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

ARSONOPHENYL-CINCHONINIC ACID (ARSONOCINCHOPHEN) AND DERIVATIVES. II

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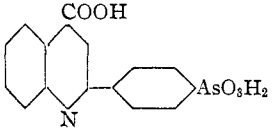
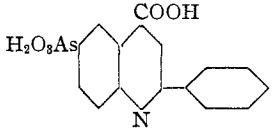
In the preceding paper,[2] an arsonophenyl-cinchoninic acid was produced in which the arsonic acid group was substituted in the phenyl radical (I). This second investigation had as its purpose the preparation of an arsonophenyl-cinchoninic acid with the arsonic acid group substituted in the benzene portion of the quinoline nucleus (II).



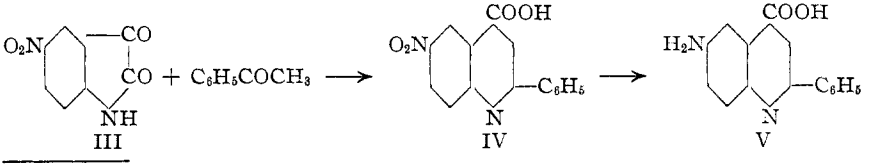
I



II

Methods which might lead to arsonoquinoline or derivatives have been studied by other investigators. Frankel and Lowy[3] have attempted a Skraup synthesis using arsanilic acid in place of aniline, a Knorr synthesis with arsanilic acid and ethyl aceto-acetate, and a Döbner and Miller synthesis from arsanilic acid, acetaldehyde and hydrogen bromide. These were all entirely unsuccessful except the last, which gave only a small yield of product. An attempt by Ogden and Adams to prepare an arsonoquinoline by condensing arsanilic acid with chloral and hydroxylamine sulfate to produce arsono-isatin which could then be condensed with acetophenone to a quinoline derivative also met with failure.

A successful synthesis of an arsonoquinoline, in particular 2-phenyl 4-carboxy-6-arsonoquinoline (arsonocinchophen) was accomplished by replacing an amino group in phenyl-cinchoninic acid by an arsonic acid radical according to the method of Bart. Of the various methods by which the aminocinchophen might be produced, only one proved to be readily carried out, namely, the nitration of isatin to a mononitro derivative (III), condensation with acetophenone to nitrophenyl-cinchoninic acid (IV) and final reduction to the amino compound (V).



III IV V

[1] This communication is an abstract of a portion of a thesis submitted by H. O. Calvery in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Ogden with Adams, THIS JOURNAL, **47**, 826 (1925).

[3] Frankel and Lowy, *Ber.*, **46**, 2546 (1913).

In attempting other obvious procedures for preparing aminophenyl-cinchoninic acid, difficulties were encountered (I) in the direct nitration of phenyl-cinchoninic acid, (2) in the condensation of *p*-nitro-aniline to give nitro-isatin, (3) in the reduction of nitro-isatin to amino-isatin.

The arsonophenyl-cinchoninic acid (II) prepared by the method described above could be reduced to an arseno compound by the usual methods. It formed a neutral, water-soluble disodium salt.

Both the arsono and arseno compounds were tested pharmacologically by Dr. G. W. Raiziss of Philadelphia. The results showed that they were both trypanocidal in character but were too toxic for ordinary use.

Experimental Part

5-Nitro-isatin,[4] III.—A solution of 14.7 g. (0.1 mole) of isatin in 66 g. of concd. sulfuric acid was cooled to 0° in an ice-salt-bath. To this was added slowly, drop by drop, 6.3 g. of fuming nitric acid (d., 1.50), and the temperature was kept near 0°. The reaction mixture was allowed to stand for about 30 minutes and then poured over 500 g. of cracked ice. A yellow precipitate separated immediately; yield, 15 g., or 85%. After recrystallization from 50% methyl alcohol, the substance melted at 254–255° (corr.).[5]

2-Phenyl-4-carboxy-6-nitroquinoline,[6] IV (Nitrocinchophen).—In a 2-liter flask was placed a solution of 48 g. of potassium hydroxide in 500 cc. of water. To this was added 38.4 g. of crude 5-nitro-isatin and then 48 g. of acetophenone in 360 cc. of 95% alcohol. The mixture was refluxed overnight (14 hours) on the steam cone and then cooled in an ice-bath to 0°. The potassium salt crystallized and was filtered off and washed once with 50 cc. of cold water by rubbing to a paste and filtering again. The moist salt was dissolved in hot 50% alcohol, the solution filtered hot and the filtrate acidified with 10% acetic acid. The bright yellow nitro acid formed was filtered off and washed twice with 200cc. portions of boiling water by rubbing to a paste in a beaker each time; yield (dry), 12 g. or 20%. It decomposes at about 350–355° and darkens considerably below that temperature.

