CCCCI.—*Heterocyclic Compounds containing Arsenic. Part II. Derivatives of* 1 : 4-*Benz*isooxazine.

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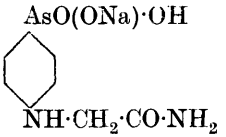
THE therapeutic importance of tryparsamide (sodium hydrogen phenylarsinate 4-glycineamide; I) and of stovarsol (3-acetamido-4-hydroxyphenylarsinic acid; II) suggested the desirability of preparing some hitherto undescribed products of the type of 3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid* (III) for pharmacological comparison.



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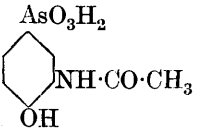

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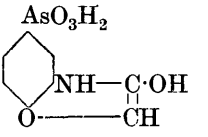
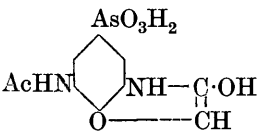


(III.)

The arsinic acid (III) was first prepared by reduction of 2-nitrophenoxyacetic acid 4-arsinic acid, the intermediate 2-amino-compound losing water under the conditions employed. It was also obtained from 3-chloroacetamido-4-hydroxyphenylarsinic acid (Raiziss and Fisher, *J. Amer. Chem. Soc.*, 1926, **48**, 1326), which readily loses hydrogen chloride in alkaline solution. Similarly, 3-chloroacetamido-5-acetamido-4-hydroxyphenylarsinic acid yielded 8-*acetamido*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid* (IV).



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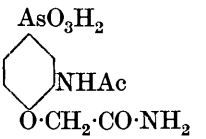

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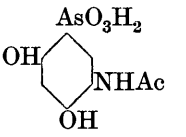


(VI.)

By using α-bromopropionyl chloride and α-bromobutyryl chloride in place of chloroacetyl chloride homologous 2-*alkylbenz*isooxazines were obtained.

2-*Acetamidophenoxyacetic acid* 4-*arsinic acid* and the corresponding *amide* (V), itself of pharmacological interest in its relationship to compounds (I) and (II), were obtained from sodium 3-acetamido-4-hydroxyphenylarsinate by the action of chloroacetic acid and chloroacetamide, respectively. Either, by the action of alkalis or mineral acids, underwent ring closure to form 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid. Similarly, 2 : 6-diacetamidophenoxyacetic acid 4-arsinic acid, on mild treatment by alkali or acid, gave the 8-acetamido-derivative (IV); complete hydrolysis gave the

corresponding amino-derivative. Finally, 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid was obtained from 6-amino-3-hydroxy-1 : 4-benz*iso*oxazine by the Bart reaction.

The diminution of toxicity and enhancement of curative effect in mice infected with *Trypanosoma equiperdum* shown by the acetamido-derivative (IV), when administered orally or intravenously, as compared with the parent substance (III) (Ewins and Everett, *Brit. J. Venereal Diseases*, 1927, **3**, 1; 1928, **4**, 181) made it desirable to prepare a number of other 8-derivatives and also some of its eleven structural isomerides.

Attempts to prepare the 8-hydroxy-derivative have, however, proved unsuccessful. None could be isolated by the thermal decomposition of the diazo-derivative of 8-amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid, nor could 3 : 4-dihydroxyphenylarsinic acid or its 5-nitro- or 5-amino-derivative be synthesised as a starting point for ring formation (compare Fargher, J., 1920, **117**, 865).

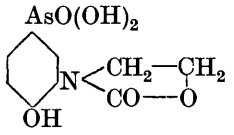
5-*Acetamido*-2 : 4-*dihydroxyphenylarsinic acid* (VI) and the corresponding 3 : 7-*dihydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid* were also prepared for comparison from 5-nitro-2 : 4-dihydroxyphenylarsinic acid (Bauer, *Ber.*, 1915, **48**, 515).

The nitration of 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid gave a mixture of 5-*nitro*-, 7-*nitro*-, and 8-*nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acids*. The last was present in 1—3% yield only and was better prepared from 5-nitro-3-amino-4-hydroxyphenylarsinic acid by the chloroacetyl chloride method. The proportion of the 5- and 7-nitro-compounds varied with the temperature of nitration. The 5-isomeride, the formation of which is favoured by low temperature, is the more soluble in water and may be separated by repeated fractional crystallisation, but is best separated by means of its neutral di-ammonium salt. Reduction of each by the method of Jacobs, Heidelberger, and Rolf (*J. Amer. Chem. Soc.*, 1918, **40**, 1580) gave the corresponding amino-compounds, the behaviour of which with nitrous acid gave the clue to their orientation: 5-*amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid* gave an insoluble *triazole* (compare 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine; preceding paper) and the 7-*amino*-compound gave a diazo-compound which coupled normally with alkaline β-naphthol, etc. This conclusion was fully confirmed by dearsenication of the amino-compounds, 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid giving with boiling 5*N*-hydrochloric acid a quantitative yield of 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine. The 7-amino-derivative, treated similarly, gave a small yield of a chlorinated product, m. p. 245°, apparently 6-chloro-7-amino-3-hydroxy-1 : 4-benz*iso*oxazine, but when boiled with sodium bi-

sulphite solution, it de-arsenicated smoothly with the formation in good yield of 7-amino-3-hydroxy-1 : 4-benz*iso*oxazine.

Attempts to prepare 2 : 3-*dihydro*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid* (VIII) by the action of ethylene chlorohydrin on 3-amino-4-hydroxyphenylarsinic acid with the intermediate formation of 3-β-hydroxyethylamino-4-hydroxyphenylarsinic acid were unsuccessful, but the application of the method of Adams and Segur (*J. Amer. Chem. Soc.*, 1923, **45**, 785) led to fair yields of the cyclic acid.

