LXVIII.—*The Bromination of some Derivatives of Veratrole.*

By JOHN LIONEL SIMONSEN and MADYAR GOPALA RAU.

IN previous communications (T., 1917, **111**, 69, 220; this vol., p. 22), the results of experiments were described on the nitration of some acetylamino-derivatives of veratrole and methoxybenzoic acids, and attention was directed to the relative orientating influence of methoxy-groups having positive or negative groups in the ortho- or para-positions. In continuation of these experiments, it appeared to us to be a matter of some interest to investigate the effect of bromination on the same series of compounds in order to determine whether substitution would proceed similarly. When these experiments were nearing completion, a paper by Jones and Robinson (T., 1917, **111**, 903) appeared which has anticipated our work in some directions.

We selected for our experiments the two isomeric acetylamino-veratroles and the three acetylaminoveratric acids, and the results obtained are shown diagrammatically below.

The bromination was performed either in chloroform or in glacial acetic acid solution, the sparingly soluble bromo-amide which separated was decomposed with water, and the product isolated in a suitable manner. As will be observed, the bromine always entered the nucleus in the para-position with respect to the acetyl-amino-group, except in the case of 6-acetylaminoveratric acid (XIV), when, this position being already occupied, the carboxyl group was eliminated with the formation of 5-bromo-4-acetylaminoveratrole (IX). Only in one case was the formation of an isomeride detected, namely, when 3-acetylaminoveratrole (I) was brominated under special conditions (see p. 786). It has not, unfortunately, proved possible to orientate this isomeride, which must be either the 4- or 5-bromo-derivative (III or IIIa), since on the elimination of the amino-group it yielded 4-bromoveratrole. From analogy, it is most probably the 4-isomeride, and this view receives

support from the fact that traces of this bromide were also formed during the bromination of 2-acetylaminoveratric acid (X).

The constitution of the main product of the bromination of 3-acetylaminoveratrole, 6-bromo-3-acetylaminoveratrole (II), was determined by eliminating the amino-group with the formation of 3-bromoveratrole (IV), a substance which was also prepared from 3-aminoveratrole (V), the bromide from each source being converted by nitration into 6-bromo-4-nitroveratrole (VI), which has already been described by Jones and Robinson (*loc. cit.*, p. 918).

The bromination of 4-acetylaminoveratrole (VIII) has already been investigated by Jones and Robinson (*loc. cit.*, p. 913), who found that 5-bromo-4-acetylaminoveratrole (IX) was formed. This result we are able to confirm, but we have found that the compound melted at 127—128°, and not at 140° as stated by these authors. In view of the ease with which this substance was obtained in a pure state, it appears to us probable that the melting point quoted by Jones and Robinson is due to a misprint.*

The determination of the constitution of the isomeric bromo-acetylaminoveratric acids (XI, XIII) obtained by the bromination of 2- and 5-acetylaminoveratric acids (X, XII) offered no difficulty, the corresponding bromoveratric acids being obtained on displacement of the amino-group by hydrogen.

In view of the fact that the formation of the bromo-amide always preceded substitution in the nucleus, which was therefore indirect, these experiments cannot be said to have thrown any light on the mechanism of the nitration of this type of substance. If indirect substitution directed by the methoxy-group does take place on nitration, it should prove possible by choice of suitable conditions to isolate this salt, and it is hoped to make further experiments with the object of throwing light on this problem.

EXPERIMENTAL.

Bromination of 3-Acetylaminoveratrole (I). 6-Bromo-3-acetylaminoveratrole (II).

In one experiment, 3-acetylaminoveratrole (3 grams) was dissolved in chloroform (9 c.c.), and to the ice-cold solution bromine (2.64 grams) dissolved in chloroform (3 c.c.) was gradually added, when bromination took place readily with the separation of the sparingly soluble yellow bromo-amide. After remaining for fifteen minutes, the precipitate was decomposed by the addition of water, the chloroform solution separated, washed with a little

* Prof. Robinson has since informed me that this is the case.—J. L. S.

dilute alkali, dried, and evaporated, when a theoretical yield of the bromoacetylamine was obtained. It was purified by crystallisation from dilute acetic acid:

0.1942 gave 0.1332 AgBr. Br=29.3.

0.1544 „ 7.6 c.c. N₂ at 30° and 758 mm. N=5.3.

