

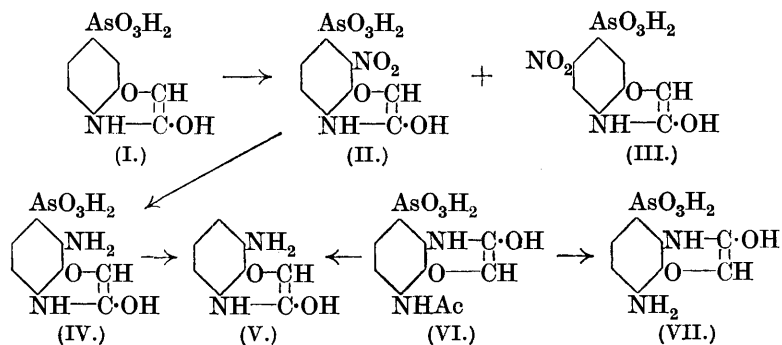
CCCCII.—*Heterocyclic Compounds containing Arsenic.*
Part III. Some Derivatives of 4-Amino-3-hydroxyphenylarsinic Acid.

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IN Part II (preceding paper) the heterocyclic compounds described were prepared mainly from 3-amino-4-hydroxyphenylarsinic acid. Similar derivatives of 4-amino-3-hydroxyphenylarsinic acid will now be described. Ewins and Everett (*Brit. J. Venereal Diseases*, 1927, **3**, 1) have shown that 3-hydroxy-1:4-benzisooxazine-6-arsinic acid and its 8-acetamido-derivative have $C/T = 1/25$ and $1/80$, respectively, *per os*, ratios sufficiently good to render desirable the study of further compounds of the same series.

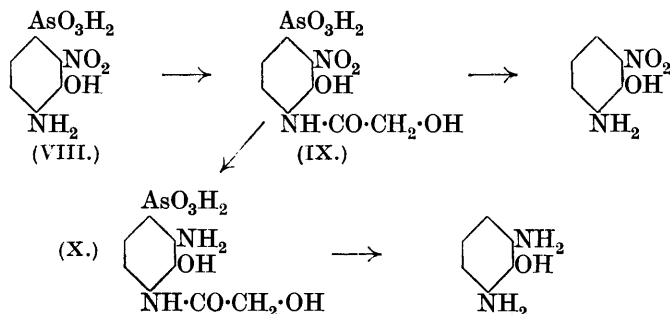
When 4-amino-3-hydroxyphenylarsinic acid is treated with chloroacetyl chloride in aqueous sodium hydroxide solution, 3-hydroxy-1:4-benzisooxazine-7-arsinic acid (I) (compare Aschan, *Ber.*, 1887, **20**, 1523) is obtained. On nitration of this acid a mixture of two isomeric nitro-derivatives is obtained. These represent 8-nitro-3-hydroxy-1:4-benzisooxazine-7-arsinic acid (II) and 6(?) -nitro-3-hydroxy-1:4-benzisooxazine-7-arsinic acid (III), respectively, because 8-amino-3-hydroxy-1:4-benzisooxazine-7-arsinic acid (IV), the reduction product of (II), on de-arsenication with 16% hydrochloric acid yields 8-amino-3-hydroxy-1:4-benzisooxazine (V). This amine is also obtained by the acid hydrolysis of 8-acetamido-

3-hydroxy-1 : 4-benzisooxazine-5-arsinic acid (VI) (compare Benda, *Ber.*, 1914, 47, 995), which is prepared from 2-amino-4-acetamido-3-hydroxyphenylarsinic acid (Balaban, this vol., p. 809), whereas the alkaline hydrolysis proceeds normally, giving 8-amino-3-hydroxy-1 : 4-benzisooxazine-5-arsinic acid (VII).



Although (III) has not been submitted to similar treatment owing to lack of material, nevertheless it is reasonable to assume *op*-nitration of the benzisooxazine arsinic acid under examination. Attempts to de-arsenate the nitro-compounds by acid hydrolysis were unsuccessful.

