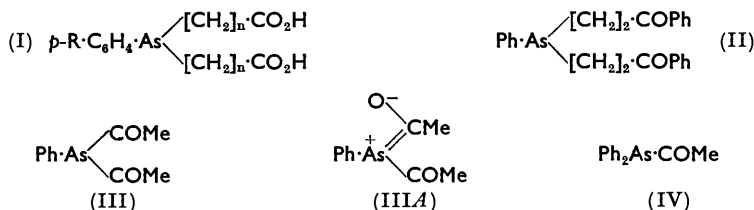


643. *Aliphatic Carboxylic Acids containing Arsenic. Di(carboxymethyl)phenylarsine and Related Compounds.*

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

The rather critical conditions for the preparation of di(carboxymethyl)phenylarsine by the Meyer reaction have been elucidated. The investigation of certain of its chemical and physical properties, and their comparison with those of closely related acids, have revealed three types of oxidation product; di(carboxymethyl)- and di-(3-carboxypropyl)-phenylarsine give the normal oxides, their di-(2-carboxyethyl) analogues give dihydroxide dilactones, and 2-carboxyethylphenylarsine gives a zwitterion of the betaine type.

SEVERAL tertiary dialkylarylsines are known in which the arsenic bears one or two radicals containing the carbonyl function of a ketonic or carboxylic group. For example, Cookson and Mann¹ prepared di-(2-carboxyethyl)phenylarsine (I; R = H, n = 2) and di-(2-benzoyl)ethyl)phenylarsine² (II) from di-(2-cyanoethyl)phenylarsine, and also prepared di-(3-carboxypropyl)phenylarsine (I; R = H, n = 3).² Compounds of this type, in which the arsenic atom is separated from electron-withdrawing groups, *e.g.*, carboxyl, by two or more methylene units, are stable, but compounds such as (III)³ and (IV)⁴ in which



these groups are directly joined, and which can be regarded as arsenic analogues of acid amides, have a low stability; they are readily oxidised and easily decomposed by dilute mineral acids. It is probable that stabilisation by structures such as (IIIA) would require energetically unfavourable $d_{\pi}-p_{\pi}$ bonding between arsenic and carbon.

We have now synthesised di(carboxymethyl)phenylarsine (IX), the first member of a series of dibasic acids intermediate in type between those discussed above. Quick and Adams⁵ have shown that dichlorophenylarsine (V), when subjected at room temperature to a Meyer reaction⁶ with aqueous sodium hydroxide and sodium chloroacetate, gives carboxymethylphenylarsinic acid (VI), which, when reduced in hydrochloric acid with sulphur dioxide, gives carboxymethylchlorophenylarsine (VII). We find that this compound, when subjected to a repetition of this Meyer reaction in boiling solution, gives

¹ R. C. Cookson and Mann, *J.*, 1947, 618.

² R. C. Cookson and Mann, *J.*, 1949, 67.

³ Job, Reich, and Vergnaud, *Bull. Soc. chim. France*, 1924, **35**, 1404.

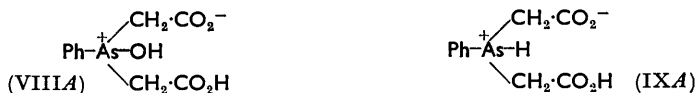
⁴ Steinkopf, Schubart, and Schmidt, *Ber.*, 1928, **61**, 678.

⁵ Quick and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 813.

⁶ Meyer, *Ber.*, 1883, **16**, 1440.

While the marked effervescence at the melting point of the oxidised acid (VIII) suggested a zwitterionic structure such as (VIIIA), no confirmatory evidence could be obtained from its infrared spectrum, nor did that of the acid (IX) in any way support the analogous possibility (IXA).

The positions of the absorption bands in the O-H and C=O bond stretching frequency regions of the spectra of the acid (IX) and certain other analogous derivatives of trivalent arsenic and phosphorus are given in the Table. The characteristic frequencies in the 900—950 cm^{-1} region, easily identifiable as rather broad-based bands of medium or high intensity, which are assigned to out-of-plane deformation of carboxyl group hydroxyl functions,¹¹ are also recorded. Bonner and Hofstadter¹² consider this band to be caused by the dimeric forms of carboxylic acids.

