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ARSENICALS. PART II. DERIVATIVES OF N^1-(*p*-ARSONOBENZYL)-SULFANILAMIDE

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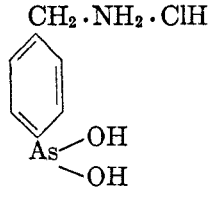
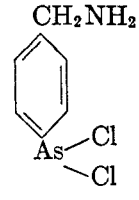
In a previous paper (1), the author described the preparation of compounds containing substituted benzenesulfonyl groups linked to aromatic arsenicals *via* an oxygen or nitrogen bridge. The present study is an extension of that work and concerns the preparation of sulfanilamido derivatives of *p*-arsonobenzylamine (homoarsanilic acid) and their reduction products.

Since the interposition of a methylene group between the para-amino group and the benzene nucleus of sulfanilamide resulted in a compound of marked therapeutic value (Marfanil), it was hoped that a similar interposition in the arsanilic acid molecule might also result in therapeutically interesting compounds. Some indication of the validity of this thesis was found in the results obtained by Eagle and his co-workers (2), who first tested *p*-arsenosobenzylamine and its acetyl derivative, and found them to be strongly trypanocidal but inferior to Mapharsen in treponemicidal:toxic ratios.

In the present study, benzylamine was acetylated with acetic anhydride and the acetylation mixture was added to fuming nitric acid in the cold to give, predominantly, *p*-nitrobenzylacetamide (I). The *p*-nitro compound was then catalytically reduced to *p*-aminobenzylacetamide (II). The amine, upon subjection to the Bart reaction (4), gave N-(*p*-arsonobenzyl)acetamide (III), in the form of white needles. Reduction of the arsonic acid yielded N-(*p*-arsenosobenzyl)-acetamide (V) and its deacetylation gave *p*-arsonobenzylamine (IV). The latter compound was then reduced with sulfur dioxide and potassium iodide in dilute hydrochloric acid solution to give directly *p*-arsonosobenzylamine hydrochloride (formula A)



(A)



(B)

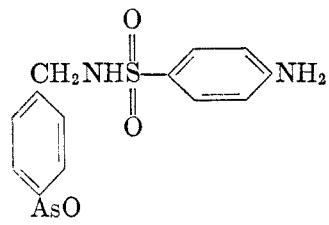
Formula A—Calc'd, As = 29.8; Cl = 14.9. Found, As = 29.8; Cl = 14.1.
Formula B—[Doak (3)], Calc'd, As = 29.7. Found, As = 29.6.

Doak and his co-workers (3) reduced *p*-arsonobenzylamine with the same reagents and isolated a compound which they regarded as the arsendichloride, and which they characterized as being completely resistant to hydrolysis with sodium bicarbonate. They further stated that, "the arsenoxide could be obtained only by

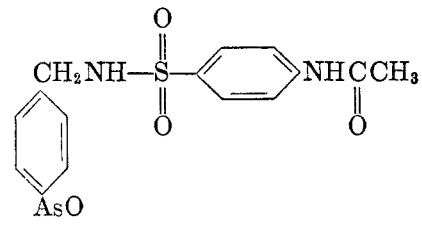
hydrolyzing with sodium hydroxide solution." Formula (B), deduced from the empiric formula assigned to the arsendichloride, cannot be regarded as a likely structure since the coexistence of the highly basic free amino group and the alkali-sensitive arsendichloride moiety is improbable. Furthermore, it was found that the reduction product obtained in these laboratories contained one atom of chlorine, even when the reduction was carried out in the presence of 3 *N* hydrochloric acid. It is most probable, therefore, that Doak and his co-workers had actually obtained *p*-arsonosobenzylamine hydrochloride (formula A) rather than the arsendichloride. On the basis of the structure presented by formula A, the resistance to hydrolysis with sodium bicarbonate noted by those investigators, was due to the inability of the bicarbonate ion to decompose the benzylammonium chloride. When sodium hydroxide was used, they obtained *p*-arsenosobenzylamine. In these laboratories, concentrated ammonium hydroxide was used instead of sodium hydroxide and a hydrated modification of *p*-arsenosobenzylamine was obtained which melted at 142.5°.

