CXXXII.—*Some Derivatives of Arylthioarsinous Acids.*

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THE formation of metallic derivatives of almost all aliphatic and aromatic thiol compounds is well known; of particular interest are those derived from a thiol compound containing an acidic group capable of forming neutral salts, *e.g.*, α-thiolacetic acid. The metallic thiolacetates constitute a means of obtaining metals in neutral aqueous solution in a non-ionised condition and may therefore find therapeutic application. The great therapeutic activity of aromatic arsenicals containing tervalent arsenic as compared with the corresponding arsinic acids renders the preparation of soluble

derivatives of these important and it seemed likely that thiol-acetates and other compounds of that type could be obtained from arylarsenious oxides and dihalogenoarsines in the same way as from arsenious oxide. This was found to be the case, the normal reaction to be expected taking place with formation of an arylthioarsinite :

$$Ar{\cdot}As{:}O + 2RSH \longrightarrow Ar{\cdot}As(SR)_2 + H_2O.$$

The part of the present work dealing with the above reaction has been anticipated in some degree by Kharasch in an American patent (No. 1,677,392).

A study of the properties and reactions of the di(carboxymethyl) arylthioarsinites led to the discovery that in acid, alkaline, or neutral solution the thiol group of an organic thiol compound reduces the quinquevalent arsenic atom of an arsinic acid to the tervalent state, and the compound produced combines with the excess of the thiol compound, giving the same compound as would be produced from the tervalent arsenic derivative according to the above equation. The reaction is represented thus :

$$Ar{\cdot}AsO(OH)_2 + 4RSH \longrightarrow Ar{\cdot}As(SR)_2 + 3H_2O + RS{\cdot}SR.$$

This method serves for the preparation of all the compounds of the above type for which it has been tested up to the present and is of much wider application than that involving the tervalent arsenic derivative, since it is frequently a matter of some difficulty to prepare the arylarsenious oxide or dihalogenoarsine by the usual methods from the arsinic acid.

The di(carboxymethyl) arylthioarsinites are in general well-defined crystalline solids. Acid does not liberate thiolacetic acid ; nor does hydrolytic fission occur with alkali, as the alkali-metal salts of the di(carboxymethyl) arylthioarsinites can be obtained from strongly alkaline solutions. These salts are neutral and generally extremely soluble in water and have pronounced therapeutic activity. In alkaline solution the arylthioarsinites give an intense nitroprusside reaction, although it has been shown that no fission to free thiol compound has occurred. They can be titrated with iodine in acid or in bicarbonate solution,

$$Ar{\cdot}As(SR)_2 + 2I_2 + 3H_2O \longrightarrow Ar{\cdot}AsO(OH)_2 + 4HI + RS{\cdot}SR ;$$

the same end-point is obtained with nitroprusside as an external indicator as with starch. This shows that the oxidation does not involve oxidation of the thiol or potential thiol groups, followed by the oxidation of the tervalent arsenic atom to the quinquevalent state. The arylthioarsinites are oxidised in alkaline solution by atmospheric oxygen to the parent arsinic acids, this process being much more rapid than is the case with the corresponding aryl-

arsenious oxides. Moreover the oxidation of the latter is accelerated by the presence of the disulphide form of the thiol compound.

This oxidation is being studied in detail, as it is obviously a type of reaction which may occur in the body on administration of such thiol compounds. The biological significance of this reaction and the reduction of arsinic acids by thiol groups will probably be discussed elsewhere. The arylthioarsinites are reduced by sodium hyposulphite to the corresponding arseno-compounds in the same way as are arsinic acids and arylarsenious oxides.

The molecular-weight figures are those found by means of iodine titration according to the equation given above.

EXPERIMENTAL.

Di(carboxymethyl) 4-Aminophenylthioarsinite, $NH_2 \cdot C_6H_4 \cdot As(S \cdot CH_2 \cdot CO_2H)_2$.—4-Aminophenylarsinic acid (2·2 g.) is added to a neutral solution of thiolacetic acid (3·8 g.) in 40 c.c. of *N*-sodium hydroxide. The arsinic acid dissolves and the solution remains neutral. On acidification with acetic acid the *thioarsinite* crystallises. It is sparingly soluble in cold water, more readily in hot, readily soluble in glacial acetic acid, and crystallises from hot water or dilute acetic acid in needles, m. p. 142—143° (Found: As, 22·1; N, 4·2; *M*, by iodine titration, 356. $C_{10}H_{12}O_4NS_2As$ requires As, 21·5; N, 4·0%; *M*, 349).

Di(carbethoxymethyl) 4-Aminophenylthioarsinite.—A solution of 4-aminophenylarsinic acid (2·2 g.) in 2*N*-hydrochloric acid (20 c.c.) is stirred with ethyl thiolacetate (5 g.) and after an hour the *hydrochloride* of the required ester is collected, washed free from ethyl dithiodiacetate with ether, and recrystallised by solution in water and addition of excess of hydrochloric acid. It forms needles, m. p. 100—105°, soluble in but hydrolysed by water; it is also soluble in alcohol and acetic acid but insoluble in ether (Found: As, 16·7. $C_{14}H_{20}O_4NS_2As,HCl$ requires As, 17·0%). The free base has only been obtained as an oil insoluble in water but readily soluble in organic solvents. In cold alkali the carbethoxy-group is hydrolysed, the di(carboxymethyl) thioarsinite being formed.

