CCCXXIII.—*Trypanocidal Action and Chemical Constitution. Part VIII. Derivatives of β-Aminoethyl- and γ-Aminopropyl-arsinic Acids.*

By George Aleck Crocker Gough and Harold King.

The great success which has attended the treatment of diseases of protozoal and allied origin with aromatic arsenic compounds arose essentially from Ehrlich's discovery that trypanocidally active atoxyl contains arsenic directly linked to the aromatic nucleus, and is, in fact, *p*-aminophenylarsinic acid. From this starting point many aromatic arsenic compounds may be readily synthesised, and since these often show the active properties of the parent substance in an enhanced degree, the attention of chemists and pharmacologists has been directed almost exclusively to this type of compound. In the aliphatic series, the position is quite different. Apart from the work of the early pioneers, which had no primary therapeutic aim, only two important attempts have been made to develop this field—one by the French firm of Poulenc Frères and the other by R. Adams and his co-workers in America. The position, however, is still unsatisfactory, since the aliphatic compounds which have been hitherto examined for trypanocidal action are without the amphoteric characteristics which so often accompany activity in the aromatic series. Thus it is important that any new investigation in this field should include the synthesis of a series of amino-aliphatic arsinic acids, which, by reason of their small molecular weight and their similarity to the amino-acids derived from the tissues, should possess a greater power of penetration and a more favourable distribution. It was therefore decided to prepare a series of compounds of the general type $R_1R_2N\cdot[CH_2]_n\cdot AsO_3H_2$, where R_1 and R_2 are hydrogen, aliphatic, or alicyclic radicals. Two methods of synthesis of such compounds suggest themselves: (*a*) the action of sodium arsenite on chloroamines of the type $R_1R_2N\cdot[CH_2]_n\cdot Cl$ (Meyer's reaction), and (*b*) the action of amines on chloro-acids of the type $Cl\cdot[CH_2]_n\cdot AsO_3H_2$. Since no acids of the latter type have been described, an initial examination of the first method was made,

but the use of β-chloroethyldiethylamine, $CH_2Cl{\cdot}CH_2{\cdot}NEt_2$, β-bromoethyldiethylamine, and *methyl-β-chloroethyldiethylammonium chloride*, $[CH_2Cl{\cdot}CH_2{\cdot}NMeEt_2]Cl$, under various conditions, gave no indication of the formation of arsinic acids. It occurred to us, however, in view of the similarity between *p*-toluenesulphonic esters of aliphatic alcohols and the corresponding halide esters, exemplified from several aspects by Ferns and Lapworth (J., 1912, **101**, 285; compare Kenyon, Phillips, and Turley, J., 1925, **127**, 405) and by Clemo and Walton's extension (this vol., p. 723) of their use to the Friedel–Crafts reaction, that the reactivity of aliphatic toluenesulphonic esters might be applied to the preparation of aliphatic arsinic acids by treatment with sodium arsenite. Such indeed has proved to be the case, for methyl *p*-toluenesulphonate and sodium arsenite give a small yield of methylarsinic acid. In order to extend the scope of the reaction to two cases in which we were interested, an attempt was made to prepare the *p*-toluenesulphonyl ester of diethylaminoethanol and the mono-ester from trimethyleneglycol. In the first case the only product isolated was *tetraethylpiperazinium di*-p-*toluenesulphonate*,

$$\left[\begin{matrix}Et\\Et\end{matrix}\!>\!N\!<\!\begin{matrix}CH_2{\cdot}CH_2\\CH_2{\cdot}CH_2\end{matrix}\!>\!N\!<\!\begin{matrix}Et\\Et\end{matrix}\right](C_7H_7SO_3)_2,$$

characterised as its *di-iodide* and *dichloroaurate*, products which were identical with those prepared from the product of the polymerisation of β-chloroethyldiethylamine. In the second case the chief products were *trimethyleneglycol di*-p-*toluenesulphonate* and *propane-αγ-dipyridinium di*-p-*toluenesulphonate*,

$$[C_5H_5N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C_5H_5N](C_7H_7SO_3)_2,$$

the latter being characterised as its *dichloride*, *dichloroaurate*, *tetramercurichloride*, and *dipicrate*. Meanwhile, further examination of this extension of the Meyer reaction has been postponed, as the synthesis of the required arsinic acids by method (*b*) has given the desired products.

This alternative method of preparation raised the problem of the synthesis of the chloro-aliphatic arsinic acids. By the interaction of ethylene and arsenious chloride in the presence of aluminium chloride, Renshaw and Ware (*J. Amer. Chem. Soc.*, 1925, **47**, 2991) prepared β-chloroethyldichloroarsine, $CH_2Cl{\cdot}CH_2{\cdot}AsCl_2$. The yield obtained by following their directions is poor and the method, although capable of improvement, was not found convenient for our purpose. As an alternative method, and one which would give access to the higher homologues, the synthesis of hydroxyalkylarsinic acids of the type $CH_2OH{\cdot}[CH_2]_n{\cdot}AsO_3H_2$ was investigated. β-Hydroxyethylarsinic acid has been prepared by the action of sodium arsenite on ethylenechlorohydrin (Poulenc Frères,

B.P. 191028, 1922; Edee, *J. Amer. Chem. Soc.*, 1928, **50**, 1394) and the reaction is also applicable to the preparation of *γ-hydroxypropylarsinic acid*. When these syrupy acids were dissolved in concentrated hydrochloric acid and reduced with sulphur dioxide in presence of hydrogen iodide, yellow oils separated which, when allowed to react with a petroleum solution of thionyl chloride, gave β-chloroethyldichloroarsine and γ-chloropropyldichloroarsine, respectively. The intermediate yellow oils were purified for chemical examination by distillation at 0·02 mm., and were then found to be the complex arsenious esters resulting from the intermolecular condensation of the primarily formed hydroxyalkyldichloroarsines. In particular, the di-ester of *γ-hydroxypropyldichloroarsine* and *γ-hydroxypropylarsinous acid* was obtained pure,

$$OH{\cdot}C_3H_6{\cdot}As\langle\begin{matrix}O{\cdot}C_3H_6{\cdot}AsCl_2\\O{\cdot}C_3H_6{\cdot}AsCl_2\end{matrix}.$$

The higher-boiling fractions, which could not be purified, were found to contain an even larger proportion of arsenic to chlorine, and thus were probably still more highly condensed compounds of the general formula $H(OC_3H_6As)_{2n-1}Cl_{2n}$, where n is the number of times that the condensation has been effected (*e.g.*, in the above case, 2; in the compound containing 7 arsenic atoms, 3). Analysis of a sample of the freshly-prepared oil, which had not been subjected to any heat treatment, showed that the first stage of the condensation had already taken place to a large extent.

The interaction of γ-chloropropylarsinic acid and aliphatic or alicyclic amines proceeds normally to yield the corresponding substituted aminopropylarsinic acids. In this way, the arsinic acids produced by the action of ammonia, di- and tri-methylamine, *n*-propylamine, *n*-hexylamine, piperidine, 2 : 2 : 6-*trimethylpiperidine*, 3-carbethoxypiperidine, 4-hydroxy-2 : 2 : 6-trimethylpiperidine, *l*-α-phenylethylamine, and piperazine were prepared, and from these a number of substitution products. Owing to the extreme solubility of these simple arsinic acids or their hydrochlorides in water, their isolation has proved a difficult problem, but almost all have been obtained crystalline by the use of appropriate organic solvents. A common impurity which complicated the isolation is probably the corresponding non-crystalline γ-hydroxypropylarsinic acid.