Upon treatment of *p*-arsonobenzylamine with *p*-acetamidobenzenesulfonyl chloride in the presence of alkali, *N'*-(*p'*-arsonobenzyl)-*p*-acetamidobenzenesulfonamide (VIII) was obtained. This compound was reduced with phenyl hydrazine to give the corresponding arsenoxide (IX). Compound VIII was deacetylated according to the method of Kwartler (5) to give N^1-(*p*-arsonobenzyl)-sulfanilamide (X) which on reduction with phenylhydrazine yielded the arsenoxide (XI). The reduction of the arsonic acids VIII and X with sodium hydrosulfite gave respectively N,N'-(*p'*-arsenobenzyl)-bis-(*p*-acetamidobenzenesulfonamide) (XII) and N,N'-(*p'*-arsenobenzyl)-bis-(*p*-aminobenzenesulfonamide) (XIII).

Chemotherapeutic studies by R. J. Schnitzer of these laboratories confirmed the results obtained by Eagle (2) anent the activities of *p*-arsenosobenzylamine and its acetyl derivative. All of the sulfanilamido derivatives possessed varying degrees of spirochetocidal and/or trypanocidal activity but none of them were outstandingly effective. The arsenoxides N^1-(*p*-arsenosobenzyl)sulfanilamide (formula C) and its acetylated derivative (formula D)



(C)



(D)

both showed good spirochetocidal activity combined with low toxicity and had chemotherapeutic indices comparable to that of Mapharsen in mouse relapsing fever.

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The author is also indebted to Dr. A. Steyermark for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

I. p-Nitrobenzylacetamide. The procedure of Amsel and Hofmann (6) was modified as follows: To 216 g. of benzylamine was added dropwise 207 g. of acetic anhydride. The mixture was then refluxed for ½ hour to ensure complete acetylation. The cooled mixture, consisting of benzylacetamide in acetic acid solution was then added dropwise with stirring to 800 cc. of fuming nitric acid (sp. gr. 1.49–1.50) at 0°. Stirring was continued at 0° for 2½ hours after addition was complete. The mixture was poured onto 1000 g. of ice and was neutralized with concentrated ammonium hydroxide. On cooling the hot solution, the product precipitated out. Recrystallization from dilute alcohol resulted in pale yellow plates melting at 130–131°; yield 199 g. [Literature m.p. 125° (6) 133° (7)].

IIa. p-Aminobenzylacetamide. A solution of 188 g. of the nitro compound in ethyl alcohol was reduced with hydrogen in the presence of Raney nickel at 200 lb. pressure and room temperature. The product was obtained in quantitative yield. Upon recrystallization from benzene it precipitated in the form of near-white needles and plates melting at 93–95° [Doak (3) 85–86°].

Anal. Calc'd for $C_9H_{12}N_2O$: C, 65.7; H, 7.3; N, 17.1.
Found: C, 66.0; H, 7.6; N, 17.2.

IIb. p-Aminobenzylacetamide dihydrochloride. The reduction of the nitro compound may also be effected as follows: Forty grams of the nitro compound dissolved in 50 cc. of concentrated hydrochloric acid and 300 cc. of water was reduced at room temperature and 500 lbs. hydrogen pressure with 4 g. of palladium charcoal (wet) (10% Pd). The reaction mixture was filtered and most of the solvent was distilled off under vacuum. The residue, upon stirring with acetone yielded 20 g. of the dihydrochloride m.p. 186–189°.

Anal. Calc'd for $C_9H_{12}N_2O \cdot 2\,HCl$: C, 45.6; H, 6.0; N, 11.8.
Found: C, 45.5; H, 6.4; N, 12.3.