Di(carbamylmethyl) 4-aminophenylthioarsinite may be obtained from the preceding ester and aqueous ammonia but is most readily prepared by adding 4-aminophenylarsinic acid (2·2 g.) to a hot solution of thiolacetamide (3·8 g.) in 50 c.c. of water; on cooling, it separates in colourless needles, m. p. 145°, sparingly soluble in cold water, readily soluble in hot water and glacial acetic acid (Found: As, 21·6; N, 11·9; *M*, by iodine titration, 347. $C_{10}H_{14}O_2N_3S_2As$ requires As, 21·6; N, 12·1%; *M*, 347).

Di(carboxymethyl) 3-Amino-4-hydroxyphenylthioarsinite.—This is prepared from 3-amino-4-hydroxyphenylarsinic acid (2·3 g.) by the method used for the 4-amino-compound. It is dissolved in the minimum quantity of 25% sodium hydroxide solution required to give a solution neutral to litmus, and excess of alcohol added; the disodium salt then crystallises in needles. The pure *acid* recovered from this crystallises in colourless prismatic needles, m. p. 157—158°, sparingly soluble in cold water and alcohol, more readily soluble in hot, and readily soluble in glacial acetic acid (Found: As, 20·2; N, 3·8; S, 17·6; *M*, by iodine titration, 363. $C_{10}H_{12}O_5NS_2As$ requires As, 20·5; N, 3·8; S, 17·5%; *M*, 365).

Di(carbamylmethyl) 3-amino-4-hydroxyphenylthioarsinite forms needles, m. p. 132—133° (Found: As, 21·1; N, 11·5; *M*, 363. $C_{10}H_{14}O_3N_3S_2As$ requires As, 20·65; N, 11·6%; *M*, 363).

Di(β-carboxy-β-aminoethyl) 3-Amino-4-hydroxyphenylthioarsinite.—A warm solution of 3-amino-4-hydroxyphenylarsinic acid (2·3 g.) and cysteine hydrochloride (6·5 g.) in 100 c.c. of water is neutralised with ammonia, and the product filtered off rapidly before the cystine produced crystallises. The product, after solution in dilute hydrochloric acid (charcoal) and recovery, crystallises in very fine, matted needles (Found: As, 17·5; N, 9·9. $C_{12}H_{18}O_5N_3S_2As$ requires As, 17·7; N, 9·9%).

Di(carboxymethyl) 5-Acetamido-2-hydroxyphenylthioarsinite.—5-Acetamido-2-hydroxyphenylarsinic acid (5·5 g.) is added to a solution of thiolacetic acid (7·5 g.) in benzene (50 c.c.) and stirred well for a few minutes. The arsinic acid changes to a clear oil which then rapidly crystallises. The *product* is filtered off, washed with ethyl acetate (to remove dithiodiacetic acid), and recrystallised from hot water; m. p. 172—174° (Found: As, 18·6; *M*, 403. $C_{12}H_{10}O_4N_3S_2As$ requires As, 18·5%; *M*, 405).

Di(carboxymethyl) 4-Carbamylmethylaminophenylthioarsinite.—Sodium *N*-phenylglycineamide-4-arsinate (" tryparsamide ") (6·1 g.) is dissolved in water (50 c.c.), and thiolacetic acid (7·2 g.) in 2*N*-sodium hydroxide (40 c.c.) added. On acidification with hydrochloric acid the *product* is obtained as an oil which crystallises. It is purified through its sodium salt (square plates) and obtained from hot water in long slender prisms, m. p. 90° (Found: As, 18·1; *M*, 407. $C_{12}H_{15}O_5N_2S_2As$ requires As, 18·5%; *M*, 406).

Di(carboxymethyl) 8-acetamido-3-hydroxy-1:4-benzisooxazine-6-thioarsinite is obtained from the corresponding arsinic acid (Newbery, Phillips, and Stickings, J., 1928, 3060) in a similar way, and crystallises in needles, m. p. 212° (decomp.) (Found: As, 16·1; *M*, 460. $C_{14}H_{15}O_7N_2S_2As$ requires As, 16·2%; *M*, 462).

Di(carbamylmethyl) 8-acetamido-3-hydroxy-1:4-benzisooxazine-

6-*thioarsinite*, obtained in the usual way from the arsinic acid and thiolacetamide in aqueous solution, forms needles, m. p. 233—235°, from 25% acetic acid (Found: As, 16·9; *M*, 464. $C_{14}H_{17}O_5N_4S_2As$ requires As, 16·3%; *M*, 460).

Di(β-*carboxy*-β-*aminoethyl*) 8-*acetamido*-3-*hydroxy*-1 : 4-*benziso*-*oxazine*-6-*thioarsinite*, obtained from the arsinic acid and cysteine hydrochloride in the manner described above for the 3-amino-4-hydroxyphenylarsinic acid, crystallises in extremely fine, matted needles which set to a gel-like substance (Found: As, 13·8. $C_{16}H_{21}O_7N_4S_2As$ requires As, 14·4%).

Di(β-*hydroxyethyl*) 8-*acetamido*-3-*hydroxy*-1 : 4-*benzisooxazine* 6-*thioarsinite*, obtained from the arsinic acid (3·3 g.), dissolved in a slight excess of dilute aqueous ammonia, and β-hydroxyethyl mercaptan (3·2 g.), crystallises in needles (Found: As, 17·8. $C_{14}H_{19}O_5N_2S_2As$ requires As, 17·3%).

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