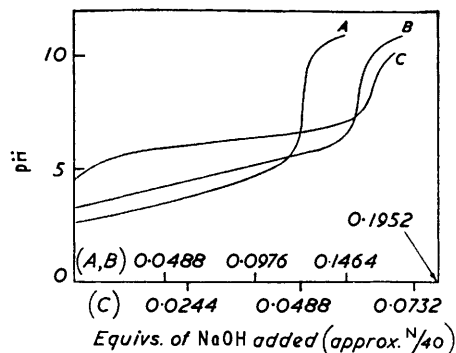


The high-frequency hydroxyl absorption patterns closely resemble that exhibited, for example, by glutaric acid¹⁴ and characterise dimeric hydrogen bonding of the carboxylic acids in the solid state. In the case of the acid (I; R = Cl, n = 2), additional absorption

FIG. 1. Potentiometric titration curves of aqueous solutions of the dibasic acids:

(A) Di(carboxymethyl)phenylarsine oxide (XIV; n = 1) (17.73 mg.). (B) Di(carboxymethyl)phenylarsine (IX) (21.08 mg.). (C) Di-(2-carboxymethyl)phenylarsine dihydroxide dilactone (XVI; R = H) (9.23 mg.).

The values of g.-equivs. of sodium hydroxide for (A) and (B) are given above, and those for (C) below, the horizontal axis.



at 2750 cm^{-1} , and the appearance of a second carbonyl band at 1717 cm^{-1} , suggest that the *para*-chloro-atom causes some additional interaction between carboxyl groups.

Infrared studies by Flett¹⁵ show that the C=O absorption band of several aliphatic dicarboxylic acids is also split, owing to carboxyl interaction; for example, the maxima

The O-H and C=O bands, determined with solid samples, in Nujol or hexachlorobutadiene mulls.

Compound	ν_{OH} (cm^{-1})	ν_{CO} (cm^{-1})	ν_{OH} (cm^{-1})
(I; R = H, n = 3) ¹	2640, 2560	1700	940
(I; R = H, n = 2) ¹	2630, 2550	1693	956
(I; R = Cl, n = 2) ¹	2750, 2660, 2560	1717, 1690	939, 925
(VII)	2640, 2540	1683	945, 920
(IX)	2640, 2540	1677	924, 904
$\text{Ph}_2\text{As}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ¹	2725, 2640, 2570	1712	938
$\text{Ph}_2\text{P}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ¹³	2725, 2630, 2540	1707	940

for anhydrous oxalic acid occur at 1710 and 1690 cm^{-1} . The effect becomes less marked as the number of intervening methylene groups increases, and adipic acid shows simple absorption at 1700 cm^{-1} .

¹¹ Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 1956, p. 148.

¹² Bonner and Hofstadter, *J. Chem. Phys.*, 1938, **6**, 531.

¹³ Mann and Millar, *J.*, 1952, 4453.

¹⁴ Bratoz, Hadzi, and Sheppard, *Spectrochim. Acta*, 1956, **8**, 249.

¹⁵ Flett, *J.*, 1951, 962.

The absorption of the C=O groups of the di-(3-carboxypropyl) acid (I; R = H, n = 3) is here regarded as normal (ν_{CO} 1700 cm^{-1}). A shift of ν_{CO} to lower frequencies occurs in the series as the methylene chains become shorter; this is correlated with the correspondingly increasing inductive effect of the arsenic atom, which, being less electronegative than carbon, exerts an influence opposite, for example, to that of halogen.¹⁵ (Thus β -chloropropionic acid shows carbonyl absorption at 1710 cm^{-1} , and the α -isomer does so at 1730 cm^{-1}) When halogen is attached to arsenic, as in the compound (VII), the two opposing effects give rise to a small resultant increase in carbonyl absorption frequency. A similar, but greater, shift is shown by the 2-carboxyethyldiphenyl-arsine and -phosphine included in the Table, and may be attributable to electron-withdrawal by the additional aromatic nucleus.