An unexpected result was obtained by the action of chloroacetyl chloride on 2-nitro-4-amino-3-hydroxyphenylarsinic acid (VIII), for the only product isolated was 2-nitro-4- ω -hydroxyacetamido-3-hydroxyphenylarsinic acid (IX). This is in contrast with the behaviour of 5-nitro-3-amino-4-hydroxyphenylarsinic acid (Part II), which gives a benzisooxazine derivative normally, and it can only be concluded that the influence of the nitro-group in this case is strong enough to inhibit ring closure. This fact was definitely



established by (a) de-arsenication of (IX) and subsequent isolation of 2-nitro-6-aminophenol, and (b) its reduction to 2-amino-4- ω -hydroxyacetamido-3-hydroxyphenylarsinic acid (X) and de-arsenication,

the 2 : 6-diaminophenol produced being identified in the forms of its di- and tri-acetyl derivatives.

When 3-nitrobenzoxazolone-5-arsinic acid, which is the main nitration product of benzoxazolone-5-arsinic acid, was boiled with 2*N*-sodium hydroxide for 3 hours, ammonia was evolved and the only identifiable product was 5-nitro-4-amino-3-hydroxyphenylarsinic acid, obtained in 41.0% yield. With hydrochloric acid, only unchanged material was recovered.

EXPERIMENTAL.

3-Hydroxy-1 : 4-benzisooxazine-7-arsinic Acid (I).—4-Amino-3-hydroxyphenylarsinic acid (23.3 g.), dissolved in 2*N*-sodium hydroxide, was treated with chloroacetyl chloride (15 c.c.); the chloroacetyl derivative which separated was redissolved by further additions of alkali. After heating on the water-bath for $\frac{1}{2}$ hour, the solution was acidified with hydrochloric acid, 12.9 g. of the desired acid (yield, 47.2%) being obtained. This acid crystallises from boiling water (10 parts) in rhomboids containing 1H₂O, and is identical with the compound obtained from 7-amino-3-hydroxy-1 : 4-benzisooxazine by the Bart-Schmidt reaction (Found on air-dried material: loss at 100°, 6.2. C₈H₁₀O₅NAs.H₂O requires H₂O, 6.2%. Found on material dried at 100°: As, 27.1; N, 4.9. C₈H₁₀O₅NAs requires As, 27.4; N, 5.1%). It is soluble in hot alcohol and moderately easily soluble in glacial acetic acid, from which it crystallises in rhomboids. The calcium salt crystallises in bunches of spikes, the magnesium and barium salts are amorphous.

Nitration of 3-Hydroxy-1 : 4-benzisooxazine-7-arsinic Acid.—The acid (10 g.) was nitrated at 0°, and on pouring the solution on ice and keeping, 6.6 g. of nitro-compounds, m. p. 275° (decomp.), were obtained. The mother-liquor deposited a further 1.8 g. (total yield, 72.4%). After recrystallisation from water the two crops were obtained in very pale yellow needles and colourless rectangular plates, respectively, representing the 8-nitro- and 6(?) -nitro-3-hydroxy-1 : 4-benzisooxazine-7-arsinic acids.

8-Nitro-3-hydroxy-1 : 4-benzisooxazine-7-arsinic acid (II) (Found on air-dried material: As, 23.8; N, 8.7. C₈H₇O₇N₂As requires As, 23.6; N, 8.8%) and *6(?) -nitro-3-hydroxy-1 : 4-benzisooxazine-7-arsinic acid* (III) (Found on air-dried material: As, 23.6. N, 8.5%) both decompose at 280°, the latter violently. Both acids are sparingly soluble in glacial acetic acid, from which they crystallise in rods and rectangular plates, respectively, and are insoluble in alcohol. The magnesium salts are amorphous, but the calcium salt of the 6(?) -nitro-acid crystallises in bunches of needles and the barium salt in diamond-shaped crystals.

8-Amino-3-hydroxy-1:4-benzisooxazine-7-arsinic acid (IV), prepared from (II) by the ferrous sulphate method (yield, 66.6%), crystallised from boiling 2*N*-acetic acid (20 parts) in clusters of almost colourless, fine, silky needles containing $\frac{3}{4}$ H₂O (Found on air-dried material: loss at 100°, 4.7; As, 25.0; N, 9.2. C₈H₉O₅N₂As, $\frac{3}{4}$ H₂O requires $\frac{3}{4}$ H₂O, 4.5; As, 24.9; N, 9.3%. Found on substance dried at 100°: As, 26.0. C₈H₉O₅N₂As requires As, 26.0%). It is readily soluble in 2*N*-hydrochloric acid and 80% formic acid, sparingly soluble in glacial acetic acid, and insoluble in alcohol. After diazotisation it gives with sodium β-naphthoxide a bright red solution. The barium salt forms fine needles, the calcium salt is micro-crystalline, and the magnesium salt amorphous.

