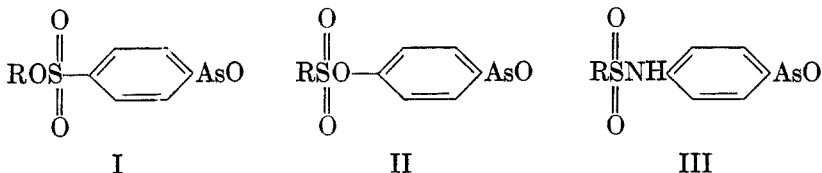


ARSENICALS. PART I. SULFONYLOXY, SULFONAMIDO, AND
BENZYLOXY DERIVATIVES OF PHENYLARSONIC
ACIDS AND THEIR REDUCTION PRODUCTS

H. HERBERT FOX

Received July 10, 1947

The experimental work in this paper was completed several years ago and was based, in the main, upon the idea of combining within the framework of one molecule, structures reminiscent of the sulfonamides and the aromatic arsenicals, in the hope of effecting a significant increase in spirocheticidal, trypanocidal, or bacteriostatic activity. An increasing number of arsenicals containing sulfonyl residues have appeared in the recent literature (1, 2, 3, 4, 5, 6). To date, however, most of the compounds reported have had the sulfur and arsenic atoms linked directly to the same nucleus, (formula I) whereas in the present study, the sulfur atom has been linked to the arsenic-bearing nucleus *via* an oxygen or nitrogen bridge (formula II and III).



The synthesis of both types of compounds was effected by condensing *p*-acetamidobenzenesulfonyl chloride with the appropriate arsenical. In the case of arsanilic acid, the condensation did not take place and the arsanilic acid was recovered unchanged. Upon reduction of the arsono group to the arsenoxide, however, condensation was easily effected. With 3-amino-4-hydroxyphenylarsonic acid, condensation took place readily, but not in the anticipated direction. The *p*-acetamidobenzenesulfonyl chloride reacted only with the hydroxyl group and left the amino group untouched. The resistance of the amino group to the Hipsberg reaction may be attributed to the influence of the arsonic acid moiety.

In addition to the two types of compounds outlined above, another series was prepared with a view to ascertaining the influence of the benzyl group when used to block the hydroxyl group of 3-amino-4-hydroxyphenylarsonic acid and its reduction products. Two of the compounds in this series were previously reported by Balaban (7), who prepared 3-nitro-4-benzyloxyphenylarsonic acid in 36% yield by heating 3-nitro-4-hydroxyphenylarsonic acid with benzyl chloride for 20 hours in alkaline solution. In the present study, slight modification of conditions resulted in a 74.5% yield of the same compound in 2 hours.

In order to hydrolyze the acetamido group in the presence of hydrolysis-sensitive sulfonyloxy and sulfonamide linkages, recourse was had to the method of Kwartler (8) involving the use of alcoholic hydrogen chloride and a small quantity of concentrated hydrochloric acid at room temperature.

The trypanocidal and spirochetocidal activity of the arsenicals described in this report was tested by R. J. Schnitzer of the Chemotherapy Division of these laboratories. Tests were conducted in rabbit syphilis and on mice infected with *T. equiperdum* and *Borrelia novyi*. Though some of the compounds were quite active in rabbit syphilis and relapsing fever (*Borrelia novyi*), none of them could be considered superior to Mapharsen. Some miscellaneous tests conducted by Schnitzer also showed that none of the compounds possessed bactericidal activity *in vivo*.

Acknowledgment. The author wishes to acknowledge his gratitude and appreciation to Dr. H. M. Wuest for suggestions made at the time this work was in progress.

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

EXPERIMENTAL

All melting points are corrected.

4-(p-Acetamidobenzenesulfonamido)phenylarsenoxide dihydrate. Twenty grams of *p*-aminophenylarsenoxide (obtained by the reduction of arsanilic acid with phenylhydrazine) and 25 g. of *p*-acetamidobenzenesulfonyl chloride are dissolved in acetone and 8 g. of pyridine are added to the solution. Heat is evolved and the mixture separates into 2 phases, the acetone is removed *in vacuo*, and the residue is dissolved in dilute sodium hydroxide. The solution is chilled and the product is precipitated at pH 7 with acetic acid. The slightly gummy precipitate hardens on standing. Repeated precipitation from dilute ammonium hydroxide with dilute acetic acid results in a yield of 27 g. of white powder melting at 198°.

Anal. Calc'd for $C_{14}H_{13}AsN_2O_4 \cdot 2H_2O$: As, 18; Mol. wt., 416.

Found: As, 17.8; Mol. wt. (iodine titration), 420.

4-(p-Aminobenzenesulfonamido)phenylarsenoxide dihydrate. The chemotherapeutic properties of this compound were reported by Eagle, *et al.* (9) who obtained the material from the Squibb Institute. Since no preparative procedure was given in their report, the synthesis is described here.

