Anal. Calcd. for $C_9H_{13}O_4AsClN$: N, 4.7. Found: N, 4.7.

p-Amidinophenylarsonous Acid Hydrochloride (VI).—Six grams of finely pulverized iminoether hydrochloride (V) was suspended in 60 cc. of a 10% solution of dry ammonia in absolute alcohol. The suspension was warmed in a closed vessel for four hours at 60°, with frequent shaking. The mixture was filtered, and to the filtrate there was added five times its volume of absolute ether. This threw down the amidine hydrochloride as a white voluminous precipitate, which was filtered out rapidly, to avoid prolonged contact with moist air, and placed immediately in a vacuum desiccator over calcium chloride; yield, 4 g., or 80%. It crystallized in colorless needles when its absolute alcohol solution was concentrated. When heated to 210°, it decomposed with foaming. It was very hygroscopic, soluble in water or alcohol, insoluble in ether or acetone. The sample used for analysis was dried at 60° and 20 mm.

Anal. Calcd. for $C_7H_{10}O_2AsClN_2$: As, 28.3; N, 10.6. Found: As, 28.1; N, 10.7.

Due to its great solubility in water, this acid could not be prepared satisfactorily by the reduction of *p*-amidinophenylarsonic acid with sulfur dioxide.

p-Amidinophenyldichloroarsine Hydrochloride (VII).—A solution of 4 g. of *p*-amidinophenylarsonous acid hydrochloride (VI) in 12 cc. of ice-cold 2 *N* hydrochloric acid was filtered into 30 cc. of concentrated hydrochloric acid cooled to 0°. A crystalline precipitate formed and increased in amount on standing overnight in the icebox. The precipitate was collected, washed with ice-cold concentrated hydrochloric acid, and then left for twenty-four hours over solid sodium hydroxide in a desiccator; yield, 4 g. (89%). For further purification, the product was precipitated from its concentrated aqueous solution with cold concentrated hydrochloric acid, and dried over solid sodium hydroxide at 80° and 20 mm. It was easily soluble in water or alcohol, crystallizing from the latter in small colorless prisms. When heated, it sintered at 202°, and melted at 208° with decomposition.

Anal. Calcd. for $C_7H_8AsCl_3N_2$: N, 9.3. Found: N, 9.2.

p-Amidinophenyldibromoarsine Hydrobromide (VIII).—Two g. of *p*-amidinophenylarsonous acid hydrochloride (VI) was dissolved in 4 cc. of dilute cold hydrobromic acid (2 cc. of concentrated hydrobromic acid to 30 cc. of water). The filtered solution was added to 8 cc. of ice-cold concentrated hydrobromic acid. After the mixture had been standing for several hours at 0°, the pale yellow precipitate was collected and purified by a series of precipitations of its aqueous solution by concentrated hydrobromic acid. The pure salt formed starry clusters of elongated prisms, melting with decomposition at 219°; soluble in water, alcohol, or dilute mineral acids; yield, nearly that calculated. The sample for analysis was dried over solid sodium hydroxide at 80° and 20 mm., in an Abderhalden pistol.

Anal. Calcd. for $C_7H_8AsBr_3N_2$: N, 6.4. Found: N, 6.4.

The compound was soluble in water, alcohol, or dilute mineral acids, and was hygroscopic.

p-Arsonobenziminoether Hydrochloride, $ROC(=NH)-C_6H_4AsO_3H_2$.—In our previous article,[2] the formation of this compound from *p*-cyanophenylarsonic acid was described, but the crude product was converted immediately into the corresponding amidino compound.

We have since purified this crude product by drying it *in vacuo* over solid caustic soda, and crystallizing it by concentration of its alcoholic solution. It formed colorless prisms which decomposed at 130° with strong effervescence.

Anal. Calcd. for $C_9H_{13}O_4AsClN$: N, 4.5. Found: N, 4.3.

Summary

1. *p*-Cyanophenylarsonous acid has been prepared by reduction of *p*-cyanophenylarsonic acid, and also from *p*-aminophenylarsine oxide dihydrate by the diazo reaction.

2. This cyano arsonous acid has been converted, through its imino ether, into the *p*-amidinophenylarsonous acid and, from the latter, the *p*-amidinophenyldihalo arsines have been prepared.

