XV and the amine isolated by distilling the solvent. The amine was dissolved in 123 cc. of hot dry ethyl acetate and 9.9 cc. of ethyl chlorocarbonate added. Some hydrochloride of the amine separated as an oil and the ethyl acetate solution of the carbethoxyamino derivative was decanted from the oil. The ethyl acetate was distilled and the oily residue dissolved in hot toluene, from which it crystallized. All of the procedure involving the amine had to be performed in a carbon dioxide atmosphere to avoid air oxidation.

α - Methyl - β - 3 - carbethoxyaminophenoxyethanol, XVII.—α-Methyl-β-3-nitrophenoxyethanol (8.39 g.) was reduced and the amine isolated and treated with 2.6 cc. of ethyl chlorocarbonate following the procedure outlined in the synthesis of XVI. Removal of the solvent left the product as an uncrystallizable oil which was purified by fractional distillation under reduced pressure.

Structure Proof.—The structures of β-3-carbethoxy-amino-6-arsonophenoxyethanol and of α-methyl-β-3-carbethoxyamino-6-arsonophenoxyethanol were proved by suspending these arsonic acids in acetone and treating them with molecular hydrogen at 40 lb. (2.67 atm.) pressure in the presence of Raney nickel catalyst. This treatment replaced the arsono group with an atom of hydrogen. The residues were isolated and proved to be identical with β-3-carbethoxyaminophenol and α-methyl-β-3-carbethoxyaminophenol prepared as described above.

Summary

The 4-acetyl-, 4-carbo-n-propoxy-, and 4-carbobenzoxyamino-2-hydroxyphenyl-arsonic acids were prepared from 4-amino-2-hydroxyphenylarsonic acid. The arsenated phenylglycol ethers β-3-carbethoxy- and α-methyl-β-3-carbobenzoxy-amino-6-arsonophenoxyethanol were prepared from the corresponding hydroxy compounds while β-3-amino-6-arsonophenoxyethanol and the α-methyl derivative were derived by hydrolysis of the last two ethers in the preceding group. α-Methyl-β-3-carbethoxyamino-6-arsonophenoxy-ethanol was prepared from the corresponding amino compound. 4-Carbethoxy-, 4-carbo-n-propoxy- and 4-carbobenzoxyamino-2-hydroxyphenylarsenious oxides and 6,6'-arseno-3,3'-dicarbethoxyamino-di-β-phenoxyethanol were obtained by reduction of the arsonic acids. The non-arsenated ethers, β-3-acetyl-, β-3-carbethoxy- and α-methyl-β-3-carbethoxyaminophenoxyethanol were newly prepared during this investigation.

LINCOLN, NEBRASKA   RECEIVED OCTOBER 31, 1938

Arsenic Derivatives of Phenylmethylcarbinol

BY C. KENNETH BANKS[1] AND CLIFF S. HAMILTON

Although numerous aromatic arsonic acids with aliphatic side chains containing alcohol groups connected to the nucleus through oxygen or nitrogen have been prepared, little work has been done on arsenic derivatives of the phenyl-alkylcarbinols. Fourneau and Lestrange[2] prepared the only compounds of this type listed in the literature. Their work dealt with the three arsonobenzyl alcohols and the ortho and para arsono-2-phenylethanols, all of which were found to have some therapeutic value. It was felt that the arsenic derivatives of phenylmethyl-carbinol, containing an optically active secondary alcohol group, might have even greater value.

The only practical method available for the synthesis of such compounds was the reduction of arsonoacetophenones to the corresponding secondary alcohols. A number of arsonoacetophenones are known[3-5] but none of these compounds

seemed to have the properties desired. Therefore the arsenic derivatives of p-hydroxyacetophenone were investigated because they have no ortho substituents which might form hetero rings on reduction.

3-Arsono-4-hydroxyacetophenone was prepared by the Bart reaction[6] from the corresponding amine hydrochloride previously prepared by Edkins and Linnell[7] and was found to be sensitive to acids, cleaving arsenic trioxide. This property was not entirely unexpected as previous work had indicated that an arsono group substituted ortho to an hydroxyl group was very unstable[4,8,9] in the presence of acids. In order to obtain a more stable arsenic compound, 3-arsono-4-methoxyacetophenone was prepared.