The action of β-chloroethyl chlorocarbonate on sodium 3-amino-4-hydroxyphenylarsinate gave 3-ω-*chlorocarbethoxyamino*-4-*hydroxyphenylarsinic acid*, which, with caustic soda, gave the required acid. It is assumed that there is formed as an intermediate product 2′-hydroxy-2-keto-3-phenyl-4 : 5-dihydro-1 : 3-*iso*oxazole-5′-arsinic acid (VII).



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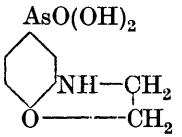

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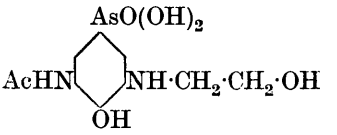

(IX.)

The mechanism by which this loses carbon dioxide to form the acid (VIII) is obscure, especially since attempts to form 8-acetamido-2 : 3-dihydro-1 : 4-benz*iso*oxazine-6-arsinic acid by an analogous method led to the formation of 5-acetamido-3-β-hydroxyethylamino-4-hydroxyphenylarsinic acid (IX), which was isolated as the corresponding *arseno*-compound readily soluble in caustic alkalis. In this case, therefore, ring closure does not occur.

In the 3-hydroxy-1 : 4-benz*iso*oxazine-8-arsinic acid series, the *parent* substance was obtained from 3-amino-2-hydroxyphenylarsinic acid by the chloroacetyl chloride method and also from 8-amino-3-hydroxy-1 : 4-benz*iso*oxazine by the Bart method. Its amino-derivative was obtained similarly from 3-amino-5-acetamido-2-hydroxyphenylarsinic acid and also from 3 : 5-diamino-2-hydroxyphenylarsinic acid (King, J., 1927, 1050) by chloroacetylation in alkaline solution.

Experimental.

A. 3-*Hydroxy*-1 : 4-*benz*iso*oxazine*-5-*arsinic Acid.*

2-Nitro-3-hydroxyphenylarsinic acid was prepared almost as described in D.R.-P. 256343 (1913). The 2-nitro-3-carbethoxyaminophenylarsinic acid (120 g.), however, was refluxed with 5*N*-sodium hydroxide (600 c.c.) for 1 hour; on acidification (Congo-red), a 50% yield of nearly pure nitrohydroxy-acid was obtained.

It formed rich yellow, hexagonal plates, m. p.* 208° (decomp.) (Found : As, 28·5; N, 5·3. Calc. : As, 28·5; N, 5·3%).

2-Amino-3-hydroxyphenylarsinic acid (compare Fourneau, Tréfouel, and Bénoit, *Bull. Soc. chim.*, 1927, **41**, 499) was obtained in 52% yield by reducing the above nitrohydroxy-acid (55 g. in 330 c.c. of hot water and 58 g. of sodium hydroxide) with glucose (44 g.). The mixture was gently boiled for 5 minutes and, after 1 hour, acidified markedly to Congo-red. Treatment with charcoal, filtration, and neutralisation to Congo-red with 10*N*-sodium hydroxide gave the amino-compound, which, after purification (compare Christiansen, *J. Amer. Chem. Soc.*, 1920, **42**, 2403), formed characteristic wedge-shaped crystals (Found : As, 32·2; N, 5·9. Calc. : As, 32·2; N, 6·0%). The calcium salt formed hexagonal plates and the acetyl derivative rectangular plates, m. p. 207—210° (decomp.) (Found : As, 27·4. Calc. : As, 27·3%).

3-*Hydroxy*-1 : 4-*benz*isoo*xazine*-5-*arsinic Acid.*—2-Amino-3-hydroxyphenylarsinic acid (20 g.), dissolved in 2*N*-sodium hydroxide (50 c.c.), was treated alternately with chloroacetyl chloride (15 c.c. in all) and 25% sodium hydroxide solution at 50°. The mixture was made strongly alkaline and heated at 90° for 10 minutes, more alkali being added as acidity developed. The cyclic *arsinic acid*, obtained in 60% yield on acidification, crystallised from boiling water in colourless rhombs, m. p. 245—248° (decomp.) (Found : As, 27·5; N, 5·0. $C_8H_8O_5NAs$ requires As, 27·5; N, 5·1%). The calcium, barium, and magnesium salts were amorphous, white solids. The orientations of this compound and of 2-nitro-3-carbethoxyaminophenylarsinic acid were confirmed by reduction of the latter by glucose and alkali giving 2 : 3-diaminophenylarsinic acid, m. p. 198° (decomp.) (compare D.R.-P. 256343).

B. 3-*Hydroxy*-1 : 4-*benz*isoo*xazine*-6-*arsinic Acid and its Derivatives.*

Preparation of the Acid.—(a) 2-Nitrophenoxyacetic acid 4-arsinic acid (Christiansen, *J. Amer. Chem. Soc.*, 1922, **44**, 2339), reduced by ferrous hydroxide (Jacobs, Heidelberger, and Rolf, *loc. cit.*), gave the *acid* in 57% yield. It crystallised from boiling water in rhombs, not molten at 300°, and was insoluble in cold water, dilute hydrochloric acid, and the usual organic solvents but soluble in alkalis and alkali carbonates (Found : As, 27·3; N, 5·25%). The calcium salt formed rosettes of needles, but the magnesium salt was amorphous.

(b) 2-*Acetamidophenoxyacetic acid* 4-*arsinic acid.* To 3-acetamido-

* All decomposition points above 200° were determined by rapid heating in a sulphuric acid bath at an initial temperature of 200°.

4-hydroxyphenylarsinic acid (45·5 g.) suspended in water (110 c.c.), sodium hydroxide (20 g.) in water (20 c.c.), followed by chloroacetic acid (16 g.), was added and the mixture was refluxed until it was acid to litmus (¾ hour). A further 7 g. of sodium hydroxide in water (7 c.c.) and chloroacetic acid (8 g.) were added and the boiling was continued until acidity to litmus again developed; the mixture was then acidified to Congo-red and, after cooling, the *arsinic acid* collected. After purification by solution in alkali, addition of acetic acid, filtration from a small amount of unchanged material, and acidification of the filtrate to Congo-red, it crystallised in long pointed needles, not molten at 280° (yield, 66%) (Found: As, 22·5; N, 4·15. $C_{10}H_{12}O_7NAs$ requires As, 22·5; N, 4·2%). The magnesium salt was amorphous.