3. Certain of these new products are now being tested pharmacologically.

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[CONTRIBUTION FROM VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

p-Arsenosobenzoylurea and Related Compounds[1]

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

In previous papers of this series[2] we have described various amide-substituted aromatic arsenoso compounds.[3] Because of the interesting effect of the amide group in modifying the pharmacologic properties of arsenoso compounds we have extended the study to include compounds in which two or more amide groups were connected on a single side chain.

Two methods were used for the preparation of these compounds: namely, (1) the customary Bart reaction or the Scheller modification[4] with the corresponding amines and (2) the coupling of the appropriate dichloroarsinoacyl chlorides with the desired aliphatic amino acids or directly with the amino acid amides when available. All nitro compounds were reduced catalytically to the corresponding amines by the method of Stevinson and Hamilton.[5]

Experimental Part

p-Arsenosobenzoylurea.—*p*-Aminobenzoylurea[6] yielded *p*-**arsonobenzoylurea** with the customary Bart reaction. *p*-Arsenosobenzoylurea was obtained on reduction with

(1) Paper VI in the Series Entitled "The Preparation of Phenylarsenoxides."

(2) Doak, Steinman and Eagle, THIS JOURNAL, **62**, 3012 (1940); **63**, 99 (1941).

(3) In this and succeeding papers from this Laboratory, wherever practicable, new arsenicals will be named according to the system of nomenclature used in *Chemical Abstracts*.

(4) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).

(5) Stevinson and Hamilton, *ibid.*, **57**, 1298 (1935).

(6) Jacobs and Heidelberger, *ibid.*, **39**, 2418 (1917).

sulfur dioxide in the usual manner. Attempts to prepare the arsenoso compound directly by treating *p*-dichloroarsinobenzoyl chloride with either (a) urea in pyridine, (b) sodium urea in benzene, or (c) silver cyanate in benzene followed by ammonia, proved unsuccessful.

The action of sodium urethan upon *p*-dichloroarsinobenzoyl chloride in benzene or in pyridine gave products of indefinite composition. In ether a white solid which analyzed for the **ethyl ester of bis-(*p*-arsenosobenzoyl)-carbamic acid** was obtained.

Anal. Calcd. for $C_{17}H_{13}As_2NO_5$: As, 31.4; N, 2.94. Found: As, 31.2; N, 2.85.

***p*-Nitrobenzoyl Isocyanate.**—This substance was prepared in 63% yield by refluxing *p*-nitrobenzoyl chloride with silver cyanate in benzene for seventy-two hours.[7] It was recrystallized from ethyl acetate under anhydrous conditions in rectangular prisms, m. p. 209–210°.

Anal. Calcd. for $C_8H_4N_2O_4$: N, 14.6. Found: N, 14.7.

1-(*p*-Arsenosobenzoyl)-3-(2-hydroxyethyl)-urea.—*p*-Nitrobenzoyl isocyanate condensed with 2-aminoethanol in benzene to give **1-(*p*-nitrobenzoyl)-3-(2-hydroxyethyl)-urea** in 30% yield. On recrystallization from water needles melting at 186–187° were obtained.

Anal. Calcd. for $C_{10}H_{11}N_3O_5$: N, 16.6. Found: N, 16.3.

Catalytic reduction gave **1-(*p*-aminobenzoyl)-3-(2-hydroxyethyl)-urea** in 70% yield. It crystallized from water in long colorless needles, m. p. 230.5–231.5°.[8]

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: N, 18.8. Found: N, 18,7.

The amine derivative underwent the Bart reaction to give **1-(*p*-arsonobenzoyl)-3-(2-hydroxyethyl)-urea,** from which the arsenoso compound was obtained on reduction with sulfur dioxide. An attempt to prepare this compound by heating ***p*-arsonobenzoyl chloride**[9] with silver cyanate and then treating the reaction mixture with 2-aminoethanol was unsuccessful.

Attempted Preparation of 1-(*p*-Arsenosobenzoyl)-3-(2,3-dihydroxypropyl)-urea.—3-Amino-1,2-propanediol was condensed with *p*-nitrobenzoyl isocyanate to give **1-(*p*-nitrobenzoyl)-3-(2,3-dihydroxypropyl)-urea.** It was recrystallized first from alcohol and finally from water, m. p. 197–199°; yield 22%.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: N, 14.8. Found: N, 15.1.

