75. *Trypanocidal Action and Chemical Constitution. Part XII. Arylthioarsinites derived from κ-Thiolundecoic Acid.*
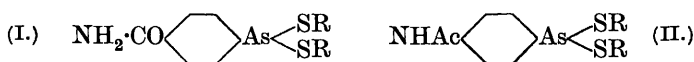
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IN Part X (Cohen, King, and Strangeways, J., 1931, 3043) the preparation and chemical properties of a number of arylthioarsinites were described and their therapeutic value in experimental trypanosomiasis in mice was discussed. These compounds were representatives of the types (I) and (II), derived from benzamide- and acetanilide-p-arsenoxides, in which R was an aliphatic or aromatic

$$\text{(I.)} \quad NH_2 \cdot CO \langle \bigcirc \rangle As \overset{SR}{\underset{SR}{<}} \qquad NHAc \langle \bigcirc \rangle As \overset{SR}{\underset{SR}{<}} \quad \text{(II.)}$$
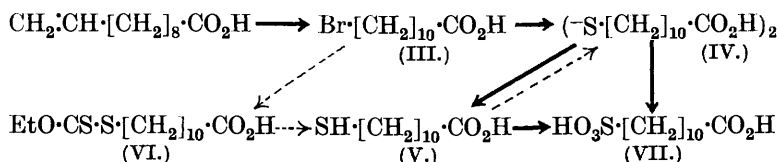
radical containing a substituent carboxyl group to permit the preparation of water-soluble sodium salts suitable for administration. The therapeutic results showed that many of these substances possessed marked trypanocidal activity. It was also found that, as the molecular weight of the thiol constituent (SR) in the above thioarsinite molecule increases, the maximum tolerated dose also tends to increase to values which are greater than those calculated from the content of the toxic arsenoxide.

The therapeutic efficiency thus exhibited by the arylthioarsinites suggested an extension of the investigation to compounds derived from higher homologues of the aliphatic thiol acid series. This communication concerns the dithioarsinites obtained by the condensation of benzamide- and acetanilide-p-arsenoxides with κ-thiolundecoic acid. These compounds conform to types (I) and (II), R being extended to a chain of eleven carbon atoms as shown below.

$$(NHAc)NH_2 \cdot CO \langle \bigcirc \rangle As \overset{S \cdot [CH_2]_{10} \cdot CO_2H}{\underset{S \cdot [CH_2]_{10} \cdot CO_2H}{<}}$$
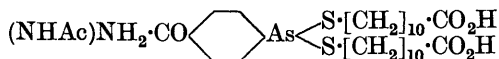
The stages by which κ-thiolundecoic acid (V) was prepared from undecenoic acid as starting material are represented in the following scheme (heavy arrows).

$$CH_2 \colon CH \cdot [CH_2]_8 \cdot CO_2H \longrightarrow Br \cdot [CH_2]_{10} \cdot CO_2H \longrightarrow (^-S \cdot [CH_2]_{10} \cdot CO_2H)_2$$
$$\text{(III.)} \qquad \text{(IV.)}$$

$$EtO \cdot CS \cdot S \cdot [CH_2]_{10} \cdot CO_2H \dashrightarrow SH \cdot [CH_2]_{10} \cdot CO_2H \longrightarrow HO_3S \cdot [CH_2]_{10} \cdot CO_2H$$
$$\text{(VI.)} \qquad \qquad \text{(V.)} \qquad \qquad \text{(VII.)}$$

Addition of hydrogen bromide to undecenoic acid may, theoretically, proceed in two ways resulting in the formation of κ- and ι-bromoundecoic acids. It was shown by Walker and Lumsden

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(J., 1901, **79**, 1192) that the bromoundecoic acid, m. p. 35°, so obtained by Brunner (*Ber.*, 1886, **19**, 2226) was probably ι-bromo-undecoic acid, and that saturation of a toluene solution of undecenoic acid with hydrogen bromide at 0° led to the formation of κ-bromo-undecoic acid (III), m. p. 51°. These conditions were adopted in the present work without success, but by following the procedure of Fairweather (*Proc. Roy. Soc. Edinburgh*, 1926, **46**, 72), according to which addition of hydrogen bromide is carried out in light petroleum solution at 0°, κ-bromoundecoic acid, m. p. 50—51°, was obtained. The product, as has been shown by previous workers, is readily isolated from the reaction mixture, being far less soluble than the ι-substituted acid. The yield, however, was about 45% of the theoretical throughout a large number of batches, which contrasts with the 90% yields reported by Flaschenträger and others (*Z. physiol. Chem.*, 1930, **192**, 245), using the same method. These authors remark, however, that the early attempts to prepare this acid were quite unsuccessful. The exact conditions which determine the addition of bromine to the terminal carbon atom are not clear, and it seems most probable that a mixture of κ- and ι-bromoundecoic acids is the usual product of this method of preparation.