The reactions of β-*chloroethylarsinic acid* were found to be in striking contrast to those of its homologue. With an excess of sodium hydroxide, dimethylamine, or any other strong base, the acid decomposes completely, forming ethylene and the corresponding arsenate and hydrochloride of the base. In the case of ammonia, where the reaction was investigated in some detail, the same decom-

position occurred in aqueous and alcoholic solution at the ordinary temperature and at 100°. When, however, ammonia or the amine was added in sufficient amount to maintain the reaction mixture neutral to litmus, normal, and generally exhaustive, substitution took place without the formation of any arsenic acid. Thus, although it was not possible to obtain such amino-acids as β-aminoethylarsinic acid, the completely substituted compounds, *triethylamine-ββ′β″-triarsinic acid*, $N(CH_2\cdot CH_2\cdot AsO_3H_2)_3$, and *methyldiethylamine-ββ′-diarsinic acid*, $NMe(CH_2\cdot CH_2\cdot AsO_3H_2)_2$ were easily obtained. In the preparation of the former compound, it was found that the ammonia could be conveniently supplied by conducting the reaction in the presence of aqueous solutions of carbamide, acetamide, or ammonium acetate, which slowly yielded the ammonia by hydrolysis. The reactive character of β-chloroethylarsinic acid is shown by the fact that some of the quaternary compound, *dimethyldiethylammonium chloride ββ′-diarsinic acid*,

$$\left[\begin{matrix}Me\\Me\end{matrix}\!>\!N\!<\!\begin{matrix}CH_2\cdot CH_2\cdot AsO_3H_2\\CH_2\cdot CH_2\cdot AsO_3H_2\end{matrix}\right]Cl\ ,$$

is formed in the preparation of *β-dimethylaminoethylarsinic acid*. The substituted arsinic acids from trimethylamine, piperidine, and piperazine were also prepared, the last forming the disubstituted piperazine,

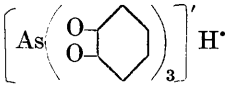
$$AsO_3H_2\cdot CH_2\cdot CH_2\cdot N\!<\!\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\!>\!N\cdot CH_2\cdot CH_2\cdot AsO_3H_2\ .$$

Whilst β-chloroethyldichloroarsine and γ-chloropropyldichloroarsine are oils, many of the amphoteric arsinic acids of both series (ethyl and propyl) form crystalline dichloroarsine hydrochlorides when sulphur dioxide is passed into a solution of the amphoteric arsinic acid in concentrated hydrochloric acid in the presence of a little hydriodic acid.

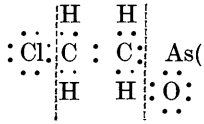
The instability of β-chloroethylarsinic acid towards bases recalls the reactions of β-chlorovinylarsinic acid (Mann and Pope, J., 1922, **121**, 1754), in which acetylene and sodium chloride and arsenate are formed by the action of sodium hydroxide. Since the use of caustic alkali in the hydrolysis of γ-chloropropylarsinic acid yields no arsenic acid, the ease of decomposition must be connected in some way with the presence of the chloro-group in the β-position to the arsinic acid grouping. This particular case of instability may be explained as an example of a general tendency of all arsinic acids. It seems probable that in alkaline solution the arsenic atom in arsinic acids tends to exert a higher co-ordination number than the normal (four), and yields complex ions by combination with one or two hydroxyl ions in which it has an outer electron shell of 10 or 12:

$$[R\cdot As{\rightarrow}O(OH)_3]' \text{ and } [R\cdot As{\rightarrow}O(OH)_4]''$$

Examples of the formation of stable compounds of a similar type are well known; *e.g.*, tripyrocatechylarsinic acid



(Rosenheim and Plato, *Ber.*, 1925, **58**, 2000). In such complex ions the arsenic–carbon linking will be weakened owing to the drift towards the carbon atom of the electron pair constituting that linking, caused by the negatively charged arsenic atom. If some decomposition can now take place which will result in the loss of two electrons from the alkyl radical (*e.g.*, the removal of a negative ion), then the two electrons forming the arsenic–carbon linking will move into the position between the α- and β-carbon atoms, with the resultant production of a double linking at this point. In the case of β-chloroethylarsinic acid, at this stage the hypothetical co-ordination compound,



consists virtually of intramolecularly ionised ethylene (Lowry, J., 1923, **123**, 822) combined with a chlorine ion and electrically neutral arsenic acid—a system which may easily become arranged into its components when the chlorine ion is removed under the influence of the sodium ions present in the solution. A similar explanation applies to the decomposition of β-chlorovinylarsinic acid.

In the case of γ-chloropropylarsinic acid, although the complex ion may be formed and the chlorine ion removed from it, the electron pair between the arsenic and the α-carbon atoms cannot move along the carbon chain to complete the octet of the terminal carbon atom, since that movement would involve the formation of a ten-electron system around the β-carbon atom. Completion of the γ-carbon octet therefore takes place in the normal way by the addition of a hydroxyl ion, with the consequent formation of γ-hydroxypropylarsinic acid.

Therapeutic Results and Considerations.

Out of more than two dozen compounds described in this communication, all of which contain one of the groups

$$>N\cdot CH_2\cdot CH_2\cdot AsO_3H_2 \text{ or } >N\cdot CH_2\cdot CH_2\cdot CH_2\cdot AsO_3H_2,$$

only two proved to have any therapeutic activity, and that of a trivial nature, when tested on experimental infections of *Trypanosoma equiperdum* in mice. These were triethylamine-ββ′β″-tri-

arsinic acid, $N(CH_2 \cdot CH_2 \cdot AsO_3H_2)_3$, and γ-piperidinopropylarsinic acid, $C_5H_{10}N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot AsO_3H_2$. For the former the maximum tolerated dose is 2·5 mg. per g. of mouse, and with a dose of 2·0 mg. the trypanosomes disappear from the peripheral blood of infected mice, but relapse occurs in 6 days; whereas for the latter the tolerated dose is 1·0 mg., and with 0·75 mg. a similar temporary "cure" is followed by relapse in 7 days. The latter compound lends itself to chemical development, but although piperidine was replaced by 2 : 2 : 6-trimethylpiperidine, 3-carbethoxypiperidine, 4-hydroxy-2 : 2 : 6-trimethylpiperidine, and piperazine, and the propyl group by the ethyl group, producing structures of similar build, there was no sign of any therapeutic activity. The results are surprising, for the majority of the compounds prepared and tested were amphoteric and extremely soluble in water—properties which should have ensured a favourable distribution in the mammalian tissues.

In seeking to arrive at some interpretation of this lack of activity, many possibilities arise, but two seem to us to be of predominant importance. Accepting the postulate that the main trypanocidal activity of active arsinic acids is due to their reduction to the corresponding oxides by the tissues, it was pointed out in Part V of this series, where another inactive series was encountered (Hewitt, King, and Murch, J., 1926, 1355; compare also Durham, Marchal, and King, *J. Pharm. Exp. Ther.*, 1926, **28**, 349), that the evidence was all in favour of the view that the inactivity of a series of aromatic arsinic acids containing the sulphonamide group, when compared with their analogously constituted active acids containing the amide group, was due to their non-reduction by the tissues to the corresponding oxides. In other words, these sulphonamide acids lay outside the zone of reduction potential of the tissues. In fact, our view is that variation of the chemotherapeutic index of derivatives of phenylarsinic acid is in part due to the variation in reduction potential produced by various substituents in the *o*-, *m*-, and *p*-positions, just as Conant and Fieser (*J. Amer. Chem. Soc.*, 1924, **46**, 1881) found that the reduction potential of quinones varies with introduction of substituents. All the acids described in this communication contain aliphatically bound arsenic with a chain of at least two methylene groups attached to the arsinic acid, and it may be that such acids are inherently difficult to reduce and that the effect on the reduction potential of wide variation of the remainder of the molecule is lost by the buffering effect of the ethylene or propylene chains.

