Duin[8] to apply the Langmuir-Harkins theory of oriented molecules to the explanation of the catalytic effects of suspended carbon particles on certain chemical reactions, to make use of the same ideas in the case of urea and urease. However, the experiments of Onodera,[9] carried on in Bayliss' laboratory, showing that urease probably has a *co-enzyme*, made up, moreover, of two parts, one dialyzable, the other not, indicate that what at first has seemed a simple reaction, must in reality be rather complicated. There is not yet available enough information regarding this reaction to let us decide what particular bonds of the urea molecule are opened by the enzyme urease.

Summary

1. Experimental data have been presented to show that the transformation of ammonium cyanate to urea is not catalyzed by urease.

2. When urea is hydrolyzed, in the presence of urease, forming ammonium carbamate, which changes into ammonium carbonate, there is a simultaneous formation of ammonium cyanate from the urea.

3. By a process of elimination it is proved that the particular reaction stage catalyzed by urease is the transformation of urea into ammonium carbamate.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY]

ARSENATED BENZOPHENONE AND ITS DERIVATIVES. II[1]

BY W. LEE LEWIS AND H. C. CHEETHAM

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The first paper[2] of this series dealt with the condensation of dichloro-*p*-arsinobenzoyl chloride with aromatic hydrocarbons and phenyl ethers in the presence of anhydrous aluminum chloride. The present paper is a further extension of the application of Friedel and Crafts' reaction, heretofore little used in the preparation of arsenicals, and takes up analogous condensations with dichloro-*o*-arsinobenzoyl chloride. An arsenated ketone, namely *p*-arsono-acetophenone was also prepared from amino-acetophenone, which necessitated a study of available methods of obtaining amino-acetophenone. The ultimate goal of this research was the preparation of a type of arsenical in which the benzoyl group with and

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[8] Kruyt and van Duin, *Rec. trav. chim.*, **40**, 249 (1921).

[9] Onodera, *Biochem. J.*, **9**, 575 (1915).

[1] This work was done under a grant from the United States Interdepartmental Social Hygiene Board, Washington, D. C. Certain of the water-soluble compounds have been submitted to Dr. A. S. Loevenhart of the University of Wisconsin for pharmacological study.

[2] Lewis and Cheetham, THIS JOURNAL, **43**, 2117 (1921).

without solubilizing groups in its nucleus should replace the hydroxyl group of arsphenamine. The successful preparation of dichloro-*o*-arsinobenzoyl chloride offered the possibility of preparing various isomers of such a compound. However, the reduction of the arsenated nitro-benzophenones to amines, as well as their further difficult reduction to the arseno compounds, presented so many obstacles that the attempt was deferred.

In the absence of nitro or amino groups in the ring, the benzophenone arsonic acids are easily and quantitatively reduced in acetic acid solution with conc. hydrobromic or hydriodic acids to derivatives of arsenious oxide. In some cases, as described, the reaction goes further, forming the beautifully colored crystalline dibromo- or di-iodo-arsines. The latter are easily converted again into the oxide by hydrolysis with dil. sodium carbonate solution.

Likewise, the arseno derivatives of the *ortho* arsenated benzophenones are easily formed by refluxing the arsonic acids, or better still the arsenious oxides, with phosphorous acid in ethyl alcohol solution.

Experimental Part

Preparation of *o*-Carboxyphenyl-arsonic Acid.—This acid is most conveniently prepared from anthranilic acid using the method of Bart.[3] One hundred and fifty g. of anthranilic acid is dissolved in 2 liters of water with 225 cc. of conc. hydrochloric acid and diazotized with 80 g. of sodium nitrite, while the temperature is kept below 5°. The arsenite solution is prepared by dissolving 140 g. of arsenic trioxide in 1200 cc. of water with 162 g. of sodium hydroxide. Forty cc. of 6 *N* copper sulfate solution is now added. The diazo solution is slowly poured into the arsenite solution with vigorous stirring, the temperature being held at 20°. The alkaline solution is then warmed on the water-bath to 60° until the evolution of nitrogen ceases, when it is acidified with hydrochloric acid and concentrated to about 1 liter. The solution is filtered hot and allowed to cool, and after it has stood for several hours a mass of crystals of *o*-carboxyphenyl-arsenic acid separates. It may be purified by recrystallization from hot water; yield, 50–60%.