III. N-(p-arsonobenzyl)acetamide. Because of some discrepancies with the results obtained by Doak (3) the synthesis of this and the succeeding compound (IV) are given in specific detail.

Seventy-eight and one-half grams of *p*-aminobenzylacetamide dissolved in 600 cc. of 6 *N* hydrochloric acid was diazotized with 33 g. of sodium nitrite in 200 cc. of water. The diazotized solution was added to a mixture consisting of 189 g. of sodium meta-arsenite, 50 cc. of 2 *N* copper sulfate, 3 l. of water and 6 l. of ice. The reaction mixture was stirred and 6 *N* sodium hydroxide was added to slight alkalinity. When the evolution of nitrogen ceased, the reaction mixture was warmed to 45° for one hour, treated with Norit, and filtered. The filtrate was acidified with concentrated hydrochloric acid to *p*H 3 (Congo Red) and was evaporated to dryness under a vacuum. The residue was extracted several times with hot methyl alcohol, and the combined extracts were evaporated to dryness. The crystalline residue was dissolved in 6 *N* sodium hydroxide, treated with Norit, filtered, and the filtrate adjusted to *p*H 3 with dilute hydrochloric acid. The resulting precipitate of crude N-(*p*-arsonobenzyl)acetamide weighed 58 g. On recrystallization from hot water, white needles were obtained which did not melt below 300°. Doak (3) described the compound as an amorphous powder.

Anal. Calc'd for $C_9H_{12}AsNO_4$: As, 27.4. Found: As, 27.5.

IV. p-Arsonobenzylamine. A solution of 50 g. of the acetyl compound in 132 cc. of 6 *N* sodium hydroxide was refluxed for 2 hours. The reaction mixture was diluted with an equal volume of water, filtered, and adjusted to *p*H 6 with acetic acid. A crystalline precipitate [Doak (3) obtained an amorphous powder] appeared, which was insoluble in water and all organic solvents and was soluble only in acids or bases. On reprecipitation from alkali with acetic acid the product was obtained as white needles which did not melt below 300°.

Anal. Calc'd for $C_7H_{10}ASNO_3$: As, 32.4. Found: As, 32.2.

V. N-(p-arsenosobenzyl)acetamide. A solution of 5 g. of the arsonic acid and 0.1 g. of potassium iodide in 100 cc. of 2 *N* hydrochloric acid was treated with sulfur dioxide for sev-

eral hours. The gummy yellow precipitate was filtered off and purified by reprecipitation from dilute sodium hydroxide with dilute acetic acid; white microcrystalline material, m.p. 223–226° [Doak (3) m.p. 224–226°].

Anal. Calc'd for $C_9H_{10}AsNO_2$: Mol. wt., 239. Found: Mol. wt., (iodine titration), 242.

VI. p-Arsonosobenzylamine hydrochloride. A stirred solution of 60 g. of *p*-arsonobenzylamine and 1 g. of potassium iodide in 500 cc. of 2 *N* hydrochloric acid was treated with sulfur dioxide at room temperature for 45 minutes. The mixture was then cooled to 0° with stirring and continued sulfur dioxide addition for three more hours. The white precipitate was filtered off, washed with a little cold water and then with acetone, and dried. A further quantity of the product was obtained by saturating the filtrate in the cold with sulfur dioxide and permitting it to stand in the refrigerator overnight; total yield of white microcrystalline powder, 46 g. The product did not melt below 300°.

Anal. Calc'd for $C_7H_{10}AsNO_2 \cdot HCl$: As, 29.8; Cl, 14.9; Mol. wt., 251.5.
Found: As, 29.8; Cl, 14.1; Mol. wt., (iodine titration), 244.

VII. p-Arsonosobenzylamine. The hydrochloride prepared above was suspended in cold concentrated ammonium hydroxide, filtered, and washed with a little cold water and then with acetone. The white powder melted at 142.5° [Doak (3) reported the anhydrous (arsenoso) modification: As = 38.0%].