In order to extend the study of inductive effects in this series of acids, the corresponding tertiary arsine oxides were required. Although all the arsines discussed above resisted atmospheric oxidation, they were readily converted by hydrogen peroxide in aqueous

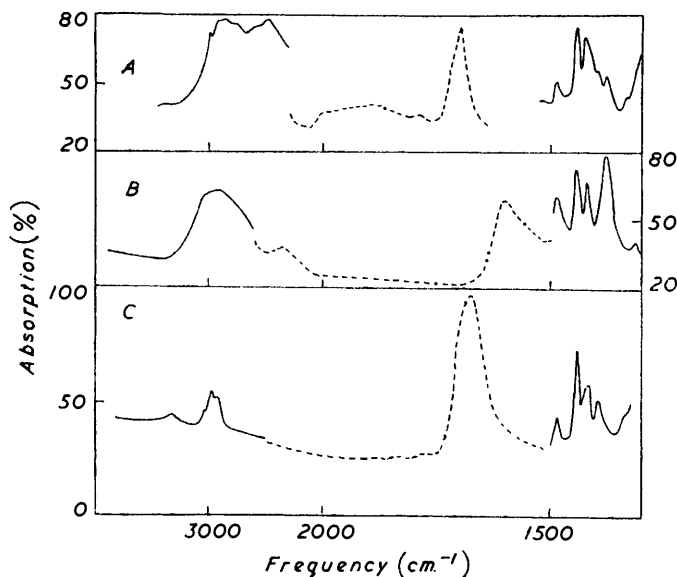


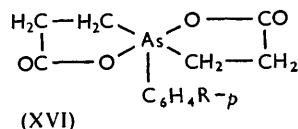
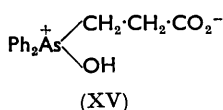
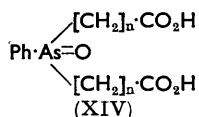
FIG. 2. Corresponding regions of the infrared spectra of solid suspensions, at arbitrary concentrations, in Nujol (-----) and hexachlorobutadiene (—), of: (A) Di(carboxymethyl)phenyl-arsine oxide (XIV; n = 1). (B) 2-Carboxyethyldiphenyl-arsine hydroxide betaine (XV). (C) Di-(2-carboxyethyl)phenyl-arsine dihydroxide dilactone (XVI; R = H).

acetone solution into stable crystalline oxidation products. Elementary analysis and infrared examination of these derivatives showed, however, that the four different types of arsine-carboxylic acid afforded three quite distinct classes of oxidation product; the contrasting structural features of these substances are clearly demonstrated by the portions of their infrared spectra (4000—1350 cm^{-1}) reproduced in Fig. 2.

The dicarboxylic acids (I; R = H, n = 3) and (IX) both yield oxides which are identical with those obtained by the Meyer reaction; they may be represented by the "normal" structure (XIV; n = 1 or 3). In the acid (XIV; n = 1) the semipolarised As=O link has a powerful effect on the carbonyl absorption frequency, which is changed by 20 cm^{-1} , in the expected direction, to 1697 cm^{-1} ; this effect is transmitted very weakly through three methylene groups in the oxidised product from (I; R = H, n = 3), causing an upward shift of only 5 cm^{-1} . The hydroxyl absorption of the compounds of type (XIV; n = 1 or 3) is particularly interesting; a rather feebly resolved system of bands centred in each case at 2480 cm^{-1} reveals "dimeric" hydrogen bonding of carboxyl OH functions in the usual way. An additional, very broad, region of absorption, centred at 1900 cm^{-1} , is due to hydroxyl bonded in some other way not possible in the parent acids and, therefore, probably involving the As=O group of the same or an adjacent molecule. At the lower-frequency end of the spectrum (not illustrated in Fig. 2) identification of the

bands due to O-H deformation is not possible with certainty, but strong bands, which occur at 815 cm^{-1} (XIV; $n = 3$) and at 844 cm^{-1} (XIV; $n = 1$), are attributed to the As=O bond.

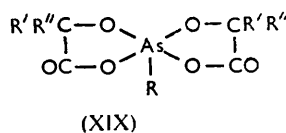
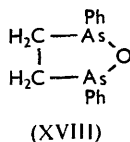
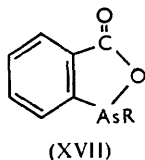
The oxidation product from 2-carboxyethyldiphenylarsine was found to have the expected composition $\text{Ph}_2\text{AsO}\cdot\text{C}_2\text{H}_4\cdot\text{CO}_2\text{H}$. Its infrared spectrum shows decisively, how-