Dichloro-*o*-arsinobenzoyl chloride, $Cl_2AsC_6H_4COCl$.—The procedure differs somewhat from that followed in the case of the *para* compound.[4] Twenty cc. of phosphorus trichloride in 20 cc. of chloroform is slowly added to 25 g. of *o*-carboxyphenyl-arsonic acid suspended in 100 cc. of cold chloroform. As soon as the evolution of hydrogen chloride ceases, 20 g. of phosphorus pentachloride is added at once and the mixture warmed on the water-bath to complete the reaction. After the solution is decanted from the sludge of phosphoric acid and impurities, the chloroform and chlorides of phosphorus are removed under diminished pressure up to 110°. The residue is used directly for condensations since it was found impossible to distil the acid chloride without decomposition, even under 15 mm. pressure.

To the crude acid chloride prepared above are added successively 75 cc. of carbon disulfide, 25 cc. of benzene, and 20 g. of anhydrous aluminum chloride. After the spontaneous evolution of hydrogen chloride has slackened somewhat, the mixture is warmed at 50° on the water-bath for 2 hours under a reflux condenser. It is then poured with stirring onto 300 g. of cracked ice; 10 cc. of conc. hydrochloric acid is added, and the

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[3] Bart, Ger. pat. 250,264 and 254,345.

[4] Poulenc, French pat. 441,215.

carbon disulfide and excess benzene are removed by distillation with steam. The reaction flask now contains a clear aqueous solution and a gummy substance which settles to the bottom. After the mixture has cooled somewhat, the aqueous solution is decanted and discarded. Four hundred cc. of dil. sodium carbonate solution and 50 cc. of 6 N sodium hydroxide are added to the flask and warmed to decompose the gummy mass which gradually goes into solution. A slight excess of the calculated amount of 3% hydrogen peroxide solution is now added. After warming for 5 minutes the solution is chilled and acidified with hydrochloric acid which precipitates the arsonic acid at once. Recrystallization from 500 cc. of 95% alcohol yields 8 g. of the product in fine needles. It is quite insoluble in hot water, ether or benzene, and soluble in warm ethyl alcohol, glacial acetic acid, alkalies, or alkali carbonates. The crystals soften at 195°, but do not melt below 250°.

Analysis. Subs., 0.2136: 27.55 cc. of 0.05016 N iodine soln. Calc. for $C_{13}H_{11}O_4As$: As, 24.51. Found: 24.25.

4-Methyl-benzophenone-2′-arsonic Acid, $CH_3C_6H_4COC_6H_4AsO_3H_2$.—This compound is made by substituting the equivalent amount of toluene for benzene in the procedure described above. Nine g. of product is obtained on recrystallization from 95% ethyl alcohol. It is easily soluble in alkalies, alkali carbonates, glacial acetic acid, or warm absolute alcohol, but is quite insoluble in water, ether, or benzene.

Analysis. Subs., 0.3730: 46.05 cc. of 0.05016 N iodine soln. Calc. for $C_{14}H_{13}O_4As$: As, 23.43. Found: 23.21.

4-Methoxy-benzophenone-2′-arsonic Acid, $CH_3OC_6H_4COC_6H_4AsO_3H_2$.—The substitution of the equivalent amount of anisole for benzene gave 10.5 g. of a beautifully crystalline arsonic acid which was recrystallized from 80% ethyl alcohol.

Analyses. Subs., 0.3283, 0.3158: 35.0 cc., 33.6 cc. of 0.05523 N iodine soln. Calc. for $C_{14}H_{13}O_5As$: As, 22.32. Found: 22.07, 22.02.

4-Ethoxy-benzophenone-2′-arsonic Acid, $C_2H_5OC_6H_4COC_6H_4AsO_3H_2$.—The equivalent amount of phenetole under similar conditions also condenses readily with the acid chloride and yields 10 g. of the arsonic acid in long colorless needles when recrystallized from 80% ethyl alcohol.

Analyses. Subs., 0.2219, 0.2257: 22.9 cc., 23.4 cc. of 0.05523 N iodine soln. Calc. for $C_{15}H_{15}O_5As$: As, 21.42. Found: 21.36, 21.45.

4-Phenoxy-benzophenone-2′-arsonic Acid, $C_6H_5OC_6H_4COC_6H_4AsO_3H_2$.—This arsonic acid is made in 40% yield by using diphenyl ether and following the procedure previously described. It is easily recrystallized from dil. alcohol.