The other possibility is that these acids are excreted from the system too readily, owing in part to their strikingly great aqueous

solubility, and in part to their lack of substantive properties for the tissues. This substantive effect of efficient medicaments, which keeps them in the body for long periods and allows them to exert a persistent and continuous action, has been emphasised in the case of Bayer 205 and its analogues (Balaban and King, J., 1927, 3078), and it undoubtedly plays an important part in the action of arsenicals (Durham, Marchal, and King, *loc. cit.*). Thus the superior activity of arseno-compounds over arsinic acids, of silver salvarsan over salvarsan, and of zinc sulpharsenol over sulpharsenol, on experimental trypanosome infections in mice, is possibly associated with such longer persistence in the body. The activity of aromatic arsinic acids and the inactivity of aliphatic arsinic acids may be due to an inherently great substantivity of the aromatic nucleus. It may be, on the other hand, that the substantivity of aromatic arsinic acids arises from the fact that, as previously suggested, they come within the zone of reduction potential of the tissues, and are accordingly reduced to the reactive oxides, and stored as such by condensation in a reversible form, whereas the aliphatic arsinic acids are non-substantive because they are outside the reduction potential of the tissues, and cannot therefore be stored as the potentially active oxides.

It is of interest that Castelli (*Arch. Schiff. Trop. Hyg.*, 1912, **16**, 605), working in Ehrlich's laboratory, found mono- and di-methylarsinic acids inactive on experimental trypanosomiasis in mice, a fact confirmed for methylarsinic acid in our laboratories, and that Ritz (*Arch. Internat. Pharmacodyn.*, 1923, **27**, 67) found allylarsinic acid to have no curative action on trypanosome infections in mice. On the other hand, Ritz found that the latter effected a temporary disappearance of *Trypanosoma brucei* in rats, on which methyl- and dimethyl-arsinic acids were inactive, whereas Voegtlin and Smith (*J. Pharm. Exp. Ther.*, 1920, **16**, 449) found methyl- and ethylarsinic acids to possess a definite action on *T. equiperdum* in rats.

We are deeply indebted to Miss F. M. Durham and Miss M. Hill, of this Department, for the painstaking care with which they have carried out the whole of the biological experiments on the toxicities of the individual arsinic acids.

EXPERIMENTAL.

β-*Chloroethylarsinic Acid and Derivatives.*

β-*Hydroxyethylarsinic Acid*, $CH_2OH{\cdot}CH_2{\cdot}AsO_3H_2$. — Ethylene chlorohydrin (80 g.) was slowly added to a solution of arsenious oxide (100 g.) and sodium hydroxide (120 g.) in water (300 c.c.) (compare B.P., 191028, 1922; Adams and Quick, *J. Amer. Chem. Soc.*, 1922, **44**, 811; Edee, *ibid.*, 1928, **50**, 1394). The mixture was

cooled and shaken during the addition in order to avoid loss of the chlorohydrin as ethylene oxide. After standing for 12 hours, the whole was warmed on the water-bath for 30 minutes, diluted with water (1500 c.c.), rendered acid with hydrochloric acid (Congo paper), and evaporated until a copious deposit of salt and arsenious oxide had separated. The solid was removed, washed twice with 96% alcohol, the united filtrates evaporated to dryness at 50°, and the residue extracted with alcohol (100 c.c.). On removal of the alcohol, a viscous syrup of crude β-hydroxyethylarsinic acid was left. Contrary to the statement of Edee (*loc. cit.*), this acid on treatment with a hot ammoniacal solution of calcium chloride yields a sparingly soluble *calcium* salt, crystallising from dilute solution in hexagonal leaflets (Found : Loss at 100°, 9·0; Ca, 17·1; As, 32·7, 33·6, 33·7. $C_2H_5O_4AsCa,H_2O$ requires H_2O, 8·0; Ca, 17·7; As, 33·2%).

β-*Chloroethyldichloroarsine*, $CH_2Cl{\cdot}CH_2{\cdot}AsCl_2$.—Crude β-hydroxyethylarsinic acid, prepared from 100 g. of ethylene chlorohydrin, was dissolved in concentrated hydrochloric acid (350 c.c.), potassium iodide solution (4 c.c. *N*) added, and the solution treated with sulphur dioxide below 50° until saturated. After standing for 48 hours, the lower layer was removed and dried by solution in carbon tetrachloride, followed by removal of the solvent by distillation. The crude oil (140 g.) was then mixed with an equal volume of light petroleum, and thionyl chloride (127 c.c.) added slowly. When the reaction ceased, the product was distilled first at ordinary pressure and finally under reduced pressure. In this manner there were obtained arsenious chloride, b. p. 39—41°/30 mm. (44 g.), and β-chloroethyldichloroarsine, b. p. 92—93°/32 mm. (60 g.). Renshaw and Ware (*J. Amer. Chem. Soc.*, 1925, **47**, 2991) give b. p. 90—93°/30 mm.

In repeating the preparation of β-chloroethyldichloroarsine from ethylene and arsenious chloride by the method of Renshaw and Ware (*loc. cit.*), it was found that the yield of product was very sensitive to slight alterations in the conditions of experiment. In one case in which freshly-distilled arsenious chloride (220 g.) and powdered, freshly sublimed aluminium chloride (29 g.) were treated with ethylene at 0°, an increase in weight of 27 g. was recorded with formation of β-chloroethyldichloroarsine (15 g.). Similar experiments were tried (*a*) with twice the above amount of aluminium chloride, and (*b*) with absorption of the ethylene at 50—60°. Whilst in both these cases a larger increase in the volume and weight was observed, the yield when the product was worked up by Renshaw and Ware's method was not appreciably altered. It was found, however, that a consistent yield (30 g.) could be obtained by using

the condition (*b*), provided the method of isolation was modified (compare Green and Price, J., 1921, **119**, 449). The reaction mixture was poured into ice-cold 4*N*-hydrochloric acid and evaporated under reduced pressure, the excess of arsenious chloride and the dichloroarsine volatilising without hydrolysis. The last portions of the dichloroarsine (often considerable) may be removed from the tarry residue by distillation in a current of the vapour of 4*N*-hydrochloric acid at 100° and 30 mm. The carbon tetrachloride extract of the total distillate was distilled to remove traces of water, and the residue distilled in a vacuum. The carbon tetrachloride extracts and the arsenious chloride underwent the curious sequence of colour changes noted by Renshaw and Ware; it is of interest that no trace of these coloured compounds was formed in the preparation of β-chloroethyldichloroarsine from β-hydroxyethylarsinic acid.

β-Chloroethylarsinic Acid.—Oxidation of the above dichloroarsine with nitric acid, by the method used by Pope and Mann (J., 1922, **121**, 1754) for the corresponding vinyl derivative, caused considerable decomposition; oxidation with chlorine in the presence of water, however, gave the chloro-acid in good yield. β-Chloroethyldichloroarsine (57 g.) was suspended in water (228 c.c.) and dissolved by the passage of chlorine below 50°. On repeated evaporation of this solution with water at 60°, followed by crystallisation of the residue from acetone, *β-chloroethylarsinic acid*, m. p. 134—135° (35 g.), was obtained as pearly plates (Found : As, 39·5. $C_2H_6O_3AsCl$ requires As, 39·8%). The maximum tolerated dose per g. of mouse is 0·2 mg.

Triethylamine-ββ'β''-triarsinic Acid.—β-Chloroethylarsinic acid (5 g.) and carbamide (6·3 g.) were heated on the water-bath with sufficient water to render the whole liquid. More water was added from time to time to liberate ammonia by hydrolysis of the carbamide. The reaction was discontinued when a sample contained no un-ionised chlorine (detected by treating a sample with excess of silver nitrate and nitric acid, filtering from silver chloride, and boiling the filtrate with excess of potassium hydroxide to hydrolyse any unreacted chloro-acid; this test was employed throughout the preparations). After excess of carbamide had been removed by extraction with boiling ethyl alcohol (30 c.c.), the residue was dissolved in water (15 c.c.) and made neutral to Congo paper. On cooling, clusters of needles of *triethylamine-ββ'β''-triarsinic acid*, m. p. 184—185°, separated (4·1 g.) (Found : As, 47·7; N, 2·7. $C_6H_{18}O_9NAs_3$ requires As, 47·6; N, 2·9%). The acid yields crystalline *calcium* and *barium* salts on treatment in ammoniacal solution with calcium and barium chlorides; the *magnesium* salt is more soluble and is amorphous. The acid is also obtained by the use of acetamide or ammonium acetate as sources of ammonia.

