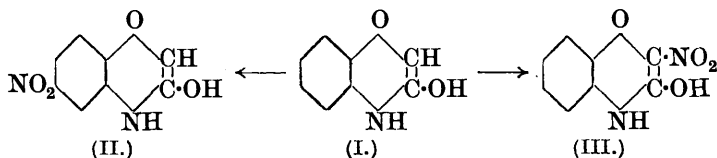


CCCL.—*The Nitration of 3-Hydroxy-1:4-benzisooxazine and its 7- and 8-Acetamido-derivatives.*

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THE present investigation was undertaken with a view to supplying materials for the preparation of hitherto unknown isomerides of 8-acetamido-3-hydroxy-1:4-benzisooxazine-6-arsinic acid, shown by Ewins and Everett (*Brit. J. Venereal Diseases*, 1927, **3**, 1) to possess a chemotherapeutic index (C/T) of 1/80 *per os*.

When 3-hydroxy-1:4-benzisooxazine (I) (Aschan, *Ber.*, 1887, **20**, 1523) is nitrated, a mixture of two nitro-compounds, melting at 235° and 155–157°, respectively, is obtained in the proportion of 1.6:1. The former is identical with the 6-nitro-3-hydroxy-

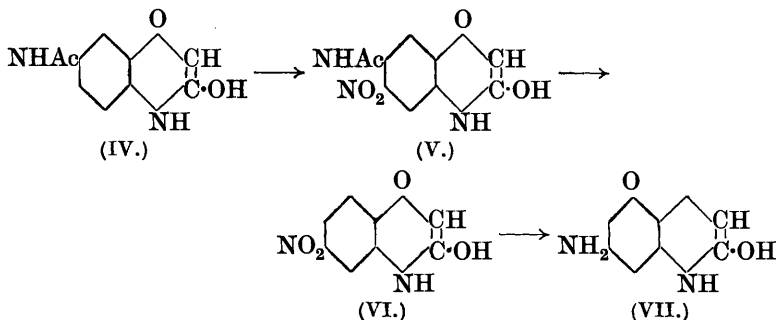


1:4-benzisooxazine (II) of Newbery and Phillips (*J.*, 1928, 3049), whereas the latter, although having the characteristics of a nitro-

benzisooxazine, is not identical with any of the nitrobenzisooxazines described by Newbery and Phillips, containing the nitro-group in the benzene portion of the nucleus. It is suggested, therefore, that the compound of m. p. 155—157° is 2-nitro-3-hydroxy-1 : 4-benzisooxazine (III), although definite proof is still lacking.

When 7-acetamido-3-hydroxy-1 : 4-benzisooxazine (IV) is nitrated, the sole product is the 6-nitro-derivative (V), oriented by identification of 6-nitro- (VI) and 6-amino-3-hydroxy-1 : 4-benzisooxazine (VII); whereas the 8-acetamido-derivative gives a mixture of the 6- and the 7-nitro-compound in the proportion of 3·4 : 1. It would appear, therefore, that the oxygen atom surpasses in directing influence the acetamido-group in the benzisooxazine ring.

The method of orientation employed was (a) elimination of the acetyl group, (b) deamination, followed by reduction, and identification of the amine formed, with known specimens by the mixed melting-point method.



EXPERIMENTAL.

The nitrations were carried out by dissolving the benzisooxazine (1 part) in concentrated sulphuric acid (4 c.c.) at 0°, and adding 1 mol. of nitric acid (*d* 1·42), dissolved in sulphuric acid, during 2 hours.

3-Hydroxy-1 : 4-benzisooxazine (I).—The crude nitration mixture (28 g.) obtained from 30 g. melted at 180—190°. After two recrystallisations from 50% acetic acid (450 c.c.) (charcoal), the m. p. was 230—232°; a further purification from 95% alcohol gave 13·38 g. of a substance, m. p. 235°, crystallising in almost colourless, rectangular prisms and identical with 6-nitro-3-hydroxy-1 : 4-benzisooxazine (II), m. p. 234° (Newbery and Phillips, *loc. cit.*). The mother-liquors deposited various crops melting at 155°, which, after recrystallisation from (a) 2*N*-acetic acid, (b) 95% alcohol, and (c) water, melted at 155—157° and amounted to 8·29 g. This substance,

which was assumed to be 2-nitro-3-hydroxy-1 : 4-benzisooxazine (III), crystallised in anhydrous, brilliant yellow, hexagonal prisms from water or 95% alcohol and in yellow rhombs from 2*N*-acetic acid (Found in air-dried material: N, 14.9, 15.1. $C_8H_6O_4N_2$ requires N, 14.4%). When reduced with iron, water, and a drop of acetic acid, it gave a base, the *acetyl* derivative of which crystallised in fine colourless needles, m. p. 283° (Found: N, 13.4. $C_{10}H_{10}O_3N_2$ requires N, 13.6%). On reduction with stannous chloride and hydrochloric acid, however, the main product was 3-hydroxy-1 : 4-benzisooxazine (87% yield), m. p. 171° (alone or mixed with an authentic specimen).