Ten grams of the acetyl compound prepared above, in 100 cc. of 25% methyl alcoholic hydrogen chloride and 4 cc. of concentrated hydrochloric acid are permitted to stand at room temperature for 48 hours. The bulk of the alcohol is then removed under vacuum and the residue is dissolved in water and filtered. The filtrate on treatment with ammonium hydroxide to slight alkalinity yields 6.9 g. of the desired product. The compound is obtained as a white powder and has no definite melting point.

Anal. Calc'd for $C_{12}H_{11}AsN_2O_3S \cdot 2H_2O$: As, 20.1; Mol. wt., 374.

Found: As, 20.2, 20.1; Mol. wt. (iodine titration), 366.

3-Amino-4-(p-acetamidobenzenesulfonyloxy)phenylarsonic acid. To 25 g. of 4-hydroxy-3-aminophenylarsonic acid [prepared by the reduction of the corresponding nitro compound with Raney nickel and hydrogen according to the method of Stevinson & Hamilton (10)] dissolved in 199 cc. of 2 *N* sodium hydroxide is added 35 g. of *p*-acetamidobenzenesulfonyl chloride in acetone. The mixture is warmed on the steam-bath for several minutes, diluted with water, and acidified to pH 3 with hydrochloric acid. The product precipitates out and is recrystallized from dilute methyl alcohol; yield 42 g. of fine white needles, m.p. (decomp.) 250°. The product does not give a phenol test and does give a test for a free amine. It is therefore the hydroxyl group which has been blocked.

Anal. Calc'd for $C_{14}H_{15}AsN_2O_7S \cdot 2H_2O$: As, 16.1. Found: As, 16.0

3-Amino-4-(p-aminobenzenesulfonyloxy)phenylarsonic acid. Deacetylation of the corresponding acetyl compound according to the method of Kwartler (8) yielded a white crystalline product. Upon recrystallization from hot water, long white needles of indefinite melting point are obtained.

Anal. Calc'd for $C_{12}H_{13}AsN_2O_6S \cdot H_2O$: As, 18.5. Found: As, 18.5, 18.3.

3-Amino-4-(p-acetamidobenzenesulfonyloxy)phenylarsenoxide. Three grams of the corresponding arsonic acid dissolved in methyl alcohol is refluxed with 2.5 g. of phenylhydrazine for one hour. The methyl alcohol is then removed under vacuum and the residue is treated with an excess of 2 *N* sodium hydroxide. The alkaline mixture is extracted several times with ether and then is neutralized with acetic acid to yield the desired arsenoxide. Purification is effected by solution in dilute sodium hydroxide, treatment with Norit, and reprecipitation with dilute acetic acid; yield 1.3 g. of white powder, m.p. 171–176°.

Anal. Calc'd for $C_{14}H_{13}AsN_2O_6S \cdot H_2O$: As, 18.1; Mol. wt., 414.

Found: As, 18.2; Mol. wt. (iodine titration), 420.

3-Amino-4-(p-aminobenzenesulfonyloxy)phenylarsenoxide. In 100 cc. of 2 *N* hydrochloric acid containing 0.5 g. of potassium iodide is dissolved 6.1 g. of the corresponding arsonic acid and the resulting solution is treated with a stream of sulfur dioxide for 4 hours at room temperature. At the end of this time, the mixture is cooled and neutralized with ammonium hydroxide. The resulting white precipitate is filtered, washed with water, and dried; yield approximately 5 g. of product melting indefinitely, but below 150°.

Anal. Calc'd for $C_{12}H_{11}AsN_3O_6S \cdot 2H_2O$: As, 19.3; Mol. wt., 390.

Found: As, 19.1; Mol. wt. (iodine titration), 386.

4,4'-bis(p-Acetamidobenzenesulfonyloxy)-3,3'-diaminoarsenobenzene. A solution of 5 g. of the corresponding arsonic acid in 10 cc. of 2 *N* sodium hydroxide and 150 cc. of water is added to a solution of 50 g. of sodium hydrosulfite and 10 g. of magnesium chloride in 400 cc. of water. The mixture is warmed to 55–60° with stirring for 2 hours. The product precipitates out as a yellow powder which may be purified by solution in acetone and reprecipitation with benzene; m.p. 177–183°, yield 4.3 g.

Anal. Calc'd for $C_{28}H_{26}As_2N_4O_8S_2$: Acetyl, 11.3. Found: Acetyl, 10.9.

4,4'-bis(p-Aminobenzenesulfonyloxy)-3,3'-diaminoarsenobenzene. Three grams of the corresponding arsonic acid are reduced with sodium hydrosulfite as described above to yield 2.5 g. of pale yellow powder. The product is purified by repeated solution in acetone and reprecipitation with benzene and finally by solution in acetone and reprecipitation with water; m.p. 139.5°.