Methyldiethylamine-ββ′-diarsinic Acid.—β-Chloroethylarsinic acid (3 g.) and water (2 c.c.) were heated to 100°, and methylamine (33% aqueous solution) added from time to time to keep the whole neutral. When all the chlorine was ionised (15 hours), the mixture was neutralised with hydrochloric acid (Congo paper), evaporated to dryness, and freed from methylammonium chloride by boiling with ethyl alcohol. The residual gum solidified after prolonged manipulation and was crystallised from a mixture of water and alcohol. *Methyldiethylamine-ββ′-diarsinic acid*, m. p. 192—194°, thus obtained forms rectangular plates (1·9 g.) (Found: As, 42·5; N, 3·8; loss on heating at 90°, 5·2, 5·1. $C_5H_{15}O_6NAs_2,H_2O$ requires As, 42·5; N, 4·0; H_2O, 5·1%). The maximum tolerated dose is 1·5 mg.

β-*Dimethylaminoethylarsinic Acid* and *Dimethyldiethylammonium Chloride ββ′-Diarsinic Acid.*—β-Chloroethylarsinic acid (6 g.) was treated with dimethylamine in a similar manner to that employed in the previous preparation. When the reaction was complete (20 hours), the mixture was acidified with hydrochloric acid, evaporated, and freed from dimethylammonium chloride by boiling with chloroform. The residue was dissolved in the minimum volume of water, and alcohol added so long as a precipitate formed. Crystallisation of this precipitate (0·5 g.) from a mixture of alcohol and water yielded compact masses of *dimethyldiethylammonium chloride ββ′-diarsinic acid*, m. p. 178° (Found: N, 3·8; Cl, 9·4. $C_6H_{18}O_6NAs_2Cl$ requires N, 3·8; Cl, 9·2%). The maximum tolerated dose is over 3 mg.

The alcoholic filtrate from the above was concentrated to a small volume (10 c.c.), and acetone (120 c.c.) slowly added. The precipitate, on crystallisation from ethyl alcohol, yielded β-*dimethylaminoethylarsinic acid hydrochloride*, m. p. 138—140° (4·9 g.) (Found: N, 6·0; Cl, 15·2. $C_4H_{12}O_3NAs,HCl$ requires N, 6·0; Cl, 15·2%).

The above quaternary ammonium compound is more readily prepared by the direct interaction of the appropriate reagents. β-Dimethylaminoethylarsinic acid (0·23 g.) and β-chloroethylarsinic acid (0·4 g.) were melted together at 100° by the addition of a few drops of alcohol and heated for 2 days. Solution of the melt in water, followed by the addition of alcohol, yielded the required compound (0·3 g.), identical with that previously prepared.

β-*Dimethylaminoethylarsinic Acid Methochloride.*—β-Chloroethylarsinic acid (4·9 g.) was treated with trimethylamine according to the method used above. When the reaction was complete, the mixture was dried, the trimethylammonium chloride removed by boiling ethyl alcohol (20 c.c.), and the residue crystallised from methyl alcohol. β-*Dimethylaminoethylarsinic acid methochloride*, m. p. 187—188° (evolution of gas), thus obtained forms elongated

plates (Found: N, 5·7. $C_5H_{15}O_3NAsCl$ requires N, 5·7%). The maximum tolerated dose is less than 0·05 mg.

β-Piperidinoethylarsinic Acid.—β-Chloroethylarsinic acid (7 g.) was dissolved in ethyl alcohol (15 c.c.), and piperidine added until the mixture was neutral to litmus; it was then refluxed, and after 3 hours the reaction again adjusted to neutrality. When interaction had ceased (6 hours), the excess piperidine was removed by basification with sodium hydroxide, followed by evaporation under reduced pressure at 50° until the distillate contained no amine. The residue was made acid with hydrochloric acid, dried, and extracted with boiling ethyl alcohol. Upon concentration of the extract, *β-piperidinoethylarsinic acid hydrochloride*, m. p. 155—157°, separated as lustrous plates (7·5 g.) (Found: Cl, 13·0; N, 5·2. $C_7H_{16}O_3NAs,HCl$ requires Cl, 13·0; N, 5·1%).

For the preparation of the corresponding dichloroarsine, the piperidino-acid (1·5 g.) was dissolved in concentrated hydrochloric acid (4 c.c.) containing a trace of potassium iodide and reduced by passing in sulphur dioxide for 15 mins. The copious precipitate was removed and recrystallised from 2*N*-hydrochloric acid. *β-Piperidinoethyldichloroarsine hydrochloride* thus obtained forms square plates, m. p. 126—127° (evolution of gas), soluble in water and in ethyl alcohol (Found: As, 26·1. $C_7H_{15}NAsCl_3$ requires As, 25·5%). By treatment of this dichloroarsine, dissolved in water (0·9 c.c.), with a saturated aqueous solution of potassium iodide (2·5 c.c.), added drop by drop, bright yellow crystals of *β-piperidinoethyldiiodoarsine hydriodide*, m. p. 158—159°, were obtained (Found: As, 13·1. $C_7H_{15}NAsI_3$ requires As, 13·2%). This substance dissolves in either water or ethyl alcohol with formation of a colourless solution.

NN′-Piperazinedi-ββ′-ethylarsinic Acid.—β-Chloroethylarsinic acid (3 g.) was treated with piperazine hydrate until neutral to litmus, and the resulting mixture heated on the water-bath. The reaction was readjusted to neutrality after 5 hours. A slight trace of un-ionised chlorine persisted after 20 hours' heating. The liquid was concentrated to 10 c.c. and acidified with hydrochloric acid. When the sides of the vessel were rubbed, hexagonal plates of *NN′-piperazinedi-ββ′-ethylarsinic acid dihydrochloride* separated. For analysis and physiological assay, they were recrystallised from 15 c.c. of boiling water; yield, 2·3 g. (Found: As, 32·2; Cl, 15·4. $C_8H_{20}O_6N_2As_2,2HCl$ requires As, 32·4; Cl, 15·3%). This salt is unmelted at 280°, but darkens progressively from 220° upwards. The maximum tolerated dose is 2·5 mg.

β-Chloroethyldiethylamine, $CH_2Cl{\cdot}CH_2{\cdot}N(C_2H_5)_2$, was prepared by a modification of the method given in B.P., 167781 of 1921.

β-Diethylaminoethanol (59 g.), dissolved in chloroform (100 c.c.), was added slowly to a mixture of thionyl chloride (120 g.) and chloroform (500 c.c.) cooled to −5°. After standing for an hour, most of the chloroform was removed on the water-bath, and the residue evaporated twice with alcohol under reduced pressure. Crystallisation of the product from alcohol–ether gave stout needles of β-chloroethyldiethylamine hydrochloride, m. p. 210—211° (69 g.). Concentration of the mother-liquors gave a further quantity (13 g.). Treatment of the amine hydrochloride (0·5 g.) in water (5 c.c.) with a hot saturated solution of picric acid (0·68 g.) in water yielded the *picrate*, m. p. 116—117°, which crystallised in a compact form from hot solutions, and in needles from cooler solutions. The *chloroaurate*, m. p. 68—71° (somewhat indefinite), crystallises from *N*-hydrochloric acid in hexagonal tablets (Found: Au, 41·1. $C_6H_{14}NCl,HAuCl_4$ requires Au, 41·4%). When the free amine, b. p. 51—52°/16 mm., was kept with an equal volume of absolute alcohol, crystals of 1 : 4-tetraethylpiperazinium dichloride (1 g.) separated, which, when treated with saturated potassium iodide solution (2·5 g. KI), yielded elongated plates of the corresponding di-iodide, identical with that obtained by the interaction of β-diethylaminoethanol and *p*-toluenesulphonyl chloride (see below). No indication of the formation of arsinic acids was obtained by the treatment of β-chloroethyldiethylamine with sodium arsenite under the conditions employed for the preparation of β-hydroxyethylarsinic acid (see above). The amine was largely unattacked, but small amounts of β-diethylaminoethanol and of an unsaturated amine were detected.