None of the usual methods for reducing the keto group were applicable. However, following a

(1) Parke, Davis and Company Fellow.
(2) E. Fourneau and Mme. Y. de Lestrange, Bull. soc. chim., **53**, 330 (1933).
(3) Gibson and Levine, J. Chem. Soc., 2388 (1931).
(4) R. E. Omer and C. S. Hamilton, THIS JOURNAL, **59**, 642 (1937).
(5) C. K. Banks and C. S. Hamilton, ibid., **60**, 1370 (1938).
(6) H. Bart, Ann., **429**, 55 (1922).
(7) R. P. Edkins and W. H. Linnell, Quart. J. Pharm. Pharmac., **9**, 75 (1936).
(8) S. B. Binkley and C. S. Hamilton, THIS JOURNAL, **59**, 1716 (1937).
(9) A. E. Beguin and C. S. Hamilton, ibid., **61**, 355 (1939).

suggestion by Stevinson,[10] solutions of the monosodium salt of 3-arsono-4-methoxyacetophenone were reduced at 80° under a pressure of 40 pounds (2.6 atm.) of hydrogen with Raney catalyst. The arsonophenylmethylcarbinol was isolated as the sodium salt. It proved to be optically inactive, showing the synthesis to be nearly symmetric.

Dehydration occurred in the side chain when solutions of the sodium salt were acidified, giving a styrene polymer. The polymer retained the arsono group and the molecular weight was found to be approximately two thousand. The presence of the alcohol group was proved by preparing the acetate ester and the arseno derivative of the alcoholarsonic acid, both of which were converted to the same compound, the diacetate ester of the arseno derivative.

The arsine oxides of the ketoarsonic acids were prepared by sulfur dioxide reduction. In addition, arseno derivatives of all of the arsonic acids were obtained by hypophosphorous acid reduction.

In the course of the investigation the oxime of 3-arsono-4-methoxyacetophenone was prepared. As no arsenic derivatives of α-phenylethylamine are recorded, the oxime was subjected to the same reduction conditions as used in the preparation of the alcoholarsonic acid and several products were isolated. Apparently some hydrolysis occurred as nearly 50% of the oxime was converted to the ketoarsonic acid and the styrene polymer. Ammonia was noticeable in the reduction container after the reaction ceased, some of it being due to elimination of nitrogen between two and three of the molecules. All three of the possible amines were isolated in varying amounts and characterized.

Experimental

Nitroacetophenones.—3 - Nitro - 4 - hydroxyacetophenone was obtained by the method of Edkins and Linnell,[7] with one variation; the nitrating agent was changed from fuming nitric acid (1.5) to a half and half mixture of fuming and concentrated nitric acids. 3-Nitro-4-methoxyacetophenone was obtained from p-methoxyacetophenone by the same procedure in 90% yields.

Aminoacetophenones were obtained from the nitroacetophenones by catalytic reductions according to the method outlined by Stevinson[10] and others,[11] using acetone as the solvent. After the reduction was complete, the catalyst

(10) M. R. Stevinson, Doctor's Thesis, University of Nebraska, 1934. In part with C. S. Hamilton, THIS JOURNAL, **57**, 1298, 1600 (1935).

(11) For details see previous articles in THIS JOURNAL listed under C. S. Hamilton.

was filtered off, the acetone removed by evaporation under reduced pressure and water added with the admission of as little air as possible. The amines crystallized on standing in a high degree of purity. **3-Amino-4-hydroxyacetophenone**, light yellow, orthorhombic crystals, m. p. 98°, 67% yield. *Anal.* Calcd. for $C_2H_9NO_8$: N, 9.26%. Found: N, 9.20%. **3-Amino-4-methoxyacetophenone**, light brown, orthorhombic crystals, m. p. 85°, 90% yield. *Anal.* Calcd. for $C_9H_{11}NO_2$: N, 8.59%. Found: N, 8.62%.

Aminoacetophenone Hydrochlorides.—The hydrochloride salts were prepared in a similar manner to the amines. The acetone solution of the amine was reduced to one-half its volume and an equal volume of anhydrous ether added. On saturating with dry hydrogen chloride gas, the amine hydrochloride precipitated in the theoretical yield. **3-Amino-4-hydroxyacetophenone hydrochloride**, orthorhombic, white crystals, m. p. >250° dec. **3-Amino-4-methoxyacetophenone hydrochloride**, white, monoclinic crystals, m. p. 170° dec. *Anal.* Calcd. for $C_9H_{11}NO_2 \cdot$ HCl: Cl, 17.58. Found: Cl, 17.52.

