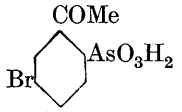
CCCXXVII.—*Benzaldehyde*-p-*arsonic Acid, Arsonic Acids of Acylphenylketones and their Derivatives. Chemotherapeutic Examination of these and other Arsonic Acids.*

By CHARLES STANLEY GIBSON and BARNETT LEVIN.

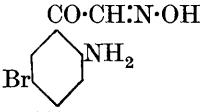
A DETAILED study has been made of substituted phenylarsonic acids in which one of the substituting groups is either an acyl (COMe, COEt) or the aldehyde group with a view to the chemotherapeutic examination of these parent substances and of their

derivatives which are readily accessible. The substances can be conveniently classified as *o*-, *m*-, and *p*-compounds according to the relative positions of the arsonic acid and the acyl or aldehyde groups in the molecule.

o-Compounds : *Acetophenone*-o-*arsonic acid*, its *semicarbazone* and *thiosemicarbazone* together with propiophenone-*o*-arsonic acid and its *semicarbazone* may be regarded as the simplest representatives. In preparing 5-*bromoacetophenone*-2-*arsonic acid* (I) by the Bart–Schmidt reaction from the hydrochloride of 5-*bromo*-2-*aminoacetophenone*, a by-product, $C_8H_7O_2N_2Br$, was obtained. This may be the *oximino*-compound (II) or the *nitroso*-compound (III), the latter being the more probable, since when once formed by the action of nitrous acid on 5-bromo-2-aminoacetophenone it escapes reaction with sodium arsenite. The constitution of 5-bromo-2-aminoacetophenone (and also of the acid I) was proved by converting it into



(I.)



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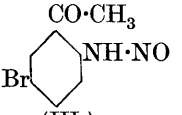


(III.)

2 : 5-dibromoacetophenone and oxidising this to 2 : 5-dibromobenzoic acid, which was identical with 2 : 5-dibromobenzoic acid prepared by bromination of anthranilic acid and subsequent replacement of the amino-group by bromine.

m-Compounds : Of the compounds belonging to this class, *acetophenone*- and *propiophenone*-m-*arsonic acids* and their *semicarbazones* are the simplest. In addition, 2-*hydroxyacetophenone*-5-*arsonic acid* and its *semicarbazone* and 4-*bromoacetophenone*-3-*arsonic acid* and its *semicarbazone* are also described. Although m-*amino*iso*valerophenone* was isolated from the mixture of reduction products of the nitration of *iso*valerophenone (compare Elson, Gibson, and Johnson, J., 1930, 1128), it was not converted into the corresponding arsonic acid, the quantity obtained being too small for the purpose. The investigation could therefore not be extended to compounds containing 5 carbon atoms in what from the point of view of this investigation may be regarded as the principal side chain (see below). The *di*-p-*toluenesulphonyl* derivative is a convenient compound for the identification of *m*-amino*iso*valerophenone. We have not succeeded in preparing benzaldehyde-*m*-arsonic acid by the Bart–Schmidt reaction (compare Balaban, this vol., p. 855), although Scott and Hamilton (*J. Amer. Chem. Soc.*, 1930, **52**, 4122) have described the *p*-nitrophenylhydrazone of this acid.

p-Compounds : For reasons which will appear later, more attention has been devoted to compounds having the principal side

chain and arsonic acid group in the para-position to each other. Acetophenone-*p*-arsonic acid (Lewis and Cheetham, *J. Amer. Chem. Soc.*, 1923, **45**, 510; Ogden and Adams, *ibid.*, 1925, **47**, 827) and benzophenone-*p*-arsonic acid may be regarded as representatives of a series of compounds which have been described (Albert, D.R.-P. 468402, 1924; U.S.Pats. 1425929, 1425930, 1425931; Deutsche Gold- und Silber-Scheideanstalt u. Albert, E.P. 249584, 249588, 1924; Margulies, F.P. 562460, 1924, E.P. 199091—3, 1922, 220668, 1923; compare Albert, *Klin. Woch.*, 1924, **3**, 2184) as yielding derivatives possessing marked activity against trypanosomes. From acetophenone-*p*-arsonic acid its *oxime*, *semicarbazone*, *thiosemicarbazone*, *ketazine*, *semioxamazone*, *phenylhydrazone*, and p-*bromophenylhydrazone* have been prepared and, incidentally, its reduction product *acetophenone*-p-*arsenious oxide*. 2-*Hydroxyacetophenone*-4-*arsonic acid* (IV) was prepared by the following series of reactions:

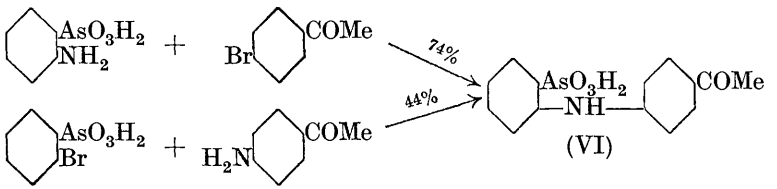
m-nitrophenol ⟶ *m*-nitroanisole ⟶ *m*-anisidine ⟶ acet-*m*-anisidide ⟶ 4-*amino*-2-*hydroxyacetophenone* ⟶ (IV)

and 3-*nitroacetophenone*-4-*arsonic acid* as well as 3-*aminoacetophenone*-4-*arsonic acid* (V) by the following reactions:

p-acetamidoacetophenone ⟶ 3-*nitro*-4-*acetamidoacetophenone* ⟶ 3-*nitro*-4-*aminoacetophenone* ⟶ 3-nitroacetophenone-4-arsonic acid ⟶ (V).

3-Bromo-4-acetamidoacetophenone (Raiford and Davis, *J. Amer. Chem. Soc.*, 1928, **50**, 158) after hydrolysis with hydrochloric acid was converted into the hydrochloride of the base and from this, by the Bart–Schmidt reaction, 3-*bromoacetophenone*-4-*arsonic acid* was obtained and converted into its *semicarbazone*.

Although not strictly belonging to this series, 4-*acetyldiphenylamine*-6′-*arsonic acid* (VI) was prepared in two ways as indicated (compare Gibson and Johnson, J., 1927, 2499):



Propiophenone-p-*arsonic acid* and its *semicarbazone* were examined as the next homologues to the corresponding acetophenone compounds. On attempting to extend the series to the *n*-valero-compounds, it was found that p-*bromo*-n-*valerophenone* (from *n*-valeryl chloride, bromobenzene, and aluminium chloride) gave on condensation with sodium arsenite a small quantity of a substance, m. p.

203°, containing arsenic which was inadequate even for complete identification; the condensation of 4-*bromo*-3-*nitro*-n-*valerophenone* with sodium arsenite also did not succeed.