De-arsenication.—When the amino-acid (2 g.) just described was heated with 16% hydrochloric acid (10 c.c.) for 1 hour, the compound of m. p. 180° (see p. 3070) was obtained in 61.4% yield.

8-Acetamido-3-hydroxy-1:4-benzisooxazine-7-arsinic acid, obtained by acetylation of the above acid in alkaline solution, crystallised from water in colourless, silky, anhydrous needles (Found on air-dried material: As, 22.6; N, 8.4. C₁₀H₁₁O₆N₂As requires As, 22.7; N, 8.5%), readily soluble in 80% formic acid, almost insoluble in glacial acetic acid, and insoluble in alcohol. The magnesium salt is gelatinous and the calcium salt separates in clusters of fine needles.

2-Nitro-4-ω-hydroxyacetamido-3-hydroxyphenylarsinic Acid (IX).—2-Nitro-4-amino-3-hydroxyphenylarsinic acid (20 g.), chloroacetylated in the usual manner, gave 13.5 g. (yield, 59.2%) of material which crystallised from water, in which it was moderately easily soluble, in golden-brown anhydrous plates, efferv. 210° (Found: As, 22.1; N, 8.2. C₈H₉O₈N₂As requires As, 22.3; N, 8.3%). The acid is sparingly soluble in alcohol and in glacial acetic acid, from which it crystallises in plates, and forms a rich red solution in aqueous sodium hydroxide.

De-arsenication. 0.5 G. of the nitro-acid, heated with 16% hydrochloric acid (2.5 c.c.) for $\frac{1}{2}$ hour, gave 2-nitro-6-aminophenol, m. p. 110° (alone or mixed with an authentic specimen).

2-Amino-4-ω-hydroxyacetamido-3-hydroxyphenylarsinic Acid (X).—The corresponding nitro-acid on reduction gave the amino-acid (85.5% yield), which crystallised from water (20 parts) in almost colourless clusters of stout anhydrous prisms (Found: As, 25.2; N, 9.1. C₈H₁₁O₆N₂As requires As, 24.5; N, 9.1%). It is soluble in excess of 2*N*-hydrochloric acid (giving a red solution after diazotisation and coupling with alkaline β-naphthol), moderately easily soluble in glacial acetic acid, very sparingly soluble in alcohol, and readily soluble in 80% formic acid. The magnesium, calcium, and barium salts are amorphous.

De-arsenication. The product of de-arsenication gave, after acetylation, the triacetyl derivative of 2 : 6-diaminophenol, m. p. ca. 200°, which after treatment with alkali gave 2 : 6-diacetamidophenol, m. p. 160°.

4-*ω*-*Hydroxyacetamido-2-acetamido-3-hydroxyphenylarsinic acid*, prepared by acetylation of the above acid, crystallised from water, in which it was moderately easily soluble, in fine, colourless, silky, anhydrous needles (Found on air-dried material : As, 22.0; N, 7.9. $C_{10}H_{13}O_7N_2As$ requires As, 21.7; N, 8.0%). It is moderately easily soluble in glacial acetic acid, but insoluble in alcohol. The magnesium salt is amorphous.

8-*Acetamido-3-hydroxy-1 : 4-benzisooxazine-5-arsinic Acid*.—10.5 G. of 2-amino-4-acetamido-3-hydroxyphenylarsinic acid, chloroacetylated as previously described, gave 2.95 g. (yield, 24.6%) of the *acid*, which crystallised from 2*N*-acetic acid, in which it was moderately easily soluble, in fine, colourless, silky, anhydrous needles (Found on air-dried substance : As, 23.1; N, 8.6. $C_{10}H_{11}O_6N_2As$ requires As, 22.7; N, 8.5%). It is readily soluble in 80% formic acid, moderately easily soluble in glacial acetic acid, very sparingly soluble in boiling water, and insoluble in alcohol. The magnesium salt is amorphous and the calcium salt forms acicular crystals.