In contrast to the behavior of the lower homolog, the nitro compound gave only *p*-aminobenzamide when reduced with Raney nickel and hydrogen.

1-(*p*-Arsenosobenzoyl)-biuret.—On refluxing *p*-nitrobenzoyl isocyanate with urea in benzene for twenty-four hours **1-(*p*-nitrobenzoyl)-biuret** was obtained as a powder melting at 203–205°; yield 50%.

Anal. Calcd. for $C_9H_8N_4O_5$: N, 22.2. Found: N, 21.8.

Reduction in alcoholic suspension with Raney nickel gave **1-(*p*-aminobenzoyl)-biuret** in 90% yield. It crystallized from alcohol in fine needles sintering about 270°.

Anal. Calcd. for $C_9H_{10}N_4O_3$: N, 25.2. Found: N, 24.4.

The Bart reaction with this amine yielded the desired **1-(*p*-arsonobenzoyl)-biuret** which was readily reduced to the arsenoso derivative.

***p*-Arsenoso-α-toluylurea.**—Urea was refluxed in benzene for eighteen hours with *p*-dichloroarsino-α-toluyl chloride. The resulting product upon hydrolysis yielded *p*-arsenoso-α-toluylurea. The Bart reaction with *p*-amino-α-toluylurea[6] did not yield any arsonic acid. An attempt to prepare the arsenoxide directly by coupling sodium urea with the methyl ester of *p*-arsenoso-α-toluic acid also failed.

N^{α}-(*p*-Arsenosophenyl)-glycylurea.—This compound was obtained from N^{α}-(*p*-arsonophenyl)-glycylurea[10] by reduction with sulfur dioxide.

α-(*p*-Arsonobenzamido)-acetamide.—*p*-Nitrobenzoyl chloride combined readily with glycinamide hydrochloride[11] in sodium bicarbonate solution to give α-(*p*-nitrobenzamido)-acetamide. It crystallized from alcohol in needles, m. p. 239–240° with decomposition.

Anal. Calcd. for $C_9H_9N_3O_4$: N, 18.8. Found: N, 18.5.

Reduction in alcoholic suspension with Raney nickel gave **α-(*p*-aminobenzamido)-acetamide** in 75% yield. It crystallized from alcohol in rectangular prisms, m. p. 228° with decomposition.

Anal. Calcd. for $C_9H_{11}N_3O_2$: N, 21.8. Found: N, 21.8.

The compound was best isolated as the **sulfate** by adding alcoholic sulfuric acid to the original alcohol solution of the amine. It separated in platelets charring above 250°.

Anal. Calcd. for $C_{18}H_{22}N_6O_4 \cdot H_2SO_4$: N, 17.4. Found: N, 17.5.

This salt yielded the desired arsonic acid with the Bart reaction.

α-(*p*-Arsenosobenzamido)-acetamide.—Although this arsenoxide could be produced by the reduction of α-(*p*-arsonobenzamido)-acetamide or by the direct ammonolysis of the methyl ester of *p*-arsenosohippuric acid,[12] it was more conveniently obtained by the direct condensation of *p*-dichloroarsinobenzoyl chloride (0.1 mole) with glycinamide hydrochloride (0.15 mole) in 10% sodium carbonate solution (500 cc.).

α-[α-(*p*-Arsenosobenzamido)-acetamido]-acetamide.—N-Glycylglycine coupled readily with *p*-dichloroarsinobenzoyl chloride in 1 *N* potassium hydroxide solution to give **N-(*p*-arsenosohippuryl)-glycine.** The methyl ester could not be prepared by esterification with methyl alcohol in the presence of anhydrous hydrogen chloride. It was prepared successfully, however, through the **silver salt.**

Anal. Calcd. for $C_{11}H_{10}AgAsN_2O_5 \cdot H_2O$; As, 16.6; N, 6.21. Found: As, 16.7; N, 6.17.

The desired **amide** was obtained on treating this ester with aqueous ammonia at −25° for several days and then allowing the ammoniacal solution to evaporate slowly.