2-*Acetamidophenoxyacetamide* 4-*arsinic acid* was prepared (yield, 26 g.) in a somewhat similar manner from 3-acetamido-4-hydroxyphenylarsinic acid (27·5 g.) and chloroacetamide (15 + 10 + 5 g.), sodium bicarbonate being added as the alkaline reaction disappeared. It crystallised from water in colourless, hexagonal plates, m. p. 236° (decomp.) (Found: As, 22·3; N, 8·15. $C_{10}H_{13}O_6N_2As$ requires As, 22·6; N, 8·4%) and formed an insoluble amorphous magnesium salt.

2-Acetamidophenoxyacetic acid 4-arsinic acid was heated (10 g.) for 1 hour at 90° with 5*N*-sodium hydroxide (20 c.c.) or refluxed (2 g.) with 4*N*-hydrochloric acid (10 c.c.). On acidification in the former case and on cooling in the latter, 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid was obtained (yields, 5·5 g. and 1 g., respectively) (Found: As, 27·3; N, 5·0%). The corresponding amide hydrolysed similarly.

(c) 6-Amino-3-hydroxy-1 : 4-benz*iso*oxazine hydrochloride (20 g.) (Newbery and Phillips, preceding paper), dissolved in water (200 c.c.) and hydrochloric acid (20 c.c.; *d* 1·12), was diazotised at 0—5° by sodium nitrite (7 g.) in solution and slowly added to a suspension of copper arsenite (prepared from arsenious oxide, 15 g., water, 40 c.c., sodium hydroxide, 6 g., and copper sulphate, 1·5 g.). The reaction of the mixture was maintained slightly alkaline by the addition of further sodium hydroxide when necessary. After heating with charcoal at 80°, the liquid was filtered, acidified to litmus, filtered from amorphous material after standing for some time, and acidified to Congo-red; the arsinic acid (12·5 g.; 46%) was then precipitated (Found: As, 27·3%).

(d) 3-Chloroacetamido-4-hydroxyphenylarsinic acid (1 g., m. p. 242°), prepared by a modification of Raiziss and Fisher's method (*loc. cit.*), was heated at 90° with sodium hydroxide (slightly more than 1 mol.) in 100 c.c. of water for 15 minutes; on acidification,

the same cyclic arsinic acid (0·6 g.) was obtained (Found : As, 27·5%).

(e) The cyclic acid (Found : As, 27·4; N, 5·1%) was also obtained directly from 3-amino-4-hydroxyphenylarsinic acid as described under 3-hydroxy-1 : 4-benz*iso*oxazine-5-arsinic acid.

2-*Nitrophenoxyacetic Acid* 4-*Dichloroarsine.*—A solution of 2-nitrophenoxyacetic acid 4-arsinic acid (10 g.) in water (10 c.c.) and hydrochloric acid (*d* 1·16; 25 c.c.) was added to a solution of potassium iodide (0·5 g. in 20 c.c. of water) saturated at 10° with sulphur dioxide. This gas was passed into the mixture at 10° for 1 hour and an equal volume of hydrochloric acid was then added. The *dichloroarsine* (7·2 g.; 70%), precipitated as rosettes of plates, was washed with hydrochloric acid and dried in a vacuum over sodium hydroxide. This compound (Found : As, 21·7; N, 4·2; Cl, 20·2. $C_8H_6O_5NCl_2As$ requires As, 21·9; N, 4·1; Cl, 20·75%) is very resistant to aqueous hydrolysis, and attempts to reduce it by stannous chloride or sodium hyposulphite were unsuccessful. Ferrous hydroxide, however, gave a small yield of 3-hydroxy-1 : 4-benz*iso*oxazine 6-arsenoxide which could not be purified.

3-*Hydroxy*-1 : 4-*benz*iso*oxazine* 6-*Arsenoxide.*—Reduction of the corresponding arsinic acid as described above under 2-nitrophenoxyacetic acid 6-dichloroarsine gave a 60% yield of 3-hydroxy-1 : 4-benz*iso*oxazine 4-dichloroarsine. This resisted purification, but gave, on solution in 2*N*-sodium hydroxide and addition of hydrochloric acid until the solution was only faintly acid to Congo-red, the *arsenoxide* in sphæro-crystals, insoluble in water or dilute mineral acids, alkali carbonates or dilute ammonia, but readily soluble in excess of dilute caustic alkali solution (Found : As, 31·3; N, 5·85. $C_8H_6O_3NAs$ requires As, 31·4; N, 5·85%). On treatment with excess of hydrochloric acid the dichloroarsine was obtained.

3 : 3′-*Dihydroxy*-6 : 6′-*arseno*-1 : 4-*benz*iso*oxazine.*—3-Hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (2·7 g.), dissolved in water (20 c.c.) and saturated sodium carbonate solution (5 c.c.), was added to a cold solution of magnesium chloride hexahydrate (2 g.) and sodium hyposulphite (10 g.) in water (200 c.c.). The filtered solution, on heating at 50—60° for 1½ hours, gave the *arseno*-compound, which, after being washed with water and dried in a vacuum over sulphuric acid, was a light yellow, amorphous solid, insoluble in water, dilute mineral acids, alkalis, and the ordinary organic solvents (Found : As, 33·2; N, 6·4. $C_{16}H_{12}O_4N_2As_2$ requires As, 33·6; N, 6·3%).

