

Summary

1. No direct or simple relationship appears to exist between the total number of isomeric hydrocarbons of the methane series and their carbon content.

2. By means of a separation of the isomeric hydrocarbons of each specified carbon content into types, arbitrarily chosen upon the basis of their structural formulas, a relationship may be established between the number of hydrocarbons and the alkyl groups of which the former may be considered to be composed. Mathematical formulas of the (finite) recursion type are advanced which permit of the calculation, from their carbon content, of the number of isomeric hydrocarbons in each of these structural types. In using these recursion formulas to calculate the total number of such hydrocarbons of any given carbon content, the total number of alkyl groups (*i. e.*, the total number of isomeric alcohols) of $N/2$ and all lesser carbon contents must be known.

3. The totals obtained by use of these mathematical formulas agree exactly through the tetradecanes with the numbers required by theory as tested by actually writing all the possible structural formulas.

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THE INFLUENCE OF THE ARSONO GROUP ON THE ACTIVITY OF NUCLEAR CHLORINE

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It has long been known that halogens in the benzene nucleus can neither be removed nor replaced by the ordinary reagents which act upon them in the aliphatic series. Nevertheless, the presence of certain groups such as nitro, cyano, carboxyl, etc., loosens the attachment and promotes substitution. Most of the experimental work in the study of replacement reactions has been done with halogeno-nitro compounds. However, as early as 1892, Heidenreich and Victor Meyer² showed that *o*-bromobenzoic acid and ammonia reacted at 200° to give diphenylamine. Later, Ullmann³ made a study of the condensation of *o*-chlorobenzoic acid with aniline and found that a catalyst was necessary, the salts of copper being most effective. The addition of potassium carbonate and the use of nitrobenzene as a solvent were also found to increase the yields.

Since the arsono group is similar in structure to the nitro, carboxyl, and sulfonic acid groups, and is meta directing, halogen in the ortho

¹ Parke, Davis and Company Fellow.

² Heidenreich and Meyer, *Ber.*, **25**, 2188 (1892).

³ Ullmann, *Ann.*, **355**, 312 (1907).

position, by analogy, should be reactive. In fact, Gibson and his co-workers⁴ have successfully applied the method of Ullmann to condensation reactions of *o*-bromophenylarsonic acid with various aromatic amines.

Thus it was suggested to make a study of the reactivity of the halogen of *o*-chlorophenylarsonic acid and to determine the value of its application to the synthesis of new arsenicals.

Condensations of the arsonic acid with primary aliphatic and aromatic amines and with ammonia were found to take place readily when they were heated in amyl alcohol with a copper catalyst and potassium carbonate. Secondary amines, benzamide and potassium phthalimide did not condense under like conditions while alcohols or alcoholates were found to replace the chlorine with the formation of the corresponding ethers.

Experimental⁵

General Procedure for the Preparation of Alkylamino-phenylarsonic Acids.—Ten grams of *o*-chlorophenylarsonic acid, 10 g. of anhydrous potassium carbonate, a trace of cuprous iodide, 6 cc. of the primary alkylamine and 25 cc. of amyl alcohol in a 50-cc. Erlenmeyer flask, fitted with a condenser with ground-glass connection, were heated in an oil-bath at 130–135° for fifteen hours, the reaction mixture being well stirred. The excess amine and amyl alcohol were removed by steam distillation, and the resulting solution was treated with decolorizing carbon. On acidification to Congo red paper with dilute hydrochloric acid, a grayish mass separated, which was crystallized from dilute acetic acid. Recrystallization from 75 cc. of hot 3 *N* hydrochloric acid gave a fine white precipitate which was identified as an alkoxyphenylarsonic acid (described later). After filtering, the alkylaminophenylarsonic acid was recovered by almost neutralizing the filtrate to Congo red paper with dilute sodium hydroxide. The portion insoluble in hydrochloric acid solution was treated again with 50 cc. of 3 *N* hydrochloric acid, and more amino compound recovered. The total yield of the alkylaminophenylarsonic acid obtained varied from 20–49% while the total yield of the ether varied from traces to as much as 7%. For analysis the amino compound was reprecipitated from a smaller amount of 3 *N* hydrochloric acid and crystallized from dilute acetic acid.