It is somewhat remarkable that of the acids now described, only acetophenone-*p*-arsonic acid can be prepared by the alternative method to the Bart–Schmidt reaction, in this case by the condensation of sodium arsenite with *p*-bromoacetophenone under the specified conditions (Deutsche Gold- und Silber-Scheideanstalt, Austr. P., 1002111, 1922).

In addition to the failures just recorded, 4-bromo-3-nitroacetophenone, 4-*bromo*-3-*aminoacetophenone*, and 2-bromo-5-nitroacetophenone all failed to react with sodium arsenite. The non-reactivity of the bromine atom having an adjacent nitro-group is unexpected (compare Borsche, Stackmann, and Makaroff-Semljanski, *Ber.*, 1916, **49**, 2222; Turner and co-workers, J., 1927, 1113; 1928, 332, 334). Actually in one experiment, when 4-bromo-3-nitroacetophenone was heated with sodium arsenite in aqueous alcohol, a certain amount of a product separated from the resulting solution in large colourless crystals, readily soluble in water. This material, after purification, appeared to be the expected sodium salt of 3-nitroacetophenone-4-arsonic acid with 4 mols. of water of crystallisation. Several careful repetitions of the experiment failed to give the same result and the conditions of the reaction appear to be narrowly prescribed (compare Hamilton and Rudermann, *J. Amer. Chem. Soc.*, 1930, **52**, 3284, who failed to effect the condensation of *o*-chloro- and *o*-bromonitrobenzenes with sodium arsenite).

From *benzaldehyde*-p-*arsonic acid*, which is the lowest member of this series, the *oxime*, *semicarbazone*, *thiosemicarbazone*, *semioxamazone*, *phenylhydrazone*, and p-*bromophenylhydrazone* have been prepared.

Some of the compounds now described have been mentioned in the patent literature, but they do not appear to have been indexed as new substances.

Chemotherapy Results.

Apart from compounds mentioned above, the results of the therapeutic examination of phenarsazinic acid and certain of its derivatives, of certain diphenylaminearsonic acids as well as of simpler acids all of which have been previously prepared in this department are given below. Most of the compounds have been examined by Professor Warrington Yorke of the Liverpool School of Tropical Medicine and Hygiene on behalf of the Chemotherapy Committee of the Medical Research Council. In these cases, mice were used as the experimental animals which were infected intraperitoneally with *T. equiperdum*. The compounds marked * were

examined by Miss F. M. Durham and those marked § by Miss Winifred Strangeways at the National Institute for Medical Research on behalf of the above Committee. In these cases, the mice were infected intravenously with the same trypanosomes. We are very greatly indebted to these collaborators. In the tables, T = the maximum tolerated dose and C = the curative dose, both expressed in mg. per 20 g. mouse; the chemotherapeutic index (C/T) can be calculated in those cases where the curative dose has been determined.

o-Compounds.	*T*.	*C*, or report on therapeutic action.
Acetophenone-*o*-arsonic acid	0·6	0
" " " semicarbazone	0·75	0
" " " thiosemicarbazone	1·25	0
Propiophenone-*o*-arsonic acid semicarbazone	0·5	0
3-Acetyldiphenylamine-6′-arsonic acid	0·125	0
3-Propionyldiphenylamine-6′-arsonic acid	0·1	0
4-Acetyldiphenylamine-6′-arsonic acid	0·125	0
3-Methyldiphenylamine-6′-arsonic acid	0·125	Very slight curative action.
2 : 4-Dinitrodiphenylamine-6′-arsonic acid	0·25	0
5-Nitro-2-methyldiphenylamine-6′-arsonic acid	0·12	0
5- " -3- " " -6′- " "	0·2	0
2-Bromo-2′-nitro-4′-methyldiphenylamine-6′-arsonic acid	1·0	0
2-Bromo-2′-amino-4′-methyldiphenylamine-6′-arsonic acid	0·5	0
Phenarsazinic acid *	0·025	0
N-Acetylphenarsazinic acid *	0·5	Some curative action in maximum doses.
N-Propionylphenarsazinic acid *	0·25	0
N-Benzoylphenarsazinic acid *	0·1	0
2-Methylphenarsazinic acid	1—2	Slight and transient curative action in maximum doses.
1(or 3) : 6-Dimethylphenarsazinic acid	0·5	Very slight curative action.
2 : 2′-Bisphenarsazinic acid	20	0
m-Compounds.		
Acetophenone-*m*-arsonic acid	6	Very slight curative action.
" " semicarbazone	15	" "
Propiophenone-*m*-arsonic acid	1·0	0
" " semicarbazone	5	0
2-Hydroxyacetophenone-5-arsonic acid	1·0	0
" " " semicarbazone	25	0
m-Methoxyphenylarsonic acid	2·5—5·0	Very slight curative action in toxic doses.
p-Compounds.		
Benzaldehyde-*p*-arsonic acid	5—10	Definite curative action in maximum doses.
" " oxime	1·0	Slight curative action in maximum doses.
" " semicarbazone	50—100	Some curative action in maximum doses.
" " thiosemicarbazone	20—30	5—10 (observed during >30 days).
" " " §	20	10 (" " ").
" " *p*-bromophenylhydrazone	2·0	0
Acetophenone-*p*-arsonic acid	1·25	Definite curative action in maximum doses.
" " oxime	1·0	Slight curative action in maximum doses.
" " semicarbazone	25	6·25 (observed during >30 days).
" " " §	15	5 (" " ").
" " thiosemicarbazone	20	Definite curative action in maximum doses.
" " ketazine	10	Very slight curative action in maximum doses.
" " phenylhydrazone	0·5	0
" " *p*-bromophenylhydrazone	1·0	0
Propiophenone-*p*-arsonic acid	1·0	0
" " semicarbazone	0·1	0
N-Acetyldiphenylamine-4-arsonic acid *	0·025	0

The results illustrate generally what has been previously observed by other workers, that those compounds having the arsonic acid

group in the *p*-position to another group are less toxic than the isomeric *o*- and *m*-compounds and are more curative (compare, for example, Gough and King, J., 1930, 671). The *o*- and *m*-compounds are not curative even in toxic doses.

The most interesting compounds from a chemotherapy standpoint are benzaldehyde-*p*-arsonic acid and acetophenone-*p*-arsonic acid and their derivatives. The acids themselves are moderately toxic, but their derivatives (with the exception of the phenylhydrazones) are very much less toxic. The small curative action of the parent acids is greatly increased in their derivatives, which reach fairly high values in the cases of benzaldehyde-*p*-arsonic acid thiosemicarbazone and acetophenone-*p*-arsonic acid semicarbazone.

It appears to us somewhat surprising that the slight curative action of the parent acids is entirely suppressed in their phenylhydrazone derivatives. It may be concluded that the diphenylamine and phenarsazinic acids are of much less value chemotherapeutically than the arsonic acids of simpler structure.

EXPERIMENTAL.

