different reactions and its absolute activity as measured by the amount of material undergoing reaction.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

ARSONOPHENYL-CINCHONINIC ACID AND DERIVATIVES

BY KATHARINE OGDEN[1] WITH ROGER ADAMS

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In an earlier paper[2] it was pointed out that a study of arsenated derivatives of compounds containing the heterocyclic nitrogen nucleus was a promising field in which to find trypanocidal compounds. A series of derivatives of phenyl-diketopyrrolidine were made by the condensation of benzaldehyde, pyruvic acid and arsanilic acid or their derivatives. The compounds thus produced were distinctly trypanocidal but had other properties which made them useless from a practical standpoint. Phenyl-cinchoninic acid (Cinchophen) and its derivatives are so useful as drugs and so comparatively non-toxic, that a study of arsenated derivatives seemed of interest. This communication describes the preparation of such compounds with the arsonic acid radical substituted in the phenyl group.

The only convenient method for the preparation of phenyl-cinchoninic acid derivatives other than the benzaldehyde, pyruvic acid and amine method, which has been shown not to be applicable to arsenic compounds is that discovered by Pfitzinger[3] which consists in the condensation of isatin with acetophenone in the presence of alkalies. The method has not attracted much attention until recently, when a very convenient and cheap method was found for the preparation of isatin and its derivatives,[4,5] from primary aromatic amines, chloral and hydroxylamine.

In place of acetophenone, certain arsono-acetophenones were condensed with isatin and substituted isatins. The reactions ran normally and yielded the corresponding arsonophenyl-cinchoninic acids (I).

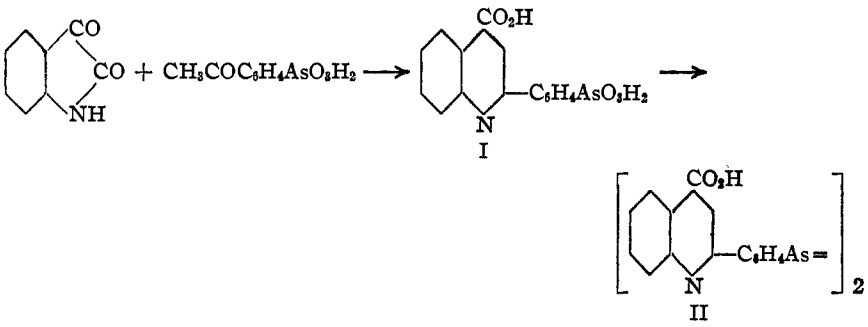
[1] This communication is an abstract of a thesis submitted by Katharine Ogden in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Johnson with Adams, THIS JOURNAL, **43**, 2255 (1921); **45**, 1307 (1923). In the first paper the condensation product of benzaldehyde, pyruvic acid and arsanilic acid was incorrectly reported as 2-phenylquinoline-4-carboxylic acid-6-arsonic acid. As shown in the second paper, it was actually a derivative of phenyl-diketopyrrolidine.

[3] Pfitzinger, *J. prakt. Chem.*, **146**, 583 (1888).

[4] Ger. pat. 301,591; *Chem. Zentr.*, **1918**, I, 148; Brit. pat. 128,122; *J. Chem. Soc., Abs.*, **116**, I, 599 (1919); Ger. pat. 320,647; *J. Chem. Soc., Abs.*, **118**, I, 682 (1920).

[5] Sandmeyer, *Helvetica chim. Acta*, **2**, 239 (1919).



These could be esterified in the usual way or reduced to the arseno compounds (II) with sodium hydrosulfite.

The arsonic acids thus formed are trypanocidal in character but are much less effective than the usual arsenic trypanocides. The arseno compounds are much more toxic than arsphenamine. Tests of effectiveness and toxicity were kindly made by Dr. G. W. Raiziss of Philadelphia.

The arsono-acetophenones are readily formed by the diazotization of amino-acetophenones and replacement by the arsonic acid group.