κ-Bromoundecoic acid was converted by sodium disulphide into κ-*disulphidoundecoic acid* (IV), m. p. 92°, which was characterised by oxidation with nitric acid to κ-*sulphoundecoic acid* (VII), and reduced to κ-*thiolundecoic acid* (V). The condensation of the latter with benzamide- and acetanilide-*p*-arsenoxides was carried out in sodium hydrogen carbonate solution (compare Cohen, King, and Strangeways, *loc. cit.*), yielding the required *dithioarsinites*.

This work was completed when the preparation of the disulphide acid (IV) and of the thiol acid (V) was reported by Bauer and Stockhausen (*J. pr. Chem.*, 1931, **130**, 40), whose procedure is shown in the above scheme by broken arrows. Starting with bromoundecoic acid, and using Biilmann's method (*Annalen*, 1906, **348**, 125), they prepared κ-xanthatoundecoic acid (VI) by reaction with potassium ethyl xanthate. This substance is said to decompose at 88°, and to give, on treatment with ammonia, κ-thiolundecoic acid, m. p. 94—95°, which is oxidised by nitric acid to the disulphide (IV), m. p. 105—106°, after crystallisation from ether. The form-ation of a sulphonic acid was not observed in the nitric acid oxidation.

In order to throw some light on the discrepancies between the findings of Bauer and Stockhausen and those of the present author, their experimental conditions were adopted, in essentials, in the preparation of the disulphide (IV) and the thiol acid (V). The products obtained were not only different from those described by

Bauer and Stockhausen, but were identical with those which had been previously prepared as described in the earlier part of this paper. The reaction between κ-bromoundecoic acid and potassium ethyl xanthate is now found to give an excellent yield of *κ-xanthato-undecoic acid*, which crystallises readily from light petroleum and melts at 49°. When this is treated with ammonia, the same thiol acid is obtained as from the reduction of the disulphide described above, and specimens of the thiol acid from both sources give the same mercaptide. Moreover, the thiol acid obtained from κ-xanthatoundecoic acid is oxidised by hydrogen peroxide or iodine to κ-disulphidoundecoic acid, m. p. 92°, identical with that which had already been obtained from κ-bromoundecoic and sodium disulphide. This thiol acid was also oxidised by nitric acid according to the directions given by Bauer and Stockhausen and κ-sulpho-undecoic acid was again isolated.

In the light of these results, the nature of the substances described by Bauer and Stockhausen is far from clear. An explanation of the discrepancies revealed above may lie in their use of a bromoundecoic acid which is possibly of doubtful constitution, since their paper contains no statement regarding the melting point or source of this starting material.

The two thioarsinites from κ-thiolundecoic acid were tested on mice infected with *Trypanosoma equiperdum*. On account of the sparing solubility of their sodium salts in water, they were unsuitable for intravenous injection; accordingly they were given subcutaneously in aqueous suspension. They effected a rapid disappearance of trypanosomes from the blood stream in common with the thioarsinites previously described (Part X, *loc. cit.*), but relapses occurred on all doses at about the same time, due no doubt to inefficient distribution of the drug. The toxicities of the benzamide and acetanilide thioarsinites are roughly represented by 0·075 and 0·2—0·3 milligram per gram of mouse, respectively.

Experimental.

κ-Bromoundecoic Acid.—A solution of undecenoic acid (20 g.) in dry light petroleum (200 c.c.), which had been shaken with concentrated sulphuric acid and redistilled, was saturated with dry hydrogen bromide at a temperature not exceeding 0° (compare Fairweather, *loc. cit.*). The product, which crystallised, was collected on a cold filter (average yield, 45·5% of the theoretical). From six such batches, a further 19 g. of crude product were obtained on concentration of the mother-liquors. Recrystallisation of 280 g. of crude product from light petroleum at − 4° yielded 200 g. of κ-bromoundecoic acid, m. p. 50—51°.