Acetophenone-o-arsonic acid was prepared from *o*-aminoacetophenone by the Bart–Schmidt reaction in a similar manner to that used for the preparation of the corresponding *m*-compound. The crude acid (75% yield) was purified by acidification of a solution of the sodium salt with concentrated hydrochloric acid. It crystallised in long colourless needles, m. p. 285—286° (decomp.) (Found: As, 30·1. $C_8H_9O_4As$ requires As, 30·7%). The *semicarbazone* was prepared and purified in exactly the same way as the analogous compound of the *m*-acid. It was obtained in colourless plates, m. p. 234—235° (decomp.) (Found: As, 25·3. $C_9H_{12}O_4N_3As$ requires As, 24·9%). The *thiosemicarbazone* was obtained by adding thiosemicarbazide to acetophenone-*o*-arsonic acid (5·5 g.) dissolved in boiling water (90 c.c.) and filtering off the crystalline precipitate after 2 hours. It was purified by dissolving it in an aqueous solution of sodium bicarbonate (charcoal) and acidifying the filtered solution with concentrated hydrochloric acid (Congo-red). It crystallised in almost colourless radiating needles (3 g.; 42% yield), m. p. 181° (decomp.). The compound is very sparingly soluble in water and insoluble in alcohol and benzene (Found: As, 23·7. $C_9H_{12}O_3N_3SAs$ requires As, 23·7%).

Propiophenone-*o*-arsonic acid was obtained from *o*-aminopropiophenone by the Bart–Schmidt reaction in 75% yield. When aqueous solutions of the acid and of acetonesemicarbazone were mixed, the *semicarbazone* crystallised in acicular needles, m. p. 206—207° (decomp.) (Found: As, 23·4. $C_{10}H_{14}O_4N_3As$ requires As, 23·8%).

5-Bromo-2-acetamidoacetophenone (compare Baeyer and Bloem, *Ber.*, 1884, **17**, 963) was prepared from *o*-acetamidoacetophenone (26·5 g.; 0·15 mol.), dissolved in a mixture of acetic acid (265 c.c.) and water (265 c.c.), by dropping in slowly and with constant shaking a solution of bromine (7·7 c.c.; 0·15 mol.) in acetic acid (150 c.c.). Towards the end of the reaction the bromo-derivative began to separate and finally the mixture set to a crystalline paste. After standing, the precipitate was collected and recrystallised from alcohol, 20 g. being obtained; m. p. 160°. The acetyl derivative was hydrolysed by boiling for 10 minutes with 25% hydrochloric acid. The hydrochloride crystallised on cooling in long thin prisms, which after drying under reduced pressure over potassium hydroxide had m. p. 180—181°. *5-Bromo-2-aminoacetophenone* was obtained from it both by treating a suspension in water with sodium hydroxide and by dissolving it in alcohol and adding an equal volume of water. This base crystallised from aqueous alcohol in colourless rectangular plates, m. p. 86—88° (Found: N, 6·6; Br, 36·7. C_8H_8ONBr requires N, 6·5; Br, 37·4%).

The Bart–Schmidt reaction on the hydrochloride of 5-bromo-2-aminoacetophenone was carried out in a similar manner to that for the preparation of 3-bromoacetophenone-4-arsonic acid. The coupled solution, after being heated on the water-bath, was filtered from tarry by-product and acidified with concentrated hydrochloric acid. The brownish solid which separated was recrystallised from alcohol (charcoal) and obtained in needles, m. p. 278° (to a red liquid). This substance contained no arsenic and is either *5-bromo-2-nitrosoaminoacetophenone* (III) or *5-bromo-2-amino-oximinoacetophenone* (II) (Found: C, 39·0; H, 2·3; N, 11·7. $C_8H_7O_2N_2Br$ requires C, 39·5; H, 2·9; N, 11·7%). The filtrate from this substance was evaporated under reduced pressure in alkaline solution, and acidification with hydrochloric acid (Congo-red) precipitated *5-bromoacetophenone-2-arsonic acid* (8 g., crude). It is soluble in water but crystallises only very slowly from this solution. It is more conveniently purified by adding hydrochloric acid to its solution in aqueous sodium carbonate. It is thus obtained in colourless crystals which turn brown at 188° but do not decompose completely until 291—293° (Found: As, 23·4. $C_8H_8O_4BrAs$ requires As, 23·2%). The sodium salt may be obtained by allowing a hot solution of the acid in concentrated sodium hydroxide or carbonate solution to crystallise, or by the addition of alcohol to the aqueous solution of the acid exactly neutralised with sodium hydroxide; it then crystallises in fine needles.

A solution of the hydrochloride of 5-bromo-2-aminoacetophenone

(13·5 g.) in hydrobromic acid (18%, 46 c.c.) was cooled to — 5° and treated with sodium nitrite (4 g.) in water (7 c.c.). The diazo-solution was poured into a solution of cuprous bromide [prepared by the reduction of a solution of copper sulphate (10·2 g.) and potassium bromide (5·1 g.) in water (46 c.c.) with sulphur dioxide] in hydrobromic acid (*d* 1·49; 19 c.c.). The mixture, after being heated on the water-bath, was allowed to cool and the solidified oil filtered off after further addition of water. This 2 : 5-*dibromoacetophenone* on recrystallisation from alcohol (charcoal) was obtained in colourless needles, m. p. 41° (Found : Br, 58·2. $C_8H_6OBr_2$ requires Br, 57·6%). On boiling this ketone with a 3% aqueous solution of potassium permanganate for 2—3 hours and passing sulphur dioxide into the concentrated filtrate from the precipitated manganese dioxide, 2 : 5-dibromobenzoic acid was obtained in quantitative yield. It crystallised from boiling water in long thin needles, m. p. 156°. It was identical with the compound obtained by brominating anthranilic acid and subjecting the resulting 5-bromoanthranilic acid hydrobromide to the Sandmeyer reaction.

For obtaining *acetophenone*-m-*arsonic acid* the following was found to be the most satisfactory method. *m*-Aminoacetophenone (10 g.), dissolved in concentrated hydrochloric acid (15 c.c.) and water (70 c.c.), was diazotised in the usual way in a 2-litre beaker with a solution of sodium nitrite (5·33 g.) in water (9 c.c.) below 0°. To the cold, mechanically stirred diazo-solution was added a concentrated aqueous solution of sodium arsenite (15 g.); considerable frothing then took place. After further stirring, the solution was made alkaline with sodium hydroxide solution (10%, 100 c.c.), care being taken to control the excessive frothing. The resulting red solution was heated on the water-bath for 15 minutes and then acidified with concentrated hydrochloric acid (Congo-red), boiled with charcoal, and filtered hot from tarry by-product. After being made alkaline, the filtrate was evaporated under reduced pressure on the water-bath to about 50 c.c.; sodium chloride then began to separate. The solution was again boiled with charcoal and filtered, and the filtrate acidified with hydrochloric acid (Congo-red). The precipitated oil rapidly solidified and a further quantity of the acid crystallised on cooling (yield, 8 g.; 45% crude). The crude product was extracted several times with alcohol and on evaporation of the filtered alcoholic solution the arsonic acid remained as an oil which rapidly crystallised. It was dissolved in the calculated quantity of standard sodium hydroxide solution, the solution treated with charcoal, and the filtrate acidified. Acetophenone-*m*-arsonic acid crystallised in long colourless needles, m. p. 156° (yield, 4·6 g.; 25%)

(Found: As, 30·5. $C_8H_9O_4As$ requires As, 30·7%). It was moderately easily soluble in hot water and in alcohol and sparingly soluble in cold water.