Methyl-β-chloroethyldiethylammonium Iodide.—Upon mixing β-chloroethyldiethylamine (26·3 g.) with methyl iodide (3·5 g.) an immediate turbidity was produced and after ½ hour the whole became solid. The excess of methyl iodide was then removed and the residue (51 g.) crystallised from methyl alcohol. *Methyl-β-chloroethyldiethylammonium iodide* thus prepared crystallises in colourless plates, m. p. 219—220°, which are slightly deliquescent and tend to become yellow or red on exposure to air, when wet with solvent (Found: I, 46·1. $C_7H_{17}NClI$ requires I, 45·7%). When treated with sodium hydroxide solution (50%), a concentrated solution of the quaternary salt (80%) yielded an oil, which became solid when the alkali was added in excess. This was found to be the original quaternary iodide liberated unchanged from solution by the "salting out" effect of the sodium hydroxide. Saturated solutions of sodium carbonate and of potassium acetate, but not those of calcium or barium chloride, exert a similar effect.

Methyl-β-chloroethyldiethylammonium chloride was prepared by treating a solution of the iodide (23·5 g.) in water (100 c.c.) with

freshly prepared silver chloride (28 g.) for 20 minutes. The silver iodide was then removed and the liquid stirred with a further quantity of silver chloride (12 g.) for 1 hour to ensure complete conversion. Removal of the water and the silver halides yielded the *chloride* as a mass of highly deliquescent needles, part of which was converted into the *chloroaurate*, m. p. 202—204°, which crystallised from 0·5*N*-hydrochloric acid in fine needles (Found: Au, 40·3. $C_7H_{17}NCl,AuCl_4$ requires Au, 40·3%). No arsinic acid could be isolated by interaction of this chloride and sodium arsenite.

Reaction between Sodium Arsenite and Methyl p-*Toluenesulphonate.*—Methyl *p*-toluenesulphonate (14·2 g.) was stirred at 100° with arsenious oxide (7·2 g.) dissolved in 22 c.c. of 10*N*-sodium hydroxide for 3 hours. When cool, the sodium *p*-toluenesulphonate was removed, and the filtrate treated with just insufficient alcohol to precipitate an oil. On keeping, a small crop of sodium methylarsinate separated in rhombs mixed with fine needles of sodium toluenesulphonate. These could be separated mechanically, and the sodium methylarsinate agreed in all its properties with a specimen prepared from methylarsinic acid. It is, however, preferable to isolate methylarsinic acid as its calcium salt. After removal of sodium toluenesulphonate, the reaction mixture was made slightly acid to Congo paper and evaporated to dryness. On dissolving the residue in water, arsenic trioxide remained undissolved and could be completely eliminated by repetition of the process. Wholly crystalline calcium methylarsinate (1·5 g.) could then be precipitated from a hot ammoniacal solution by excess of calcium chloride. For analysis, the product was dissolved in hydrochloric acid, treated with calcium chloride and reprecipitated from hot dilute solution by excess of ammonia. It then crystallised in microscopic plates (Found: Ca, 20·3. Calc. for CH_3O_3AsCa,H_2O: Ca, 20·5%) having the formula given by Klinger and Kreutz (*Annalen*, 1888, **249**, 152).

Interaction of p-*Toluenesulphonyl Chloride and* β-*Diethylaminoethanol.*—Dry diethylaminoethanol (5·8 g.) was treated with a solution of *p*-toluenesulphonyl chloride (9·5 g.) in benzene (30 c.c.) at 0°. After standing over-night, the solid which had separated was removed and crystallised from ethyl alcohol. In this way there were obtained elongated, hexagonal plates of *tetraethylpiperazinium di*-p-*toluenesulphonate*, m. p. 300—301° (decomp.) (Found: N, 5·4. $C_{26}H_{42}O_6N_2S_2$ requires N, 5·2%). Upon treatment of this salt (1 g.) with a saturated solution of potassium iodide (2·5 g.) in water, long needles of the corresponding *di-iodide*, unmelted at 300°, separated (Found: I, 55·7; N, 6·1. $C_{12}H_{28}N_2I_2$ requires I, 56·9; N, 6·2%). Treatment of the di-*p*-toluenesulphonate (0·1 g.), dissolved in hot 2*N*-hydrochloric acid (40 c.c.), with auric chloride

gave large, square plates of *tetraethylpiperazinium dichloroaurate* (Found : Au, 45·0. $C_{12}H_{28}N_2Au_2Cl_8$ requires Au, 44·9%). Both this substance and the iodide were found to be identical with the corresponding derivatives prepared from the tetraethylpiperazinium dichloride (see above) formed by the polymerisation of free β-chloroethyldiethylamine. The specimen of the chloroaurate prepared in this way gave similar figures on analysis (Found : Au, 44·9%).

γ-Chloropropylarsinic Acid and Derivatives.

γ-Trimethylene Chlorohydrin.—Preparation of the chlorohydrin from trimethylene glycol and hydrochloric acid by the method of Hultman, Davis, and Clarke (*J. Amer. Chem. Soc.*, 1921, **43**, 369) was found not as satisfactory as the following process based on the method used by Carius (*Annalen*, 1862, **124**, 257) for the preparation of ethylene chlorohydrin: Sulphur monochloride (2200 g.) was added with vigorous stirring to trimethylene glycol (1000 g.) heated to 70°, at such a rate that the evolved gases could be easily absorbed. After stirring for a further 2 hours, the mixture was cooled and filtered from suspended sulphur. Distillation of the filtrate yielded impure trimethylene dichloride (40 g.) and trimethylene chlorohydrin, b. p. 74—76°/23 mm. (850 g.).

γ-Hydroxypropylarsinic Acid.—Trimethylene chlorohydrin (95 g.) was stirred with sodium arsenite solution (100 g. As_2O_3 and 120 g. NaOH dissolved in 300 c.c. of water) at 50—60° until homogeneous. The liquid was then diluted with an equal volume of water, neutralised to Congo paper, and evaporated to dryness at 50°. Extraction of the residue with hot alcohol (150 c.c.) yielded, after removal of the alcohol, a syrup of impure *γ-hydroxypropylarsinic acid*. This acid yields a crystalline *calcium* salt (Found : As, 33·2. $C_3H_7O_4AsCa$ requires As, 33·8%).

γ-Chloropropyldichloroarsine.—γ-Hydroxypropylarsinic acid (from 95 g. of trimethylene chlorohydrin) was dissolved in concentrated hydrochloric acid (250 c.c.), containing potassium iodide (0·3 g.), and sulphur dioxide passed to saturation, the temperature being kept below 40°. After standing for 2 days, the lower layer (85 g.) was separated and dried by distilling carbon tetrachloride from it. It was then mixed with light petroleum (90 c.c.), and thionyl chloride (56 c.c.) added with cooling and agitation. After refluxing for 2 hours, the petroleum was removed and the residue distilled. In this manner there were obtained arsenious chloride, b. p. 45°/32 mm. (13 g.), and *γ-chloropropyldichloroarsine*, b. p. 120—122°/16 mm. (70 g.) (Found : As, 33·5. $C_3H_6AsCl_3$ requires As, 33·6%).