8-*Amino-3-hydroxy-1 : 4-benzisooxazine*.—0.8 G. of the above acid was heated with 16% hydrochloric acid (4.0 c.c.) for $\frac{1}{2}$ hour. On cooling, 0.5 g. of the *benzisooxazine hydrochloride* separated. It crystallises in anhydrous, stout, hexagonal prisms from water, in which it is readily soluble when hot, chars at 270°, and decomposes at ca. 300° (eff.). Its aqueous solution is acid to Congo-red (Found on air-dried material : Cl, 17.4; N, 14.4. $C_8H_8O_2N_2 \cdot HCl$ requires Cl, 17.7; N, 14.0%). It diazotises normally. The *base* crystallises from hot water, in which it is fairly soluble, in long, colourless, silky, anhydrous needles, m. p. 180° (Found on air-dried material : N, 16.9. $C_8H_8O_2N_2$ requires N, 17.1%). It is readily soluble in alcohol and acetone, sparingly soluble in ether, and almost insoluble in benzene. The nitrate (long rectangular prisms) and the sulphate (short stout rods) are very soluble in water. The *acetyl* derivative crystallises from water, in which it is sparingly soluble, in long, colourless, silky anhydrous needles, m. p. 257° (Found on air-dried material : N, 13.6. $C_{10}H_{10}O_3N_2$ requires N, 13.6%). When the amine or its acetyl derivative is warmed with concentrated nitric and sulphuric acids, a bright blue colour develops; the amine hydrochloride produces an olive-green colour.

8-*Amino-3-hydroxy-1 : 4-benzisooxazine-5-arsinic Acid*.—2 G. of the corresponding acetyl derivative were hydrolysed with 2*N*-sodium

hydroxide (20 c.c.) for $\frac{1}{2}$ hour. This *acid* crystallises from water, in which it is sparingly soluble, in long rectangular prisms which contain $\frac{1}{2}$ H₂O not lost at 100° (Found on material dried at 100° : As, 24.8; N, 9.6. C₈H₉O₅N₂As, $\frac{1}{2}$ H₂O requires As, 25.2; N, 9.4%). It is readily soluble in 2*N*-hydrochloric acid and diazotises normally. It is soluble in 80% formic acid, sparingly soluble in glacial acetic acid, from which it crystallises in rectangular prisms, and insoluble in alcohol. The magnesium salt crystallises in irregular plates, the calcium and barium salts are amorphous.

Benzoxazolone-5-arsinic Acid.—4-Amino-3-hydroxyphenylarsinic acid (20 g.) was dissolved in 2*N*-sodium hydroxide and treated with carbonyl chloride; the solid which separated (yield, 20.6 g.; 93%) was insoluble in hydrochloric acid and after treatment with nitrous acid did not couple with sodium β -naphthoxide. This acid, mentioned in E.P. 214,628, crystallises from boiling water (25 parts) in long, colourless, anhydrous, boat-shaped plates (Found : As, 29.1; N, 5.5. Calc. for C₇H₆O₅NAs : As, 29.0; N, 5.4%). It is very sparingly soluble in glacial acetic acid and alcohol, but moderately easily soluble in 80% formic acid. The magnesium salt is micro-crystalline.

Nitration of Benzoxazolone-5-arsinic Acid.—The acid (8.63 g.) was nitrated at 0°, and the mixture poured on ice; 6.7 g. (yield, 66.1%) of product were collected. A prolonged fractional crystallisation from water gave evidence of the presence of more than one compound, but actually only one substance was obtained pure, the final mother-liquor giving material which was an inseparable mixture.

3-Nitrobenzoxazolone-5-arsinic acid, the subject of U.S.P. 1539798, crystallises from boiling water (20 parts) in almost colourless, stout, anhydrous, quadrilateral prisms (Found on air-dried material : As, 24.8; N, 9.1. Calc. for C₇H₅O₇N₂As : As, 24.7; N, 9.2%). It is moderately easily soluble in glacial acetic acid and 2*N*-acetic acid, from which it crystallises in quadrilateral prisms, sparingly soluble in 80% formic acid, and almost insoluble in alcohol.