Acetophenone-m-*arsonic acid semicarbazone*, prepared by adding acetonesemicarbazone (2·25 g.) to a hot solution of the acid (4·5 g.) in water (67 c.c.), was obtained in a yield of 3·8 g. It was further purified by dissolving it in the calculated quantity of standard sodium carbonate solution (charcoal) and acidifying the filtrate with hydrochloric acid. It was thus obtained in colourless plates, undecomposed at 305° (Found: As, 25·3. $C_9H_{12}O_4N_3As$ requires As, 24·9%).

Propiophenone-m-*arsonic acid* was obtained from *m*-aminopropiophenone by the Bart–Schmidt reaction in 46% yield. It crystallised from water in colourless needles, m. p. 212° (decomp.) (Found: As, 29·4. $C_9H_{11}O_4As$ requires As, 29·1%). The corresponding *semicarbazone* was obtained in the usual way in 75% yield in large, pale yellow crystals. It was purified by solution in half the calculated quantity of sodium carbonate solution and reprecipitation with hydrochloric acid (Found: N, 12·8. $C_{10}H_{14}O_4N_3As$ requires N, 13·3%).

5-Acetamido-2-hydroxyacetophenone was prepared from phenacetin as described by Kunckell (*Ber.*, 1901, **34**, 124), acetyl chloride being used instead of acetyl bromide. The yield was poor, 24 g. from 80 g. of phenacetin. The acetyl derivative was hydrolysed by boiling with 15% hydrochloric acid for 2 hours and basifying the solution with aqueous ammonia.

2-*Hydroxyacetophenone*-5-*arsonic Acid.*—5-Amino-2-hydroxyacetophenone (15 g.), dissolved in concentrated hydrochloric acid (21 c.c.) and water (120 c.c.), was treated below 0° with a concentrated aqueous solution of sodium nitrite (7·25 g.). An aqueous solution of sodium arsenite (20·4 g.) was added with stirring, followed by a 10% aqueous solution of sodium hydroxide (140 c.c.). The resulting mixture was heated for 1 hour on the water-bath, acidified with concentrated hydrochloric acid whilst still hot, and filtered (charcoal), and the yellow filtrate was made alkaline with sodium hydroxide solution, evaporated under reduced pressure to small bulk, and acidified with hydrochloric acid (Congo-red). After 24 hours, the brown precipitate was collected and recrystallised twice from water (charcoal). The *arsonic acid* was obtained in colourless prismatic needles, m. p. 189—192° (decomp.). It is moderately easily soluble in water and its aqueous solution gives a reddish-purple coloration with ferric chloride (Found: As, 29·0. $C_8H_9O_5As$ requires As, 28·8%). Its *semicarbazone*, prepared in the usual way from acetonesemicarbazone, was purified by reprecipitation by hydrochloric acid from its solution

in sodium carbonate solution. After addition of hydrochloric acid, the solution was boiled (charcoal) and from the filtrate the compound was deposited in almost colourless needles, slowly decomposing from about 245° (Found : As, 22·9. $C_9H_{12}O_5N_3As$ requires As, 23·7%).

4-Bromo-3-nitroacetophenone (compare Borsche and co-workers, *loc. cit.*) was prepared by adding *p*-bromoacetophenone (45 g.) in small quantities to mechanically stirred nitric acid (*d* 1·5; 300 g.) cooled in a freezing mixture. The mixture was poured on ice after some 15 minutes, and the precipitate collected, washed thoroughly with water, and recrystallised from methyl alcohol. It had m. p. 120° (the melting point given by the above workers is 116·5°) and was obtained in 70% yield. It did not condense with sodium arsenite when heated in aqueous methyl alcohol in a sealed tube, and attempts to effect its reduction with iron and acetic acid and with tin and concentrated hydrochloric acid gave unsatisfactory results. In order to convert it into 4-bromo-3-aminoacetophenone, the acetyl derivative of this substance was first obtained by the method of Stephen and Keewit (this vol., p. 82). Stannous chloride crystals (7 g.) and acetic anhydride (9·2 g.) were mixed in a Claisen flask fitted with an air condenser and, after a few minutes, the above nitro-ketone (2·4 g.) was added. After the initial vigorous reaction was over, the mixture was heated on the water-bath for 45 minutes and then the acetic acid removed from the dark clear solution under reduced pressure. The thick oily residue was taken up in water, filtered, and the filtrate made alkaline with an excess of sodium hydroxide. The liquid was thoroughly extracted with ether, the ethereal solution on evaporation giving an oil which readily solidified on mixing with water. The 4-*bromo*-3-*acetamidoacetophenone* was twice crystallised from aqueous alcohol and obtained in pale yellow, hexagonal plates, m. p. 118° (yield, 1 g.) (Found : N, 5·6. $C_{10}H_{10}O_2NBr$ requires N, 5·5%). This acetyl derivative was boiled for 10 minutes with 15% hydrochloric acid; the hydrochloride then crystallised from the solution. Recrystallised from alcohol, it was obtained in needles which began to darken at 198° and melted with decomposition at 206°. The free base, 4-*bromo*-3-*aminoacetophenone*, was obtained from the hydrochloride by boiling for a few minutes with 10% sodium hydroxide solution. It separated as an oil which rapidly solidified. When recrystallised from alcohol, it was obtained in almost colourless plates, m. p. 117° (Found : N, 6·7. C_8H_8ONBr requires N, 6·5%).