κ-*Disulphidoundecoic Acid* (IV).—(a) Hydrated sodium sulphide (5·28 g. ; $Na_2S,9H_2O$) was gently heated with the addition of flowers of sulphur (0·7 g.). To the red melt was added a solution of κ-bromo-undecoic acid (10·6 g.) in water (100 c.c.) containing sodium hydrogen carbonate (3·36 g.), and the mixture was heated on a boiling water-bath for 1 hour. The disulphide acid separated (8·0 g.) on acidific-ation of the clear solution. It crystallises from acetone or glacial acetic acid in granular aggregates of small needles, m. p. 92°. Bauer and Stockhausen give m. p. 105—106° (Found : C, 60·7; H, 9·6; S, 15·0. Calc. for $C_{22}H_{42}O_4S_2$: C, 60·8; H, 9·7; S, 14·8%). It is readily soluble in warm organic solvents with the exception of ether. In common with other aliphatic disulphides (compare Part X, p. 3048), it is immediately reduced to the thiol acid by a solution of an arylarsenoxide (benzamide-*p*-arsenoxide) in aqueous sodium hydr-oxide with the development of a strong nitroprusside reaction.

(b) To a warm solution of 2·18 g. of κ-thiolundecoic acid (obtained from κ-xanthatoundecoic acid as described below) in 10 c.c. of glacial acetic acid, " perhydrol " (0·6 g.; 1 mol.) was added, and the solu-tion allowed to cool slowly. The product which crystallised (1·6 g.) contained no free thiol group (negative nitroprusside test) but on treatment with an alkaline solution of benzamide-*p*-arsenoxide developed a strong nitroprusside reaction. It separated from acetone or glacial acetic acid in crystalline nodules, m. p. 92° (Found : C, 60·0, 60·2, 60·2; H, 9·8, 9·7, 10·0; equiv., 217. Calc. for $C_{22}H_{42}O_4S_2$: C, 60·8; H, 9·7%; equiv., 217). The mixed melting point of this acid and of the product obtained as in (a) is also 92°. The same disulphide acid is also obtained if this oxidation of the thiol acid is carried out with iodine as oxidant.
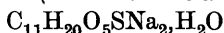
κ-*Xanthatoundecoic Acid* (VI).—κ-Bromoundecoic acid (24 g.) was dissolved in water (500 c.c.) with the addition of anhydrous sodium carbonate (4·8 g.). Potassium ethyl xanthate (16 g.) was added to the solution, which was then heated for 3 hours on a boiling water-bath. When the cooled solution was acidified to Congo-paper, κ-*xanthatoundecoic acid* was precipitated (27 g.). It crystallised from 4—5 volumes of light petroleum in lustrous leaflets, m. p. 49° (Found : C, 55·1; H, 8·5. $C_{14}H_{26}O_3S_2$ requires C, 54·9; H, 8·5%). According to Bauer and Stockhausen this xanthate derivative decomposes at 88°.

κ-*Thiolundecoic Acid* (V).—(a) The above disulphidoundecoic acid (4·34 g.) was dissolved in glacial acetic acid (30 c.c.) and hydro-chloric acid (10 c.c., *d* 1·16). The solution was gently refluxed while zinc dust (2·5 g.) was gradually added during 2 hours. The filtered solution was made turbid with dilute hydrochloric acid and cooled. The thiol acid, giving an intense nitroprusside reaction, separated

in filmy pointed leaflets (4·0 g.), m. p. 47°. Analytical data were not obtained, since attempts to recrystallise this substance resulted in gradual conversion of the thiol into the disulphide. After three crystallisations from alcohol, the melting point is 92°, alone or mixed with the disulphide. When treated with mercuric chloride in alcoholic solution, the thiol acid forms an insoluble mercaptide, separating as a white microcrystalline powder, m. p. 185—187° (decomp.).

(b) A solution of κ-xanthatoundecoic acid (10 g.) in alcohol (50 c.c.) and aqueous ammonia (20 c.c.; 25%) was kept at room temperature for 4 days, during which time a crystalline solid, probably an ammonium salt, slowly separated. The mixture was evaporated to a small bulk under reduced pressure at 50°, and dilute ammonium hydroxide (10 c.c.) was added. This was extracted with ether, and from the ethereal extracts, xanthogenamide was later isolated. The alkaline aqueous solution was acidified with hydrochloric acid (Congo-paper); the thiol acid then separated in fine pointed leaflets or needles identical in properties with the product obtained by method (a) above. Alcoholic mercuric chloride gives a mercaptide, m. p. 185—187° (decomp.) alone or mixed with the mercaptide already described (a).