Anal. Calc'd for $C_7H_{10}ASNO_2$: As, 34.9; mol. wt., 215.
Found: As, 34.5; Mol. wt., (iodine titration), 212.

VIII. N¹-(p'-arsonobenzyl)-p-acetamidobenzenesulfonamide. To 7 g. of *p*-arsonobenzylamine in 50 cc. of 2 *N* sodium hydroxide was added 9 g. of *p*-acetamidobenzenesulfonyl chloride in acetone solution. The mixture was warmed on the steam-bath for a few minutes, filtered, diluted with water, and finally adjusted to *p*H 3. The product precipitated out and on recrystallization from dilute methyl alcohol was obtained in the form of glistening white plates which melted with decomposition at 300°.

Anal. Calc'd for $C_{15}H_{17}AsN_2O_6S$: As, 17.5. Found: As, 17.8.

IX. N¹-(p-arsenosobenzyl)-p-acetamidobenzenesulfonamide. A mixture of 5 g. of the arsonic acid and 4.2 g. of phenylhydrazine in methyl alcohol was refluxed until the evolution of nitrogen ceased. The methyl alcohol was removed and the oily residue was treated with a slight excess of 1 *N* sodium hydroxide and extracted with ether. The aqueous layer was filtered and treated with a concentrated ammonium chloride solution to yield the desired product; white powder, m.p. 215–219°; soluble in methyl alcohol, acetone, and dilute hydrochloric acid.

Anal. Calc'd for $C_{15}H_{15}AsN_2O_4S \cdot 2.5\ H_2O$: As, 17.1; Mol. wt., 439.
Found: As, 16.9; Mol. wt., (iodine titration), 435.

X. N¹-(p-arsonobenzyl)sulfanilamide. Four grams of the corresponding acetyl compound was hydrolyzed according to the method of Kwartler (5). Upon recrystallization from water glistening feathery white needles were obtained, decomp. 307–308°; soluble in hot water and hot methyl alcohol and insoluble in acetone and ether. The compound gave a coupling reaction indicating the presence of the free amino group.

Anal. Calc'd for $C_{13}H_{15}AsN_2O_5S \cdot H_2O$: As, 18.6. Found: As, 18.7.

XI. N¹-(p-arsenosobenzyl)sulfanilamide. A methyl alcohol solution of 7.5 g. of the arsonic acid was reduced with phenylhydrazine as described above to yield a white powder, m.p. 122–124°.

Anal. Calc'd for $C_{13}H_{13}AsN_2O_3S \cdot 2H_2O$: As, 19.3; Mol. wt., 388.
Found: As, 18.8; Mol. wt., (iodine titration), 372.

XII. N,N'-(p-arsenobenzyl)-bis-(p'-acetamidobenzenesulfonamide). Five grams of the arsonic acid was reduced with sodium hydrosulfite in the customary manner to yield the yellow powder characteristic of the arsenobenzenes. Since the product was insoluble in all the common solvents, it could not be purified; m.p. indefinite.

Anal. Calc'd for $C_{30}H_{30}As_2N_4O_6S_2$: As, 19.8. Found: As, 18.0.

XIII. N,N'-(p-arsenobenzyl)-bis-(p-aminobenzenesulfonamide). Reduction of the cor-

responding arsonic acid with sodium hydrosulfite resulted, as above, in a yellow amorphous precipitate which could not be purified; m.p. indefinite.

Anal. Calc'd for $C_{26}H_{26}As_2N_2O_4S_2$: As, 22.3. Found: As, 23.2.

SUMMARY

Some sulfanilamido derivatives of *p*-arsonobenzylamine, and their reduction products are described in this report.

The preparation of *p*-arsonosobenzylamine and its hydrochloride are also described.

None of the compounds were outstandingly active against trypanosome and spirochetal infections though the sulfanilamido derivatives of *p*-arsonosobenzylamine possessed chemotherapeutic indices comparable to that of Mapharsen in relapsing fever experiments.

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