Analysis. Subs., 0.2408: 21.75 cc. of 0.05523 N iodine soln. Calc. for $C_{19}H_{15}As$: As, 18.84. Found: 18.66.

A few typical arseno compounds were prepared by refluxing the arsonic acid, or better, its corresponding oxide, with phosphorous acid in ethyl alcohol solution.

4,4′-Dibenzoylarsenobenzene, $C_6H_5COC_6H_4As{:}AsC_6H_4COC_6H_5$.—Two g. of benzophenone-4-arsenious oxide[5] in 50 cc. of ethyl alcohol is refluxed for 2 hours with 10 cc. of conc. phosphorous acid. The yellow powder is filtered and washed with hot alcohol. It is insoluble in water, alkalies, acids, ether or alcohol, but is slightly soluble in hot chloroform. Continued exposure to air, especially when moist, changes it to the oxide.

Analysis. Subs., 0.2083: 29.8 cc. of 0.05523 N iodine soln. Calc. for $C_{26}H_{18}O_2As_2$: As, 29.29. Found: 29.61.

2,2′-Dibenzoylarsenobenzene, $C_6H_5COC_6H_4As{:}AsC_6H_4COC_6H_5$.—Two g. of benzophenone-2-arsonic acid dissolved in 50 cc. of alcohol is refluxed for 2 hours with 10 cc.

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[5] Ref. 2, p. 2119.

of conc. phosphorous acid. The resulting yellow powder, filtered from the hot solution and washed with hot alcohol, is quite insoluble in all ordinary solvents.

Analysis. Subs., 0.2487: 29.4 cc. of 0.05176 *N* iodine soln. Calc. for $C_{26}H_{18}O_2As_2$: As, 29.29. Found: 29.40.

2,2′-Di-*p*-anisoylarsenobenzene, $CH_3OC_6H_4COC_6H_4As:AsC_6H_4COC_6H_4OCH_3$.—This compound was prepared from the corresponding arsonic acid in the usual manner. It is a yellow powder insoluble in all ordinary solvents.

Analysis. Subs., 0.1915: 26.1 cc. of 0.05176 *N* iodine soln. Calc. for $C_{28}H_{22}O_4As_2$: As, 26.22. Found: 26.44.

4,4′-Diethoxydibenzoyl-2,2′-arsenobenzene, $C_2H_5OC_6H_4COC_6H_4As:AsC_6H_4COC_6H_4OC_2H_5$.—4-Ethoxy-benzophenone-2′-arsonic acid reduced in the same manner yields a yellow powder which is similar in all respects to those described above.

Analysis. Subs., 0.1435: 18.4 cc. of 0.05176 *N* iodine soln. Calc. for $C_{30}H_{26}O_4As_2$: As, 25.00. Found: 24.87.

4-Methoxybenzophenone-2′-dibromo-arsine, $CH_3O\text{-}C_6H_4COC_6H_4AsBr_2$.—On the addition of 10 cc. of 48% hydrobromic acid to a solution of 2 g. of 4-methoxy-benzophenone-2′-arsonic acid in 25 cc. of glacial acetic acid, fine yellow needles of the dibromo-arsine separate after the mixture has stood for several hours in the cold. The solution becomes dark red, due to the liberation of free bromine. The yield after recrystallization from glacial acetic acid is 2 g. The compound is readily soluble in alcohol and aromatic hydrocarbons, insoluble in water, slowly hydrolyzed by sodium carbonate solution, more rapidly by alcoholic sodium carbonate, and melts at 161°.

Analyses. Subs., 0.2370: 21.8 cc. of 0.04711 *N* iodine soln. Subs., 0.1456: AgBr (Carius), 0.1233. Calc. for $C_{14}H_{11}O_2AsBr_2$: As, 16.81; Br, 35.85. Found: As, 16.25; Br, 36.03.

4-Ethoxybenzophenone-2′-dibromo-arsine, $C_2H_5OC_6H_4COC_6H_4AsBr_2$.—The ethyl derivative, forming yellow needles from glacial acetic acid which melt at 152°, is prepared in the same way, from the corresponding arsonic acid.

Analysis. Subs., 0.2695: AgBr (Carius), 0.2220. Calc. for $C_{15}H_{13}O_2AsBr_2$: Br, 34.76. Found: 35.05.