ever, that it possesses the zwitterion structure (XV), for the pair of strong absorption bands characteristic of $-\text{CO}_2^-$ occur at 1597 and 1375 cm^{-1} . The bands attributed to bonded O-H in the parent acid are absent, and are replaced by a rather broad, ill-defined band at 2330 cm^{-1} and (possibly) by bands which are centred at 2890 cm^{-1} and therefore not distinguishable from those due to $\cdot\text{CH}_2\cdot$ groups. It is noteworthy that there is no dominant absorption in the region 800—900 cm^{-1} , to which the As=O vibration would give rise. The zwitterion (XV) is apparently the first authentic example of such a structure in arsenic compounds: it is closely analogous in type to a betaine.

Particular interest attaches to the oxidation products of the acids (I; $\text{R} = \text{H}$, $n = 2$) and (I; $\text{R} = \text{Cl}$, $n = 2$), which have the "dilactone" structure (XVI; $\text{R} = \text{H}$ and Cl respectively).

The evidence for structure (XVI) is fourfold: (i) Repeated elementary analyses show a composition which agrees with that of (XVI). (ii) The infrared spectra of the two compounds show no absorption that could be attributed to hydroxyl groups within the molecule. On the other hand, powerful carbonyl absorption occurs at 1681 ($\text{R} = \text{H}$) and 1684 cm^{-1} ($\text{R} = \text{Cl}$); this is consistent with the structure (XVI), particularly since the As-O bond is partially polar in character. The absorption band in the region 800—850 cm^{-1} , observed in the spectra of compounds (XIV; $n = 1$ or 3) and attributed to the As=O group, is not found in that of the compounds (XVI). (iii) The dilactone (XVI; $\text{R} = \text{H}$) can be titrated smoothly with dilute aqueous sodium hydroxide; a sharp end-point is obtained potentiometrically (Fig. 1), without an intermediate "step," and the equivalent weight of (XVI; $\text{R} = \text{H}$) thus derived agrees very closely with the theoretical value. The ease of hydrolysis of (XVI; $\text{R} = \text{H}$) is shown by the low pH (4.5) of its aqueous solution before titration. (iv) The compounds cannot be the isomeric cyclic anhydrides formed by loss of water from two carboxylic groups in the oxidised acids (as XIV; $n = 2$), for it is well established that cyclic anhydrides show two carbonyl absorption bands in the regions 1870—1820 and 1800—1750 cm^{-1} .



The readiness with which arsenic participates in the formation of a five-membered internal lactone (or anhydride) ring has been known for some time; for example, derivatives of *o*-carboxyphenylarsinous acid (and also of the arsenic acid) readily cyclise to anhydrides having the ring system (XVII).¹⁶ Ethylenebis(phenylarsinous acid) immediately forms the anhydride (XVIII), and the arsenic acid behaves similarly.¹⁷ Many other examples have been recorded.¹⁸

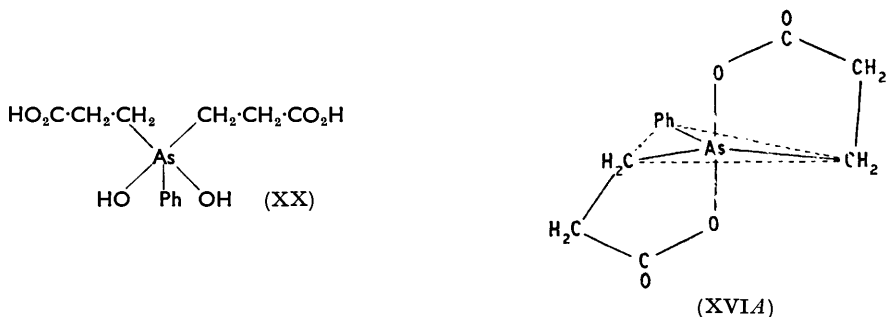
¹⁶ Aeschlimann and McClelland, *J.*, 1924, **125**, 2025.

¹⁷ Emrys R. H. Jones and Mann, *J.*, 1955, 401.

¹⁸ Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth and Silicon," Interscience Publ. Inc., New York, 1950, p. 58 ff.