By using *p*-methylisatin, condensing with *p*-arsono-acetophenone and esterifying, arsenic compounds corresponding to Neocinchophen were prepared. These had no advantage over the unsubstituted derivatives.

Experimental Part

p-Arsono-acetophenone,[6] $(p)H_2O_3AsC_6H_4COCH_3$.—This substance was prepared from *p*-amino-acetophenone; yield, about 65%.

o-Arsono-acetophenone, $(o)H_2O_3AsC_6H_4COCH_3$.—The same method was employed as for *p*-arsono-acetophenone. To separate the product, the acid solution was evaporated to dryness and the residue extracted with methyl alcohol. When water was added to a concentrated alcoholic solution, a light brown precipitate was formed. This material could be recrystallized from dil. methyl alcohol; yield, 12 g., from 27 g. of amine. It did not melt up to 250°.

Anal. Subs., 0.2615, 0.0804: 22.00 cc., 6.80 cc. of 0.0980 *N* iodine soln. Calcd. for $C_8H_9O_4As$: As, 30.70. Found: 30.91, 31.12.

2-*p*-Arsonophenyl-4-carboxy-quinoline. I.—One-half of a solution of sodium hydroxide (15 g. in 100 cc. of water) was added to 17 g. of *p*-arsono-acetophenone, while the other half was added to 10 g. of isatin. After mixing these solutions, 300 cc. of alcohol was added. The resulting clear, dark red solution was kept gently refluxing on the steam-bath for 24 hours. Then the alcohol was distilled, the solution cooled, diluted with water and carefully acidified with dil. hydrochloric acid. The product was a very finely divided, yellow solid, insoluble in most organic solvents. It was appreciably soluble in dil. hydrochloric acid, especially hot, so that this solvent could be used for recrystallization; the product was still quite colored, however. The best method that was found for purification was to dissolve the material in hot ethylene glycol in which it was readily soluble. The recrystallized product was then washed well with methyl alcohol. In order to remove the last traces of solvent, it was necessary to redissolve the

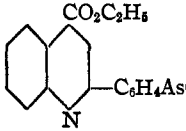
[6] *C. A.*, **16**, 4301 (1922); **17**, 1691 (1923).

solid in hot sodium hydroxide solution and precipitate again with acid. If precipitated cold, the product was so finely divided that it went through the filter. The compound, thus obtained, was a white powder which did not melt up to 270°.

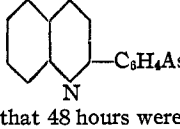
Anal. Subs., 0.1876, 0.1832 g.: 10.37 cc., 10.12 cc. of 0.0993 *N* iodine soln. Calcd. for $C_{16}H_{12}O_5NAs$: As, 20.16. Found: 20.12, 20.10.

Sodium Salts of 2-*p*-arsonophenyl-4-carboxy-quinoline.—When one molecular equivalent of standard sodium hydroxide solution was added to a definite amount of 2-*p*-arsonophenyl-4-carboxy-quinoline, only about half of the solid material dissolved. When two molecular equivalents of alkali were added a clear solution was obtained which was alkaline to methyl orange and acid to phenolphthalein. When three molecular equivalents of alkali were added, in the presence of as little water as possible, and this solution poured into an excess of methyl alcohol and chilled, a flaky precipitate was obtained. This precipitate was washed with alcohol which removed the color, leaving the salt white. It proved to be a disodium salt.

Anal. Subs., 0.2584, 0.2663: 12.45 cc., 12.95 cc. of 0.0980 *N* iodine soln. Calcd. for $C_{16}H_{10}O_5AsNa_2$: As, 18.03. Found: 18.01, 17.90.