Nitration of 3-*Hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic Acid.*—The arsinic acid (20 g.), intimately mixed with potassium nitrate (7·5 g.), was added to sulphuric acid (70 c.c.) at 0°, 10°, and 30° in three experiments. The mixtures were poured on ice and the dried

nitro-compounds were recrystallised from hot water (500 c.c.), having first been dissolved by the aid of a little sodium hydroxide, followed by acidification. The treatment of the liquors is described below under the 8-nitro-derivative. The recrystallised solid was suspended in water (40 c.c.), and 15% ammonia added until a faint smell of ammonia and a faintly alkaline reaction were produced. The ammonium salt precipitated was collected and washed with a little ice-water; on acidification of its solution in boiling water (100 c.c.), 7-nitro-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid was obtained. The liquor, which contained a di-ammonium salt, on acidification gave 5-nitro-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid. The following table indicates the relative yields of the 7- and 5-nitro-isomerides.

Temp. of nitration.	Total yield.	7-Isomeride.	5-Isomeride.
0°	72%	29%	39%
10	75	35	35
30	73	41	28

5-*Nitro*-3-*hydroxy*-1 : 4-*benz*isoo*xazine*-6-*arsinic acid* crystallises from water in yellow prisms (Found : As, 23·7. $C_8H_7O_7N_2As$ requires As, 23·6%). It forms soluble crystalline calcium, barium, and magnesium salts and a sparingly soluble mono-ammonium salt. On reduction with ferrous hydroxide the corresponding *amino*-compound was obtained in 70% yield (Found : As, 26·1; N, 9·7. $C_8H_9O_5N_2As$ requires As, 26·0; N, 9·7%). It crystallises from water in colourless prisms, changing to hexagonal plates, not molten at 300°, is soluble in excess of mineral acids, but is reprecipitated on addition of water. The calcium and barium salts crystallise in white needles, the magnesium salt is micro-crystalline. The sodium salt is sparingly soluble in water but readily soluble in excess of caustic alkali. Attempts to acetylate this arsinic acid in alkaline or acetic acid solution or by the action of acetic anhydride were unsuccessful, the unchanged arsinic acid being obtained in the first two cases. The *triazole* formed white, hexagonal tufts or prisms, m. p. 247° (decomp.), from boiling water (Found : As, 23·7; N, 12·9. $C_8H_6O_5N_3As,H_2O$ requires As, 23·7; N, 13·25%). The calcium, barium, and magnesium salts were all sparingly soluble, amorphous, white solids, the calcium salt being less soluble in boiling than in cold water.

De-arsenication of 5-*amino*-3-*hydroxy*-1 : 4-*benz*isoo*xazine*-6-*arsinic acid.* The amino-arsinic acid (10 g.) was refluxed for 1 hour with 5*N*-hydrochloric acid (50 c.c.). The filtered solution on cooling gave 5·2 g. of 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine hydrochloride. A further 1·1 g. were obtained from the filtrate by treatment with

sodium carbonate and reconversion of the crude base (total yield, 90%). The hydrochloride gave with sodium acetate 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine, m. p. 236° (not depressed by admixture with the synthetic base; preceding paper).

7-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid* crystallised from boiling water, in which it was sparingly soluble, in long, yellow prisms (Found : As, 24·0%). The calcium, barium, and magnesium salts are soluble yellow solids. On reduction with ferrous hydroxide or glucose and alkali it gave a 70% yield of 7-*amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid*, which formed white prisms, m. p. 258—260° (decomp.), on addition of water to its solution in 25% sulphuric acid (Found : As, 26·0; N, 9·5%). The barium and calcium salts are crystalline (needles), the magnesium salt is amorphous. The *acetyl* derivative crystallised in white prisms, decomp. 275° (Found : As, 22·8; N, 8·5. $C_{10}H_{11}O_6N_2As$ requires As, 22·7; N, 8·5%), and the *urethane* in long needles (Found : As, 21·1; N, 7·7. $C_{11}H_{13}O_7N_2As$ requires As, 20·9; N, 7·8%). Both form amorphous calcium and magnesium salts.

De-arsenication of 7-*amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid*. The amino-arsinic acid (5 g.) was boiled under reflux with sodium bisulphite (3 g.) in water (20 c.c.). Solution was quickly effected and 7-amino-3-hydroxy-1 : 4-benz*iso*oxazine began to separate. After 30 minutes the mixture was made alkaline with sodium carbonate. The product (2·5 g.; 85%) crystallised from water in colourless prisms, m. p. 220°, not depressed by admixture with synthetic 7-amino-3-hydroxy-1 : 4-benz*iso*oxazine (preceding paper).

3 : 7-*Dihydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic acid*, obtained in good yield from 5-amino-2 : 4-dihydroxyphenylarsinic acid (Bauer, *loc. cit.*) by chloroacetylation in alkaline solution, crystallised from boiling water in white plates, not molten at 300° (Found : As, 26·1; N, 4·9. $C_8H_8O_6NAs$ requires As, 26·0; N, 4·9%). The barium salt crystallised from boiling water in clusters of colourless prisms, the calcium and magnesium salts were amorphous.

5-*Acetamido*-2 : 4-*dihydroxyphenylarsinic acid*, obtained by acetylation of the above amino-acid in the usual way, formed colourless prisms from water (Found : As, 25·6. $C_8H_{10}O_6NAs$ requires As, 25·9%). The calcium and magnesium salts are amorphous.

8-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*-6-*arsinic Acid*.—(a) The mother-liquors from the crystallisation of the crude nitration product of 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid gave, on neutralisation with ammonia, addition of excess of magnesium chloride, and heating, a yellow, crystalline precipitate (1 g.) of the magnesium salt. This was converted into the *acid* with dilute

hydrochloric acid (0·7 g. after crystallisation from boiling water) (Found : As, 23·8%).