Anal. Calc'd for $C_{24}H_{22}As_2N_4O_8S_2 \cdot H_2O$: As, 21.6. Found: As, 21.6.

3-Nitro-4-benzoyloxyphenylarsonic acid. A mixture of 25 g. (1 mole) of 3-nitro-4-hydroxyphenylarsonic acid, 36 g. (3 moles) of benzyl chloride, 48.5 cc. (3 moles) 6 *N* sodium hydroxide, and 200 cc. of water is refluxed for 2 hours. The reaction mixture is kept alkaline by the addition of sodium hydroxide if necessary. The mixture is then cooled, extracted twice with ether, and the aqueous phase is acidified with acetic acid. The resulting precipitate (26 g. or 74.5%) is recrystallized from water to yield fine white needles melting at 250°.

Anal. Calc'd for $C_{13}H_{12}AsNO_6$: As, 21.2. Found: As, 20.7.

3-Amino-4-benzoyloxyphenylarsonic acid. Twenty grams of the nitro compound is dissolved in a mixture consisting of 74 cc. of 1 *N* sodium hydroxide, 180 cc. of water, and 550 cc. of methyl alcohol. The mixture is then reduced in the presence of Raney nickel with hydrogen at room temperature and 50 pounds pressure. Upon completion of reduction, the methyl alcohol is removed under vacuum and the aqueous residue is acidified with dilute acetic acid to yield a tan precipitate (17 g. or 78%). The product is recrystallized from dilute alcohol and is obtained in the form of slightly tan needles melting (with previous darkening) at 248–249°. Balaban reported blackening at ca 220°.

Anal. Calc'd for $C_{13}H_{14}AsNO_4$: As, 23.2. Found: As, 22.8.

3-Amino-4-benzoyloxyphenylarsenoxide. Ten grams of the arsonic acid is suspended in 100 cc. of 2 *N* hydrochloric acid containing 0.2 g. of potassium iodide. The mixture is stirred and sulfur dioxide is passed in at room temperature until all of the arsonic acid has gone into solution (ca 8 hours). The mixture is kept in the refrigerator overnight and is

then treated with ammonium hydroxide. The resulting precipitate is redissolved in dilute sodium hydroxide and reprecipitated with dilute acetic acid to yield 6.2 g. of a white powder; m.p. 67-68°.

Anal. Calc'd for $C_{13}H_{12}AsNO_2 \cdot H_2O$: As, 24.4; Mol. wt., 307.

Found: As, 24.4; Mol. wt. (iodine titration), 306.5.

4,4'-bis (Benzyloxy)-3,3'-diaminoarsenobenzene dihydrochloride. A solution of 5 g. of the arsonic acid is reduced with sodium hydrosulfite as described above to yield 4 g. of the arseno compound. The free base is dissolved in acetone and reprecipitated with dilute hydrochloric acid. The hydrochloride thus formed is dissolved in glacial acetic acid and reprecipitated with a large excess of very dilute hydrochloric acid. For final purification the product is dissolved in methyl alcohol and reprecipitated with ether. It is obtained as a yellow powder melting at 155-159°.

Anal. Calc'd for $C_{26}H_{24}As_2N_2O_2 \cdot 2HCl \cdot H_2O$: As, 23.6. Found: As, 23.6.

SUMMARY

This report concerns the preparation of 3-amino-4-(*p*-acetamidobenzene-sulfonyloxy)phenylarsonic acid, 4-(*p*-acetamidobenzene-sulfonamido)phenylarsonoxide, 3-nitro-4-benzyloxyphenylarsonic acid and the derivatives obtained from these compounds by reduction of the arsono groups and/or deacetylation.

None of the compounds possessed outstanding trypanocidal or spirochetocidal activity.

NUTLEY, N. J.

REFERENCES

- (1) DOAK, EAGLE, AND STEINMAN, *J. Am. Chem. Soc.*, **62**, 3012 (1940).
- (2) DOAK, EAGLE, AND STEINMAN, *J. Am. Chem. Soc.*, **63**, 99 (1941).
- (3) DOAK, EAGLE, AND STEINMAN, *J. Am. Chem. Soc.*, **66**, 192 (1944).
- (4) ONETO AND WAY, *J. Am. Chem. Soc.*, **63**, 762 (1941).
- (5) MORGAN AND HAMILTON, *J. Am. Chem. Soc.*, **66**, 874 (1944).
- (6) WAY AND CHAN, *J. Pharmacol.*, **81**, 278 (1944).
- (7) BALABAN, *J. Chem. Soc.*, 2473 (1931).
- (8) KWARTLER, *J. Am. Chem. Soc.*, **65**, 354 (1943).
- (9) EAGLE, HOGAN, DOAK, AND STEINMAN, *U. S. Public Health Report*, **59**, 777 (1944).
- (10) STEVINSON AND HAMILTON, *J. Am. Chem. Soc.*, **57**, 1298 (1935).