2-(2',3'-Dimethylbenzyl)-5,6-dimethylbenzoic Acid (VI).—A solution of 2-(2',3'-dimethylbenzoyl)-5,6-dimethylbenzoic acid (1 g.) in 1 *N* potassium hydroxide (100 ml.) was refluxed for forty-eight hours with zinc dust (5 g.) activated with copper sulfate. After the removal of excess zinc, the solution was acidified and afforded 0.9 g. of VI, m. p. 146–150°. After crystallization from acetic acid it melted at 152–153°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.0; H, 7.5.

2-(2',3'-Dimethylbenzyl)-3,4-dimethylbenzoic acid (V) was obtained in 75% yield from III by the same procedure. After crystallization from acetic acid it melted at 187–189°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.7; H, 7.7.

1,2,5,6-Tetramethylanthracene (VII).—2-(2',3'-Dimethylbenzyl)-5,6-dimethylbenzoic acid (0.9 g.) was mixed with anhydrous zinc chloride (2 g.) and heated at 180–185° for thirty minutes. After cooling, the melt was powdered, extracted with water and warmed with 0.1 *N* sodium carbonate to remove a trace of unaltered acid. A solution of the crude anthrone in 1 *N* sodium hydroxide (100 ml.) and ethyl alcohol (50 ml.) was refluxed for sixty hours with zinc dust (5 g.). The resulting solid was collected and extracted with benzene–alcohol. Addition of picric acid to the extract afforded almost black crystals of the picrate of 1,2,5,6-tetramethylanthracene. The picrate was recrystallized from benzene–alcohol, m. p. 187–189°.

Anal. Calcd. for $C_{18}H_{18}\cdot C_6H_3O_7N_3$: C, 62.2; H, 4.6. Found: C, 62.4; H, 4.6.

The regenerated hydrocarbon (ammonia) was crystallized from acetic acid and formed pale yellow needles, m. p. 204°. The over-all yield of 1,2,5,6-tetramethylanthracene from 1 g. of IV was 0.3 g. (37%).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.7. Found: C, 92.0; H, 8.0.

1,2,7,8-Tetramethylanthracene (VIII).—The picrate of the hydrocarbon was obtained from V by the above procedure. It formed red needles, m. p. 183–185°, from benzene–alcohol.

Anal. Calcd. for $C_{18}H_{18}\cdot C_6H_3O_7N_3$: C, 62.2; H, 4.6. Found: C, 62.3; H, 4.8.

The regenerated hydrocarbon (ammonia) formed pale yellow crystals, m. p. 140–141°. The over-all yield of hydrocarbon from the keto acid was about 35%.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.7. Found: C, 92.5; H, 8.1.

1,2,5,6-Tetramethylanthraquinone.—One gram of the keto acid IV was cyclized by treatment with concentrated sulfuric acid at 90–100° for three hours. This afforded a mixture of 1,2,5,6-tetramethylanthraquinone (IX) and a compound which is believed to be 1,2,7,8-tetramethylanthraquinone (X). Quinone IX (0.3 g.) crystallized from glacial acetic acid as yellow-brown needles, m. p. 201–202°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.5; H, 6.5.

A small amount of 1,2,5,6-tetramethylanthracene dissolved in glacial acetic acid was treated with chromic acid. The reaction product was crystallized from acetic acid and when mixed with some of the above 1,2,5,6-tetramethylanthraquinone showed no depression of the melting point.

Quinone X (0.3 g.) crystallized from dilute acetic acid as yellow-brown needles, m. p. 160–161°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.4; H, 6.3.

Because of the lack of material the authors were unable to supply a rigid proof for the structure of this compound.

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Summary

1,2,5,6-Tetramethylanthracene, of interest as a model of the carcinogen 1,2,5,6-dibenzanthracene, has been synthesized. 1,2,7,8-Tetramethylanthracene has also been synthesized and characterized in the form of the picrate.