(b) To 7·5 g. of 3-nitro-5-amino-4-hydroxyphenylarsinic acid (Newbery and Phillips, *loc. cit.*), dissolved in acetone (100 c.c.), was added chloroacetyl chloride (5 c.c.) at 25°. Removal of the bulk of solvent gave 3-*nitro*-5-*chloroacetamido*-4-*hydroxyphenylarsinic acid* (6·5 g.), which formed yellow prisms, m. p. 200° (decomp.), from boiling water (Found : As, 21·1; Cl, 9·9. $C_8H_8O_7N_2ClAs$ requires As, 21·1; Cl, 10·0%). The magnesium salt is amorphous. On treatment with slightly more than 1 mol. of sodium hydroxide a 60% yield of 8-*nitro*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid*, identical with the product from (a), was obtained. It formed almost colourless prisms, decomp. 320°. The calcium salt (yellow needles) is moderately easily soluble in cold water, and the magnesium salt (yellow needles) is insoluble, differing in this respect from the magnesium salt of the 5- and 7-nitro-compounds. Attempts to prepare this acid by nitration of 2-acetamidophenoxyacetic acid 4-arsinic acid failed, unchanged material only being obtained.

2 : 6-*Diacetamidophenoxyacetic acid* 4-*arsinic acid* was obtained in 75% yield [colourless prisms, m. p. 212° (decomp.), from water] by the action of chloroacetic acid on sodium 3 : 5-diacetamido-4-hydroxyphenylarsinate (Newbery and Phillips, *loc. cit.*) as described under 2-acetamidophenoxyacetic acid 4-arsinic acid (p. 3055) (Found : As, 19·2; N, 7·1. $C_{12}H_{15}O_8N_2As$ requires As, 19·2; N, 7·2%). The magnesium salt is amorphous. On treatment with boiling 5*N*-sodium hydroxide or 5*N*-hydrochloric acid 8-*amino*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid*, identical with the product obtained by reduction of the above 8-nitro-derivative with ferrous hydroxide, was obtained. It consisted of staggered plates, not molten at 300°, insoluble in water, but soluble in dilute mineral acids and in alkalis (Found : As, 26·0; N, 9·6%). The sulphate forms rhombs, sparingly soluble in cold water, the barium salt consists of colourless prisms, the calcium salt of white needles, and the magnesium salt is amorphous.

8-*Amino*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*hydroxychloroarsine hydrochloride* was obtained in 90% yield by reduction of the above amino-arsinic acid in 5*N*-hydrochloric acid by sulphur dioxide and potassium iodide, followed by precipitation with excess of hydrochloric acid (*d* 1·16). It formed tiny rhombs or needles (Found : As, 23·0; N, 8·1; Cl, 22·0. $C_8H_8O_3N_2ClAs,HCl$ requires As, 22·9; N, 8·6; Cl, 21·7%) and gave on treatment with water 8-*amino*-3-*hydroxy*-1 : 4-*benz*isooxazine 6-*arsenoxide hydrochloride*, which crystallised in colourless hexagonal plates, soluble in excess of water (Found : As, 25·6; Cl, 11·9. $C_8H_7O_3N_2As,HCl$ requires As, 25·8; Cl, 12·2%).

8 : 8′-*Diamino*-3 : 3′-*dihydroxy*-6 : 6′-*arseno*-1 : 4-*benz*isooxazine was obtained as a pale yellow, amorphous solid, insoluble in water, dilute caustic alkali solutions, and organic solvents, soluble in dilute hydrochloric acid (Found : As, 30·5; N, 11·7; atomic ratio As : N = 1 : 2·06. $C_{16}H_{14}O_4N_4As_2$ requires As, 31·5; N, 11·8%).

8-*Acetamido*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid*, made either by acetylation of the corresponding amino-acid or by chloroacetylation in alkaline solution of 3-amino-5-acetamido-4-hydroxyphenylarsinic acid (Newbery and Phillips, *loc. cit.*), formed colourless prisms, m. p. 275—280° (decomp.) (Found : As, 22·7; N, 8·5%). The barium and magnesium salts are amorphous. On reduction with sulphur dioxide and potassium iodide as above described, 8-*acetamido*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*dichloroarsine* (tufts of white needles) was obtained; this on treatment with water gave the *arsenoxide*, clusters of white needles, insoluble in water, sodium carbonate, or dilute mineral acids, soluble in dilute sodium hydroxide solution and in excess only of 10*N*-ammonia (Found : As, 25·3; N, 9·4. $C_{10}H_9O_4N_2As$ requires As, 25·3; N, 9·5%).

8 : 8′-*Diacetamido*-3 : 3′-*dihydroxy*-6 : 6′-*arseno*-1 : 4-*benz*isooxazine was obtained as a yellow amorphous solid, stable in air and insoluble in water, dilute mineral acids, alkalis, and organic solvents (Found : As, 26·1. $C_{20}H_{18}O_6N_4As_2$ requires As, 26·8%).

3-*Hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic Acid* 8-*Glycineamide*.—To 8-amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (13 g.) in sodium carbonate solution was gradually added, during 1 hour, chloroacetamide (5 g.) alternately with sodium bicarbonate (5 g.), a faint alkalinity to litmus being maintained. On acidification to Congo-red, the *arsinic acid* was obtained in 60% yield. It formed hexagonal plates from boiling water (Found : As, 21·5; N, 12·05. $C_{10}H_{12}O_6N_3As$ requires As, 21·7; N, 12·2%).

8-*Glycylamino*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic Acid*.—8-Amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (20 g.) in 2*N*-sodium hydroxide was treated with chloroacetyl chloride (10 c.c.) and 2*N*-sodium hydroxide by the Schotten–Baumann method. On acidification 8-chloroacetamido-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid was precipitated, which, after filtration and washing with water, was dissolved in excess of ammonia (*d* 0·880). After several hours, the mixture was heated to drive off the excess of ammonia and acidified strongly to Congo. Addition of sodium acetate to the filtered solution gave the *glycyl* derivative. Purified by solution in hydrochloric acid and neutralisation with sodium acetate, it formed minute needles, soluble in mineral acids and in alkalis (Found : As, 21·5. $C_{10}H_{12}O_6N_3As$ requires As, 21·7%).