7-Acetamido-3-hydroxy-1 : 4-benzisooxazine (IV).—The crude nitrated material from 16.4 g. weighed 17.0 g. (m. p. ca. 255°). After being twice recrystallised from 50% acetic acid (charcoal), it melted at 276° (14.4 g.).

6-Nitro-7-acetamido-3-hydroxy-1 : 4-benzisooxazine (V) crystallised from 50% acetic acid in anhydrous golden-brown prisms (Found in air-dried material: N, 16.6. $C_{10}H_9O_5N_3$ requires N, 16.7%). It was very sparingly soluble in this solvent and also in water or alcohol. When it was boiled with 16% hydrochloric acid, 6-nitro-7-amino-3-hydroxy-1 : 4-benzisooxazine was obtained, which crystallised from 50% acetic acid (1 in 400) in anhydrous, long, red, hexagonal prisms, decomp. 317° (efferv.) (Found in air-dried material: N, 19.7. $C_8H_7O_4N_3$ requires N, 20.1%), insoluble in boiling water but sparingly soluble in alcohol. The nitro-amine (2.0 g.) was deaminated by dissolution in sulphuric acid and alcohol and treatment with solid sodium nitrite at 100°; 0.6 g. of needles, m. p. 227°, was then obtained, which, on reduction with iron, water, and a drop of acetic acid, gave 6-amino-3-hydroxy-1 : 4-benzisooxazine (VII), m. p. 255° (alone or mixed with an authentic specimen).

8-Acetamido-3-hydroxy-1 : 4-benzisooxazine.—16.4 G. on nitration gave 19.4 g. of a mixture, m. p. 267°, which was finally resolved by fractional crystallisation from 50% acetic acid (charcoal) and from water (charcoal) into (a) 10.45 g., m. p. 295—297° (efferv.), and (b) 3.0 g., m. p. 254°.

6-Nitro-8-acetamido-3-hydroxy-1 : 4-benzisooxazine crystallised from 50% acetic acid in long, bright yellow, rectangular prisms containing $1H_2O$, m. p. 295—297° (efferv.) (Found: loss at 100°, 5.9; N in air-dried material, 15.8, 15.9. $C_{10}H_9O_5N_3, H_2O$ requires H_2O , 6.7; N, 15.6%). It was very sparingly soluble in 50% acetic acid and almost insoluble in water, benzene, or ether, but soluble in alcohol. This compound (4.5 g.) was deacetylated by 16% hydrochloric acid, giving a hydrochloride (4.1 g.), crystallising from

hydrochloric acid in colourless prisms, decomp. 302° , which was readily dissociated by water, giving 6-nitro-8-amino-3-hydroxy-1:4-benzisooxazine, decomp. *ca.* 300° . This amine crystallised from water, in which it was very sparingly soluble, in anhydrous, deep yellow spikes (Found in air-dried material : N, 20.3. $C_8H_7O_4N_3$ requires N, 20.1%). It was moderately easily soluble in acetic acid, but less soluble in alcohol. The nitro-amine (1.5 g.) after removal of the amino-group gave 0.7 g., m. p. $226-227^{\circ}$ (needles), which on reduction gave 6-amino-3-hydroxy-1:4-benzisooxazine, m. p. 255° (alone or mixed with an authentic specimen).

7-Nitro-8-acetamido-3-hydroxy-1:4-benzisooxazine crystallised from water (1 part dissolves in 60 parts of boiling water) in very pale yellow, prismatic needles containing $1H_2O$, m. p. 254° (Found : loss at 100° , 7.1; N in air-dried material, 15.8. $C_{10}H_9O_5N_3 \cdot H_2O$ requires H_2O , 6.7; N, 15.6%). It was moderately easily soluble in acetic acid, very sparingly soluble in alcohol, and insoluble in benzene or ether. The nitro-compound (3.0 g.) was deacetylated as previously described, giving 7-nitro-8-amino-3-hydroxy-1:4-benzisooxazine (2.2 g.), which crystallised from 50% acetic acid in anhydrous yellow prisms, m. p. 302° (decomp.) (Found in air-dried material : N, 19.6. $C_8H_7O_4N_3$ requires N, 20.1%). This was moderately easily soluble in hot alcohol, but very sparingly soluble in water. After removal of the amino-group, 7-nitro-3-hydroxy-1:4-benzisooxazine, m. p. 230° , was obtained, which on reduction (0.5 g.) gave the 7-amino-derivative, m. p. 220° (alone or mixed with an authentic specimen).

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