Tigogenin from Chlorogenone Disemicarbazone.—Sodium (1 g.) was dissolved in 25 cc. of absolute ethanol and 2.7 g. of chlorogenone disemicarbazone was added. The mixture was heated in a bomb tube at 180° for seven hours. The product was poured into water and filtered. The combined product from three bomb tubes (representing 8 g. of chlorogenone disemicarbazone) was dissolved in ethanol and this was mixed with a solution of digitonin in ethanol. The digitonide which separated after standing for one hour was collected and dried; it weighed 6.5 g. and was decomposed with pyridine. The product (1.4 g.) was recrystallized from methanol and melted at 202–205°. Recrystallized from acetone it melted at 204–206°. When mixed with tigogenin, m. p. 204–207°, it gave no depression in melting point.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 97.7; H, 10.9.

The acetate was recrystallized from acetone, m. p. 204–206°. A mixture with tigogenin acetate, m. p. 204–206°, melted at 204–206°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.2; H, 10.0.

Summary

Chlorogenin has been converted to tigogenin.

STATE COLLEGE, PENNA. RECEIVED AUGUST 6, 1940

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

The Preparation of Phenylarsenoxides. II. Derivatives of Amino- and Hydroxyphenylarsenoxides

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

Pharmacological studies[1] on the series of compounds described in the first paper of this series[2] have shown that the chemotherapeutic index of *m*- and *p*-amino- and *m*- and *p*-hydroxyphenylarsenoxides was significantly higher than that of the unsubstituted phenylarsenoxide, as judged by *in vitro* activity against *T. pallidum* and by toxicity in white mice. Accordingly, a series of arsenoxides has been prepared in which the amino or hydroxy group was either blocked, as by ether formation, or extended on a side chain.

The arsenoxides described in the present paper (Table I) were all prepared by reduction with sulfur dioxide and potassium iodide in the usual manner. Whenever possible they were recrystallized from appropriate solvents; otherwise they were dissolved in alkali and reprecipitated with acid. They usually softened on heating without giving a definite melting point.

With the exception of *p*-arsonobenzylamine, *p*-arsonobenzylacetamide and *p'*-amino-*p*-benzoylaminophenylarsonic acid, which were amorphous powders, and *p*-arsonoacetophenoneoxime, which crystallized as rhomboids, the arsonic acids all crystallized as needles.

p-Arsono-N-ethylaniline was prepared by the method of Emerson and Walters[3] applied to arsanilic acid. *p'*-Amino-*p*-benzoylaminophenylarsonic acid was prepared by reduction of the corresponding nitro compound,[4] but using Raney catalyst in a low-pressure apparatus instead of ferrous hydroxide. The precautions taken by Hamilton and Major[5] to avoid oxidation were found unnecessary with this catalytic method.

The method of Barrowcliff, Pyman and Remfry[6] for the preparation of *p*-acetoxyphenylarsonic acid, which gave a colored product, was modified in that sodium *p*-hydroxyphenylarsonate was ground with acetic anhydride, the sodium salt precipitated with ether and recrystallized from alcohol–ether mixture.

For the preparation of *p*-arsenosodimethylaniline the method of Michaelis and Rabinerson[7] in our hands failed repeatedly to give a satisfactory yield. Accordingly, the Bart reaction was applied to *p*-dimethylaminoaniline and the resulting arsonic acid reduced to the arsenoxide in the cold. At temperatures exceeding 30°, tri-(*p*-dimethylaminophenyl)-arsine was the sole product. The arsenoxide rearranged to the same product when dissolved in alkali and then acidified.

Experimental Part[8]

***p*-Cyanophenylarsonic acid**[9] was prepared in the expectation that it could be reduced to *p*-arsonobenzylamine.

(1) Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, in press.
(2) Doak, Eagle and Steinman, THIS JOURNAL, **62**, 168 (1940).
(3) Emerson and Walters, *ibid.*, **60**, 2023 (1938).
(4) King and Murch, *J. Chem. Soc.*, **125**, 2595 (1924).
(5) Hamilton and Major, THIS JOURNAL, **47**, 1128 (1925).
(6) Barrowcliff, Pyman and Remfrey, *J. Chem. Soc.*, **93**, 1893 (1908).
(7) Michaelis and Rabinerson, *Ann.*, **270**, 139 (1892).
(8) All melting points are corrected.
(9) Bertheim, *Ber.*, **41**, 1853 (1908), previously prepared this compound but failed to isolate it from solution.