4-*Bromoacetophenone*-3-*arsonic Acid*.—A suspension of the hydrochloride made by boiling 4-bromo-3-acetamidoacetophenone (9 g.) with hydrochloric acid (18%; 25 c.c.) for 5 minutes, diluting the resulting hot solution with water (40 c.c.), and rapidly cooling it to

below 0°, was diazotised by treatment with sodium nitrite (2·4 g.) in water (5 c.c.) and then treated with a concentrated aqueous solution of sodium arsenite (6·5 g.). The resulting solution was made alkaline with 10% aqueous sodium hydroxide and worked up as in previous similar experiments. The crude *4-bromoacetophenone-3-arsonic acid* precipitated on acidification was recrystallised from water and obtained in colourless plates or needles, m. p. 198° (decomp.) (Found: As, 23·2. $C_8H_8O_4BrAs$ requires As, 23·2%). The *semicarbazone*, readily prepared in the usual manner by means of acetonesemicarbazone, crystallised from the mixture of the pure reactants in colourless large plates, which were washed with water and alcohol. It was almost insoluble in water, alcohol and acetic acid and remained unmelted at 300° (Found: N, 11·15. $C_9H_{11}O_4N_3BrAs$ requires N, 11·05%).

m-*Amino*isovalerophenone.—*iso*Valerophenone (48·5 c.c.)—prepared from *iso*valeryl chloride, benzene, and aluminium chloride under analogous conditions to those used for the preparation of *p*-bromoacetophenone—was run slowly and with stirring into nitric acid (*d* 1·5) below 0°. The resulting mixture, after standing in the freezing mixture for some 30 minutes, was poured on ice (400 g.) and after extraction with ether the ethereal solution was washed with sodium carbonate solution and finally with water and dried with calcium chloride. The ether was evaporated and the residue fractionally distilled under reduced pressure. A yellow oil was obtained which distilled for the greater part at 178—181°/19 mm. This oil was evidently a mixture, as it gave an oily product on oxidation with potassium permanganate. The mixture (42 g) and tin (45 g.) were treated gradually with concentrated hydrochloric acid, and this mixture, after being heated on the water-bath for an hour, was made strongly alkaline with sodium hydroxide and steam-distilled. The steam distillate was extracted with ether, and the ethereal solution dried with sodium sulphate and evaporated, an oil (10 g.) being finally obtained, b. p. 154—157°/17·5 mm. From previous work (Elson, Gibson, and Johnson, *loc. cit.*) it seemed likely that this product volatile in steam might be reasonably pure *o*-amino-*iso*valerophenone (Found: N, 8·3. $C_{11}H_{15}ON$ requires N, 7·9%), but on conversion into the bromo*iso*valerophenone—a pale yellow liquid, b. p. 141—143°/17 mm.—and oxidation of the latter with potassium permanganate the bromobenzoic acid obtained had, after several crystallisations from water, m.p. 132—140° and was a mixture of *o*- and *m*-bromobenzoic acids. The residue from the steam distillation was extracted with ether, and this solution finally yielded an oil, b. p. 179—181°/14 mm. (Found: N, 8·0. $C_{11}H_{15}ON$ requires N, 7·9%). This was converted by the Sandmeyer reaction into the

corresponding *bromo*-compound, which was obtained as a pale yellow liquid, b. p. 153—155°/19 mm., in 50% yield (Found : Br, 32·6. $C_{11}H_{13}OBr$ requires Br, 33·2%). The latter on oxidation with potassium permanganate solution gave a quantitative yield of *m*-bromobenzoic acid, m. p. 154°, identical with an authentic specimen.

Di-p-*toluenesulphonyl*-m-*amino*i*sovalerophenone* was obtained from *m*-amino*iso*valerophenone (1·8 g.), *p*-toluenesulphonyl chloride (2·0 g.), and sodium hydroxide (*N*, 12 c.c.) under the usual conditions. The resulting oil solidified on mixing with methyl alcohol and after recrystallisation from ethyl alcohol was obtained in colourless needles (Found : C, 62·3; H, 5·6. $C_{25}H_{27}O_5N_2S$ requires C, 61·9; H, 5·6%). A small amount of the same substance was obtained from the impure *o*-amino*iso*valerophenone.

Acetophenone-*p*-arsonic acid was prepared by two methods. (a) *p*-Aminoacetophenone (20 g.)—prepared from acetanilide, acetyl chloride, carbon disulphide, and aluminium chloride—was diazotised in hydrochloric acid solution below 0°. Treatment of the diazo-solution with a concentrated solution of sodium arsenite caused excessive frothing. The resulting solution was made alkaline with 10% aqueous sodium hydroxide (200 c.c.), and the arsonic acid separated as in analogous cases. The crude acid amounted to 24 g. (66% yield) and was purified by recrystallisation from water (charcoal) and obtained in colourless needles, m. p. 175° (Found : As, 31·1. Calc. : As, 30·7%). ω-Chloro- and ω-bromo-acetophenone-*p*-arsonic acids could not be prepared by the Bart–Schmidt reaction on the corresponding amino-compounds.

(b) *p*-Bromoacetophenone was first prepared by adding redistilled acetyl chloride (100 g.) to bromobenzene (420 g.) and anhydrous aluminium chloride in a 3-litre flask fitted with a reflux condenser. After the initial vigorous reaction had abated, the mixture was heated on the water-bath for 2 hours and then, after cooling, poured on ice. The lower layer was separated and the aqueous layer extracted with ether, the ethereal solution being added to the bromobenzene layer and this mixture dried with calcium chloride. After removal of the ether and bromobenzene at the ordinary pressure, the residue was fractionated under reduced pressure. The *p*-bromoacetophenone distilled at 124—128°/12 mm.* This compound

* A similar reaction was carried out with *p*-dibromobenzene (23·6 g.), acetyl chloride (8 g.), and anhydrous aluminium chloride (13·5 g.). The dark red liquid was decomposed with ice (150 g.) and a little hydrochloric acid, and the oily layer, after separation from the aqueous layer, was extracted with carbon tetrachloride. The solvent was evaporated and the uncrystallisable red oil was treated with semicarbazide hydrochloride (3·5 g.) in concentrated

(70 g.), dissolved in alcohol (1120 c.c.), was mixed with a solution of sodium arsenite (126 g.) in water (1120 c.c.) and heated in an autoclave at 160—170° for 16 hours. The clear yellow solution was evaporated on the water-bath until free from ethyl alcohol, and the remaining solution acidified with hydrochloric acid (Congo-red), approximately 5 g. of the acetophenone-*p*-arsonic acid being obtained. The filtrate was evaporated to dryness on the water-bath, the solid residue dissolved in sodium carbonate solution, filtered from arsenious oxide, and then reprecipitated with concentrated hydrochloric acid. The precipitate was thoroughly extracted with alcohol, and the alcoholic extract evaporated; the resulting oil, which solidified on mixing with water, gave after recrystallisation from water a total amount of 24 g. (28%) of the required acid. Nitration of acetophenone-*p*-arsonic acid under analogous conditions to those previously used for the nitration of acetophenone (Elson, Gibson, and Johnson, *loc. cit.*) gave a product, colourless needles decomposing at *ca.* 200°, containing no nitrogen, which appeared to be carboxyphenyl-*p*-arsonic acid (Found: As, 29·7. Calc.: As, 30·5%).

Acetophenone-p-*arsonic acid oxime* was prepared by dissolving the acid (2·5 g.) in *N*/5-sodium hydroxide (20 c.c.) and adding hydroxylamine hydrochloride (1·5 g.). After the clear solution had been warmed for some little time over a flame, the oxime crystallised on cooling; it was recrystallised from water. It decomposed at *ca.* 188° [compare Albert, Amer. P. 1647662, who gives m. p. 157° (decomp.)]; yield, 1 g. (Found: As, 28·5. $C_8H_{10}O_4NAs$ requires As, 28·9%).