8-*Chloro*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic Acid*.—8-Amino-

3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (28 g.) was diazotised at 0°, and the diazo-compound was collected and boiled with cuprous chloride (15 g.) dissolved in saturated sodium chloride solution containing a little hydrochloric acid. After treatment with charcoal and cooling, the precipitate obtained (15 g.; 50%) was dissolved in warm alkali and reprecipitated by acid; it then formed yellow prisms, not molten at 280°, sparingly soluble in boiling water (Found: As, 24·1; N, 4·3; Cl, 11·4. $C_8H_7O_5NClAs$ requires As, 24·4; N, 4·6; Cl, 11·5%). The magnesium salt is amorphous.

3-*Hydroxy*-8-*methyl*-1 : 4-*benz*isooxazine-6-*arsinic Acid.*—*The arsination of* o-*cresol.* The method of Christiansen (*J. Amer. Chem. Soc.*, 1923, **45**, 801) for the preparation of 4-hydroxy-3-methylphenylarsinic acid was modified by preliminary distillation of the *o*-cresol–arsenic acid mixture until $\frac{1}{2}$ molecule of water had been removed. The residual mixture was then refluxed with mechanical agitation for 4 hours and worked up as suggested by Christiansen. In this way a 25% yield of sodium 4-hydroxy-3-methylphenylarsinate, *i.e.*, twice that recorded by Christiansen, was obtained.

The sodium salt on nitration (compare Benda and Bertheim, *Ber.*, 1911, **44**, 3450) gave 3-nitro-4-hydroxy-5-methylphenylarsinic acid in 70% yield. On reduction by glucose and alkali as described under 2-amino-3-hydroxyphenylarsinic acid (p. 3054), a 60% yield of the corresponding amino-acid was obtained (compare D.R.-P. 224,953; Fourneau, *Ann. Inst. Pasteur*, 1926, 944). Purified by solution in hydrochloric acid and reprecipitation by sodium acetate, it formed colourless prisms, insoluble in water but readily soluble in alkalis. The monosodium salt (white needles) is sparingly soluble in cold water.

3 : 3′-*Diacetamido*-4 : 4′-*dihydroxy*-5 : 5′-*dimethylarsenobenzene*, obtained by reduction of 3-acetamido-4-hydroxy-5-methylphenylarsinic acid (compare E.P. 254,086), was a yellow, amorphous solid, insoluble in water, mineral acids, and organic solvents, soluble in dilute sodium hydroxide solution and in 50% acetic acid (Found: As, 29·8; N, 6·0. $C_{18}H_{20}O_4N_2As_2$ requires As, 31·4; N, 5·9%).

3-*Hydroxy*-8-*methyl*-1 : 4-*benz*isooxazine-6-*arsinic acid*, made by chloroacetylation in alkaline solution of 3-amino-4-hydroxy-5-methylphenylarsinic acid, crystallised from water in white prisms soluble in alkalis (Found: As, 25·9; N, 4·4. $C_9H_{10}O_5NAs$ requires As, 26·2; N, 4·9%).

3 : 3′-*Dihydroxy*-8 : 8′-*dimethyl*-6 : 6′-*arseno*-1 : 4-*benz*isooxazine was obtained as a yellow, amorphous solid insoluble in water, dilute mineral acids, alkali, and organic solvents, but soluble in 50% acetic acid (Found: As, 30·6; N, 5·6. $C_{18}H_{16}O_4N_2As_2$ requires As, 31·6; N, 5·9%).

8-β-*Hydroxyethylamino*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic Acid*.—8-Amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (15 g.) was treated at 40—50° with β-chloroethyl chlorocarbonate (10 c.c.) and 10*N*-sodium hydroxide. On acidification, 8-ω-chlorocarbethoxyamino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid (compare 3-ω-chlorocarbethoxyamino-4-hydroxyphenylarsinic acid, below) separated; it formed white needles from 50% acetic acid. This compound (12 g.) was refluxed for 40 minutes with 5*N*-sodium hydroxide (60 c.c.); on acidification, carbon dioxide was liberated and 8-β-*hydroxyethylamino*-3-*hydroxy*-1 : 4-*benz*isooxazine-6-*arsinic acid* (white prisms from boiling water) separated (Found : As, 22·5; N, 8·4. $C_{10}H_{13}O_6N_2As$ requires As, 22·5; N, 8·4%).

3-*Hydroxy*-8-*carboxy*-1 : 4-*benz*isooxazine-6-*arsinic Acid*.—5-Aminosalicylic acid (made by the method of Armin, Fisher, and Rosenberg, *Ber.*, 1898, **31**, 81) gave, by a modification of the Bart method, a 40% yield of 4-hydroxy-3-carboxyphenylarsinic acid.

3-*Nitro*-4-*hydroxy*-5-*carboxyphenylarsinic acid* (16 g.) separated when a mixture of 4-hydroxy-3-carboxyphenylarsinic acid (20 g.) and potassium nitrate (7·7 g.), added to sulphuric acid (100 c.c.) at 5°, was poured into ice-water (500 c.c.). It formed rich yellow plates of a monohydrate from boiling water and melted at 282—284° (decomp.) when anhydrous. It is moderately easily soluble in cold water and readily soluble in alkalis, giving a deep red solution with excess of sodium hydroxide (Found : H_2O, 5·7; As, 22·8; N, 4·25. $C_7H_6O_8NAs,H_2O$ requires H_2O, 5·5; As, 23·1; N, 4·3%). The magnesium, barium, and calcium salts are amorphous. On reduction with glucose and alkali, 3-*amino*-4-*hydroxy*-5-*carboxyphenylarsinic acid* was obtained; it formed white rhombs, not molten at 300°, from water (Found : As, 27·0; N, 4·8. $C_7H_8O_6NAs$ requires As, 27·1; N, 5·0%). The calcium, barium, and magnesium salts are amorphous. The acid is soluble in excess only of dilute mineral acids, but readily soluble in sodium hydroxide, forming a monosodium salt (needles) which is less soluble in water than the disodium salt.