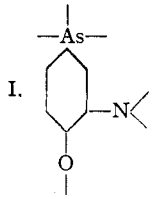
EDMONTON, ALBERTA, CANADA RECEIVED APRIL 28, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

Derivatives of 3-Amino-4-hydroxybenzenearsonic Acid

BY L. A. SWEET, JOHN CONTROULIS, E. W. TILLOTSON[1] AND C. K. BANKS

A large portion of the compounds used as treponemicidal agents have the basic structure I.



One of the most active of the pentavalent arsenicals derived from this nucleus is 3-amino-4-β-hydroxyethoxybenzenearsonic acid.[2,3] In a systematic investigation of further derivatives having the 4-β-hydroxyethoxyl group, a number of substituted 3-amino compounds were prepared. These were analogous to derivatives of *p*-arsanilic acid previously examined, principally tryparsamide,[4] arsonophenylglycine[5] and *p*-biguanidobenzenearsonic acid.[6]

3-Amino-4-β-hydroxyethoxybenzenearsonic acid reacted with chloroacetic acid and chloroacetamide to yield the glycine and glycineamide derivatives respectively. In common with many other arsenicals of structure I, the products isolated from solution and dried of superficial moisture had one or more molecules of water associated with

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(2) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).

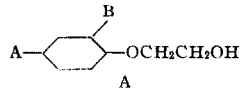
(3) Tatum, *et al.*, *J. Pharmacol.*, **59**, 241 (1937).

(4) Jacobs and Heidelberger, THIS JOURNAL, **41**, 1587 (1919).

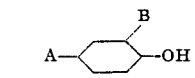
(5) Jacobs and Heidelberger, *ibid.*, **41**, 1440 (1919).

(6) Banks, *et al.*, *ibid.*, **68**, 2102 (1946).

TABLE I



A	B	Yield, %	Empirical formula	Analyses, % As[a] Calcd.	Found
—$AsO_3H_2 \cdot 2H_2O$	—NHC(NH)NHC(NH)NH_2	86	$C_{10}H_{20}AsN_5O_7$	18.86	18.70
—AsO_3H_2	—NHC(NH)NHC(NH)NH_2	86	$C_{10}H_{16}AsN_5O_5$	20.74	20.74
—AsO_3HNa	—NHC(NH)NHC(NH)NH_2	84	$C_{10}H_{15}AsN_5NaO_5$	19.54	19.44
—$AsO_3H_2 \cdot H_2O$	—$NHCH_2COOH$	55	$C_{10}H_{16}AsNO_8$	21.21	21.16
—AsO_3H_2	—$NHCH_2COOH$	55	$C_{10}H_{14}AsNO_7$	22.35	22.45
—As=	—$NHCH_2COONa$	89	$(C_{10}H_{11}AsNNaO_4)_x$	24.39	24.30
—$AsO_3H_2 \cdot H_2O$	—$NHCH_2CONH_2$	78	$C_{10}H_{17}AsN_2O_7$	21.28	21.20
—AsO_3H_2	—$NHCH_2CONH_2$	78	$C_{10}H_{15}AsN_2O_6$	22.41	22.43
—AsO_3HNa	—$NHCH_2CONH_2$	80	$C_{10}H_{14}AsN_2NaO_6$	21.04	21.12
—AsO_3H_2	—$NHOCCH_2Cl$	60	$C_{10}H_{13}AsClNO_6$	21.18	21.30
—$AsO_3H_2 \cdot H_2O$	—$NHOCCH_2SO_3H$	76	$C_{10}H_{16}AsNO_{10}S$	17.95	18.04



—$AsO_3H_2 \cdot 2H_2O$	—NHC(NH)NHC(NH)NH_2	78	$C_8H_{16}AsN_5O_6$	21.21	21.11
—AsO_3H_2	—NHC(NH)NHC(NH)NH_2	78	$C_8H_{12}AsN_5O_4$	23.62	23.52
—AsO_3H_2	—$NHCONH_2$	68	$C_7H_9AsN_2O_5$	27.12	26.85

[a] Arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). Performed by A. W. Spang of our laboratories.

their structure. This water was lost on drying *in vacuo* at 100°. Condensation of dicyandiamide with the aminoarsonic acid yielded the biguanido compound.