γ-Chloropropylarsinic Acid.—Chlorine was passed into a suspension of γ-chloropropyldichloroarsine (40 g.) in water (160 g.) until solution

was complete. By repeated evaporation of the solution with water, followed by crystallisation of the residue from water, elongated hexagonal plates of *γ-chloropropylarsinic acid*, m. p. 146—148°, were obtained (Found: As, 37·1. $C_3H_8O_3AsCl$ requires As, 37·0%). This acid yields crystalline *barium* and *calcium* salts with ammoniacal barium and calcium chlorides. The maximum tolerated dose is 0·1 mg.

The Reaction between γ-Hydroxypropylarsinic Acid and Sulphur Dioxide.—The oil which separated when the hydroxy-acid was treated with sulphur dioxide in hydrochloric acid solution was dried as already described. Complete decomposition occurred at 140° when the oil was heated at 15 mm.; at 0·15 mm., however, there was little decomposition and the crude product (15 g.) gave a very volatile substance (arsenious chloride), a light yellow, mobile liquid, b. p. 34—35° (8·5 g.), a darker liquid, b. p. 35—75°, and a residue (5·2 g.). The second fraction was redistilled, b. p. 35°/0·16 mm., and left only a minute residue. Analysis showed it to be the *di-ester* of *γ-hydroxypropyldichloroarsine* and *γ-hydroxypropylarsinous acid*, $(AsCl_2{\cdot}C_3H_6{\cdot}O)_2As{\cdot}C_3H_6{\cdot}OH$ (Found: As, 41·3; Cl, 26·6. $C_9H_{19}O_3As_3Cl_4$ requires As, 41·5; Cl, 26·2. γ-Hydroxypropyldichloroarsine, $C_3H_7OAsCl_2$, requires As, 36·6; Cl, 34·6%). The third fraction and the residue appeared to contain small amounts of more complex condensation compounds (Found: In the third fraction, As, 41·3; in the residue, As, 42·3%). The ester, b. p. 35°/0·16 mm. (10 g.), on treatment with thionyl chloride (8 c.c.) at 0° yielded finally γ-chloropropyldichloroarsine (4·9 g.).

γ-Aminopropylarsinic Acid.—γ-Chloropropylarsinic acid (7 g.) was found to react completely with ammonia (*d* 0·88; 50 c.c.) without the production of arsenic acid, when heated at 110° for 8 hours. After the excess of free ammonia had been removed by warming under reduced pressure, the product was made alkaline with sodium hydroxide and distilled at 50° until the distillate was neutral. The residue was then made acid (Congo paper) with hydrochloric acid, evaporated to dryness, and the organic matter separated from the salt by extraction with alcohol. After removal of the alcohol, the residue was dissolved in water, neutralised to litmus paper with sodium hydroxide, evaporated to dryness, and extracted with pure methyl alcohol. Gradual addition of acetone to the extract yielded the amino-acid which was now sparingly soluble in methyl alcohol. It was freed from a trace of a substance containing ionic chlorine by boiling with a little methyl alcohol. *γ-Aminopropylarsinic acid*, m. p. 212—214° (evolution of gas), obtained in this way, forms compact, microscopic prisms which are extremely soluble in water, but insoluble in ethyl alcohol (Found: N, 7·5. $C_3H_{10}O_3NAs$ requires N, 7·6%). The maximum tolerated dose is 0·4 mg.

γ-Dimethylaminopropylarsinic Acid.—γ-Chloropropylarsinic acid (6 g.) was heated with a methyl-alcoholic solution of dimethylamine (6 c.c. of 33%) at 110° for 8 hours and the excess of amine removed by distillation with sodium hydroxide solution under reduced pressure. The residue was acidified with hydrochloric acid, evaporated to dryness at 50°, and extracted with alcohol. Gradual addition of acetone to this gave a precipitate, which was removed and recrystallised from ethyl alcohol (6 c.c.). *γ-Dimethylaminopropylarsinic acid hydrochloride*, m. p. 108—110°, thus obtained forms slightly deliquescent needles (Found: Cl, 14·4; N, 5·7; As, 30·4. $C_5H_{14}O_3NAs,HCl$ requires Cl, 14·3; N, 5·7; As, 30·3%). The maximum tolerated dose is 0·4 mg.

γ-Dimethylaminopropylarsinic Acid Methochloride.—The chloro-acid (6 g.) was heated with trimethylamine (30 c.c. of 33% aqueous solution) at 100°. After 3 hours the water and excess of amine were removed and the residue extracted with chloroform (30 c.c.) to remove trimethylammonium chloride. The residue, which solidified on being kept for 2 days, was dissolved in the minimum volume of water at 70°, and ethyl alcohol added at that temperature until a turbidity was produced. On cooling, compact prisms of *γ-dimethylaminopropylarsinic acid methochloride* separated, m. p. 174—176° (Found: Cl, 13·5; N, 5·4. $C_6H_{17}O_3NAsCl$ requires Cl, 13·6; N, 5·4%), which did not yield a sparingly soluble picrate or chloroaurate. The maximum tolerated dose is 0·3 mg.

γ-n-Propylaminopropylarsinic Acid.—γ-Chloropropylarsinic acid (6 g.) was refluxed with alcohol (40 c.c.) and *n*-propylamine (10 g.; 6 mols.) for 12 hours. When the reaction was complete, the excess amine and alcohol were removed, first by distillation alone and then with sodium hydroxide under reduced pressure. The residue, when acidified with hydrochloric acid, dried, and extracted with alcohol, yielded *γ-n-propylaminopropylarsinic acid hydrochloride*, m. p. 210—212° (Found: As, 28·2; N, 5·3; Cl, 13·6. $C_6H_{16}O_3NAs,HCl$ requires As, 28·6; N, 5·4; Cl, 13·6%). The maximum tolerated dose is 0·5 mg. The acid, prepared by treatment of the hydrochloride (0·47 g.) with sodium hydroxide (1 mol.) followed by evaporation to dryness, was extracted from the residue with methyl alcohol (2 c.c.); on addition of ethyl alcohol (12 c.c.), in which it is insoluble, needles of *γ-n-propylaminopropylarsinic acid*, m. p. 222—224°, slowly separated (Found: N, 6·1. $C_6H_{16}O_3NAs$ requires N, 6·2%). The acid is neutral to litmus, and yields a white, basic arseno-compound on warming with hypophosphorous acid containing a trace of potassium iodide.

m-Nitrobenzopropylamidopropylarsinic Acid.—*γ-n*-Propylaminopropylarsinic acid hydrochloride (1·5 g.), dissolved in 2*N*-sodium

hydroxide (9 c.c.), was shaken with powdered *m*-nitrobenzoyl chloride (1·45 g.). After 10 minutes equal additional quantities of the latter two reagents were introduced. After further shaking, the mixture was acidified with hydrochloric acid and the resultant system of oil, solid, and water extracted thrice with ether. The oil and the aqueous portion were then evaporated to dryness and extracted with ethyl alcohol. Evaporation of the alcohol left an oil which crystallised after long contact with ethyl acetate. Crystallisation of this solid from aqueous alcohol yielded m-*nitrobenzopropylamidopropylarsinic acid*, m. p. 132—134° (Found: As, 19·9. $C_{13}H_{19}O_6N_2As$ requires As, 20·0%). The corresponding *benzoyl* compound is an oil which could not be crystallised.

γ-n-*Propylaminopropyldichloroarsine Hydrochloride*.—A solution of the amino-acid hydrochloride (1 g.) in concentrated hydrochloric acid (4 c.c.) containing a trace of potassium iodide was treated with sulphur dioxide until saturated. The crystals which separated on chilling were removed and recrystallised from concentrated hydrochloric acid (5 c.c.) with sufficient water to complete solution at the boiling point. γ-n-*Propylaminopropyldichloroarsine hydrochloride*, m. p. 195—196°, thus obtained forms elongated hexagonal tablets, which rapidly reduce a solution of iodine in potassium iodide and yield a yellow solid on treatment with saturated potassium iodide solution (Found: As, 26·4. $C_6H_{14}NAsCl_2,HCl$ requires As, 26·6%). The maximum tolerated dose is 0·0075 mg. It rendered trypanosomes non-infective at a dilution of 1 : 40,000 in horse-serum after 4·5 hours' contact.