3-*Acetamido*-4-*hydroxy*-5-*carboxyphenylarsinic acid*, prepared from the above amino-acid by acetylation in alkaline solution, crystallised from boiling water in long, colourless needles, m. p. 250—254° (decomp.). The magnesium and calcium salts are amorphous (Found : As, 23·4; N, 4·6. $C_9H_{10}O_7NAs$ requires As, 23·5; N, 4·4%).

3-*Hydroxy*-8-*carboxy*-1 : 4-*benz*isooxazine-6-*arsinic acid*, made by chloroacetylation in alkaline solution of 3-amino-4-hydroxy-5-carboxyphenylarsinic acid, formed white rhombs, m. p. 300—305° (decomp.), from water. It was soluble in alkalis, giving neutral

solutions, but was sparingly soluble in cold water (Found: As, 23·4; N, 4·5. $C_9H_8O_7NAs$ requires As, 23·6; N, 4·4%).

3-*Hydroxy*-2-*methyl*-1 : 4-*benz*isooxazine-6-*arsinic acid* was obtained from 3-amino-4-hydroxyphenylarsinic acid as described under 3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid, α-bromopropionyl bromide being used instead of chloroacetyl chloride. It formed colourless, pointed needles, not molten at 300°, from water. The calcium salt consists of tufts of needles, and the magnesium salt is amorphous (Found: As, 26·3; N, 4·8. $C_9H_{10}O_5NAs$ requires As, 26·2; N, 4·9%).

3-*Hydroxy*-2-*ethyl*-1 : 4-*benz*isooxazine-6-*arsinic acid*, obtained similarly by means of α-bromobutyryl chloride, formed colourless needles, not molten at 280°, from water. The calcium salt consists of tiny polyhedral crystals, the *magnesium* salt is amorphous (Found: As, 25·2; N, 4·35. $C_{10}H_{12}O_5NAs$ requires As, 24·9; N, 4·65%).

8-*Acetamido*-3-*hydroxy*-2-*methyl*-1 : 4-*benz*isooxazine-6-*arsinic acid*, obtained from 3-amino-5-acetamido-4-hydroxyphenylarsinic acid and α-bromopropionyl bromide, formed white prisms from boiling water. It decomposes at 265° and forms an amorphous magnesium salt (Found: As, 21·7; N, 8·05. $C_{11}H_{13}O_6N_2As$ requires As, 21·8; N, 8·1%).

8-*Acetamido*-3-*hydroxy*-2-*ethyl*-1 : 4-*benz*isooxazine-6-*arsinic acid* formed colourless needles from boiling water (Found: As, 20·7; N, 7·9. $C_{12}H_{15}O_6N_2As$ requires As, 20·9; N, 7·8%).

3-ω-*Chlorocarbethoxyamino*-4-*hydroxyphenylarsinic Acid*.—To 10 g. of 3-amino-4-hydroxyphenylarsinic acid in 30 c.c. of 2*N*-sodium hydroxide at 30° were added alternately β-chloroethyl chlorocarbonate (7 c.c.) and 10*N*-sodium hydroxide, the temperature being maintained between 35° and 40° and the reaction mixture being kept alkaline to litmus but not to phenolphthalein. The filtered solution was acidified to Congo-red, and the *arsinic acid* obtained was purified by acidification of its warm solution in sodium carbonate (yield, 9·5 g.; 63%). It formed colourless rhombic crystals, m. p. 209° (decomp.), insoluble in cold water, the alcohols or in dilute mineral acids, but readily soluble in alkalis (Found: As, 22·1; N, 4·1; Cl, 10·2. $C_9H_{11}O_6NClAs$ requires As, 22·1; N, 4·1; Cl, 10·45%). The magnesium salt is amorphous.

2 : 3-*Dihydro*-1 : 4-*benz*isooxazine-6-*arsinic Acid*.—The above chloro-acid (9 g.) was refluxed for 15 minutes with 30 c.c. of 4*N*-sodium hydroxide. When the filtered solution was acidified to Congo-red, carbon dioxide was evolved and the required *arsinic acid* precipitated. Crystallised by acidification of its hot alkaline solution, it formed white or buff-coloured, hexagonal prisms, not molten at 300°, insoluble in water and in most organic solvents

but readily soluble in alkalis (Found : As, 29·1 ; N, 5·6. $C_8H_{10}O_4NAs$ requires As, 29·0 ; N, 5·4%). It forms a white, amorphous magnesium salt.

2 : 3-*Dihydro*-1 : 4-*benz*isooxazine-6-*arsenoxide* was obtained by reduction of the corresponding arsinic acid, dissolved in 7 times its weight of hydrochloric acid (*d* 1·16), with sulphur dioxide and potassium iodide as described earlier. On addition of excess of hydrochloric acid, a gum separated, which later crystallised. The crude dichloroarsine was converted into the *oxide* by treatment with water. Purified by addition of hydrochloric acid to its solution in sodium hydroxide, it consisted of a white, amorphous solid insoluble in water, sodium carbonate, ammonia and organic solvents (Found : As, 34·0. $C_8H_8O_2NAs$ requires As, 33·3%). By treatment with excess of hydrochloric acid the dichloroarsine was formed as white prisms.

6 : 6′-*Arseno* (2 : 3-*dihydro*-1 : 4-*benz*isooxazine), obtained from the arsinic acid by hyposulphite reduction in the normal manner, is a yellow amorphous solid insoluble in water, caustic alkalis, dilute mineral acids, and the ordinary organic solvents (Found : As, 35·7 ; N, 6·6. $C_{16}H_{16}O_2N_2As_2$ requires As, 35·9 ; N, 6·7%).