TABLE I
ALKYLAMINOPHENYLARSONIC ACID

-Aminophenylarsonic acids	Yield, %	M. p., °C. (corr.)	Analyses, %			
			Arsenic		Nitrogen	
			Calcd.	Found	Calcd.	Found
<i>o</i> - <i>n</i> -Propyl-	20	128	28.94	28.87	5.41	5.40
<i>o</i> - <i>n</i> -Butyl-	40	126	27.45	27.37	5.13	5.11
<i>o</i> - <i>n</i> -Amyl-	48	98	26.11	26.09	4.88	4.87
<i>o</i> -Isoamyl-	49	115	26.11	26.12	4.88	4.77
<i>o</i> - β -Hydroxyethyl-	45	141–143	28.71	28.67	5.37	5.35
Carboxy-methyl-	30	178d	27.25	27.30	5.09	5.05

⁴ Burton and Gibson, *J. Chem. Soc.*, 247 (1927); Gibson and Johnson, *ibid.*, 2499 (1927); 2204 (1928).

⁵ The potentiometric method of Cislak and Hamilton, *THIS JOURNAL*, 52, 638 (1930), was used for the quantitative determination of arsenic in the compounds prepared. The analyses are given in duplicate when the proof of the structures of the compounds hinged upon the arsenic analyses, and the amount of the purified sample permitted.

o-Arsonophenyl-*N*-butyl-nitrosamine.—To 5 g. of *o*-*n*-butylaminophenylarsonic acid in 100 cc. of 3 *N* hydrochloric acid, a solution of 8 g. of sodium nitrite in 25 cc. of water was slowly added, with stirring. The nitrosamine which formed was filtered, washed with water and dried. It was purified by treating with 40 cc. of hot ethyl acetate, cooling, and then crystallizing the residue from 400 cc. of hot water; yield 4.57 g. The cream-colored needle-like crystals melted with decomposition at 147° (corr.).

Anal. Calcd. for $C_{10}H_{15}O_4N_2As$: As, 24.73. Found: As, 24.82, 24.73.

Reaction with Ammonium Carbonate in Sealed Tubes.—Ten grams of *o*-chlorophenylarsonic acid, 10 g. of anhydrous potassium carbonate, 0.5 g. of copper acetate and 25 cc. of amyl alcohol were placed in a bomb tube and thoroughly mixed while heating in a steam-bath. After cooling, 10 g. of ammonium carbonate was mixed with the contents and the tube sealed. The tube was heated in a bomb oven for fifty hours at 135°. The mixtures from three tubes, prepared and treated as above, were combined and steam distilled, and the remaining solution decolorized and strongly acidified. The tarry substance (see below) which formed was removed, and the solution made just alkaline to Congo red paper (acid to litmus), and evaporated to dryness. The solid residue was extracted with portions of hot absolute alcohol which were combined, and the alcohol removed by evaporation. The oily substance which remained was dissolved in a small amount of water, decolorized and the water allowed to evaporate. At first an oil separated, followed by white crystals. By gently warming with a little water, the crystals dissolved, leaving most of the oily substance. By two such extractions a small amount of white needle-like crystals was obtained which melted at 151–152° (corr.). The melting point of *o*-arsanilic acid given by Jacobs, Heidelberger and Rolf⁶ is 153°. A solution of the crystals when diazotized gave an orange dye with R-salt.

Anal. Calcd. for $C_6H_5O_3NAs$ (*o*-arsanilic acid): As, 34.54. Found: As, 34.34.

The tarry substance (see above), which was insoluble in the acid solution, was treated with boiling 6 *N* hydrochloric acid. It formed a clear solution from which a small quantity of a non-identified substance slowly separated (from hot solution) as white needles. The substance did not melt below 240°, was soluble in dilute sodium hydroxide, but insoluble in hot 6 *N* hydrochloric acid. A qualitative test showed the presence of nitrogen and the absence of chlorine. The arsenic content was found to be 27.64%. The filtrate from the acid treatment above was allowed to cool. Long white needles separated which were recrystallized from hot 6 *N* hydrochloric acid, dissolved in alkali, decolorized and reprecipitated with acid. When air dried, the substance melted at 132–136° with foaming. However, when dried *in vacuo* over sulfuric acid, or in the oven at 100°, the substance melted at 198–200° (corr.). A test for nitrogen was positive, while one for chlorine was negative. The arsenic analysis corresponded to that for diphenylamine-*o,o'*-diarsonic acid.