γ-n-*Hexylaminopropylarsinic Acid*.—The chloro-acid (6 g.) and *n*-hexylamine (18 g.) were heated at 100° for 20 hours. After removal of the excess of amine, by distillation first under reduced pressure and then in the presence of sodium hydroxide, the residue was acidified with hydrochloric acid, evaporated to dryness, and extracted with ethyl alcohol (15 c.c.). The crystalline product, obtained by cooling the extract in ice, was recrystallised from ethyl alcohol and then yielded short, flat plates of γ-n-*hexylaminopropylarsinic acid hydrochloride*, m. p. 221—223° (6·2 g.). The maximum tolerated dose is 0·025 mg. The m-*nitrobenzoyl* derivative, m. p. 118—120°, prepared from the amino-acid hydrochloride (3·5 g.), *m*-nitrobenzoyl chloride (4·4 g.), and 2*N*-sodium hydroxide (35 c.c.) by the method already described, formed white plates (Found: As, 18·4. $C_{16}H_{25}O_6N_2As$ requires As, 18·0%). The maximum tolerated dose is less than 0·025 mg. The corresponding m-*aminobenzoyl* compound, formed by reduction with ferrous hydroxide, could not be obtained in a crystalline state either free or as the hydrochloride.

γ-Carbethoxy-n-*hexylaminopropylarsinic Acid.*—Ethyl chloroformate (1·2 g.) was added in small amounts with vigorous stirring to an ice-cold solution of the amino-acid (1 g.) in *N*-sodium hydroxide (6 c.c.). When the odour of the chloroformate had disappeared, the solution was acidified with hydrochloric acid and the precipitated oil removed. After prolonged manipulation and keeping at −5°, this solidified and was crystallised from ether–light petroleum. *γ-Carbethoxy*-n-*hexylaminopropylarsinic acid*, m. p. 58—60°, thus obtained, formed long, flat plates (Found : N, 4·1. $C_{12}H_{26}O_5NAs$ requires N, 4·1%). The maximum tolerated dose is 0·005 mg.

γ-Phenylcarbamyl-n-*hexylaminopropylarsinic Acid.*—Phenylcarbimide (4 g.) was added drop by drop to an ice-cold solution of the amino-acid hydrochloride (3 g.) in *N*-sodium hydroxide (25 c.c.) with vigorous stirring. The diphenylcarbamide that separated was removed and the filtrate made acid (Congo paper). The precipitated oil, which solidified after long keeping at 0°, was crystallised from aqueous alcohol and yielded *γ-phenylcarbamyl*-n-*hexylaminopropylarsinic acid*, m. p. 118—124° (indef.). The maximum tolerated dose is 0·01 mg.

γ-n-*Hexylaminopropyldichloroarsine hydrochloride*, prepared in a similar manner to that employed for the corresponding propyl compound from the amino-acid hydrochloride (3 g.) and concentrated hydrochloric acid (30 c.c.), forms large hexagonal plates, m. p. 190—192°, when crystallised from 2*N*-hydrochloric acid (100 c.c.) (Found : As, 23·1. $C_9H_{20}NAsCl_2,HCl$ requires As, 23·1%).

l-*α*-*Phenylethylaminopropyldichloroarsine Hydrochloride.*—The interaction of *l*-*α*-phenylethylamine (3·1 g.) and the chloro-acid (1·5 g.) was carried out in a manner similar to that employed for the preparation of the hexylamino-acid. The product, which remained as a glassy gum, could not be obtained pure and was converted directly into the dichloroarsine by treatment with hydrochloric acid and sulphur dioxide. The precipitate was crystallised from 2*N*-hydrochloric acid and the l-*α*-*phenylethylaminopropyldichloroarsine hydrochloride*, m. p. 194—196°, thus obtained, formed large hexagonal plates (Found : As, 21·9. $C_{11}H_{16}NAsCl_2,HCl$ requires As, 21·8%). The maximum tolerated dose is 0·005 mg.

γ-Piperidinopropylarsinic Acid.—A mixture of the chloro-acid (6 g.) and piperidine (26 g.) was heated for 6 hours at 100°, crystals of piperidine hydrochloride being deposited almost immediately. When the chlorine was completely ionised, the excess of free and combined piperidine was removed, the residue acidified with hydrochloric acid, and evaporated to dryness at 50°. The ethyl-alcoholic extract of the residue, when concentrated and chilled, deposited crystals which were recrystallised from boiling alcohol. *γ-Piperidino-*

propylarsinic acid hydrochloride thus obtained (5 g.) formed square plates, m. p. 162—164° (Found : N, 4·8; Cl, 12·4. $C_8H_{18}O_3NAs,HCl$ requires N, 4·9; Cl, 12·3%).

γ-Piperidinopropyldichloroarsine hydrochloride was prepared by treatment of the acid hydrochloride (3 g.), dissolved in concentrated hydrochloric acid (9 c.c.), with sulphur dioxide. The precipitated solid yielded hexagonal plates, m. p. 194—196° (2·4 g.), when crystallised from 4*N*-hydrochloric acid. The maximum tolerated dose is 0·01 mg.

γ-4-Hydroxy-2 : 2 : 6-trimethylpiperidinopropylarsinic Acid.—The chloro-acid (2 g.) was heated with vinyldiacetonealkamine (6·9 g.) and ethyl alcohol (20 c.c.) for 2 days. After basification with sodium hydroxide, followed by evaporation to dryness, the excess of amine was removed by exhaustive extraction with benzene, and the residue dissolved in water and made neutral to methyl-orange. The liquid was then evaporated to dryness and extracted with boiling methyl alcohol. On concentration of the extract, white, microscopic crystals separated. Recrystallisation of these from methyl alcohol yielded deliquescent *γ-4-hydroxy-2 : 2 : 6-trimethylpiperidinopropylarsinic acid*, m. p. 162° (Found : N, 4·7. $C_{11}H_{24}O_4NAs$ requires N, 4·5%). The maximum tolerated dose is 0·2 mg.

γ-2 : 2 : 6-Trimethylpiperidinopropylarsinic Acid and 2 : 2 : 6-Trimethylpiperidine. — 4-Bromo-2 : 2 : 6-trimethylpiperidine hydrobromide (44 g.), prepared from vinyldiacetonealkamine by the method of Pauly and Harries (*Ber.*, 1898, **31**, 667), was reduced by heating with glacial acetic acid (240 c.c.) and zinc dust (66 g.) for 6 hours. The solids were then removed and washed with hot acetic acid. The acid was then removed from the combined filtrates by distillation under reduced pressure, and the basified residue distilled in a current of steam until the distillate was neutral. The ethereal extract of the latter distillate yielded *2 : 2 : 6-trimethylpiperidine*, b. p. 138—139° (20 g.); *hydrochloride*, m. p. 236—237° (Found : Cl, 21·6. $C_8H_{17}N,HCl$ requires Cl, 21·7%). The following characteristic colour reactions are given by addition of this and similar amines (0·02 c.c.) to a 0·5% solution of sodium nitroprusside (20 c.c.) containing acetaldehyde (0·02 c.c.) (Lewin, *Ber.*, 1899, **32**, 3388): piperidine, initially violet-blue, unchanged after 4 hours; 2 : 2 : 6-trimethylpiperidine, initially wine-red, finally magenta; 3-carbethoxypiperidine, initially blue, finally green. The *chloroaurate*, prepared by treating a solution of the amine (0·1 g.) in 2*N*-hydrochloric acid (4 c.c.) with aqueous auric chloride until no further turbidity was produced, followed by crystallisation of the oil from *N*-hydrochloric acid, forms octahedra, m. p. 127—129° (Found : Au, 42·0. $C_8H_{17}N,HAuCl_4$ requires Au, 42·2%). The

picrate, prepared by the action of saturated aqueous picric acid on the amine (0·1 g.), followed by crystallisation of the precipitated oil from water, forms well-developed rhombs, m. p. 195—196°. For the preparation of the substituted aminopropylarsinic acid, γ-chloropropylarsinic acid (2·5 g.) was heated on the water-bath with the amine (10 g.) and alcohol (10 c.c.) for 6 hours. The solvent and free amine were then removed by distillation in the presence of sodium hydroxide, and the residue acidified with hydrochloric acid and evaporated to dryness. The ethyl-alcoholic extract of this yielded the amino-acid hydrochloride, which could not be obtained in a crystalline state; it was therefore converted into the free acid by adjusting the reaction to neutrality to litmus, evaporating the water, and extracting the residue with boiling methyl alcohol. Addition of dry ether to this extract yielded deliquescent, microscopic crystals of γ-2 : 2 : 6-*trimethylpiperidinopropylarsinic acid*, m. p. 150—160° (indef.) (Found : N, 4·4. $C_{11}H_{24}O_3NAs$ requires N, 4·8%). The maximum tolerated dose is 2·0 mg.