Arsonoacetophenones.—The arsonoacetophenones were obtained by the Bart reaction.[6] The amine hydrochloride (0.1 mole) was dissolved in water, three equivalents of hydrochloric acid added and the solution cooled to −5°. The solution was diazotized by an equivalent of sodium nitrite and then added to a coupling solution containing arsenic trioxide (0.2 mole), sodium hydroxide (0.5 mole), and cupric chloride (1 g.) in 100 ml. of water and 100 g. of ice. After the reaction had subsided, the solution was allowed to stand overnight, heated to 70° and filtered. The filtrate was made acid to litmus paper, concentrated to 100 ml., charcoaled and filtered. The filtrate was made acid to congo red paper and cooled, precipitating the crude arsonic acid. On recrystallization from water the pure arsonic acid was obtained.

Acetylphenylarsine Oxides.—The above preparation was followed except that the product was not isolated. The acidified solution was heated to 50°, a trace of potassium iodide added and saturated with sulfur dioxide. After standing twenty-four hours, the arsine oxide precipitated and was filtered off. The crude product was purified by re-solution in N alkali, charcoaling, filtering and reprecipitating with acid.

Monosodium Salt of d,l-α-Methyl-3-arsono-4-methoxybenzyl Alcohol.—3-Arsono-4-methoxyacetophenone (10 g.) was dissolved in water (50 ml.) containing an equivalent of sodium hydroxide (2 g.). The solution was placed in a reduction container, heated to 80°, Raney catalyst added and then reduced with electrolytic hydrogen at 40 pounds (2.67 atm.) pressure. After the reduction was complete, the catalyst was removed and the filtrate concentrated to a thick sirup. A small portion of the sirup was added to 10 ml. of absolute ethyl alcohol, causing precipitation of some crystals. The remainder was added to isopropyl alcohol, the product separating as an oil. On adding the seed crystals in ethyl alcohol, the entire yield crystallized. The product was filtered off and was of such a degree of purity as to need no further purification.

α-Methyl-3-arsono-4-methoxybenzyl Acetate.—The sodium salt of the arsonobenzyl alcohol (4 g.) was added to hot acetic anhydride (15 ml.). After heating for several

TABLE I

COMPOUNDS AND PROPERTIES

	Compound	Description	M. p., °C.	Yield, %	Formula	As analysis,[12] % Calcd.	Found
1	3-Arsono-4-hydroxyacetophenone	White tetra. crystals	225	35	$C_8H_9O_5As$	28.81	28.75
2	3-Arsono-4-methoxyacetophenone	White tetra. crystals	212	60	$C_9H_{11}O_5As$	27.33	27.32
3	2-Hydroxy-5-acetylphenylarsine oxide	White powder	104	50	$C_8H_9O_3As \cdot H_2O$	30.70	30.61
4	2-Methoxy-5-acetylphenylarsine oxide	White powder	294 dec.	70	$C_9H_9O_3As \cdot H_2O$	29.03	29.01
5	2,2'-Dihydroxy-5,5'-diacetylarsenobenzene	Dark yellow powder	193–198 dec.	80	$C_{16}H_{14}O_4As_2$	35.71	35.80
6	2,2'-Dimethoxy-5,5'-diacetylarsenobenzene	Light yellow powder	168 dec.	80	$C_{18}H_{18}O_4As_2$	33.43	33.39
7	Monosodium salt of d,l-α-methyl-3-arsono-4-methoxybenzyl alcohol	Pearly white granules	>300 dec.	98	$C_9H_{12}O_5AsNa$	25.13	25.02
8	N-Methyl-3-arsono-4-methoxybenzyl acetate	White orthorhombic crystals	Approx. 320 dec.	40	$C_{11}H_{16}O_6As$	23.62	23.59
9	2,2'-Dimethoxy-5,5'-(α,α'-dihydroxy)-diethylarsenobenzene	Light yellow powder	245–250 dec.	50	$C_{18}H_{22}O_4As_2$	33.10	33.17
10	2,2'-Dimethoxy-5,5'-(α,α'-diacetoxy)-diethylarsenobenzene	Light yellow powder	268 dec.	80	$C_{22}H_{26}O_6As_2$	27.95	27.89
11	Polymer of 3-arsono-4-methoxystyrene	Light brown	295–320	65	$(C_9H_{11}O_4As)_x$	29.03	29.09
12	Polymer of 2,2'-dimethoxy-5,5'-divinylarsenobenzene	Brown powder	>300	60	$(C_{18}H_{18}O_2As_2)_x$	36.01	36.10
13	3-Arsono-4-methoxyacetophenone oxime	White orthorhombic	200	90	$C_9H_{12}O_5NAs$	25.91	26.06
14	2,2'-Dimethoxy-5,5'-(α,α'-diisonitroso)-diethylarsenobenzene	Yellow powder	135 subl.	50	$C_{18}H_{20}O_4N_2As_2$	31.29	31.27
15	3-Arsono-4-methoxy-α-phenylethylamine	White crystals	248 dec.	5	$C_9H_{14}O_4NAs$	27.24	27.17
16	N-Di-(3-arsono-4-methoxy-α-phenylethyl)-acetamide	White crystals	278 dec.	10	$C_{20}H_{27}O_8NAs_2$	26.80	26.73
17	N-Tri-(3-arsono-4-methoxy-α-phenylethyl)-amine	Tetra. needles	205	1	$C_{27}H_{36}O_{12}NAs_3$	28.41	28.34
18	N-3-Arsono-4-methoxy-α-phenylethyl-acetamide	White crystals	>300	64	$C_{11}H_{16}O_6NAs$	23.71	23.63