The *semicarbazone* was obtained by adding acetonesemicarbazone to an aqueous solution of the acid and allowing the solution to stand for 24 hours. It was purified by dissolving it in the calculated quantity of aqueous sodium carbonate (charcoal), filtering the solution, and acidifying it with hydrochloric acid. The colourless microcrystalline powder froths without changing colour at about 210° and thereafter remains unchanged up to 300° (Found: As, 24·3. $C_9H_{12}O_4N_3As$ requires As, 24·9%). When alcohol is added to a solution of the semicarbazone in the calculated quantity of 2*N*-sodium carbonate, the sodium salt crystallises in flat colourless prisms.

Acetophenone-p-*arsonic acid thiosemicarbazone* was prepared by adding thiosemicarbazide (0·3 g.) to the pure acid (0·8 g.) dissolved

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sodium acetate solution (20 c.c.) and then with an equal volume of alcohol. The crystalline solid which separated was recrystallised from alcohol and obtained in thin prisms, m. p. 201°. It proved to be p-*bromoacetophenone-semicarbazone* (Found: N, 16·0. $C_9H_{10}ON_3Br$ requires N, 16·4%), identical with an authentic specimen prepared from *p*-bromoacetophenone.

in hot water (4 c.c.). The compound separated immediately and was further purified by dissolving it in the calculated quantity of 2*N*-sodium carbonate, filtering the solution, and precipitating the thiosemicarbazone with concentrated hydrochloric acid. It does not decompose below 290° (Found in material dried at 110°: As, 24·4. $C_9H_{12}O_3N_3SAs$ requires As, 23·7%).

Acetophenone-p-*arsonic acid ketazine*, $[AsO_3H_2{\cdot}C_6H_4{\cdot}CMe{:}N{\cdot}]_2$, was obtained in attempting to prepare the hydrazone. The acid (6 g.) in hot water (8 c.c.) was mixed with hydrazine hydrate (1 c.c.) and acetic acid (3 g.), and the mixture heated for a short time on the water-bath. The ketazine crystallised in small, pale yellow plates which remained undecomposed at 290° (Found: N, 6·2. $C_{16}H_{18}O_6N_2As_2$ requires N, 5·8%).

Acetophenone-p-*arsonic acid semioxamazone*,

$$AsO_3H_2{\cdot}C_6H_4{\cdot}CMe{:}N{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}NH_2,$$

was deposited almost immediately on addition of semioxamazide (1·03 g.) to a solution of the acid (2·44 g.) in water (10 c.c.). It was recrystallised from water, in which it was moderately easily soluble, and obtained in yellow needles which turned black at *ca.* 217° (Found: As, 22·6. $C_{10}H_{12}O_5N_3As$ requires As, 22·8%). The sodium salt crystallised from a solution of the semioxamazide in 2*N*-sodium carbonate. The *phenylhydrazone* was prepared by adding phenylhydrazine (0·7 g.) in acetic acid (4 c.c.) to a hot solution of acetophenone-*p*-arsonic acid (1·1 g.) in water (10 c.c.). The precipitated phenylhydrazone was dissolved in alcohol (50 c.c.), and water added until crystallisation commenced. It was obtained in pale yellow leaflets, m. p. 225° (decomp.) (Found: As, 22·4. $C_{14}H_{15}O_3N_2As$ requires As, 22·5%). The p-*bromophenylhydrazone* was prepared similarly from *p*-bromophenylhydrazine. It was recrystallised twice from 60% aqueous alcohol and obtained in yellow needles, m. p. 227° (decomp.) (Found: N, 6·9. $C_{14}H_{14}O_3N_2BrAs$ requires N, 6·8%).

Acetophenone-p-*arsenious oxide*, prepared by dissolving acetophenone-*p*-dichloroarsine (Elson and Gibson, this vol., p. 2387) in warm sodium hydroxide solution, was precipitated when carbon dioxide was passed through the solution. It was washed thoroughly with water and dried at 110°. It is a white powder which does not decompose below 300° (Found: As, 34·9. $C_8H_7O_2As$ requires As, 35·7%).

m-Nitrophenol (40 g.), dissolved in sodium hydroxide solution (15 g. in water, 90 c.c.), was treated fairly rapidly with methyl sulphate (30 g.), the mixture being kept cool in ice. The precipitate was collected after some hours; it was well washed with dilute sodium hydroxide solution and, after drying in air, was used for the

preparation of *m*-anisidine. The *m*-nitroanisole (35 g.) was mixed with tin (50 g.) and hydrochloric acid (equal vols. of conc. acid and water, 160 c.c.), and a trace of graphite added. The mixture was cautiously heated until the vigorous reaction had started and, when this had subsided, it was boiled for 2 hours. The resulting solution was basified with sodium hydroxide solution and extracted with ether, the ethereal solution dried with anhydrous sodium sulphate, and the ether evaporated. The residual crude *m*-anisidine was heated with acetic anhydride on the water-bath for 1 hour and the acet-*m*-anisidide, which solidified after treatment with water, was recrystallised from aqueous alcohol.

For the preparation of 4-*acetamido*-2-*hydroxyacetophenone*, acet-*m*-anisidide (74 g.) in dry carbon disulphide (160 c.c.) was treated with acetyl chloride (96·6 g.); a colourless crystalline mass was then deposited. To this mixture was added powdered aluminium chloride (210 g.) in seven equal portions, a vigorous reaction taking place. The mixture was heated for 1—2 hours on a hot plate, the carbon disulphide decanted as far as possible, the dark viscous layer treated cautiously with crushed ice and then with dilute hydrochloric acid, and the semi-solid material separated from the aqueous layer. The ketone was obtained solid by dissolving it in 10% aqueous alcohol and allowing the solution to crystallise. This crystalline material was then twice recrystallised from 30% aqueous alcohol (charcoal). It may also be purified by crystallisation from benzene, in which the liquid impurities are more soluble. The ketone crystallised from either alcohol or benzene in thin, pale yellow needles, m. p. 91°. The yield was variable, the best being 35% of the theoretical (Found: N, 7·2. $C_{10}H_{11}O_3N$ requires N, 7·2%).

4-*Amino*-2-*hydroxyacetophenone* was obtained by boiling the above acetyl derivative (17 g.) with 15% hydrochloric acid (25 c.c.) for 1 hour. The resulting dark red solution was basified with sodium carbonate, and the precipitated base recrystallised three times from 60% aqueous alcohol. It was obtained in colourless plates, m. p. 122—123° (to a red liquid), which turn brown on exposure to air (Found: N, 9·2. $C_8H_9O_2N$ requires N, 9·3%). Acet-*o*-anisidide, when submitted to the Friedel–Crafts reaction, gave an oil which could not be purified; when this was taken up in aqueous alcohol, crystalline material separated in insufficient amount for fuller investigation.