2-*p*-Arsonophenyl-4-carbo-ethoxy-quinoline,  .—To 2 g. of the crude acid was added 20 cc. of absolute ethyl alcohol that had been saturated with hydrogen chloride. The solid material dissolved slowly. The solution was kept gently refluxing on the steam-bath for 24 hours. At the end of that time, crystals had formed so that when the mixture was cooled, it was a semisolid. The crystals were filtered off and dissolved in ethyl alcohol in which they were readily soluble. They were recrystallized by treating the hot solution with Filtchar and then adding water until the milkiness just became permanent. On cooling this solution, crystals formed that were practically white. The neutral equivalent was determined. The end-point with phenolphthalein was reached when just two molecular equivalents of alkali had been added. The substance melted with decomposition at 117–119°. It was difficult to drive all the alcohol out of the material as the latter could not be heated above 60–70° without darkening. Four recrystallizations and drying at 60° for five hours gave a satisfactory product; yield of crude material, 1.5 g., or 70%.

Anal. Subs., 0.1809, 0.1643: 9.15 cc., 8.32 cc. of 0.0993 *N* iodine soln. Calcd. for $C_{18}H_{16}O_5NAs$: As, 18.7. Found: 18.41, 18.43.

2-*p*-Arsonophenyl-4-carbomethoxy-quinoline,  .—Following the procedure used for the ethyl ester, except that 48 hours were required for esterification in this case, 2 g. of acid was treated with methyl alcohol that had been saturated with hydrogen chloride. The material was difficult to purify, as it had a decided tendency to come out of solution as an oil. By using Filtchar, however, with dil. methyl alcohol, a flaky solid was obtained; m. p., 153° (sharp); yield, 1 g., or 45%.

Anal. Subs., 0.1770, 0.1852: 9.35 cc., 9.77 cc. of 0.0993 *N* iodine soln. Calcd. for $C_{17}H_{14}O_5NAs$: As, 19.37. Found: 19.23, 19.21.

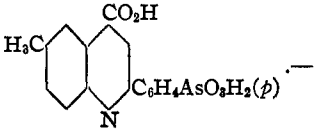
Arseno Derivative of 2-*p*-Arsonophenyl-4-carboxy-quinoline. II.—To a solution of 24 g. of sodium hydrosulfite in 70 cc. of water and 50 cc. of *N* sodium hydroxide was

added 12 g. of magnesium chloride. The magnesium hydroxide was filtered off and to the clear solution, 4 g. of arsonic acid derivative in 20 cc. of *N* sodium hydroxide solution was added. The solution was stirred at 50–60° for three hours and then allowed to stand overnight. After five to ten minutes of heating, a yellow precipitate gradually separated. It was very gelatinous, filtering slowly. After the solid material had been washed with water it was dissolved in a known amount of alkali, the solution filtered and the substance reprecipitated with an equivalent amount of hydrochloric acid. The arseno derivative was then filtered again, washed well with water and dried in a vacuum oven at 50°. The material was a reddish-brown powder soluble in alkali, but insoluble in organic solvents. It did not melt up to 250°. A neutral solution was obtained when one equivalent of alkali was added for each half of the molecule.

Anal. (dried material). Subs., 0.2147, 0.1962: 13.53 cc., 12.50 cc. of 0.0993 *N* iodine soln. Calcd. for $C_{32}H_{20}O_4N_2As_2$: As, 23.2. Found: 22.9, 23.1.

Hypophosphorous acid could also be used as a reducing agent but an impure product resulted.

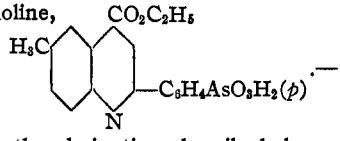
2-*p*-Arsonophenyl-4-carboxy-6-methyl-quinoline,



The same method was used here as with isatin. *p*-Methylisatin and *p*-arsono-acetophenone were condensed. The product was recrystallized from ethylene glycol. It was a fine powder, practically white, which did not melt below 250°; yield, 92%.