5-Nitro-4-amino-3-hydroxyphenylarsinic Acid.—4 G. of the above acid were heated with 2*N*-sodium hydroxide (40 c.c.) for 4 hours, ammonia being evolved and the solution acquiring a deep reddish-violet colour. On acidification the desired *acid* was obtained in 41.0% yield. The mother-liquor gave with ferric chloride an intense bluish-green colour, indicating the presence of a pyrocatechol derivative; only a trace of crystalline material, however, could be isolated from it. This acid crystallises from water in bright yellow spikes containing 1H₂O which is not lost at 100° (Found on material dried at 100° : As, 25.7; N, 8.8. C₆H₇O₆N₂As, H₂O requires As,

25.4; N, 9.4%). It is sparingly soluble in water, almost insoluble in glacial acetic acid and alcohol, soluble in formic acid and concentrated hydrochloric acid, and diazotises normally. The calcium salt separates in laminae.

6-Nitrobenzoxazolone-5-arsinic Acid.—2-Nitro-4-amino-3-hydroxyphenylarsinic acid (6 g.) was treated with carbonyl chloride as previously described; the collected solid (3.9 g.; 59.6%) was insoluble in hydrochloric acid and after treatment with nitrous acid did not couple with sodium β -naphthoxide. This *acid* crystallises from water, in which it is very sparingly soluble, in long, pale brown, anhydrous, hexagonal plates (Found on material dried at 100°: As, 24.7; N, 9.2. $C_7H_5O_7N_2As$ requires As, 24.7; N, 9.2%). It is almost insoluble in alcohol and glacial acetic acid. The magnesium and barium salts are microcrystalline.

6-Aminobenzoxazolone-5-arsinic Acid.—The above nitro-acid on reduction gave an 82.4% yield of the *amino-acid*, which crystallised from 30 volumes of boiling water in colourless hexagonal laminae, containing $1H_2O$ which is lost at 100° (Found on air-dried material: loss at 100°, 6.0; As, 25.8. $C_7H_7O_5N_2As \cdot H_2O$ requires H_2O , 6.2; As, 25.7%. Found on material dried at 100°: As, 27.0; N, 10.5. $C_7H_7O_5N_2As$ requires As, 27.4; N, 10.2%). It is soluble in concentrated hydrochloric acid and diazotises normally, is readily soluble in 80% formic acid, very sparingly soluble in glacial acetic acid, and insoluble in alcohol. The magnesium, calcium, and barium salts are all microcrystalline.

6-Acetamidobenzoxazolone-5-arsinic acid, prepared by acetylation of the above acid, crystallised from 2*N*-acetic acid in colourless anhydrous leaflets (Found on air-dried material: As, 23.9. $C_9H_9O_6N_2As$ requires As, 23.7%). It is sparingly soluble in glacial acetic acid, from which it crystallises in minute rods. The magnesium salt is amorphous and the calcium salt microcrystalline.

6-Acetamidobenzoxazolone-3-arsinic Acid.—2-Amino-4-acetamido-3-hydroxyphenylarsinic acid (10 g.) was treated with carbonyl chloride as previously described. The product (9.0 g.; 81.8%) was insoluble in hydrochloric acid and after treatment with nitrous acid gave no coloration with sodium β -naphthoxide. This *acid* crystallises in anhydrous colourless leaflets from 2*N*-acetic acid, in which it is sparingly soluble (Found on air-dried material: As, 23.9; N, 8.7. $C_9H_9O_6N_2As$ requires As, 23.7; N, 8.9%). It is fairly readily soluble in water and almost insoluble in glacial acetic acid. The magnesium, calcium, and barium salts are amorphous.

The author desires to thank Mr. R. H. Klein, F.I.C., for the analyses recorded in this and the previous paper (this vol., p. 809),

and Mr. J. G. Everett, B.Sc., A.I.C., for the experimental results obtained with mice (see Ewins and Everett, *Brit. J. Venereal Diseases*, 1928, 4, 181) and also for the results detailed in the previous paper (*loc. cit.*).

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[Received, September 17th, 1928.]