κ-*Sulphoundecoic Acid* (VII).—Nitric acid (d 1·4; 20 c.c.) was added to the disulphide acid (4·34 g.). When the vigorous reaction had subsided, the mixture was heated on the water-bath for 4 hours. The liquid was diluted with water, and a small quantity of amorphous solid was filtered off. The solution, on repeated evaporation with water to remove nitric acid, yielded a waxy crystalline solid (2·5 g.) when strongly cooled (− 4°). This was dissolved in the minimum volume of warm concentrated hydrochloric acid, from which the *sulphonic acid* crystallised in long flat needles or leaflets, m. p. 63—65°. It is exceedingly soluble in water, methyl and ethyl alcohols and acetic acid, but not in benzene or light petroleum. On account of its highly hygroscopic nature reliable analytical data could not be obtained from combustions (Found : C, 46·1; H, 8·8; S, 11·7; equiv., 139. $C_{11}H_{22}O_5S$ requires C, 49·6; H, 8·3; S, 12·0%; equiv., 133). The characteristic *disodium* salt separates in needles from a solution of the acid in excess of concentrated aqueous sodium hydroxide (Found : loss at 95°, 5·55.

$$C_{11}H_{20}O_5SNa_2,H_2O$$

requires H_2O, 5·5%. Found for anhydrous material : Na, 14·8. $C_{11}H_{20}O_5SNa_2$ requires Na, 14·8%).

Action of Nitric Acid (d 1·2) *on* κ-*Thiolundecoic Acid*.—The thiol acid (2·3 g.) obtained from κ-xanthatoundecoic acid was treated with water (3 c.c.) and nitric acid (d 1·2 ; 6 c.c.) and heated on the

water-bath for 2 hours (compare Bauer and Stockhausen, *loc. cit.*). During the ensuing vigorous reaction the solid gradually dissolved. The liquid was diluted and cooled and the solid which separated was collected. This did not appear to be homogeneous. The absence of free thiol groups was shown by a negative nitroprusside test, and the presence of some disulphide by a positive reaction when the product was treated with alkaline benzamide-*p*-arsenoxide. On evaporation of the mother-liquor a crystalline solid (0·9 g.) was obtained. Crystallisation from concentrated hydrochloric acid yielded κ-sulphoundecoic acid, identical with that already described and giving the same disodium salt.

Thioarsinites derived from κ-Thiolundecoic Acid.—In the preparation of each of the following thioarsinites, the same product was obtained whether the thiol acid used was prepared by ammoniacal decomposition of the xanthate acid or by reduction of the disulphido-acid.

Di-(κ-carboxydecyl) benzamide-p-thioarsinite. Benzamide-*p*-arsenoxide (1·05 g.), added to a solution of κ-thiolundecoic acid (2·18 g.) in water (100 c.c.) containing sodium hydrogen carbonate (1 g.), dissolved when the mixture was boiled for some minutes. The solution was filtered and acidified. The *thioarsinite* (3 g.) separated from glacial acetic acid in microcrystalline granules, m. p. 270° (decomp.) after sintering at a lower temperature (Found : As, 11·5. $C_{29}H_{48}O_5NS_2As$ requires As, 11·9%). A solution of the thioarsinite in hot sodium hydrogen carbonate deposits a crystalline sodium salt imparting a characteristic sheen to the suspension. The latter gives no coloration with sodium nitroprusside, but an intense nitroprusside reaction is observed in sodium hydroxide solution.

Di-(κ-carboxydecyl) acetanilide-p-thioarsinite. By using acetanilide-*p*-arsenoxide (2·4 g.) and κ-thiolundecoic acid (4·36 g.), this *thioarsinite* was prepared in a similar manner to that described above for the benzamide analogue. Yield, 5·35 g. It crystallised from glacial acetic acid in boat-shaped leaflets, m. p. 117—118° (Found : As, 11·5. $C_{30}H_{50}O_5NS_2As$ requires As, 11·7%). A sparingly soluble sodium salt is formed in sodium hydrogen carbonate solution, and the normal nitroprusside reactions are exhibited by this compound.