C₁₀H₁₂O₃NBr requires Br=29.2; N=5.1 per cent.

6-Bromo-3-acetylaminoveratrole crystallises in prismatic needles melting at 78°. It is readily soluble in all the ordinary organic solvents with the exception of benzene and light petroleum. The same bromoacetylamine was found to be the sole product when glacial acetic acid was used as the solvent in place of chloroform.

6-Bromo-3-aminoveratrole was formed when the acetyl derivative was heated on the water-bath for some hours with hydrochloric acid (50 per cent.). It crystallises from dilute methyl alcohol in colourless needles melting at 66°, and is readily soluble in the ordinary organic solvents:

0.119 gave 6.6 c.c. N₂ at 30° and 759 mm. N=6.0.

C₈H₁₀O₂NBr requires N=6.0 per cent.

The benzoyl derivative crystallised from dilute alcohol in minute, radiating needles melting at 75°:

0.1935 gave 8.0 c.c. N₂ at 30° and 760 mm. N=4.4.

C₁₅H₁₄O₃NBr requires N=4.1 per cent.

3-Bromoveratrole (IV) and 6-Bromo-4-nitroveratrole (VI).

1. For the determination of the constitution of the bromo-amide described above, it was necessary to prepare 3-bromoveratrole. This substance, which does not appear to have been previously described, was readily obtained when 3-aminoveratrole (Gibson, Simonsen, and Rau, *loc. cit.*, p. 79) was diazotised and treated with cuprous bromide in the usual manner. It was purified by distillation in a current of steam and subsequent distillation under diminished pressure, when it was obtained as a somewhat viscid oil boiling at 114°/5 mm.:

0.1287 gave 0.1117 AgBr. Br=36.9.

C₈H₉O₂Br requires Br=36.9 per cent.

When 3-bromoveratrole was dissolved in acetic acid and treated with nitric acid (D 1.4), it yielded 6-bromo-4-nitroveratrole, which crystallised from alcohol in needles melting at 112—113°, and was found by direct comparison to be identical with the substance described by Jones and Robinson (*loc. cit.*, p. 918) (Found: N=5.5. Calc.: N=5.3 per cent.).

II. 3-Bromoveratrole was also formed when 6-bromo-3-amino-

veratrole (see above) was diazotised in alcoholic solution with amyl nitrite in the usual manner. It was identified by conversion into 6-bromo-4-nitroveratrole melting at 112—113° (Found: N=5.5. Calc.: N=5.3 per cent.).

4- or 5-Bromo-3-acetylaminoveratrole (III or IIIa).

For the preparation of this substance, the following method was found to be the most convenient. The acetylamine (5 grams) was dissolved in acetic acid (50 per cent.: 20 c.c.) and bromine (4.2 grams) was gradually added to the well-cooled solution. When bromination was complete, the mixture was diluted with water and ammonia added until a nearly neutral solution was obtained. On remaining overnight, the bromination product, A, separated; this was collected and the filtrate repeatedly extracted with ether. The ether was evaporated and the residual oil triturated with cold acetone, when a sparingly soluble solid remained. This was mixed with the product A (see above) and purified by crystallisation from acetone, when it separated in well-defined octahedra melting at 151° (yield, 2 grams):

0.1966 gave 0.136 AgBr. Br=29.4.

0.1842 , 9.4 c.c. N₂ at 30° and 756 mm. N=5.3.

C₁₀H₁₂O₃NBr requires Br=29.2; N=5.1 per cent.

4- or 5-Bromo-3-acetylaminoveratrole is readily soluble in alcohol or acetic acid, more sparingly so in benzene, acetone, ether, or light petroleum.

The corresponding *amine* was obtained by heating the acetyl derivative for one hour on the water-bath with sulphuric acid (50 per cent.). It separated from dilute methyl alcohol in colourless needles melting at 49°:

0.1268 gave 0.1023 AgBr. Br=34.4.

C₈H₁₀O₂NBr requires Br=34.4 per cent.

The *benzoyl* derivative, C₁₅H₁₄O₃NBr, crystallised from dilute alcohol in needles melting at 146°.

The *platinochloride* separated from dilute hydrochloric acid in aggregates of yellowish-brown prisms which darkened at 200° and gradually decomposed when heated above this temperature:

0.1659 gave 0.0402 Pt. Pt=24.2

(C₈H₁₀O₂NBr)₂H₂PtCl₄ requires Pt=24.3 per cent.