minutes, the acetylating solution was poured into water. On standing, the acetate precipitated. The crude product was recrystallized from water.

Polymer of 3-Arsono-4-methoxystyrene.—The sodium salt of the arsonobenzyl alcohol (5 g.) was dissolved in water and the solution made strongly acid. On evaporation to dryness, a gum was obtained. By continued solution in hot water and reprecipitation on cooling, a light brown, glassy solid was obtained. It was soluble in hot water and alkalies, insoluble in cold water and all organic solvents.

3-Arsono-4-methoxyacetophenone Oxime.—3-Arsono-4-methoxyacetophenone was dissolved in sodium hydroxide (80 ml. of N), hydroxylamine hydrochloride (12 g.) added and the solution warmed. On standing, the oxime precipitated and was recrystallized from water.

Arsenobenzenes.—2,2' - Dimethoxy - 5,5' - (α,α' - dihydroxy)-diethylarsenobenzene was prepared by adding the sodium salt of the arsonobenzyl alcohol to hot, 50% hypophosphorous acid with stirring. The precipitated product was filtered off, recrystallized from ethyl alcohol and dried.

The remainder of the arseno derivatives were prepared from the corresponding arsonic acids by solution in 25% hypophosphorous acid, heating for ten minutes and filtering. The precipitated arseno derivative was washed well, treated with alcohol and ether and dried. **2,2'-Dimethoxy-5,5'-(α,α'-diacetoxy)-diethylarsenobenzene** also was prepared from the unacetylated product described above by heating with acetic anhydride.

Reduction of Oxime.—3-Arsono-4-methoxyacetophenone oxime (20 g.) was dissolved in a slight excess of N sodium hydroxide (80 ml.). The solution was placed in a reduction container, heated to 80° and Raney catalyst added. The reduction was carried out under 45 pounds

(12) See Cislak and Hamilton, *This Journal*, **52**, 638 (1930).

(3 atm.) pressure of hydrogen. After the reduction was complete, the catalyst was removed and the solution concentrated, filtered and made strongly acid, precipitating 3-arsono-4-methoxyacetophenone. After removing the ketoarsonic acid the solution was taken to dryness and the solid taken up in 4 N hydrochloric acid. The undissolved residue (styrene polymer) was filtered off and the filtrate was made neutral to congo red paper, precipitating some solid material (a). After removing the solid material, the solution was made basic to congo red paper but not to litmus paper. After standing overnight, 3-arsono-4-methoxy-α-phenylethylamine was precipitated. It was purified by recrystallization from water. The other solid material (a) was crystallized fractionally from hot water. The less soluble portion proved to be unreacted oxime. The more soluble fraction was treated with acetic anhydride. On decomposing the excess anhydride, the acetylated secondary amine was precipitated. After filtering off the acetylated material, the filtrate was made nearly neutral and concentrated. On long standing, the tertiary amine was deposited in a crystalline form.

