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

Arsenicals Containing the Furan Nucleus

BY WESLEY G. LOWE[1] AND CLIFF S. HAMILTON

Although considerable work has been done on heterocyclic arsenicals, no furan arsenicals have as yet been reported.[2] Since recent investigations of furan have indicated that it possesses certain superaromatic properties,[3] it is of interest to study the carbon–arsenic bond in these arsenicals as contrasted with that linkage in aromatic and heterocyclic chemistry in general. There is also a possibility that furan arsenicals might possess valuable properties in medicine.

2-Aminofuran[3] has not been isolated. Consequently the Bart reaction,[4] which couples arsenic to carbon by means of the diazonium salt and sodium arsenite, is not applicable. The problem was attacked successfully in this investigation through the furan mercurials,[5] and the properties of the arsenicals thus far isolated are such that it seems unlikely that a Bart reaction could be applied if the furan diazonium salt were available.

The difficulties encountered in isolating the furan arsenicals arise from three properties of these unstable compounds: (1) the ease of ring scission leading to a series of organic arsenicals of an aliphatic type, (2) the ease of rupture of the carbon–arsenic bond yielding furan and inorganic arsenic, (3) the ease of resin formation in the presence of excess arsenic trichloride.

Ring scission occurs on hydrolysis of the compound formed by the action of arsenic trichloride on 2,5-dichloromercurifuran, leading to the arsenicals of an aliphatic type. The structures of these compounds will be the subject of further research. No parallel behavior has been observed in arsenicals obtained from 2-chloromercurifuran.

True furan arsenicals have been prepared by the action of arsenic trichloride on 2-chloromercurifuran

$$C_4H_3OHgCl + AsCl_3 \longrightarrow C_4H_3OAsCl_2 + (C_4H_3O)_2AsCl + (C_4H_3O)_3As + HgCl_2$$

The action of undiluted arsenic trichloride on 2-chloromercurifuran leads to resinification if heat is applied. At room temperature the action is slow and incomplete, but in the presence of benzene as a diluent the mercurial reacts rapidly and completely at reflux temperature without detectable decomposition. These arsenicals are very readily decomposed in the presence of excess arsenic trichloride. Attempts to distil them at 10 mm., a pressure suitable for the corresponding thiophene arsenicals,[6] resulted in extensive decomposition. At pressures of 1.0 to 0.1 mm. the distillation is possible since the arsenic trichloride is completely removed at room temperature under these conditions. Purification of the individual compounds requires numerous fractionations and the gradual loss of furan arsenicals due to resin formation during this process makes the final yield very low.

The arsenicals fractionated by this method show unusual properties. Furyldichloroarsine and difurylchloroarsine are both destroyed by the action of boiling water or alcohol, the carbon–arsenic bond being cleaved and furan (identified as 2-chloromercurifuran) evolved from the solution. Trifurylarsine is more stable and can be steam-distilled, but the carbon–arsenic linkage is much more easily broken than in the case of triphenylarsine.[7] Under conditions that lead to the formation of the addition compound, triphenylarsine mercuric chloride, by reaction of triphenylarsine and mercuric chloride,[8] trifurylarsine forms instead 2-chloromercurifuran. Iodination of triphenylarsine yields triphenyltetraiodoarsine[9] and iodination of trifurylarsine under the same conditions yields 2-iodofuran.

By conducting dry hydrogen sulfide through a cold alcoholic solution of furyldichloroarsine or difurylchloroarsine, it is possible to prepare the corresponding sulfides without loss of furan. These compounds exhibit the same type of instability as do the furylchloroarsines.

Finzi[10] in a synthesis of thiophene arsenicals from the corresponding mercurials avoided distillation of the thienylchloroarsines by hydrolyzing the reaction mixture, oxidizing with hydrogen peroxide and isolating thienylarsonic acid and di-

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[1] Parke, Davis and Company Fellow.

[2] Gilman and Kirkpatrick, *Chem. Abstr.*, **28**, 6714 (1934).

[3] Gilman and Wright, *Chem. Rev.*, **11**, 323 (1932).

[4] Bart, *Ann.*, **429**, 55 (1922).

[5] Gilman and Wright, THIS JOURNAL, **55**, 3302 (1933).

[6] Steinkopf and Bauermeister, *Ann.*, **413**, 330 (1917).

[7] La Coste and Michaelis, *Ber.*, **11**, 1887 (1878).

[8] La Coste and Michaelis, *Ann.*, **201**, 241 (1880).

[9] Michaelis, *ibid.*, **321**, 164 (1902).