When the above-mentioned bromo-amine was diazotised, it yielded 4-bromoveratrole, which was identified by conversion into 4-bromo-5-nitroveratrole melting at 123° (Jones and Robinson,

loc. cit., give 125° as the melting point of this substance (Found: $N=5.3$. Calc.: $N=5.2$ per cent.).

The acetone solution from which the 4- or 5-bromo-3-acetylaminoveratrole had been separated was evaporated, and the residue (5.5 grams) was repeatedly crystallised from alcohol, when a substance melting at 78° was isolated and found by direct comparison to be 6-bromo-3-acetylaminoveratrole.

Bromination of 4-Acetylaminoveratrole (VIII). 5-Bromo-4-acetylaminoveratrole (IX).

As has already been mentioned in the introduction (p. 784), the bromination of 4-acetylaminoveratrole has already been investigated by Jones and Robinson (*loc. cit.*, p. 913), who found that 5-bromo-4-acetylaminoveratrole was formed. We have investigated this bromination both in chloroform and in acetic acid solutions, when the 5-bromo-derivative was obtained as the sole product. It crystallised from hot water in long, slender needles which melted at $127-128^{\circ}$. Attention has already been directed to the discrepancy between this melting point and that found by Jones and Robinson:

0.1981 gave 0.1352 AgBr. Br = 29.3.

$C_{10}H_{12}O_3NBr$ requires Br = 29.2 per cent.

5-Bromo-4-aminoveratrole, which has not been described previously, was obtained only with considerable difficulty, owing to the ease with which it decomposed. Ultimately, the following method was found to be fairly satisfactory. The bromoacetylamine was dissolved in a methyl-alcoholic solution of potassium hydroxide (15 per cent. KOH) and heated on the water-bath for three hours, the excess of potassium hydroxide removed by carbon dioxide, the solution filtered, and the methyl alcohol evaporated in a vacuum at the ordinary temperature. The residue was extracted with ether, the ether evaporated, when the base was obtained as a viscid oil which rapidly crystallised. After draining on porous porcelain, it was recrystallised from dilute methyl alcohol, from which it separated in colourless needles melting at 51° . When exposed to the air, the base rapidly darkened in colour:

0.0844 gave 0.0682 AgBr. Br = 34.4.

$C_8H_{10}O_2NBr$ requires Br = 34.4 per cent.

The *benzoyl* derivative, $C_{15}H_{14}O_3NBr$, crystallised in needles melting at 142° .

The constitution of this bromo-amine was readily determined by conversion into 4:5-dibromoveratrole. The bromo-amine (1 gram) was dissolved in hydrobromic acid (30 per cent.: 5 c.c.) and diazo-

H H*

tised by the addition of sodium nitrite (0.4 gram). After remaining in the cold for half an hour, the mixture was poured into hydrobromic acid (5 c.c.) containing a little copper powder and allowed to remain in the cold overnight. The solution was warmed on the water-bath, extracted with ether, the ether evaporated, and the residue crystallised from alcohol, when 4:5-dibromoveratrole separated in needles melting at 92° , which melting point was not changed on admixture with a specimen of the compound obtained from a different source.

Bromination of 2-Acetylaminoveratric Acid (X). 5-Bromo-2-acetylaminoveratric Acid (XI).

I. 2-Acetylaminoveratric acid (2 grams) was suspended in acetic acid (4 c.c.) and mixed with bromine (1.3 grams) dissolved in acetic acid (2 c.c.); the mixture was sealed up and allowed to remain, with occasional shaking, for twenty-four hours, when the colour of the bromine had completely disappeared and a yellow, unstable bromo-amide had separated. On the addition of water, a clear solution was obtained, from which the bromo-acid gradually crystallised. This was collected, and a further quantity obtained by extracting the filtrate with ether (yield, 2.1 grams). On trituration with dilute sodium carbonate solution, a small quantity of a neutral substance (0.1 gram) remained undissolved. This crystallised from alcohol in needles melting at about 168° , but it was not obtained in sufficient quantity for investigation. The acid which separated from the alkaline filtrate on acidification was found to be quite homogeneous, and was purified by crystallisation from ethyl acetate:

0.1534 gave 0.0908 AgBr. $\text{Br} = 25.2$.

$\text{C}_{11}\text{H}_{12}\text{O}_5\text{NBr}$ requires $\text{Br} = 25.1$ per cent.

