XXVII.—*The Supposed Formation of Ergotoxine Ethyl Ester from Ergotinine. A Correction.*

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SOME years ago (T., 1910, **97**, 284) we obtained a crystalline phosphate by boiling ergotinine in alcoholic solution with phosphoric acid, and we concluded that the salt was the phosphate of ergotoxine ethyl ester. This is not so; it is the phosphate of ergotoxine itself. Ergotoxine, $C_{35}H_{41}O_6N_5$, is the hydrate of ergotoxine, $C_{35}H_{39}O_5N_5$ (Barger and Carr, T., 1907, **91**, 337), and at the time of our previous work the phosphate of ergotoxine (the first salt to be crystallised) had been obtained exclusively in the form of fine needles (T., 1910, **97**, 286, Fig. 2), whilst our supposed ester salt crystallised in broad plates (*loc. cit.*, Fig. 1). Similar differences of crystalline form were observed in the hydrochlorides (*loc. cit.*, Figs. 3 and 4), and oxalates, prepared from the two phosphates. (On the other hand, each pair of salts had approximately the same melting point.) We chiefly relied, however, on an analysis (1 per cent. more carbon than in ergotoxine phosphate, as calculated) and a Zeisel determination of the ethoxy-group. (Found, 5·97. Calc., 5·82 per cent.)

Some years later, Mr. F. H. Carr and Dr. F. L. Pyman determined the methoxy- and methylimino-groups in ergotoxine and in ergotinine, and drew the conclusion that both alkaloids contain one *O*-methyl and one *N*-methyl group. In that case we ought to have found two alkyloxy-groups in the ester, as Messrs. Carr and Pyman pointed out to us. Their determinations were as follows:

Ergotinine.—The substance was of good colour and crystalline appearance, and melted at 231°. It suffered no appreciable loss on drying even at 130°.

1. 0·4051 gave 0·1241 AgI below 180°. OMe = 4·0.
and 0·1004 AgI above 290°. NMe = 3·1.
2. 0·3019 gave 0·0851 AgI below 180°. OMe = 3·7.
and 0·0942 AgI above 290°. NMe = 3·9.
3. After a blank distillation of the hydriodic acid yielding 0·0053 AgI:
0·1457 gave 0·0258 AgI below 180°. OMe = 2·3.
4. After a blank distillation of the hydriodic acid yielding 0·0123 AgI:
0·4128 gave 0·0794 AgI below 180°. OMe = 2·5.
and 0·1139 AgI above 290°. NMe = 3·4.

5. After a blank distillation of the hydriodic acid (10 c.c.) yielding 0.0098 AgI and the subsequent addition of 5 c.c. of acetic anhydride:

0.4127 gave 0.1548 AgI below 180°. OMe = 4.9.
and 0.0688 AgI above 290°. NMe = 2.1.

6. After a blank distillation of the hydriodic acid (10 c.c.) yielding 0.0218 AgI, and the subsequent addition of 5 c.c. of acetic anhydride:

0.4130 gave 0.1401 AgI below 180°. OMe = 4.5.
and 0.0764 AgI above 290°. NMe = 2.3.

7. Blank distillation with 10 c.c. of hydriodic acid for one hour gave 0.0027 AgI, after addition of 5 c.c. of acetic anhydride, and a double distillation for two hours gave 0.0183 AgI, after a further double distillation for two and one-third hours gave 0.0025 AgI:

0.4966 gave 0.1501 AgI below 180°. OMe = 4.0.
and 0.0713 AgI above 290°. NMe = 1.7.
 $C_{35}H_{39}O_5N_5$ requires OMe = 5.1; NMe = 4.8 per cent.

Ergotoxine Phosphate.—

1. 0.3976 gave 0.1204 AgI at 140—195°. OMe = 4.0.
2. 0.3926 „ 0.1614 AgI „, 140—195°. OMe = 5.4.
3. 0.2302 „ 0.0732 AgI „, 140—195°. OMe = 4.2.
4. 0.3954 gave 0.1055 AgI below 180°. OMe = 3.5.
and 0.0663 AgI above 290°. NMe = 2.1.
5. 0.3914 gave 0.0982 AgI below 180°. OMe = 3.3.
and 0.0678 AgI above 290°. NMe = 2.0.
6. 0.1420 gave 0.0494 AgI below 180°. OMe = 4.6.
and 0.0364 AgI above 290°. NMe = 3.2.