β-(*p*-Arsenosobenzamido)-propionamide.—β-Alaninamide was prepared by the Raney nickel reduction of α-cyanoacetamide in absolute alcohol. The hydrochloride was isolated by acidifying the reaction mixture to *p*H 7.7 with alcoholic hydrogen chloride and cooling overnight at −25°. On recrystallization from methanol it was obtained in 70% yield, m. p. 149°.[13] When condensed with *p*-dichloroarsinobenzoyl chloride in the usual manner (sodium carbonate solution) the desired β-(*p*-arsenosobenzamido)-propionamide was formed.

α-Amino-N^{α}-(*p*-arsenoso-α-toluyl)-acetamide.—*p*-Dichloroarsino-α-toluyl chloride was added to glycinamide hydrochloride in sodium carbonate solution and the reaction mixture concentrated at 40° on the water pump to one-third the original volume. On standing overnight at 5° the desired amide precipitated out.

α-(*p*-Arsenosophenylsulfonamido)-acetamide.—Similarly, *p*-arsenosobenzenesulfonyl chloride prepared by the partial hydrolysis of *p*-dichloroarsinobenzenesulfonyl chloride yielded α-(*p*-arsenosophenylsulfonamido)-acetamide on coupling with glycinamide hydrochloride as above.

(7) *Cf.* Billeter, *Ber.*, **36**, 3218 (1903).

(8) Charlton and Day [*J. Org. Chem.*, **1**, 552 (1937)] prepared the isomeric β-*p*-nitrobenzoxyethylurea which melted at 183–183.4° (cor.). That this compound is different from the urea derivative reported here is shown by the fact that the amino derivative which Charlton and Day obtained melted at 203° (cor.).

(9) *p*-Dichloroarsinobenzoyl chloride in carbon tetrachloride was oxidized with chlorine to *p*-tetrachloroarsinobenzoyl chloride. This was converted to *p*-arsonobenzoyl chloride on partial hydrolysis with cold water. *Anal.* Calcd. for $C_7H_4AsClO_4$: As, 28.3; Cl, 13.4. Found: As, 28.4; Cl, 13.6.

(10) Jacobs and Heidelberger, THIS JOURNAL, **41**, 1600 (1919).

(11) Bergell and Wülfing, *Z. physiol. Chem.*, **64**, 348 (1910).

(12) Cohen, King and Strangeways, *J. Chem. Soc.*, 3236 (1931).

(13) *Cf.* Franchimont and Friedmann, *Rec. trav. chim.*, **25**, 75 (1906).

TABLE I

ARSONIC ACIDS AND ARSENOSO COMPOUNDS DERIVED FROM BENZOYLUREA AND RELATED COMPOUNDS

Compound	Description	M. p., °C.	Yield, %	Formula	As analyses, % Calcd.	As analyses, % Found	N analyses, % Calcd.	N analyses, % Found
R = Arsono								
p-R-benzoylurea	Amorphous (W)	326.5	17	$C_8H_9AsN_2O_5$	26.0	25.6	9.73	9.78
1-(*p*-R-benzoyl)-3-(2-hydroxyethyl)-urea	Rectangular plates (W)	238–238.5 w. dec.	50	$C_{10}H_{13}AsN_2O_6$	22.6	22.5	8.44	8.50
1-(*p*-R-benzoyl)-biur t	Rectangular plates (W)	> 360	17	$C_9H_{10}AsN_3O_6$	22.6	22.7	12.7	12.9
α-(*p*-R-benzamido)-acetamide	Platelets (W)	211–213 w. dec.	5	$C_9H_{11}AsN_2O_5$	24.8	24.7	9.28	9.26
R = Arsenoso								
p-R-benzoylurea	Amorphous	270–271	75	$C_8H_7AsN_2O_3 \cdot H_2O$	27.5	28.0	10.3	10.4
1-(*p*-R-benzoyl)-3-(2-hydroxyethyl)-urea	Amorphous	...	67	$C_{10}H_{11}AsN_2O_4$	25.1	25.2	9.40	9.15
1-(*p*-R-benzoyl)-biuret	Needles (W)	> 360	84	$C_9H_8AsN_3O_4 \cdot 3H_2O$	21.3	21.5	12.0	12.0
p-R-α-toluylurea	Shiny plates (W)	Chars > 272	45	$C_9H_9AsN_2O_3$	28.0	27.5	10.5	9.86
N^{α}-(*p*-R-phenyl)-glycylurea	Amorphous	166–168 w. dec.	75	$C_9H_{10}AsN_3O_3 \cdot 2H_2O$	23.5	23.5	13.2	13.6
α-(*p*-R-benzamido)-acetamide	Rectangular prisms (W)	Chars > 285	65	$C_9H_9AsN_3O_3$	28.0	28.1	10.5	10.5
N-(*p*-R-hippuryl)-glycine	Amorphous	Dec. > 220	75	$C_{11}H_{11}AsN_2O_5 \cdot H_2O$	21.8	21.3	8.14	7.92
N-(*p*-R-hippuryl)-glycine, methyl ester	Amorphous	Chars > 240	30	$C_{12}H_{13}AsN_2O_5 \cdot H_2O$	20.9	20.8	7.83	7.80
α-[α-(*p*-R-benzamido)-acetamido]-acetamide	Rectangular prisms (W)	Chars > 240	50	$C_{11}H_{12}AsN_3O_4 \cdot H_2O$	21.8	21.9	12.3	12.0
β-(*p*-R-benzamido)-propionamide	Needles (W)	283–285 w. dec.	50	$C_{10}H_{11}AsN_2O_3$	26.6	26.6	9.94	9.94
α-Amino-N^{α}-(*p*-R-α-toluyl)-acetamide	Needles (W)	133 w. dec.	50	$C_{10}H_{11}AsN_2O_3 \cdot 2H_2O$	23.6	23.5	8.81	8.40
α-(*p*-R-phenylsulfonamido)-acetamide	Amorphous	193–195 w. dec.	55	$C_8H_9AsN_2O_4S$	24.6	24.4	9.22	8.89