3-Amino-4-β-hydroxyethoxybenzenearsonic acid was also treated with chloroacetyl chloride and the resulting chloroacetamide converted to the sulfoacetamide. The carbamyl and guanidoguanyl derivatives of 3-amino-4-hydroxybenzenearsonic acid were also prepared.

Experimental

3-Biguanido Compounds.—The appropriate arsonic acid (0.1 mole) and dicyandiamide (0.12 mole) were refluxed in 500 ml. of water for one hour. On cooling the biguanido compound separated in the hydrated arsonate form. The compounds were dehydrated by heating *in vacuo* at 100°.

2-β-Hydroxyethoxy-5-arsonophenylglycine.—A neutral solution containing 90 g. of 3-amino-4-β-hydroxyethoxybenzenearsonic acid and 60 g. of chloroacetic acid in 300 ml. of water was made strongly alkaline with 100 ml. of 6 *N* sodium hydroxide and refluxed for three hours. On acidifying to congo red paper and cooling, the product crystallized. It was purified by recrystallization from water. The hydrated form was dehydrated by heating at 100° *in vacuo*.

Disodium bis-(3-Carboxymethylamino-4-β-hydroxyethoxy)-arsenobenzene.—The above arsonic acid (20 g.) was warmed to 50° with 50 ml. of water and 50 ml. of 50% hypophosphorous acid for two hours. After cooling, the solution was diluted to 500 ml., made neutral to congo red paper and the product filtered off under nitrogen. It was washed on the filter with water, a small quantity of absolute ethanol and then ether. The nearly dry product was suspended in 100 ml. of water, dissolved with a slight excess of sodium hydroxide and precipitated by adding 6 volumes of absolute alcohol and then 4 volumes of ether. The yellow product was dried *in vacuo*.

2-β-Hydroxyethoxy-5-arsonophenylglycineamide.—A solution of 27.8 g. of 3-amino-4-β-hydroxyethoxybenzenearsonic acid, 20 g. of chloroacetamide and 4 g. of sodium hydroxide in 100 ml. of water was refluxed two hours. The product separated on acidification and was recrystallized from hot water. The hydrated form was obtained when dried *in vacuo* over phosphorus pentoxide and the anhydrous form by drying at 100°.

3-Chloroacetamino-4-β-hydroxyethoxybenzenearsonic Acid.—3-Amino-4-β-hydroxyethoxybenzenearsonic acid (35 g.) was dissolved in 100 ml. of saturated sodium acetate solution, 150 ml. of glacial acetic acid and 50 ml. of water. The solution was cooled to 10° and 35 g. of chloroacetyl chloride added with stirring. When the reaction was completed, the solution was acidified to congo red paper, chilled to 0°, and the product which crystallized filtered off and dried *in vacuo* over phosphorus pentoxide.

N-(2-β-Hydroxyethoxy-5-arsonophenyl)-sulfoacetamide.—The above chloroacetamide (32 g.) was dissolved in 3.6 g. of sodium hydroxide, 15 g. of sodium sulfate and 150 ml. of water and the mixture refluxed for forty minutes. The product, which precipitated when the cold solution was made strongly acid to congo red paper, was recrystallized from water.

3-Carbamido-4-β-hydroxyethoxybenzenearsonic Acid.—3-Amino-4-β-hydroxyethoxybenzenearsonic acid (0.1 mole) and potassium cyanate (0.2 mole) were dissolved in 200 ml. of water and 25 ml. of glacial acid added. After standing at room temperature for twenty-four hours, 75 ml. of concentrated hydrochloric acid was added and the solution chilled until the product crystallized. It was purified by recrystallization from hot water.

Sodium Salts.—All sodium salts were obtained by the technique described in a previous paper.[7]

Summary

The preparation of a number of 3-substituted amino derivatives of 4-β-hydroxyethoxybenzenearsonic acid has been reported.

DETROIT, MICH. RECEIVED APRIL 30, 1947

(7) Banks, *et al.*, THIS JOURNAL, **66**, 1771 (1944).