Anal. Calcd. for $C_{12}H_{15}O_6NAs_2$: As, 35.95. Found: As, 36.00, 36.02.

Reaction with Monomethylaniline.—A mixture of 10 g. of *o*-chlorophenylarsonic acid, 12 g. of anhydrous potassium carbonate, copper powder and 30 cc. of monomethylaniline (no solvent) was heated for fifteen hours at 140–150°, with stirring. After removing the methylaniline by steam distillation, the resulting solution was decolorized and acidified. The substance which separated was treated with hot acetone, cooled and filtered. The portion insoluble in acetone was further purified by dissolving in alkali, decolorizing, and reprecipitating with acid. The substance was dried in a desiccator over sulfuric acid and there was no further loss in weight on drying for ten hours in an oven at 100°. The yield was 1.65 g. A qualitative analysis showed the absence of ni-

⁶ Jacobs, Heidelberger and Rolf, *THIS JOURNAL*, 40, 1583 (1918).

trogen and chlorine. The arsenic analysis corresponded to diphenyl ether *o,o'*-diarsonic acid. The substance softened and darkened at 240°.

Anal. Calcd. for C₁₂H₁₂O₇As₂: As, 35.87. Found: As, 35.97, 35.97.

General Procedure for the Preparation of Alkoxyphenylarsonic Acids.—Ten grams of *o*-chlorophenylarsonic acid, 10 g. of anhydrous potassium carbonate, a little copper powder, and 35 cc. of an alcohol containing 1.6 g. of potassium (or an equivalent amount of sodium) were heated at 130–135° for fifteen hours with stirring. After steam distillation and treatment with activated charcoal the alkoxyphenylarsonic acid was precipitated by acidifying with concd. hydrochloric acid. The yield was 30–49%.⁷

TABLE II
ALKOXYPHENYLARSONIC ACIDS

-Phenylarsonic acid	Yield, %	M. p., °C. (corr.)	Arsenic analyses, %	
			Calcd.	Found
<i>o-n</i> -Butoxy-	30	200	27.55	27.56
<i>o</i> -Isoamoxy-	43	201	26.02	26.00
<i>o</i> -Phenoxy-	49	174	25.49	25.40

Discussion

In beginning a study of the reactions of *o*-chlorophenylarsonic acid, a series of about sixty condensation reactions with aniline was carried out under different experimental conditions. Specific examples have been chosen from this series to show the various effects. In general, 5 g. of the arsonic acid, 5 g. of anhydrous potassium carbonate, a trace of copper powder, and 20 cc. of aniline (no solvent) were heated in the apparatus described in the Experimental Part for fifteen hours, at 135°. In the tables only the conditions or amounts which differ from the general procedure are given. The yields indicated are based upon the amounts obtained after steam distillation, acidification, and a single crystallization from acetone and water.

Only two catalysts, copper and cuprous iodide, were tried in this series of reactions. Cuprous iodide gave a better yield but the product obtained when using copper was found to be purer. No yield was obtained in the absence of a catalyst. Freshly prepared cuprous iodide was more efficient than that which had been kept for some time.

TABLE III
THE EFFECT OF CHANGES IN TEMPERATURE

Temp., °C.....	115	135	160	185
Time, hrs.....	10	10	10	10
Yield, %.....	Trace	56	7	Trace

⁷ In the case of *o*-phenoxyphenylarsonic, acidification with concd. hydrochloric acid gave an oil. The water layer was removed and the oily substance treated with ether. A white crystalline precipitate formed which was dissolved in the calcd. amount of dilute sodium hydroxide, decolorized with charcoal and reprecipitated by the slow addition of hydrochloric acid. The product was further purified by recrystallization from an acetone–water solution.