[10] Finzi, *Gazz. chim. ital.*, **55**, 824 (1925).

thienylarsinic acid. Repeated attempts to follow this procedure with furan arsenicals failed, a result explained by the decomposition of these compounds in water. This unusual activity of the carbon–arsenic bond is in accord with the observed ease of decarboxylation of furoic acid, the ease of mercuration of furan, the behavior of difuryldiphenyllead, and the superaromatic properties in general which have been studied by Gilman.[11]

Apparatus

The apparatus employed for the fractionation of the arsenicals was built in two units. The distillation unit was composed of five parts: a distilling flask, a fractionating column, a condenser, a receiver and a modified McLeod gage. The flask (100 cc. volume) had a side arm attached for the introduction of the arsenicals and was sealed to a fractionating column of the notched type, 25 cm. long and 2 cm. in diameter. This was enclosed by a glass jacket in which glycerol, electrically heated and air stirred, circulated. The flask was immersed in a glycerol bath and independently heated. The condenser, a vertical tube with an inseal extending to the bottom and an outlet at the top, was connected by a stopcock to the receiver. Tubes sealed to the side and base of the receiver and drawn to capillary points permitted the removal of the arsenicals with minimum disturbance of vacuum.

The second unit, connected with first by suction tubing, was composed of a combustion tube sealed to a calcium chloride tube containing cotton fiber. The combustion tube was built of heavy-walled Pyrex, 60 cm. in length and 2 cm. outside diameter. It was filled with copper oxide and heated electrically during distillation to a dull red to protect the pump from organic fumes. During distillation of the arsenicals the pressure fell continuously from an initial value of 1 or 2 mm. to a final value of 0.1 mm.

Experimental

Furyldichloroarsine.—In a 500-cc. flask was placed 147 g. of 2-chloromercurifuran, 200 cc. of benzene and 66 g. of arsenic trichloride, and the mixture was refluxed for four hours. The mercuric chloride was filtered off and the filtrate freed from benzene by distillation from a water-bath. The viscous dark-colored oil remaining (40 cc.) was introduced into the vacuum-distillation apparatus, the condenser and receiver chilled with Dry-Ice and the pressure reduced. The temperature of the flask was then slowly raised to 100° while the column was kept at 25°. The distillation was interrupted, the arsenic trichloride and benzene melted and removed from the condenser, and distillation resumed immediately. With the flask at a temperature of 120° and the column at 80°, 12 g. of crude furyldichloroarsine distilled over. This material was contaminated with arsenic trichloride and difurylchloroarsine. In order to obtain a pure sample four more fractionations were necessary. Resinification during this process caused considerable loss of the arsenical. One gram of pure furyldichloroarsine was isolated. It is colorless when kept under vacuum but in contact with the air turns green and finally sets to a resin. Its vapors possess powerful lachrymatory and vesicatory properties. Boiling water liberates furan from the compound; d^{25}_4 1.930.

Anal. Calcd. for $(C_4H_3O)AsCl_2$: As, 35.20; Cl, 33.79. Found: As, 35.27; Cl, 33.83.

Difurylchloroarsine.—By raising the temperature of the column to 120° and the flask to 140°, 25 g. of impure difurylchloroarsine was obtained. During the distillation of this material the Dry-Ice was removed from the condenser since at low temperature difurylchloroarsine became so viscous that it blocked up the delivery tube. It was readily condensed at room temperature. This fraction was purified by three more fractionations, 2 g. of pure material being obtained. It is a colorless oily liquid which turns slightly green in contact with the air but shows no signs of resinification on long standing. Its action on the skin is less rapid but more painful than that of furyldichloroarsine, since it penetrates deeply before hydrolyzing. Boiling water and alcohol liberate furan rather slowly; d^{25}_4 1.717.

Anal. Calcd. for $(C_4H_3O)_2AsCl$: As, 30.65; Cl, 14.51. Found: As, 30.70; Cl, 14.70.

Trifurylarsine.—The temperature of the fractionating column was finally raised to 160° and the flask to 170°. Two grams of trifurylarsine containing some difurylchloroarsine was obtained. This fraction was readily purified by steam distillation since the difurylchloroarsine present is broken down in the process. One gram of a colorless oil was obtained which turned slightly yellow on standing. It was collected in ether, the ether dried and evaporated, and on standing trifurylarsine crystallized in plates; m. p. 35°. It is soluble in all the common organic solvents.

Anal. Calcd. for $(C_4H_3O)_3As$: As, 27.14; mol. wt., 276. Found: As, 27.01, 27.09; mol. wt., by boiling point rise of benzene, 261, 262.

The yield of arsenicals, calculated on the basis of mercuric chloride precipitated, is practically quantitative; on the basis of the distillate after one fractionation, 50–60%.

Furylarsine Sulfide.—One gram of furyldichloroarsine was placed in 10 cc. of cold alcohol and dry hydrogen sulfide passed through the solution. The gas escaping from the solution was passed through concentrated sulfuric acid to test for the presence of furan vapor. None was detected. A pale yellow precipitate formed immediately in the alcohol. After thirty minutes the solution was filtered and the filtrate found to be free of furyldichloroarsine. The furylarsine sulfide was washed with alcohol and dried; m. p. 125° with decomposition. It was insoluble in carbon disulfide and hot benzene, but dissolved in 1 *N* sodium hydroxide on heating. On boiling, this solution evolved furan.

Anal. Calcd. for $(C_4H_5O)AsS$: As, 43.05. Found: As, 43.09, 43.00.

