Di-α-hydroxybenzyl phenylarsine (Phenylarsine and Benzaldehyde).—The procedure for the preparation of this substance is similar to the one just described. When 20 g. of phenylarsine, 29 g. of pure benzaldehyde and a few drops of hydrochloric acid are mixed, heat is evolved and within a few minutes the mixture has solidified. The crude product crystallized directly from benzene yields fine white needles with a constant m. p. of 193°. The compound must be dried to constant weight at 110° before it is analyzed.

For the analysis for arsenic, the method of Erwins[3] was used.

Subs., 0.2187, 0.2163; CO_2, 0.5301, 0.4471; H_2O, 0.0895, 0.0709.

Subs., 0.2163, 0.2296: 14.0 cc., 14.95 cc. iodine (1 cc. = 0.0031 g. As).

Calc. for $C_{20}H_{19}O_2As$: C, 65.58; H, 5.19; As, 20.66. Found: C, 66.06, 66.28; H, 4.53, 4.31; As, 20.07, 20.19.

The substance is stable to water, dil. hydrochloric acid and in alkali. It is soluble in most organic solvents, but insoluble in water.

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[1] Palmer, *Ber.*, **34**, 3597 (1901).

[2] Little, *J. Chem. Soc.*, **95**, 478 (1909).

[3] Erwins, *ibid.*, **109**, 1356 (1916).

Summary.

1. Phenylarsine has been condensed with butyraldehyde and benzaldehyde to give compounds consisting of two moles of aldehyde and one of arsine and probably having the following structure, $C_6H_5As(CHOH)_2R$.

2. The condensation products are stable toward dilute acid, alkali and water.

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THE HUMIN FORMED BY THE ACID HYDROLYSIS OF PROTEINS. VI. THE EFFECT OF ACID HYDROLYSIS UPON TRYPTOPHANE.[1]

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In previous articles of this series[2] we have shown "that the formation of black acid insoluble humin in a normal protein hydrolysate is dependent upon the presence of tryptophane in the protein molecule." While tryptophane reacts readily with aldehydes to give a black insoluble product, it also undergoes some unknown reaction even when allowed to stand in an acid solution. This was noted by Abderhalden[3] who found that the mother liquor from a tryptophane preparation, which had been allowed to stand for a long time, slowly darkened, lost its ability to absorb bromine, gave no glyoxylic test, and finally deposited a dark brown product, soluble in acids and alkalies, and which when heated gave a strong indole odor.

Harries and Langheld[4] studied the effect of ozone upon hydrolytic products of proteins and found that tryptophane treated with ozone colored very dark, gave no glyoxylic reaction, reduced Fehling's solution in the cold, was precipitated by barium hydroxide, lead acetate, basic lead acetate, and liberated ammonia when treated with sodium hydroxide.

Van Slyke states[5] "tryptophane is known to be precipitated partially by phosphotungstic acid even from fairly dilute solution. When it is boiled with mineral acids, however, it is, to a large extent, at least, destroyed, the nature and fate of the products being unknown." In order to ascertain the behavior of tryptophane under the conditions of protein

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[2] Gortner and Blish, THIS JOURNAL, **37**, 1630–36 (1915); Gortner, *J. Biol. Chem.*, **26**, 177–204 (1916); Gortner and Holm, THIS JOURNAL, **39**, 2477–2501 (1917); **42**, 821–827 (1920); Holm and Gortner, *ibid.*, **42**, 632–40 (1920).

[3] Abderhalden, *Z. physiol. Chem.*, **78**, 159–160 (1912).

[4] Harries and Langheld, *ibid.*, **51**, 371–383 (1907).

[5] Van Slyke, *J. Biol. Chem.*, **10**, 39 (1911).