4-Amino-2-hydroxyacetophenone was converted into 2-*hydroxyacetophenone*-4-*arsonic acid* by the Bart–Schmidt reaction under analogous conditions for the preparation of 2-hydroxyacetophenone-5-arsonic acid. The crude acid, obtained in small yield, was recrystallised from water, in which it was readily soluble, and obtained in

prismatic needles, m. p. 156° (Found : As, 28·7. $C_8H_9O_5As$ requires As, 28·8%).

3-*Nitro*-4-*acetamidoacetophenone* was prepared by adding *p*-acetamidoacetophenone (20 g.) during ½ hour to well-stirred nitric acid (*d* 1·5; 100 c.c.) at 0°. After standing for some 15 minutes, the mixture was poured on ice (400 g.), and the precipitated nitro-compound recrystallised from alcohol and obtained in yellow needles (21 g.), m. p. 137° (Found : N, 13·2. $C_{10}H_{10}O_4N_2$ requires N, 12·6%). This compound was converted into 3-*nitro*-4-*amino-acetophenone* by boiling with concentrated hydrochloric acid for a few minutes, a red oil being formed which rapidly solidified. This was recrystallised from aqueous alcohol and obtained in long yellow needles, m. p. 148—149° (Found : N, 15·8. $C_8H_8O_3N_2$ requires N, 15·6%). A further quantity may be obtained by basifying the aqueous solution. On oxidation in the usual way with potassium permanganate (3% aqueous solution) 3-nitro-4-acetamidoaceto-phenone gave an almost quantitative yield of 3-nitro-4-acetamido-benzoic acid having, after recrystallisation from aqueous alcohol, m. p. 282—283°, identical with the acid obtained in the same way from 3-nitro-4-acetamidotoluene.

The insolubility of 3-nitro-4-aminoacetophenone necessitated a slight modification of the usual conditions for producing 3-*nitro-acetophenone*-4-*arsonic acid*. 3-Nitro-4-acetamidoacetophenone (10 g.) was boiled for 10 minutes with concentrated hydrochloric acid (30 c.c.) and this solution, separated from a small quantity of oily material, was added slowly after cooling to a mechanically stirred solution of sodium nitrite (3·6 g.) in water (50 c.c.) at − 5°. A concentrated aqueous solution of sodium arsenite (10 g.), followed by sufficient 10% aqueous sodium hydroxide, was added to render the mixture alkaline. After being stirred for some time, the mixture was heated on the water-bath until the vigorous evolution of nitrogen had subsided. The arsonic acid was obtained in the usual way after acidification with concentrated hydrochloric acid. This material was extracted thoroughly with absolute alcohol, the solvent evaporated, and the residue crystallised from water, in which it was sparingly soluble. It was obtained in rectangular plates, m. p. 228—230° (Found : As, 25·8. $C_8H_8O_6NAs$ requires As, 25·9%). For preparative purposes, it is sufficient to purify the crude acid by acidification of its solution in 2*N*-sodium carbonate. The attempted preparation of this acid by (a) the action of nitric acid (*d* 1·5) on a solution of acetophenone-*p*-arsonic acid in concentrated sulphuric acid, (b) slow addition of acetophenone-*p*-arsonic acid to concentrated nitric acid, and (c) the action of a mixture of nitric and acetic acids on a solution of the arsonic acid in a mixture of acetic

acid and acetic anhydride was unsuccessful. From the solution in (b) carboxyphenyl-4-arsonic acid was isolated in good yield.

3-Nitroacetophenone-4-arsonic acid (5 g.) in 25% sodium hydroxide solution (4 c.c.) and water (5 c.c.) was added to a hot suspension of ferrous hydroxide [ferrous sulphate crystals (42 g.), water (125 c.c.), 25% sodium hydroxide solution (40 c.c.)], the mixture shaken thoroughly for 10 minutes and filtered, and the precipitate washed. The filtrate was boiled with barium chloride solution, filtered from the barium sulphate, and concentrated under reduced pressure. After separation from sodium chloride, the solution was acidified, and the precipitated acid recrystallised from water, in which it was readily soluble when hot. *3-Aminoacetophenone-4-arsonic acid* was thus obtained in somewhat reddish prisms, unmelted at 290° (Found: As, 28·8. $C_8H_{10}O_4NAs$ requires As, 28·9%) [compare Austr. P. 102211, where the compound is described as having m. p. 230° (decomp.), which has not been confirmed; further, an attempt to prepare this acid by the method described in this patent, *viz.*, by heating 4-bromo-3-aminoacetophenone with sodium arsenite and copper powder, was unsuccessful, although a material which after recrystallisation from water remained unmelted at 290° was obtained, but the amount was inadequate for fuller investigation].

On boiling 3-bromo-4-acetamidoacetophenone (Raiford and Davis, *loc. cit.*) with 20% hydrochloric acid, the hydrochloride of the base was obtained. To a suspension of this hydrochloride (17·5 g.), obtained by rapidly cooling its solution in hot concentrated hydrochloric acid (25 c.c.) and water (62 c.c.) below 0°, was added a solution of sodium nitrite (4·75 g.) under the usual conditions. After the diazotisation, concentrated sodium arsenite (13 g.) solution was added, nitrogen being evolved, and finally the solution was made alkaline with 10% aqueous sodium hydroxide. This solution was worked up in the usual way and *3-bromoacetophenone-4-arsonic acid* obtained. This was recrystallised from water (charcoal) and obtained in colourless prisms having hexagonal ends, m. p. 190—191° (slight decomp.) (yield, 4 g.) (Found: As, 22·9; Br, 24·8. $C_8H_8O_4BrAs$ requires As, 23·2; Br, 24·75%). The *semicarbazone* was obtained in 80% yield from acetonesemicarbazone in the usual manner. It was almost insoluble in water and having been prepared from pure materials it was sufficient to purify it by the addition of hydrochloric acid to its filtered solution in the calculated quantity of 2*N*-sodium carbonate (Found in material dried at 110°: N, 10·7. $C_9H_{11}O_4N_3BrAs$ requires N, 11·1%). The semicarbazone was dissolved in hot concentrated sodium carbonate solution or sodium hydroxide solution; the sodium salt crystallised on cooling.

4-*Acetyldiphenylamine*-6′-*arsonic acid* was prepared in two ways. (a) *p*-Bromoacetophenone (25·6 g.), *o*-aminophenylarsonic acid (27·8 g.), potassium carbonate (22·4 g.), and amyl alcohol (128 c.c.) together with a trace of copper powder were boiled for 5 hours. The product was isolated as previously described (compare Gibson and Johnson, *loc. cit.*) and the crude acid amounted to 74% of the theoretical amount. It was first repeatedly recrystallised from dilute acetic acid (charcoal) and then from aqueous alcohol, and obtained in brownish crystals, m. p. 205—208° (Found : As, 21·8. $C_{14}H_{14}O_4NAs$ requires As, 22·4%).