TABLE I

ARSONIC ACIDS AND ARSENOXIDES WITH SUBSTITUTED AMINO AND HYDROXY GROUPS

Compound R = Arsono	Yield, %	Formula	As analyses, % Calcd.	Found
p-R-dimethylaniline[a]	24	$C_8H_{12}O_3NAs$	30.6	30.5
p-R-N-ethylaniline	5	$C_8H_{12}O_3NAs$	30.6	30.4
m-R-acetanilide[b]	50	$C_8H_{10}O_4NAs$	28.9	28.8
p-R-benzonitrile	12	$C_7H_6O_3NAs$	33.0	32.8
Sodium salt[c]	21.5	$C_7H_4O_3NNa_2As \cdot H_2O$	25.9	25.8
p-R-benzylacetamide[d]	62	$C_9H_{12}O_4NAs$[e]	27.4	27.8
p-R-benzylamine[f]	47	$C_7H_{10}O_3NAs$[g]	32.4	32.1
p'-Amino-*p*-benzoylaminophenylarsonic acid	100	$C_{13}H_{13}O_4N_2As$	22.3	22.5
p'-Acetylamino-*p*-benzoylaminophenylarsonic acid	100	$C_{15}H_{15}O_5N_2As$	19.8	19.8
Sodium *p*-acetoxyphenylarsonic acid	100	$C_8H_8O_5NaAs$	26.6	26.7
R = Arsenoso				
p-R-dimethylaniline	74	$C_8H_{10}ONAs$	35.5	35.5
m-R-acetanilide[h]	70	$C_8H_8O_2NAs$	33.3	33.2
p-R-benzylacetamide[i]	60	$C_9H_{10}O_2NAs$	31.4	31.3
p-R-benzylamine[j]	40	C_7H_8ONAs	38.0	38.0
p-Benzoylaminophenylarsenoxide	90	$C_{13}H_{10}O_2NAs$	26.1	26.3
p'-Amino-*p*-benzoylaminophenylarsenoxide[k]	..	$C_{13}H_{11}O_2N_2As$	24.8	24.7
p'-Acetylamino-*p*-benzoylaminophenylarsenoxide[k]	..	$C_{15}H_{13}O_3N_2As$	21.8	21.8
p-Acetoxyphenylarsenoxide	66	$C_8H_7O_3As$	33.2	33.5
p-R-acetophenoneoxime[l]	56	$C_8H_8O_2NAs$	33.3	33.3
p-R-β-phenoxyethanol[m]	70	$C_8H_9O_3As$	32.9	32.9

[a] Best results were obtained by allowing the nitrogen to evolve spontaneously for several days. [b] M. p. 208–209°. The acetylation of *m*-arsonoaniline was facilitated by the use of fused sodium acetate. [c] H_2O calcd.: 6.2, loss at 100°, 6.1. [d] *p*-Aminobenzylacetamide, from which this arsonic acid was prepared, was obtained by the reduction of *p*-nitrobenzylacetamide [Amsel and Hofman, *Ber.*, **19**, 1284 (1886)], using Raney catalyst in alcoholic solution. It crystallized from ether in shiny platelets, yield 74%, m. p. 85–86°. *Anal.* Calcd. for $C_9H_{12}ON_2$: N, 17.1. Found: N, 17.2. [e] N Calcd.: 5.1. Found: 5.1. [f] *p*-Arsonobenzylacetamide was hydrolyzed with a 3% solution of hydrogen chloride in methyl alcohol. Following removal of the solvent the free base was liberated with ammonia. It was insoluble in water and organic solvents, charred above 300°, and probably possesses the zwitterion form. [g] N Calcd.: 6.1. Found: 6.0. [h] Needles from water; m. p. 139–140°. [i] M. p. 224–226°. [j] The dichloroarsine failed to hydrolyze with sodium bicarbonate. (*Anal.* Calcd. for $C_7H_8NCl_2As$: As, 29.7. Found: As, 29.6.) The arsenoxide could be obtained only by hydrolyzing with sodium hydroxide solution. [k] These compounds when washed with water formed colloidal solutions. Yields are not given because of losses in washing. [l] *p*-Arsonoacetophenone was prepared by the Scheller modification with approximately the same yield as obtained by the customary Bart procedure [Gibson and Levin, *J. Chem. Soc.*, 2388 (1931)]. All attempts to reduce *p*-arsenosoacetophenoneoxime to the corresponding β-phenylethylamine with sodium and alcohol regenerated the ketone in the theoretical yields. [m] This compound has previously been prepared by L. A. Sweet (personal communication).

A mixture of 44 g. potassium cyanide and 23.7 g. nickelous chloride in 200 cc. of water was heated on the steam-bath, and diazotized arsanilic acid (0.1 mole) slowly added. Heating was continued for three hours, when the mixture was cooled and acidified to congo red. The heavy brown precipitate was filtered off and extracted twice with boiling water. The combined filtrate and washings were made alkaline with ammonia, and the magnesium salt precipitated by boiling with magnesia mixture. This was extracted with 10% sodium hydroxide and the sodium salt precipitated as fine needles with alcohol. Several crystallizations and treatment with charcoal failed to remove the light brown color. The yield was 21.5%. The free acid obtained by acidifying the sodium salt was difficult to purify because of its remarkable solubility. A more satisfactory result was obtained by dissolving the magnesium salt in acetic acid and precipitating the lead salt with lead acetate. This was decomposed with the calculated amount of sulfuric acid, filtered, and the filtrate evaporated to dryness. It crystallized from water in needles, melting at 360–361°.

***p*-β-Hydroxyethylphenyldichloroarsine.**—Reduction of the corresponding arsonic acid[10] gave the dichloroarsine which was purified by crystallization from alcohol. We were unable to prepare the arsenoxide from the dichloroarsine. It was not hydrolyzed with sodium bicarbonate, and when dissolved in 10% sodium hydroxide a deep vermilion color developed which was not discharged with acid.

Anal. Calcd. for $C_8H_9OCl_2As$: As, 28.1. Found: As, 28.0.

Summary

The preparation is described of a series of monosubstituted arsonic acids and phenylarsenoxides in which amino and hydroxy groups have been extended on side chains or substituted (—NHR, —NR_2, —OR, —CH_2NH_2, —CH_2NHR, and —CH_2OH).

BALTIMORE, MD. RECEIVED JULY 17, 1940

(10) Fourneau and Lestrange, *Bull. soc. chim.*, [4] **53**, 330 (1933).