Tetrafuryldiarsine Sulfide.—One gram of difurylchloroarsine was placed in 10 cc. of cold alcohol and dry hydrogen sulfide passed through the solution. There was no precipitation. After standing for twelve hours the solution was evaporated to dryness in the cold, an oil separating.

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[11] Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932); Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933); Gilman and Young, *ibid.*, **56**, 464 (1934).

No odor of difurylchloroarsine remained. Attempts to steam distil the oil failed, the compound being broken down into furan, arsenious sulfide and arsenic trioxide. The oil was dissolved in ether without further purification, the solution dried and evaporated. On standing the oil turned a light yellow but did not crystallize at the temperature of Dry-Ice; d^{25}_4 1.583.

Anal. Calcd. for $((C_4H_3O)_2As)_2S$: As, 33.30. Found: As, 33.36, 33.44.

2-Chloromercurifuran from Trifurylarsine.—One gram of trifurylarsine was dissolved in 20 cc. of alcohol, a solution of 3.2 g. of mercuric chloride in 100 cc. of water alcohol added, and the solution was heated to boiling and set aside to cool. Well-defined crystals of 2-chloromercurifuran formed and after addition of water to complete the precipitation they were filtered, dried and weighed; yield 1.6 g. or 50%. This material was identified by an analysis for mercury and chlorine and checked against the known compound by a mixed melting point.

Iodination of Trifurylarsine.—One gram of trifurylarsine and 3 g. of iodine were placed in 10 cc. of ether and refluxed for two hours. After evaporating the ether, 20 cc. of water was added. The resulting solution was neutralized with sodium carbonate and the excess iodine removed with sodium thiosulfate. On distillation, 0.6 g. of 2-iodofuran was obtained, 28%. Mercuration of this product gave 5-iodo-2-chloromercurifuran, m. p. 169°.

2,5-Furyldiarsine Tetrachloride.—Sixty grams of 2,5-chloromercurifuran was placed in a 250-cc. flask and 90 g. of arsenic trichloride added, and after standing for three days at room temperature the precipitate of mercuric chloride was filtered out. Removal of excess arsenic trichloride from the filtrate by low pressure distillation left a black viscous material from which nothing organic was distillable at 0.01 mm. Therefore, one-sixth of the filtrate was placed in a 100-cc. flask and 5 g. of iodine in 15 cc. of carbon tetrachloride added. After refluxing for three hours the contents were subjected to steam distillation; yield of 2,5-diodofuran 1.0 g. or 17%.

The production of 2,5-diiodofuran from this arsenical indicates that the original product of arsenation contains the furan nucleus and that the arsenic is in the 2 and 5 positions as expected from the synthesis. However, all products that have been formed at this time by the action of water on this arsenical have only one arsenic atom in the molecule and do not contain the furan nucleus. Their structure will be the subject of further research.

Appreciation is due Dr. Henry Gilman for certain suggestions.

Summary

Some furan arsenicals obtainable from 2-chloromercurifuran have been isolated and described. Evidence has been reported indicating that the carbon–arsenic bond in these arsenicals is cleaved with unusual ease. A furan arsenical has been prepared from 2,5-dichloromercurifuran and its structure determined indirectly. Compounds derivable from this arsenical by the action of water do not contain the furan nucleus.

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Cinchona Alkaloids in Pneumonia. III. Apocupreines (Apoquinine)

BY C. L. BUTLER AND LEONARD H. CRETCHER

Recent favorable results with ethylapoquinine in the study of experimental and clinical pneumonia[1] have made the chemistry of apoquinine (the alkali-soluble product resulting from the action of demethylating agents on quinine) of great importance. The present paper describes experiments dealing with the preparation of apoquinine which it is believed will be of help in explaining the confusing data in the literature on this subject. Data on the pneumococcicidal action and toxicity of some apoquinine fractions are also presented.

This confusion in the older literature has recently been pointed out by Henry and Solomon[2] and is strikingly shown by the following data on the melting point and specific rotation, respectively, of apoquinine: 160 and −178.1°;[3] 210 and −217°;[4] 160 and −196.4°;[5] 190 and −190.5°;[6] 170 and −216°;[7] 184 and −214°.[2]

Using hydrochloric and sulfuric acids as reagents, we have succeeded in the preparation of apoquinine in two analytically pure forms showing a marked difference in properties. Since a rearrangement, probably of the vinyl group from $-CH{=}CH_2$ to $=CH-CH_3$, invariably accom-

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[1] Maclachlan, Permar, Johnston and Kenney, *Am. J. Med. Sci.*, **188**, 699 (1934).

[2] Henry and Solomon, *J. Chem. Soc.*, 1923 (1934).

[3] Hesse, *Ann.*, **205**, 314 (1880).

[4] Lippmann and Fleissner, *Monatsh.*, **16**, 34 (1895); *Ber.*, **28**, 1972 (1895).

[5] Fränkel and Buhlea, *ibid.*, **58**, 559 (1925).

[6] Jarzyński, Ludwiczakówna and Suszko, *Rec. trav. chim.*, **52**, 839 (1933).

[7] Miura and Okamoto, *Jap. J. Med. Sci.*, [1] **5** 1 (1930).