Spirocyclic dilactones have not, however, hitherto been described, although compounds of closely related structures (XIX) have been claimed by Salmi and his co-workers¹⁹ to result from the interaction of arsonic acids and α -hydroxycarboxylic acids. The novel "lactonisation" which we now report involves reactive groupings without imposed rigidity (cf. XVII), and, unlike (XIX), is intramolecular in origin; it appears certain that the ring-closure proceeds *via* the dihydroxy-compound (XX), produced by hydration of the initial arsine oxide.

The probable spatial configuration of compounds of type (XVI) is shown in (XVIA);



coplanarity of the bonds from arsenic to both methylene groups and the aromatic nucleus will be derived from trigonal sp^2 hybridisation, while both cyclic oxygen atoms will be collinear with arsenic if the remaining pair of arsenic electrons undergo pd hybridisation. This structure would be analogous to that of the tertiary stibine dihalides.²⁰

This structure (XVIA) should allow the molecule to show optical activity, but the strong tendency to ring-opening in hydroxylic solvents would probably cause very rapid racemisation.

EXPERIMENTAL

All compounds were colourless.

Carboxymethylchlorophenylarsine (VII).—This was prepared by method of Quick and Adams,⁵ with the precautions stated above.

Di(carboxymethyl)phenylarsine (IX).—The chloroarsine (VII) (10 g.) and chloroacetic acid (4.3 g., 1 mol.) were added in this order to a solution of sodium hydroxide (7.8 g.) in water (100 c.c.), which was then boiled vigorously under reflux for 3 hr. The cold solution was poured into water (200 c.c.), made just acid to Congo-red with dilute hydrochloric acid, and, after the addition of potassium iodide (0.1 g.), cooled to 5–10° whilst being saturated with sulphur dioxide. After *ca.* 30 min., the crystalline almost pure *acid* (IX) (9 g., 82%) had separated: it had m. p. 126–127°, after crystallisation from water (Found: C, 44.3; H, 3.9%; equiv. wt., 135. $C_{10}H_{11}O_4As$ requires C, 44.4; H, 4.1%; equiv. wt., 135).

If the above reaction and acidification are carried out in more concentrated solution, the crystalline arsine oxide (see below) may separate. It can be dissolved in cold dilute acid and reduced as above.

Solutions of the acid (IX) and of an excess of hydrogen peroxide (20-vol.), each in acetone, when mixed and warmed, became initially cloudy as oily droplets separated, and finally became clear. On cooling, the solution deposited *di(carboxymethyl)phenylarsine oxide* (VIII), m. p. 148° (effervescence) after crystallisation from water (Found: C, 41.8; H, 3.4%; equiv. wt., 142. $C_{10}H_{11}O_5As$ requires C, 42.0; H, 3.85%; equiv. wt., 143).

The acid (IX) was unaffected when its solution in methyl iodide, in methanolic methyl iodide, and in nitromethane–methyl iodide was boiled under reflux.

Di-(3-carboxypropyl)phenylarsine oxide (XIV; $n = 3$) was prepared by the oxidation of the arsine (I; R = H, $n = 3$) in acetone–hydrogen peroxide solution, which, when concentrated,

¹⁹ Salmi, Merivuori, and Laaksonen, *Suomen Kem.*, 1946, **19**, B, 102.

²⁰ Wells, *Z. Krist.*, 1938, **99**, 367.

cooled, and diluted with acetone, deposited the oxide, m. p. 131—132°, after crystallisation from ethanol (lit.,¹ m. p. 133—136°).

2-Carboxyethyldiphenylarsine oxide (XV), prepared as the oxide (VIII), had m. p. 158°, from water (Found : C, 56.5; H, 4.6. $C_{15}H_{15}O_3As$ requires C, 56.6; H, 4.7%).

Di-(2-carboxyethyl)phenylarsine dihydroxide dilactone (XVI; R = H), similarly prepared, had m. p. 235° after crystallisation from water (Found : C, 48.7; 48.8; H, 4.3, 4.4%; equiv. wt., 146. $C_{12}H_{13}O_4As$ requires C, 48.7; H, 4.4%; equiv. wt., 148).

Di-(2-carboxyethyl)-p-chlorophenylarsine dihydroxide dilactone (XVI; R = Cl), similarly prepared, had m. p. 223° (from water) (Found : C, 43.4; H, 3.9; Cl, 10.7, 10.5. $C_{12}H_{12}O_4ClAs$ requires C, 43.6; H, 3.7; Cl, 10.7%).

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