3-ω-*Chlorocarbethoxyamino*-5-*acetamido*-4-*hydroxyphenylarsinic acid*, obtained from 3-amino-5-acetamido-4-hydroxyphenylarsinic acid by treatment with β-chloroethyl chlorocarbonate and caustic soda as described under 3-ω-chlorocarbethoxyamino-4-hydroxyphenylarsinic acid, crystallised from 30% acetic acid in long needles, m. p. 189° (decomp.). Its magnesium salt is amorphous (Found : As, 19·15 ; N, 7·0 ; Cl, 8·65. $C_{11}H_{14}O_7N_2ClAs$ requires As, 18·9 ; N, 7·1 ; Cl, 8·9%).

3 : 3′-*Di*(β-*hydroxyethylamino*)-5 : 5′-*diacetamido*-4 : 4′-*dihydroxyarsenobenzene*.—3-ω-Chlorocarbethoxyamino-5-acetamido-4-hydroxyphenylarsinic acid (5 g.) was heated in the water-bath for 30 minutes with 10% sodium hydroxide solution (20 c.c.). The mixture was then cooled and added to a solution of sodium hyposulphite (20 g.) and magnesium chloride hexahydrate (2 g.) in water (200 c.c.). After 2 hours' heating at 55°, the *arseno*-compound was collected, washed, and dried at 90°. It is a stable, pale yellow, amorphous solid, insoluble in water, sodium carbonate, dilute hydrochloric acid, or the usual organic solvents, but readily soluble in dilute caustic alkali solutions (Found : As, 26·2 ; N, 9·4. $C_{20}H_{26}O_6N_4As_2$ requires As, 26·4 ; N, 9·8%).

C. 3-*Hydroxy*-1 : 4-*benz*isooxazine-8-*arsinic Acid*.

6-Nitro-2-aminophenol, obtained as described in the previous paper, gave, by a modification of the Bart reaction, a 50% yield of

3-nitro-2-hydroxyphenylarsinic acid (compare Fourneau, Tréfouel, and Bénoit, *loc. cit.*), which formed characteristic yellow nodules, m. p. 252—254° (decomp.) (Found: As, 28·8%). The calcium, barium, and magnesium salts were yellow, amorphous solids. On reduction as described under 2-amino-3-hydroxyphenylarsinic acid, a 62% yield of 3-amino-2-hydroxyphenylarsinic acid (m. p. over 300°; magnesium and calcium salts amorphous), was obtained (Found: As, 32·2%). 3-Acetamido-2-hydroxyphenylarsinic acid (compare Fourneau, etc., *loc. cit.*) forms stout plates, m. p. 205° (decomp.), from water. Its calcium salt is amorphous and its barium salt microcrystalline (Found: As, 27·5; N, 5·0. Calc.: As, 27·3; N, 5·1%).

3-*Hydroxy*-1 : 4-*benz*isoo*xazine*-8-*arsinic acid*, obtained either from 3-amino-2-hydroxyphenylarsinic acid by chloroacetylation in alkaline solution as described above under the isomeric acids, or by the Bart reaction on 8-amino-3-hydroxy-1 : 4-benz*iso*oxazine (see previous paper), formed white needles, m. p. 298° (decomp.), from boiling water (Found: As, 27·5; N, 5·0%). The magnesium salt consists of clusters of needles, the calcium salt of characteristic, many-sided nodules, and the barium salt of white prisms. The sodium salt forms white needles readily soluble in water to give a solution neutral to litmus.

6-*Amino*-3-*hydroxy*-1 : 4-*benz*isoo*xazine*-8-*arsinic Acid.*—This was obtained in good yield from 3 : 5-diamino-2-hydroxyphenylarsinic acid (King, *loc. cit.*) by chloroacetylation in alkaline solution as in the preparation of 3-hydroxy-1 : 4-benz*iso*oxazine-5-arsinic acid (p. 3054), an excess of chloroacetyl chloride being used. Presumably the intermediately-formed 6-chloroacetamido-3-hydroxy-1 : 4-benz*iso*oxazine-8-arsinic acid is decomposed during the reaction.

6-*Amino*-3-*hydroxy*-1 : 4-*benz*isoo*xazine*-8-*arsinic acid* (Found: As, 26·0; N, 9·6%), obtained as above or by hydrolysis of the acetyl derivative, formed white prisms, not molten at 300°, from water. It is insoluble in cold water and organic solvents, but readily soluble in alkalis and in dilute hydrochloric and sulphuric acids, the sparingly soluble hydrochloride (prisms) and sulphate (rhombs) separating on standing. The barium salt forms white prisms, and the calcium salt rhombs; the magnesium salt is amorphous or microcrystalline. This acid is more basic than 7- and 5-amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acids, but less basic than 8-amino-3-hydroxy-1 : 4-benz*iso*oxazine-6-arsinic acid: 2·5 g. of the 6-amino-8-arsinic acid, 8-amino-6-arsinic acid, 7-amino-6-arsinic acid, and 5-amino-6-arsinic acid, suspended in 10 c.c. of water, require, respectively, 2·5, 4·3, 7, and 15 c.c. of 10*N*-sulphuric acid

for solution. Only the solutions of the last two amino-acids are hydrolysed by addition of water.

6-*Acetamido*-3-*hydroxy*-1 : 4-*benz*isooxazine-8-*arsinic acid*, obtained in 80% yield by acetylation of the corresponding amino-acid or in 50% yield by chloroacetylation in alkaline solution of 3-amino-5-acetamido-2-hydroxyphenylarsinic acid (Newbery and Phillips, *loc. cit.*), consists of white needles, not molten at 300°. It is insoluble in cold, sparingly soluble in boiling water (Found : As, 22·9; N, 8·5%). The magnesium salt is a white, amorphous solid.

6 : 6′-*Diacetamido*-3 : 3′-*dihydroxy*-8 : 8′-*arseno*-1 : 4-*benz*isooxazine, made by hyposulphite reduction of the above arsinic acid, is a pale yellow, amorphous solid, fairly stable in air. It is insoluble in water, alkalis, dilute mineral acids, and ordinary organic solvents (Found : As, 25·7; N, 9·5. $C_{20}H_{18}O_6N_4As_2$ requires As, 26·8; N, 10·0%).

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