γ-*Piperazinopropylarsinic Acid*.—The product obtained by heating the chloro-acid (4 g.) with piperazine hydrate (24 g.) at 100° for 20 hours, was freed from piperazine by distillation in a current of steam at 100° under reduced pressure in the presence of sodium hydroxide. When the distillate no longer gave a precipitate with picric acid, the residue was acidified with hydrochloric acid (Congo paper), dried, and extracted with boiling ethyl alcohol. Upon concentration and cooling of the extract, a thick syrup separated which slowly solidified. Crystallisation of this from ethyl alcohol (30 c.c.) yielded γ-*piperazinopropylarsinic acid dihydrochloride* (Found : Cl, 21·9. $C_7H_{17}O_3N_2As,2HCl$ requires Cl, 21·8%). The maximum tolerated dose is 2·0 mg. The benzoyl derivative was obtained by the Schotten–Baumann method from the amino-acid hydrochloride (3·3 g.), benzoyl chloride (3·0 g.), and 2*N*-sodium hydroxide (35 c.c.). After the benzoic acid had been removed from the acidified reaction mixture by extraction with ether, the residue was evaporated to dryness and extracted with ethyl alcohol. This extract yielded a white solid which, when crystallised from aqueous acetone, yielded γ-4-*benzoylpiperazinopropylarsinic acid*, m. p. 204—206° (decomp., eff.) (Found : N, 8·0. $C_{14}H_{21}O_4N_2As$ requires N, 7·9%). The maximum tolerated dose is 0·2 mg.

γ-3-*Carbethoxypiperidinopropylarsinic Acid*.—The chloro-acid (3·1 g.) was heated with ethyl nipecotinate (15·7 g.) (prepared from nicotine by the method of Adams and McElvain, *J. Amer. Chem. Soc.*, 1923, **45**, 2745) for 15 hours at 90°. The ethyl nipecotinate was then removed by adding sodium hydroxide (8 c.c.; 40%) to a solution of the product in water (30 c.c.) at 0°, followed by extraction

with ether. The aqueous residue was then made acid with hydrochloric acid (methyl-orange) and evaporated to dryness at 50°. Extraction of this solid with boiling methyl alcohol (20 c.c.), followed by the addition of ethyl alcohol, yielded the desired amino-acid in an impure condition. For analysis and physiological testing, it was dissolved in methyl alcohol (15 c.c.) and poured into dry ether (120 c.c.). *γ-3-Carbethoxypiperidinopropylarsinic acid* thus obtained was dried in a vacuum in the presence of sulphuric acid and sodium hydroxide and ground under dry ether; it then formed an amorphous, deliquescent solid (Found : N, 4·3; As, 22·9. $C_{11}H_{22}O_5NAs$ requires N, 4·3; As 23·2%). The maximum tolerated dose is 1·5 mg.

Interaction of Trimethylene Glycol and p-*Toluenesulphonyl Chloride in the Presence of Pyridine.*

p-Toluenesulphonyl chloride (19 g.) was added in small portions to a mixture of trimethylene glycol (4 g.) and pyridine (8 g.) at 0°. Crystals of pyridine hydrochloride filled the liquid after about ½ hour, but became smaller in bulk after 20 hours, whereupon the whole was treated with water (100 c.c.). The oil which separated was removed and washed twice with dilute hydrochloric acid and with water. Since it possessed a pronounced smell of trimethylene dichloride, it was distilled with water under reduced pressure. By this treatment a small amount of volatile oil was obtained which, when extracted with ether and dried, gave trimethylene dichloride, b. p. 120—122°. The semi-solid residue of the steam distillation, after being dried in a vacuum, was extracted with ether, and the insoluble portion crystallised from methyl alcohol (6 c.c.). It separated in hexagonal plates (2·5 g.) which proved to be *trimethylene glycol di-p-toluenesulphonate*, m. p. 93—94° (Found : C, 52·8; H, 5·4. $C_{17}H_{20}O_6S_2$ requires C, 53·1; H, 5·3%). The aqueous extract of the original reaction mixture was freed from pyridine by distillation with sodium hydroxide under reduced pressure, concentrated (to 20 c.c.), and made neutral to litmus with hydrochloric acid; addition of saturated aqueous mercuric chloride solution then yielded a crystalline *mercury* salt, which in turn afforded an amine hydrochloride in the usual way. For examination of the properties of this amine the original reaction was conducted under modified conditions calculated to favour the production of a quaternary compound. Trimethylene glycol (4 g.) and pyridine (8 g.) were mixed with *p*-toluenesulphonyl chloride (19 g.) in a single addition and the reaction was allowed to proceed without cooling. When the reaction had subsided, the mixture was warmed on the water-bath for 2 hours. The crop of large, crystalline plates which separated

on cooling was washed with ether to remove pyridine and crystallised from acetone (30 c.c.). The deposited crystals (3·1 g.) were free from ionised chlorine and proved to be *propane-αγ-dipyridinium di-p-toluenesulphonate*, m. p. 118—120° (Found : N, 5·2. $C_{27}H_{30}O_6N_2S_2$ requires N, 5·2%). When treated with a saturated aqueous solution of mercuric chloride, this substance is converted into the corresponding *mercurichloride*. Crystallisation of the precipitated salt from boiling water gave a product from which the mercuric chloride was found to have partly dissociated (Found : Cl, 26·1; Hg, 57·5. $C_{13}H_{16}N_2Cl_2,4HgCl_2$ requires Cl, 26·1; Hg, 59·1%); but crystallisation in the presence of an excess of mercuric chloride yielded clusters of radiating needles of the pure mercurichloride (Found : Cl, 26·1; Hg, 59·5%). The combination of four molecules of mercuric chloride with one molecule of a diquaternary compound has been observed previously in a few cases (*e.g.*, Curtius and Clemm, *J. pr. Chem.*, 1900, **62**, 194). For the preparation of the diquaternary dichloride the *mercurichloride* was suspended in warm water and decomposed with hydrogen sulphide in the usual way. Evaporation of the aqueous product to dryness yielded an oil which, when dried in a vacuum, formed a mass of needle-like crystals, and recrystallisation from alcohol–ether gave pure *propane-αγ-dipyridinium dichloride* (Found : Cl, 26·3. $C_{13}H_{16}N_2Cl_2$ requires Cl, 26·1%). Treatment of this salt (0·1 g.) in boiling *N*-hydrochloric acid (40 c.c.) with aqueous auric chloride yielded, on cooling, elongated rectangular plates of the *dichloroaurate*, which became dark yellow when heated and were unmelted at 300°; on cooling, the original light yellow colour is restored (Found : Au, 44·7. $C_{13}H_{16}N_2Au_2Cl_8$ requires Au, 44·9%). The corresponding *dipicrate* crystallises from water in long, stout prisms, m. p. 176°.

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