As indicated in Table III, the best yields were obtained at a temperature of about 135°.

TABLE IV
THE EFFECT OF CHANGES IN REACTION TIME

Time, hrs.....	3	5	10	20
Yield, %.....	52	58	56	52

From the data in Table IV, apparently the reaction was finished in from three to five hours.

TABLE V
THE EFFECT OF SOLVENTS (Cu₂I₂ WAS USED AS THE CATALYST)

Aniline, cc.	Solvent	Yield, %
15	None	61
25	None	61
15	Amyl alcohol (4 cc.)	69
15	Amyl alcohol (8 cc.)	65
5	Amyl alcohol (25 cc.)	68
15	Nitrobenzene (8 cc.)	56
15	Nitrobenzene (25 cc.)	Small
15	Amyl alcohol (25 cc.) and water (1 cc.)	60
15	Amyl alcohol (25 cc.) and water (5 cc.)	48
15	Water (5 cc.)	48

Slightly better yields were obtained using amyl alcohol as the solvent. The action of nitrobenzene was unfavorable. Small amounts of water, which hinder the ordinary Ullmann reaction, did not greatly affect the yield.

Condensations did not take place when sodium carbonate or sodium acetate was substituted for the potassium carbonate. In no case was a triphenylamine-diarsonic acid isolated. Theoretically such a compound could be formed by the reaction of two molecules of *o*-chlorophenylarsonic acid with one molecule of aniline.

Incidentally, it was found that *o*-chlorophenylarsonic acid, when heated to boiling with water containing a slight excess of aniline, formed a crystalline aniline salt. Aniline was liberated again on treating with alkali.

A series of condensations was also carried out with primary aliphatic amines. The amines (iso- and *n*-amyl, *n*-butyl, and *n*-propyl) readily condensed with *o*-chlorophenylarsonic acid under the conditions found favorable in the experiments with aniline. The products, after the usual recrystallizations, etc., were found to be mixtures. This was indicated by slight changes in the melting points on recrystallization and also by the fact that nitrogen determinations were consistently low. By crystallizing from hot 3 *N* hydrochloric acid, a white crystalline substance separated on cooling which did not contain nitrogen and which corresponded in properties to a compound (*o*-amoxyphenylarsonic acid) obtained by treating *o*-chlorophenylarsonic acid with potassium amylylate, under the usual experimental conditions. Smaller yields were obtained with butyl- and propylamines, probably due to their lower boiling points and to the greater solubilities of their condensation products. A sealed tube reaction with ethylamine was

carried out and a small quantity of a substance obtained which melted at 126–127°. The melting point given in the literature⁸ for *o*-ethylaminophenylarsonic acid is 128–129°.

Ethanolamine (b. p. 168°, uncorr.) in the absence of a solvent condensed very readily with *o*-chlorophenylarsonic acid to form *o*- β -hydroxyethyl-aminophenylarsonic acid. This product has previously been prepared by Rodewald and Adams⁹ by treating *o*-arsanilic acid with β -chloroethyl-chlorocarbonate and hydrolyzing the resulting product with alkali. The nitrosamine was prepared to prove an amino rather than an ether linkage.

Glycine condensed, in the presence of amyl alcohol, to give fair yields of phenylglycine-*o*-arsonic acid. To avoid steam distilling, the amyl alcohol was removed by extractions with ether.

It was desired to include in this study the reaction of *o*-chlorophenylarsonic acid with ammonia. This reaction was carried out in sealed tubes using ammonium carbonate as the source of ammonia. Copper acetate was used as the catalyst, since due to its solubility it was easily dispersed throughout the reaction mixture. Theoretically one, two, or three hydrogen atoms of ammonia could be replaced by phenylarsonic acid radicals to give (1) *o*-arsanilic acid, (2) a diphenylamine-diarsonic acid, and (3) a triphenylamine-triarsonic acid. From the reaction mixture, *o*-arsanilic acid was identified by means of its melting point, its reaction with R-salt, and by its arsenic analysis. A small amount of a second substance containing nitrogen was obtained which was soluble in hot 6 *N* hydrochloric acid, but crystallized on cooling. Its arsenic analysis corresponded to that calculated for a diphenylamine-diarsonic acid. A third product was isolated which contained nitrogen and arsenic (27.64%) which was insoluble in hot 6 *N* hydrochloric acid, and did not melt below 240°. The nature of this substance was not determined.