Anal. Subs., 0.2313, 0.1090: 12.47 cc., 5.90 cc. of 0.0993 *N* iodone soln. Calcd. for $C_{17}H_{14}O_5NAs$: As, 19.37. Found: 19.62, 19.61.

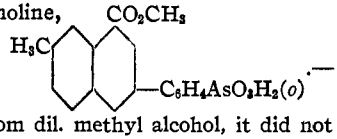
2-*p*-Arsonophenyl-4-carbo-ethoxy-6-methyl-quinoline,



The same method was used as in the esterification of other derivatives described above. The slightly yellow product after two crystallizations from dil. ethyl alcohol did not melt under 275°; yield, 60%.

Anal. Subs., 0.1695: 8.50 cc. of 0.0957 *N* iodine soln. Calcd. for $C_{19}H_{18}O_5NAs$: As, 18.07. Found: 18.20.

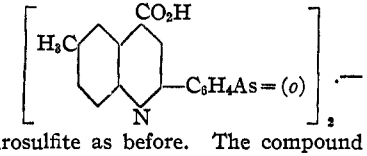
2-*p*-Arsonophenyl-4-carbomethoxy-6-methyl-quinoline,



The product was light brown. After purification from dil. methyl alcohol, it did not melt under 275°; yield, 40%.

Anal. Subs., 0.1778, 0.1533: 8.75 cc., 7.55 cc. of 0.0957 *N* iodine soln. Calcd. for $C_{18}H_{16}O_5NAs$: As, 18.70. Found: 18.01, 18.13.

Arseno Derivative of 2-*p*-Arsonophenyl-4-carboxy-6-methyl-quinoline,



The reduction was carried out with sodium hydrosulfite as before. The compound

obtained was reddish-brown, insoluble in organic solvents, and did not melt under 250°; yield, 45%.

Anal. Subs., 0.1585, 0.2067: 9.35 cc., 12.20 cc. of 0.0957 *N* iodine soln. Calcd. for $C_{34}H_{24}O_4N_2As_2$: As, 22.25. Found: 21.71, 21.72.

Summary

By the condensation of isatin or substituted isatins with arsono-acetophenones, arsonophenyl-cinchoninic acids have been prepared. The corresponding esters and arseno derivatives are easily produced. All of these substances proved to be much more toxic than arsphenamine or arsanilic acid and not as trypanocidal.

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MERCURY DERIVATIVES OF SOME IMIDES

BY EDWARD LYONS

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Amides and imides yield mercury derivatives in which the mercury is attached to nitrogen. Succinimide[1] gives the compound $(CH_2CO)_2N-Hg-N(CH_2CO)_2$; phthalimide[1c] similarly gives $C_6H_4(CO)_2N-Hg-N(CO)_2C_6H_4$. Saccharin[2] has been reported to yield compounds that are either insoluble, or soluble only in physiological salt solution.

The present paper describes the preparation and properties of a new class of mercury compounds, obtained from imides, containing the characteristic groupings =C(O,O)Hg, and ≡S(O,O)Hg.

New Mercury Compounds of Imides

When imides such as succinimide, phthalimide or saccharin react in alkaline solution with freshly prepared mercuric oxide, or better, with mercuric salts and an excess of base, there are formed alkali salts of substances containing mercury linked to =C=O or ≡S=O groups. The number of mercury atoms which can be introduced is limited to the number of these doubly-linked oxygen atoms. Thus, succinimide gives a mono- and dimercury compound (I and II). Phthalimide presents similar possibilities (III and IV). Saccharin gives three compounds, which may be represented by V, VI and VII.

[1] (a) Dessaignes, *Ann.*, **82**, 234 (1852). (b) Menschutkin, *Ann.*, **162**, 171 (1871). (c) Landsberg, *Ann.*, **215**, 209 (1883).

[2] Dufournel, *Bul. soc. chim.*, [3] **25**, 326 (1901). Auld, *J. Chem. Soc.*, **91**, 1048, (1907). Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., **1921**, p. 309.