4-Methoxybenzophenone-2′-arsenious Acid, $CH_3OC_6H_4COC_6H_4AsO_2H_2$.—Two g. of the corresponding dibromide is dissolved in 25 cc. of alcohol and warmed with dil. sodium carbonate solution for 2 minutes. After diluting with water to 150 cc. and warming almost to the boiling point, dil. sulfuric acid is added, precipitating the arsenious acid in shiny plates. The crystals retain their form and water of hydration when heated to 105° for 3 hours.

Analysis. Subs., 0.1736: 23.00 cc. of 0.04711 *N* iodine soln. Calc. for $C_{14}H_{13}O_4As$: As, 23.43. Found: 23.39.

4-Methoxybenzophenone-2′-dichloro-arsine, $CH_3OC_6H_4COC_6H_4AsCl_2$.—Two g. of the above acid is dissolved in hot glacial acetic acid and refluxed for 15 minutes with 20 cc. of conc. hydrochloric acid. As the solution cools, colorless crystals of the dichloride, melting at 148°, separate.

Analysis. Subs., 0.1010: AgCl (Carius), 0.0820. Calc. for $C_{14}H_{11}O_2AsCl_2$: Cl, 19.87. Found: 20.09.

4-Methoxybenzophenone-2′-di-iodo-arsine, $CH_3OC_6H_4COC_6H_4AsI_2$.—Ten cc. of conc. hydriodic acid is added to a solution of 2 g. of 4-methoxybenzophenone-2′-arsonic acid in 25 cc. of glacial acetic acid. After the mixture has stood for 2 hours in the cold, the precipitated di-iodo-arsine is filtered and recrystallized from glacial acetic acid, yielding bright red crystals which melt at 137°.

Analysis. Subs., 0.1238: AgI (Carius), 0.1077. Calc. for $C_{14}H_{11}O_2AsI_2$: I, 47.02. Found: 46.97.

4-Ethoxybenzophenone-2'-di-iodo-arsine, $C_2H_5OC_6H_4COC_6H_4AsI_2$.—This compound is prepared as described above from 4-ethoxybenzophenone-2'-arsonic acid. Orange-colored crystals are formed from glacial acetic acid, melting at 151°.

Analysis. Subs., 0.0807: AgI (Carius), 0.0687. Calc. for $C_{15}H_{13}O_2AsI_2$: I, 45.83. Found: 45.94.

4-Methoxybenzophenone-4'-dichloro-arsine, $CH_3OC_6H_4COC_6H_4AsCl_2$.—Two g. of the corresponding oxide is dissolved in 25 cc. of glacial acetic acid and refluxed with 20 cc. of conc. hydrochloric acid for 15 minutes. On standing overnight in the cold long colorless crystals of the dichloro-arsine separate. The compound melts at 152°.

Analysis. Subs., 0.0765: AgCl (Carius), 0.0626. Calc. for $C_{14}H_{11}O_2AsCl_2$. Cl, 19.87. Found: 20.21.

4-Methoxybenzophenone-4'-dibromo-arsine, $CH_3OC_6H_4COC_6H_4AsBr_2$.—The analogous dibromo-arsine is prepared as described above using 10 cc. of 48% hydrobromic acid. It forms light yellow crystals melting at 136°.

Analysis. Subs., 0.2186: AgBr (Carius), 0.1857. Calc. for $C_{14}H_{11}O_2AsBr_2$: Br, 35.85. Found: 36.14.

4-Methoxybenzophenone-4'-di-iodo-arsine, $CH_3OC_6H_4COC_6H_4AsI_2$.—By using hydriodic acid in the above reaction, red crystals of the di-iodo compound, melting at 105°, are formed.

Analysis. Subs., 0.1135: AgI, 0.0997. Calc. for $C_{14}H_{11}O_2AsI_2$: I, 47.02. Found: 47.43.

Aliphatic-aromatic arsinic acids[6] may be easily prepared from the dibromo or di-iodo-arsines of this series by condensing them with halogenated aliphatic compounds in the presence of strong alkalies. The reactions take place in the cold and the resulting products are generally obtained in good yield and crystalline form.