Specimen No. 1 was prepared from ergotinine, the rest from ergot. Nos. 4–6 were dried at 100° and analysed with the addition of acetic anhydride. The melting point was 187—188°.

0.1482, dried at 100° (mixed with CuO), gave 0.3120 CO₂ and 0.0900 H₂O. C = 57.4; H = 6.8.

$C_{35}H_{41}O_6N_5 \cdot H_3PO_4$ requires C = 57.9; H = 6.1; OMe = 4.3;
NMe = 4.0 per cent.

On receipt of the above data we re-examined the action of alcoholic phosphoric acid on ergotinine, on a larger scale than was originally possible. We were able to transform the salt, first obtained as needles, into plates by recrystallisation from alcohol.

One gram of ergotinine was suspended in 15 c.c. of absolute alcohol, and rather more than one molecular proportion of syrupy phosphoric acid was added. On heating under reflux on the water-

bath the ergotinine dissolved, but after a total heating of thirty to forty-five minutes the solution became almost solid with a mass of prismatic needles, which were collected.

The yield was 0.95 gram, or 80 per cent. of the theoretical; the melting point, 189—190°. After drying at 100°:

0.5720 gave 0.0246 AgI (two hours at 140—150°). OMe=0.56.

On recrystallisation from alcohol, plates were formed, melting at 190°, which were analysed:

0.4216 gave 0.0412 AgI (two hours at 150°). OMe=1.3.

From these experiments we conclude that the phosphate was that of ergotoxine, and that no ethyl ester grouping was present, for it would have been readily removed under the analytical conditions employed.

We next examined the action of hydriodic acid on ergotinine, using in each case 10 c.c. of acid (D 1.7) and 5 c.c. of acetic anhydride, the bath being heated for two hours at the temperature intervals indicated.

A. Ergotinine, older (less pure) specimen:

0.4127 gave 0.1259 AgI at 150—195° and 0.0389 AgI at 340—350°. Total AgI=0.1648. OMe=5.3 or NMe=4.9.

B. Ergotinine, purer specimen:

0.4129 gave 0.0105 AgI at 140—145°, 0.1333 AgI at 180—200°, and 0.0303 AgI at 300—370°. Total AgI=0.1741. OMe=5.6 or NMe=5.2.

$C_{35}H_{39}O_5N_5$ requires OMe=5.1; NMe=4.8 per cent.

We have calculated our results from the total silver iodide formed, for we believe that only one methyl group is present, and think that this methyl group is attached to nitrogen. Messrs. Carr and Pyman's six analyses, in which heating was continued to 290°, when calculated as NMe only, give the mean 6.4 per cent., which is one-third more than the theoretical. In our opinion the amount of silver iodide is, however, insufficient to account for a methoxy- as well as a methylimino-group. There is abundant evidence that many methylimino-groups give off part of their methyl as methyl iodide on merely boiling with hydriodic acid, particularly if carbonyl groups are adjacent (Busch, *Ber.*, 1902, **35**, 1565; Goldschmiedt and Hönigschmid, *Ber.*, 1903, **36**, 1850; *Monatsh.*, 1906, **27**, 849; Kirpal, *Ber.*, 1908, **41**, 819). Decker (*Ber.*, 1903, **36**, 2895) has pointed out that in this way *N*-alkyl may be mistaken for *O*-alkyl, and Herzig (*Monatsh.*, 1908, **29**, 295) states that with nitrogenous substances, unless the formation of silver iodide begins soon after the hydriodic acid boils, and proceeds rapidly to an end, it is unsafe to conclude that a methoxyl group is present. In

our own experiments the evolution of methyl iodide from the boiling acid was slow and incomplete, whence our conclusion, that ergotinine and ergotoxine contain one *N*-methyl group, but no methoxy-group.

We desire to thank Messrs. Carr and Pyman for having directed our attention to the error in our former paper, and for having placed their analytical results at our disposal.

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