(b) *p*-Aminoacetophenone (8·0 g.), *o*-bromophenylarsonic acid (16·67 g.), potassium carbonate (12·9 g.), amyl alcohol (52 c.c.) and a trace of copper powder were heated together and the resulting mixture was worked up in exactly the same manner as in the previous experiment, the crude acid being obtained in 44% yield. It was recrystallised from aqueous alcohol and obtained in brownish crystals, m. p. 205—208°, identical with the previous product.

Propiophenone-p-*arsonic acid*, prepared in the usual way from *p*-aminopropiophenone, was purified by solution in sodium hydroxide solution (charcoal) and reprecipitation from this filtered solution by means of hydrochloric acid ; it was then recrystallised from boiling water and obtained in colourless prismatic needles, remaining undecomposed at 295°. It is moderately easily soluble in hot water, but sparingly soluble in water and alcohol at the ordinary temperature (Found : As, 29·0. $C_9H_{11}O_4As$ requires As, 29·1%). The *semicarbazone* was prepared in the usual way from the acid (3 g.) in water (20 c.c.) and acetonesemicarbazone (1·5 g.), 2·75 g. being obtained (Found : As, 23·5. $C_{10}H_{14}O_4N_3As$ requires As, 23·8%).

An attempt to prepare *p*-acetamido-*n*-valerophenone from *n*-valeryl chloride, aluminium chloride, and acetanilide in carbon disulphide was unsuccessful. Substitution of *n*-valeryl bromide for the chloride led to no better result.

n-*Valeryl bromide*, which does not appear to have been previously described, was prepared by dropping phosphorus tribromide (25 g.) on *n*-valeric acid (28 g.). After the addition was complete the mixture was heated on the water-bath for 2 hours, the upper layer was separated from the lower viscous layer and distilled through a fractionating column. *n*-Valeryl bromide was obtained as a colourless fuming liquid, b. p. 64°/66 mm., in 50% yield (Found : Br, 48·9. C_5H_9OBr requires Br, 48·4%).

p-*Bromo*-n-*valerophenone*, prepared from *n*-valeryl chloride, bromobenzene, and aluminium chloride in the same manner as *p*-bromoacetophenone, distilled at 168—169°/20 mm. and solidified to a colourless mass (yield, 45%). On recrystallisation from aqueous

alcohol, it was obtained in colourless plates, m. p. 37—38° (Found : Br, 33·4. $C_{11}H_{13}OBr$ requires Br, 33·2%). When this ketone was heated with sodium arsenite in aqueous methyl alcohol in a sealed tube as in the preparation of acetophenone-*p*-arsonic acid, only a small amount of solid material containing arsenic and having m. p. 203° was obtained.

4-*Bromo*-3-*nitro*-n-*valerophenone* was prepared by adding a mixture of nitric acid (*d* 1·5; 6 c.c.) and concentrated sulphuric acid (20 c.c.) to a solution of *p*-bromo-*n*-valerophenone (29 g.) in sulphuric acid (200 g.), the temperature being maintained below — 5°. The mixture was kept at this temperature for 1 hour and then poured on ice, and the precipitated solid, after being freed as far as possible from acid, was recrystallised from benzene or aqueous alcohol. The yield of yellowish-brown needles, m. p. 196—197°, was poor (Found : N, 5·5. $C_{11}H_{12}O_3NBr$ requires N, 4·9%). This compound did not condense with sodium arsenite under the same conditions as those mentioned above.

A 22% yield of *benzaldehyde*-p-*arsonic acid* can be readily obtained if the following details are followed. *p*-Aminobenzaldehyde (20 g.) is treated with hydrochloric acid (34 c.c.) and water (40 c.c.) and allowed to stand for several hours to ensure as complete solution as possible. After the addition of further water (120 c.c.) the solution is diazotised below — 5° with sodium nitrite (12 g.) in water (20 c.c.). The diazotised solution is coupled with a concentrated solution of sodium arsenite (33·3 g.), and 10% sodium carbonate solution (120 c.c.) added. The crude acid obtained in the usual way is extracted with absolute alcohol, and the alcohol evaporated on the water-bath, the resulting oil rapidly solidifying on mixing with water. It is obtained in colourless needles on recrystallisation from 50% aqueous acetic acid or from water. It crystallises in colourless needles undecomposed at 280° (Found in material dried at 110° : As, 33·0. $C_7H_7O_4As$ requires As, 32·6%). Benzaldehyde-*m*-arsonic acid could not be prepared in an analogous manner.

Benzaldehyde-p-*arsonic acid oxime* was prepared from the arsonic acid in the same way as acetophenone-*p*-arsonic acid oxime. On recrystallisation from hot water, in which it was moderately easily soluble, it was obtained in colourless needles, m. p. 157° (decomp.) (Found : N, 6·0. $C_7H_8O_4NAs$ requires N, 5·7%). The corresponding *semicarbazone*, prepared in the usual way from the arsonic acid and acetonesemicarbazone, was recrystallised from water, in which it was sparingly soluble, and was obtained in prismatic needles, undecomposed below 300° (Found : N, 14·8. $C_8H_{10}O_4N_3As$ requires N, 14·6%). The sodium salt of this semicarbazone was obtained by the addition of alcohol to an exactly neutralised solution

in 2*N*-sodium carbonate. It crystallised from alcohol in colourless needles.

Benzaldehyde-p-*arsonic acid thiosemicarbazone*, obtained in the usual way by the condensation of equimolecular proportions of the reactants in aqueous solution, was recrystallised from hot water, in which it was very sparingly soluble, and obtained in pale yellow prisms, almost unchanged at 300° (Found : N, 13·6. $C_8H_{10}O_3N_3SAs$ requires N, 13·9%). The *phenylhydrazone*, prepared from the acid (1 g.) in water (8 c.c.) by addition of phenylhydrazine (0·7 g.) in acetic acid (4 c.c.), was recrystallised from aqueous alcohol and obtained in yellow needles, m. p. 186° (Found : N, 8·9. $C_{13}H_{13}O_3N_2As$ requires N, 8·8%). The p-*bromophenylhydrazone* was prepared in an analogous manner to the corresponding derivative of acetophenone-*p*-arsonic acid. On recrystallisation from aqueous alcohol it was obtained in brownish-yellow needles, m. p. 233° (decomp.) (Found : N, 7·0. $C_{13}H_{12}O_3N_2BrAs$ requires N, 7·0%). The *semioxamazone*, also prepared similarly to the corresponding derivative of acetophenone-*p*-arsonic acid, was recrystallised from water, in which it was somewhat sparingly soluble, and obtained in colourless fine needles, undecomposed at 300° (Found : As, 23·6. $C_9H_{10}O_5N_3As$ requires As, 23·8%).

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