desired hydroxyamine hydrochloride, which crystallizes in fine, colorless needles, m. p. 170°.

Anal. Calcd. for $C_{12}H_{20}O_3NCl$: C, 55.05; H, 7.71. Found: C, 55.33; H, 7.91.

2,5 - Dimethoxy - α - dimethylaminopropiophenone.—The method of Hyde, Browning and Adams[4] gave very good results in this case. It was necessary, in order to remove dimethylamine completely, to wash the ether solution of the base with water. The tertiary amino ketones of this type are reasonably stable. The hydrochloride crystallizes in slender, practically colorless prisms, melting at 154–156° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.00; H, 7.37. Found: C, 56.89; H, 7.57.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropyldimethylamine Hydrochloride (IIIb).—Catalytic reduction of the preceding α-dimethylaminopropiophenone gave the desired compound. The hydrochloride crystallizes in fine, colorless needles, melting at 198° (dec.).

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.60; H, 8.05. Found: C, 56.52; H, 8.25.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropyltrimethylammonium Chloride (IIIc).—The methiodide, prepared from the above tertiary base, was converted into the chloride by the silver chloride method. After recrystallization, the chloride forms fine, colorless, felted needles, melting at 221–223° (dec.).

Anal. Calcd. for $C_{14}H_{24}O_3NCl$: C, 57.99; H, 8.33. Found: C, 58.08; H, 8.62.

Melting points are all corrected. Those for the hydrochlorides were determined on material dried *in vacuo* at 100° for several hours. The authors wish to make the same acknowledgments to Mr. W. S. Ide and Dr. C. W. Ferry as were made in Part I.

Summary

The projected series of 2,5-dimethoxyphenylalkyl- and alkanolamines has been completed by the preparation of the alkanolamines, β-(2,5-dimethoxyphenyl)-β-hydroxyethylamine hydrochloride, β-(2,5-dimethoxyphenyl)-β-hydroxypropylamine hydrochloride, and β-(2,5-dimethoxyphenyl)-β-hydroxyisopropylamine hydrochloride, together with the corresponding secondary and tertiary amine hydrochlorides and the quaternary chlorides.

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[CONTRIBUTION FROM THE SYPHILIS DIVISION OF THE DEPARTMENT OF MEDICINE, JOHNS HOPKINS MEDICAL SCHOOL, BALTIMORE, MARYLAND, AND THE UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.]

A Modified Bart Reaction

BY G. O. DOAK

Indirect methods for preparing sulfonic and sulfamido substituted arsonic acids are tedious and give low yields. Although Oneto[1] recently has succeeded in preparing *p*-sulfophenyl- and *p*-sulfamidophenylarsonic acids by means of the Bart reaction, in this Laboratory this method failed with the corresponding *m*- and *o*- compounds. The alcoholic Bart reaction described by Scheller[2] has received but scant attention in the literature.[3a,b] When this modification proved successful in this Laboratory with both *p*- and *m*-sulfamidophenylarsonic acids, it was extended to include other arsonic acids, difficult to prepare by the customary Bart procedure. It was found that while anilines substituted in the ring by nitro, carboxy, or sulfamido groups gave excellent results, the reaction failed with 2,6- and 3,5-dimethylanilines. It also failed with metanilic acid. When applicable, the method gave higher yields, was less time consuming, and gave a product more easily purified than the customary Bart procedure.

Experimental Part

The amine, 0.1 mole in 250 cc. absolute alcohol with 10 g. of sulfuric acid and 28 g. arsenous chloride cooled to 0°, was diazotized with a saturated aqueous solution of the calculated amount of sodium nitrite, using starch–iodide paper to protect the end-point. Then, and not before, 1 g. of cuprous bromide[4] was added, the mixture thoroughly stirred, warmed to 60° until no more nitrogen was evolved, and then distilled with steam. The separated arsonic acid was recrystallized.

***p*-Sulfamidophenylarsonic Acid.**—This compound was obtained in 57% yield from sulfanilamide, crystallizing from water in small needles.

Anal. Calcd. for $C_6H_8NO_5SAs$: As, 26.7. Found: As, 26.8.

***m*-Sulfamidophenylarsonic Acid.**—*m*-Aminobenzenesulfonamide, 0.2 mole, gave 32.7 g. (58% yield) of *m*-sulfamidophenylarsonic acid, which crystallized from water in warty aggregates. When placed in a bath at 215° and the temperature slowly raised, it melted at 218–219°, but

(1) Oneto, THIS JOURNAL, **60**, 2058 (1938); **61**, 2105 (1939).

(2) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 229 (1927).

(3) (a) Steinkopf, *J. prakt. Chem.*, **128**, 63 (1930); (b) Cherline and Iacoubovitch, *Bull. soc. chim.*, [5] **1**, 1367 (1934).