Attempted Preparation of Sulfur Ureas.—In contrast to the behavior of urea, sulfamide[14] did not condense with *p*-nitrobenzoyl chloride when refluxed in benzene for forty-eight hours or in ethyl acetate for twenty-four hours. Potassium sulfamide[15] also failed to condense with either *p*-nitrobenzoyl chloride or *p*-nitrobenzenesulfonyl chloride when refluxed in benzene for forty-eight hours.

The table lists the arsonic acids and arsenoso compounds which were prepared. Recrystallization was done from water (W). Melting points below 200° were taken in a double-walled sulfuric acid bath using Anschütz thermometers with a Bureau of Standards report; no stem correction was made. Melting points above 200° were made in a copper block with a thermometer standardized against the same set of Anschütz thermometers. All analytical results were the average of two or more determinations.

(14) Kindly supplied through the courtesy of Doctor E. F. Degering, Purdue University.

(15) Franklin and Stafford, *Am. Chem. J.*, **28**, 83 (1902).

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Summary

A number of arsonic acids and arsenoso compounds containing two or more amide groups on a single side chain have been prepared.

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[CONTRIBUTION FROM THE VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

Arsenoso Compounds Containing Amide Groups[1]

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

Among the various types of aromatic arsenoso compounds which have been described in previous publications from this Laboratory, those containing amide groups have been of particular interest from the pharmacological viewpoint. The present paper gives the results of further research on this class of compounds.

For the oxidation of tolylarsonic acids and the esterification of the resulting arsonobenzoic acids the methods of Cohen, King and Strangeways[2] were used. The catalytic method of Stevinson and Hamilton[3] was used for the reduction of nitrobenzenearsonic acids to the corresponding amino compounds. Cyanobenzenearsonic acids were prepared and isolated by the method previously described,[4] except that cuprous cyanide was substituted for nickel cyanide. In contrast to the findings of Korczynski and Fandrich[5] with non-arsenated aromatic amines the use of cuprous cyanide gave a larger yield in this particular reaction. The Scheller–Bart reaction[6] was used for the preparation of **4-nitro-, and 5-nitro-*o*-toluenearsonic acids.** While the yields were larger by this procedure as compared to the

(1) Paper VII in the Series Entitled "The Preparation of Phenylarsenoxides."

(2) Cohen, King and Strangeways, *J. Chem. Soc.*, 3236 (1931).

(3) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).

(4) Doak, Eagle and Steinman, *ibid.*, **62**, 3010 (1940).

(5) Korczynski and Fandrich, *Compt. rend.*, **183**, 421 (1926).

(6) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).