N - 3 - Arsono - 4 - methoxy - α - phenylethylacetamide.—One gram of the primary amine obtained above was heated with 10 ml. of acetic anhydride and poured into water precipitating the crude product. It was purified by recrystallization from water.

Summary

1. A number of new aromatic arsonic acids were prepared by standard synthetic methods, including arsenic derivatives of phenylmethylcarbinol and α-phenylethylamine.

2. The arseno derivatives of the above arsonic acids were obtained by hypophosphorous acid reduction of the parent compounds.

Two new arsine oxides were also formed.

3. Two styrene polymers were obtained which retained the properties of the arsono and arseno groups.

4. Several intermediates were prepared for the first time; other intermediates were obtained by new methods in good yields.

The Mechanism of the Autoxidation of ψ-Cumohydroquinone

BY G. KORNFELD AND A. WEISSBERGER

James, Snell and Weissberger[1] reported that the rate of absorption of oxygen by solutions of hydroquinone and its homologs is proportional to the square of the hydroxyl-ion concentration, and, with hydroquinone, methylhydroquinone, and the dimethylhydroquinones, to the concentration of these compounds. Accordingly, it was assumed that the reaction proceeds over the doubly charged hydroquinone ions. With tetramethyl hydroquinone (durohydroquinone), besides this dependency, a linear dependency on the concentration of the oxidation product, duroquinone, was observed,[2] and it was assumed that the doubly charged ion of durohydroquinone reacted with one molecule of duroquinone to form two singly charged ions of a semiquinone. The production of their semiquinone ions was further assumed to be the rate-controlling process of the quinone-catalyzed reaction, which was automatically followed by their oxidation to quinone, since the reaction rate of the auto-catalyzed reaction was found to be independent of the oxygen pressure. The same independence of the oxygen pressure as well as the linear dependence on the quinone concentration was found for the oxidation rate of trimethylhydroquinone (ψ-cumohydroquinone), but only as long as the ψ-cumoquinone concentrations were kept sufficiently low. With increasing concentration of ψ-cumoquinone, the reaction rate became increasingly independent of it, and, at the same time, the influence of the oxygen pressure on the reaction rate increased. Since the autoxidation rates of hydroquinone and its mono- and dimethyl homologs depend linearly on the oxygen pressure and were found to be independent of their quinone concentrations, the oxidation of ψ-cumohydroquinone represents a transition be-

tween the oxidation of the fully substituted durohydroquinone and the oxidation of hydroquinone and its mono- and dimethyl homologs. Therefore, it seems the more necessary to gain an insight into the mechanism which prevents the catalytic action of higher concentrations of ψ-cumoquinone, in the autoxidation of ψ-cumohydroquinone.

To compare quantitatively the results of theoretical considerations with the observed data, we went back to the original experiments. We wish to thank Dr. T. H. James of these Laboratories for permission to use them.

The reaction rate, $\Delta x/\Delta t$, was calculated from point to point for each experimental run. The decrease of ψ-cumohydroquinone was determined by the uptake of oxygen. At the same time it indicated the increase of ψ-cumoquinone from the start of the reaction. The initial rate was found to be very accurately proportional to the initial concentrations of ψ-cumohydroquinone. Accordingly, the reaction rate for each time interval was divided by the average ψ-cumohydroquinone concentration during this interval, and this expression (indicated by crosses in Fig. 1) was plotted against the average ψ-cumoquinone concentration. Curve I in Fig. 1 gives an example of the dependence of this reduced reaction rate on the ψ-cumoquinone concentration during the course of an experimental run. The concentrations are expressed in millimoles per liter, and the time is expressed in minutes. For this particular experiment, the initial concentration of ψ-cumohydroquinone was 5 millimoles per liter, and the pH 7.46. Other experiments (13 in number) in which the ψ-cumohydroquinone concentration, pH, and oxygen pressure varied, but in which, just as in the run represented in Fig. 1, no ψ-cumohydroquinone was added at the start, gave the same type of curve, except that most of them

(1) James, Snell and Weissberger, THIS JOURNAL, **60**, 2084 (1938).

(2) Ibid., **60**, 98 (1938).