All attempts to condense with secondary aliphatic amines (di-isoamyl-, di-*n*-butyl-, and diethylamines) were unsuccessful. The reactions were carried out at various temperatures in the absence of a solvent, but no reaction product was obtained. When amyl alcohol was used as a solvent, amoxyphenylarsonic acid was formed in yields as high as 20%.

Although Gibson and Johnson¹⁰ have found it possible to condense *o*-bromophenylarsonic acid with monomethylaniline, the reaction under similar conditions with *o*-chlorophenylarsonic acid gave no product containing nitrogen. When heated under the usual conditions to 140–150° with monomethylaniline (no solvent), a product was obtained which was insoluble in acetone or dilute hydrochloric acid but was readily soluble in alkali. The arsenic content was found to correspond to that calculated for a diphenyl ether diarsonic acid. Theoretically this could be formed if part of the *o*-chlorophenylarsonic acid were hydrolyzed to form *o*-hydroxyphenylarsonic acid, which in turn reacted with some of the remaining *o*-chlorophenylarsonic acid. The latter reaction would be probable since phenol was found to react readily to form diphenyl ether *o*-arsonic acid. While no evidence has been obtained of the formation of *o*-hydroxyphenylarsonic acid in any of the reactions studied thus far, still it is possible that certain reagents may bring about the hydrolysis of *o*-chlorophenylarsonic acid. In fact, Tuttle¹¹ found that *o*-chlorobenzoic acid when heated with piperidine yielded salicylic acid, but none was obtained when heated with a potassium hydroxide solution. Since the usual methods of splitting ethers are not applicable to diphenyl ethers, and since no suitable derivative

⁸ Burton and Gibson, *J. Chem. Soc.*, 2387 (1927).

⁹ Rodewald and Adams, *THIS JOURNAL*, **45**, 3102 (1923).

¹⁰ Gibson and Johnson, *J. Chem. Soc.*, 2499 (1927).

¹¹ Tuttle, *THIS JOURNAL*, **45**, 1906 (1923).

with known constants could be found, no final proof of the structure of this compound was made.

In the course of this work a few other reactions were attempted which were unsuccessful. The formation of ethers from alcohols or alcoholates, and the work of Hurltley,¹² who, in studying the replacement of halogen in *o*-bromobenzoic acid, condensed that acid with malonic ester, acetoacetic ester and benzoylacetone, suggested like condensations with *o*-chlorophenylarsonic acid. However, under similar conditions the corresponding reactions did not take place. Benzamide and potassium phthalimide also failed to react under conditions similar to the amino condensations or at higher temperature.

Summary

1. A study was made of the effects of changes in the reaction conditions, such as temperature, time, catalyst, solvent, etc., on the reaction of *o*-chlorophenylarsonic acid with aniline.

2. *o*-Chlorophenylarsonic acid was condensed with a series of aliphatic amines and amino compounds, namely, isoamyl-, *n*-butyl-, *n*-propyl-, and ethanolamines, and with glycine. The nitrosamine derivatives of *n*-butyl-, and β -hydroxyethylaminophenylarsonic acids were also prepared.

3. A sealed tube reaction with ammonium carbonate gave a reaction mixture from which *o*-arsanilic acid, and diphenylamine-*o,o'*-diarsonic acid were isolated.

4. Attempts to condense *o*-chlorophenylarsonic acid with monomethyl-aniline yielded a product which analyzed for diphenyl ether *o,o'*-diarsonic acid.

5. The alcoholates of isoamyl and *n*-butyl alcohols and also phenol were condensed with *o*-chlorophenylarsonic acid to give isoamoxy-, *n*-butoxyphenylarsonic acids, and diphenyl ether *o*-arsonic acid, respectively.

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¹² Hurltley, *J. Chem. Soc.*, 1870 (1929).