4-Methoxybenzophenone-4'-arsino Acetic Acid, $CH_3OC_6H_4COC_6H_4As(O_2H)CH_2CO_2H$.—A mixture of 2 g. of 4-methoxybenzophenone-4'-dibromo-arsine and 0.7 g. of sodium hydroxide in 20 cc. of water is cooled, and to this solution is added gradually with shaking 1 g. of chloro-acetic acid dissolved in the necessary amount of 6 *N* alkali. The mixture is allowed to stand for about 3 hours, when it is made acid to phenolphthalein, and filtered to remove a small amount of the oxide. Acidification of the filtrate to congo red precipitates the arsinic acid in colorless crystals. The product may be purified by recrystallization from hot water.

Analysis. Subs., 0.2004: 25.8 cc. of 0.0413 *N* iodine soln. Calc. for $C_{16}H_{15}O_6As$: As, 19.82. Found: 19.95.

With a view to the preparation of a series of arsenic derivatives of a mixed ketone, containing an aliphatic and an aromatic radical, available methods of preparing *p*-amino-acetophenone were studied.[7] The best results were obtained by slight modification of a method of H. T. Clarke.[8]

Fifteen hundred g. of crude acetanilide, 2250 g. of acetic anhydride, and 750 g. of anhydrous zinc chloride are refluxed in a 12-liter flask on a sand-bath for 6 hours. The reaction mixture is allowed to cool until boiling has stopped, when 2.5 liters of 15% hydrochloric acid is added. The refluxing is further continued for 5 hours, and the acetic acid finally removed by distillation under reduced pressure until the volume of the

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[6] Quick and Adams, THIS JOURNAL, **44**, 805 (1922).

[7] These compounds were prepared by Mr. C. R. Wilcox in this Laboratory.

[8] Private communication from H. T. Clarke, Eastman Kodak Co.

mixture has been reduced to 1.5 liters. It is then poured into an open vessel to cool. The resulting tar is worked up in 200 g. lots, each lot being treated thoroughly with 300 cc. of 6 *N* sodium hydroxide solution. The brown oil which separates is extracted with ether and the ethereal extract fractionated at 17 mm. The oil coming over above 210° forms a yellow solid, crystallizable from alcohol, forming bright yellow crystals melting at 106°. A yield of 327 g. or 22% was obtained.

Preparation of acetophenone-*p*-arsonic acid, $CH_3COC_6H_4AsO_3H_2$.—Twenty-five g. of *p*-amino-acetophenone is diazotized in the usual manner and treated with a solution of sodium arsenite according to the method of Bart already described. The compound is insoluble in water but soluble in alkalies and glacial acetic acid.

Analyses. Subs., 0.2830, 0.3299: 49.3, 58.00 cc. of 0.0471 *N* iodine soln. Calc. for $C_8H_9O_4As$: As, 30.73. Found: 30.76, 31.03.

Summary

The application of the Friedel and Crafts reaction has been further extended to the preparation of new arsenated ketones and their derivatives. Dichloro-*o*-arsinobenzoyl chloride has been condensed with aromatic hydrocarbons, and various aromatic ethers and the arseno and halogen derivatives of these compounds have been studied. An arsenated mixed ketone, namely, acetophenone-*p*-arsonic acid has been prepared.

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

A STUDY OF THE FORMATION OF HYDROXAMIC ACIDS FROM KETENE

BY CHARLES DEWITT HURD AND PAUL B. COCHRAN

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Much has been written concerning the structure of hydroxylamine. Although a unity of thought is still to be desired, the following facts stand out prominently in all such discussions. Towards alkylating agents, the 3 hydrogens in hydroxylamine are replaced successively by alkyl groups which are all joined directly to the nitrogen; towards acylating agents the process is different but equally characteristic. In this case, the first and the third acyl groups to enter the molecule are joined directly to the nitrogen, whereas the second is attached to the oxygen.

Several different kinds of acylating agents have been used successfully in the preparation of hydroxamic acids. For example, in standard methods for preparing hydroxamic acids from hydroxylamine, the use of acid chlorides, of acid anhydrides, of esters, and of amides are all advocated. Ketenes, which have been shown to be ideal acylating agents, are the newest addition to this list. A year ago it was demonstrated that diphenyl-acethydroxamic acid may be prepared from diphenyl ketene.[1]

In the work described in this paper, the simplest ketene, $CH_2:C:O$,

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[1] Jones and Hurd, THIS JOURNAL, **43**, 2433 (1921).