Anal. Subs., 0.1942: 26.08 cc. of 0.0495 *N* HCl. Calcd. for $C_{16}H_{10}O_4N_2$: N, 9.52. Found: 9.41.

2-Phenyl-4-carboxy-6-aminoquinoline[6] (V).—To a suspension of 10 g. of crude nitrocinchophen in 250 cc. of concd. hydrochloric acid was added 50 g. of stannous chloride ($SnCl_2.H_2O$), and the mixture was stirred at 35° for two hours. It first turned a greenish yellow and then orange, due to the precipitation of the amine hydrochloride. This was filtered off and placed in a flask with 200 cc. of water. At first it formed a deep red solution from which a dark product soon precipitated. This was not filtered off but the mixture was made alkaline with 10% sodium carbonate solution, turning a pale, milky yellow. This liquid was then filtered. As the sodium salt is insoluble in an excess of sodium carbonate solution, the residue on the filter was dissolved in 50 cc. of water and the solution filtered again. The combined filtrates were acidified with 10% acetic acid and the bright orange precipitate formed was filtered off, washed with water

[4] (a) Baeyer, *Ber.*, **12**, 1312 (1879); (b) Ger. pat. 221,529 (1910); (c) Friedländer, "Fortschritte der Tierfarbenfabrikation," J. Springer, Berlin, **10**, 520 (1910–1912).

[5] Baeyer reports 226–230°; Ger. pat. 221,529 reports 248–250° and 253–255°.

[6] Ger. pat. 287,804 (1915); Ref. 4 c, **12**, 725 (1914–1916).

and dried; yield, 8.5 g., or 96.6%. After crystallization from 50% acetic acid it shrinks at 240° and melts at 259–260° (corr.), with decomposition.

Anal. Subs., 0.2476: 36.83 cc. of 0.0495 *N* HCl. Calcd. for $C_{16}H_{12}O_2N_2$: N, 10.64. Found: 10.62.

2-Phenyl-4-carboxy-6-arsonoquinoline, II.—A suspension of 5.36 g. of crude, powdered 2-phenyl-4-carboxy-6-aminoquinoline in 30 cc. of 2 *N* hydrochloric acid and 20 cc. of water was cooled to 0–5°, diazotized with 10 cc. of 2 *N* sodium nitrite solution and stirred for about three hours at 5°. A solution of 2.9 g. of arsenious oxide and 5.6 g. of potassium hydroxide in 24 cc. of water, 15 cc. of 4 *N* sodium carbonate, and 200 cc. of water was placed in a large beaker and cooled to —5°. To this was added 0.5 g. of cupric sulfate dissolved in a little water. The whole of the diazo solution was then immediately added to the sodium arsenite solution at one time. After nitrous acid could no longer be detected in the mixture it was allowed to stand for an hour during frequent stirring. It was then warmed slowly to 60° and filtered. When the clear, reddish-brown solution was acidified with dil. hydrochloric acid a brown precipitate settled out. This was dissolved in a little alkali and the alkaline solution was acidified until a precipitate just began to form. The dark brown solution was boiled with Norite until it was colorless. It was then acidified with hydrochloric acid and a white, flocculent precipitate settled which, when dry, weighed 1.8 g. It was further purified by recrystallization from *n*-butyl alcohol. It did not melt below 360°. It was insoluble in all the ordinary organic solvents and water but was slightly soluble in butyl alcohol.

Anal. Subs., 0.1931: 10.55 cc. of 0.0983 *N* I soln. Calcd. for $C_{16}H_{12}O_5AsN$: As, 20.10. Found: 20.13.

2,2'-Phenyl-4,4'-carboxy-6,6'-arsenoquinoline.—To 5.3 g. of hydrated magnesium chloride in 130 cc. of water at 8° was added 30 g. of sodium hydrosulfite. To this was added gradually during 1.5 minutes a cold solution of 2 g. of 2-phenyl-4-carboxy-6-arsonoquinoline in 46 cc. of water containing 0.66 g. of sodium hydroxide. This solution was then treated with 1 g. of Norite and the mixture heated rapidly to 40°, filtered, and heated quickly to 55°. The temperature was kept at this point for 90 minutes during which period the product separated. It was filtered off, washed and dried in a vacuum over sodium hydroxide. The resulting red compound was insoluble in all the organic solvents and in water but was soluble in sodium hydroxide solution. It did not melt below 300°.

Anal. Subs., 0.2132, 0.1921: 13.85, 12.42 cc. of 0.0983 *N* I soln. Calcd. for $C_{32}H_{20}O_4As_2N_2$: As, 23.07. Found: As, 23.20, 23.12.

Summary

1. An arsonocinchophen is described. It has trypanocidal properties but is too toxic for practical use.

2. The method of preparation consisted in the replacement of the amino group in aminocinchophen by the arsonic acid radical. The aminocinchophen was prepared by condensation of nitro-isatin with acetophenone and reduction of the resulting nitrocinchophen.

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