(4) Cuprous bromide was found to give slightly better yields than the cuprous chloride as recommended by Scheller.

resolidified, probably to the anhydride, which charred without melting. It was extremely resistant to hydrolysis. After heating in a pressure bottle with concentrated hydrochloric acid at 100°, the compound was recovered unchanged, and it was only partially hydrolyzed with cold concentrated sulfuric acid after twenty-four hours.

Anal. Calcd. for $C_6H_8NO_5SAs$: As, 26.7. Found: As, 26.3.

***m*-Nitrophenylarsonic Acid.**—*m*-Nitroaniline, 138 g. (1 mole) gave 133.5 g. (54% yield) of *m*-nitrophenylarsonic acid, after one recrystallization from water.

3-Nitro-4-methylphenylarsonic Acid.—2-Nitro-4-aminotoluene gave a 40% yield of 3-nitro-4-methylphenylarsonic acid by the modified method.

***m*-Carboxyphenylarsonic Acid.**—*m*-Aminobenzoic acid gave a 76% yield by the modified procedure.

Analyses of these last three substances for arsonic acid gave percentages of arsenic in close agreement with the theoretical requirements.

Attempted Preparation of *m*-Sulfophenylarsonic Acid.—When metanilic acid was subjected to the modified Bart reaction, no crystals separated from the aqueous solution. An attempt to isolate the compound by means of the barium salt yielded only *m*-phenolsulfonic acid. Similarly, 2,6-dimethyl- and 3,5-dimethylanilines gave only the corresponding xylenols when subjected to the modified Bart reaction. In the case of the 2,6- compound, this failure cannot be due to any steric factor, since 2,6-dimethylphenylarsonic acid was prepared in a 30% yield by the usual Bart procedure.

The advantage of the modified Bart procedure may be shown by the following percentage yield figures, the first figure in each case corresponding to the ordinary procedure and the second figure to the modified one: *p*-sulfamido,[1] 25, 57; *m*-sulfamido, 0, 58; *m*-nitro,[5a] 28, 54; 3-nitro-4-methyl,[5b] 15.5, 40; *m*-carboxy,[5a] 36.6, 76.

Summary

The method of Scheller for the preparation of arsonic acids by an alcoholic Bart reaction has been tried with a series of aromatic amines. With sulfamido-, carboxy-, or nitro-substituted amines the reaction gave larger yields of the arsonic acid than the usual Bart procedure, but with two dimethylanilines and metanilic acid, the modification did not prove applicable.

(5) (a) Bart, *Ann.*, **429**, 55 (1922); (b) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1580 (1918).

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The Preparation of Phenylarsenoxides in Relation to a Projected Study of their Chemotherapeutic Activity. I. Monosubstituted Derivatives

BY G. O. DOAK, HARRY EAGLE, AND H. G. STEINMAN

There is now a considerable body of evidence to show that the chemotherapeutic action of arsonic acids and arseno compounds is due to their conversion *in vivo* to the corresponding arsenoxide. Thus, Voegtlin and Smith[1] concluded that both the arsonic acids and the arseno compounds are not in themselves trypanocidal but become active only after conversion to the arsenoxides in the animal body. Further, Tatum and Cooper[2] have shown that "Mapharsen," 3-amino-4-hydroxyphenylarsenoxide, while much more toxic, actually possesses a higher therapeutic index than neoarsphenamine. More recently, Eagle[3] has shown that although the arsphenamines are directly treponemicidal *in vitro*, that activity is primarily due to their rapid oxidation in solution by molecular oxygen, and is either absent or minimal if the experiment is carried out under nitrogen.

While considerable work has been done in attempting to correlate the chemical structure and chemotherapeutic activity of arsonic acids and arseno compounds, the arsenoxides themselves have received much less attention. The present investigation was therefore undertaken in an attempt to correlate the chemical structure of the arsenoxides with their treponemicidal activity, using as the test organism *Treponema pallidum*, the causative agent of syphilis. Although the majority of investigators have hitherto used trypanosomes in testing arsenicals, compounds active against one species of trypanosome will not necessarily be active against *T. pallidum*,[4] or even against another species of trypanosome.[5] The chemical preparation and properties of the arsenoxides will be presented here; data relating to their treponemicidal activity, toxicity, and potential therapeutic utility will be published elsewhere.

The initial series consisted of the parent com-

(1) Voegtlin and Smith, *J. Pharmacol.*, **15**, 475 (1920).
(2) Tatum and Cooper, *ibid.*, **50**, 198 (1934).
(3) Eagle, *ibid.*, **66**, 423 (1939).
(4) Ehrlich and Hata, "The Experimental Chemotherapy of Spirilloses," Redman Co., New York, 1911, p. 126; Probey and McCoy, *U. S. Publ. Health Repts.*, **45**, 1716 (1930).
(5) Kuhs and Tatum, *J. Pharmacol.*, **61**, 451 (1937).