5-Bromo-2-acetylaminoveratric acid separates in fine needles melting at $188-189^{\circ}$. It is readily soluble in acetone, alcohol, ethyl acetate, or chloroform, more sparingly so in water, benzene, or ether, and very sparingly so in light petroleum.

II. 2-Acetylaminoveratric acid (2 grams) was mixed with chloroform (4 c.c.) and treated with bromine (1.3 grams) dissolved in chloroform (2 c.c.); the bromo-amide gradually separated, and, after remaining for twenty-four hours, the mixture was treated with water, the chloroform separated, washed with a little dilute alkali, dried, and evaporated, when a small quantity of a neutral substance remained. This was crystallised from a little dilute methyl alcohol, when it crystallised in octahedra melting at 151° , and was found to be 4- or 5-bromo-3-acetylaminoveratrole.

The alkaline washings yielded on acidification 5-bromo-2-acetylaminoveratric acid.

5-Bromo-2-aminoveratric acid was obtained when the acetyl derivative was hydrolysed with either hydrochloric acid or concentrated sulphuric acid. It crystallises from alcohol in colourless prisms melting at 158—159°:

0.1114 gave 5.6 c.c. N_2 at 31° and 758 mm. $N=5.4$.

$C_9H_{10}O_4NBr$ requires $N=5.1$ per cent.

The constitution of this amino-acid was readily proved by the elimination of the amino-group, when 5-bromoveratric acid melting at 191° was obtained (Found: $Br=30.5$. Calc.: $Br=30.6$ per cent.).

Bromination of 5-Acetylaminoveratric Acid (XII).

2-Bromo-5-acetylaminoveratric Acid (XIII).

The acid (2 grams) was dissolved in acetic acid (4 c.c.) and treated with the calculated quantity of bromine dissolved in a little acetic acid. The clear solution rapidly became cloudy, and a voluminous precipitate of the reddish-yellow bromo-amide separated. After remaining for ten minutes, water was carefully added, when a clear solution was obtained, from which the bromo-acid slowly crystallised. This was collected and recrystallised from dilute alcohol, from which it separated in fine needles:

0.1862 gave 0.1096 AgBr. $Br=25.1$.

$C_{11}H_{12}O_5NBr$ requires $Br=25.1$ per cent.

2-Bromo-5-acetylaminoveratric acid melts at 221°. It is readily soluble in hot alcohol or acetone, more sparingly so in the cold solvents; in water or benzene it is sparingly soluble.

On hydrolysis of the acetyl-amino-acid with hydrochloric acid (50 per cent.), the amino-acid was obtained as a viscid oil which rapidly crystallised. It was recrystallised from dilute alcohol, from which it separated in glistening prisms melting at 183°. It is readily soluble in hot alcohol or acetone, but only sparingly so in water, chloroform, or benzene:

0.151 gave 0.1021 AgBr. $Br=28.8$.

$C_9H_{10}O_4NBr$ requires $Br=28.9$ per cent.

When diazotised in alcoholic solution with amyl nitrite, it yielded 2-bromoveratric acid, which after crystallisation from methyl alcohol melted at 201—202° (Found: $Br=30.2$. Calc.: $Br=30.6$ per cent.).

*Bromination of 6-Acetylaminoveratric Acid (XIV).**5-Bromo-4-acetylaminoveratrole (IX).*

The finely divided acid (2 grams) was suspended in chloroform and the calculated quantity of bromine dissolved in chloroform gradually added. The bromine was rapidly absorbed, and simultaneously a small amount of gas (carbon dioxide) was evolved. After remaining overnight, water was added to the pasty mass, when a vigorous evolution of gas was observed. A small quantity of unchanged acid was removed by filtration, the chloroform separated, washed with a little dilute alkali, dried, and evaporated. The deep brown residue rapidly solidified to a hard, crystalline cake, and was purified by crystallisation from hot water, from which it separated in slender, colourless needles melting at 127—128°, and was identical in every way with the compound obtained by the bromination of 4-acetylaminoveratrole. No trace of any other product could be isolated:

0.1144 gave 0.0775 AgBr. Br=28.9.

$C_{10}H_{12}O_3NBr$ requires Br=29.2 per cent.

THE PRESIDENCY COLLEGE,
MADRAS.

[Received, May 16, 1918.]