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THE ALKALOIDS OF ERGOT

PART II.

LONDON SCHOOL OF TROPICAL MEDICINE
NOT TO BE TAKEN AWAY.

BY

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AND

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XXX.—*The Alkaloids of Ergot. Part II.*

By GEORGE BARGER and ARTHUR JAMES EWINS.

IN a previous communication on this subject (Trans., 1907, **91**, 337), one of us, in conjunction with F. H. Carr, described the new amorphous alkaloid ergotoxine, $C_{35}H_{41}O_6N_5$, and assigned to Tanret's crystalline ergotinine the formula $C_{35}H_{39}O_5N_5$. The crystalline alkaloid was thus proved to be the anhydride of the amorphous one, as was first surmised by Kraft.*

The transformation of ergotoxine into ergotinine takes place by boiling with methyl alcohol (Kraft), or with acetic anhydride. When, on the other hand, ergotinine was warmed on the water-bath with very dilute phosphoric acid, Barger and Carr obtained from it the crystalline phosphate of an amorphous base, which closely resembled ergotoxine phosphate in physiological action and had the same melting point; the crystalline form was, however, entirely different. Ergotoxine phosphate crystallises in thin needles (Fig. 2), the new phosphate formed rhomb-shaped, triangular, or hexagonal plates (Fig. 1), and the difference persisted after the bases had been liberated, dissolved in ether, and again converted into their phosphates by precipitation with alcoholic phosphoric acid.

We have now found the cause of this difference between the two salts. When ergotinine is heated with a solution of phosphoric acid in ethyl alcohol, there is formed, not ergotoxine phosphate, but the phosphate of ergotoxine ethyl ester, and it is the latter salt which crystallises in plates. The hydrochlorides of the two bases are also quite different (Figs. 3 and 4). That the new base is an ethyl ester was shown by analysis, and especially by a determination of the ethoxy-group by Zeisel's method.

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* The identity of Kraft's hydroergotinine (*Arch. Pharm.*, 1906, **244**, 336) with ergotoxine was recently doubted by Vahlen (*Arch. exp. Path. Pharm.*, 1908, **60**, 42) on physiological grounds, but an analysis of hydroergotinine sulphate by Kraft (*Arch. Pharm.*, 1907, **245**, 644) and a comparative physiological examination by Dale (*Arch. exp. Path. Pharm.*, 1909, **61**, 113) leave no doubt that hydroergotinine and ergotoxine are synonymous terms.

It thus follows that ergotoxine contains a carboxyl group, and that ergotinine is its lactone (or lactam). In accordance with this view, ergotoxine is soluble in sodium hydroxide, but ergotinine is not, nor is the ester-base above referred to. Esterification probably takes place to some extent when ergotoxine is boiled with alcohol (in the absence of phosphoric acid). We have noticed repeatedly in converting ergotoxine into ergotinine by boiling with methyl alcohol (Kraft's method) that the yield is far from quantitative; some of the ergotoxine is probably converted by this process into the very soluble ethyl ester, instead of the crystalline anhydride. It is, moreover, quite likely that ergotinine itself when boiled with alcohol forms ergotoxine ester to some extent; this behaviour would explain the loss of ergotoxine on recrystallisation which we ourselves and others (Tanret, Meulenhoff) have noticed. The fall in optical rotation shown by alcoholic ergotinine solutions, especially on boiling, is also probably due to the formation of an ergotoxine ester.

Besides proving the presence of a carboxyl group in ergotoxine, we have been able to establish the presence of a somewhat larger and more characteristic fragment of the complicated molecule of the ergot alkaloids. On destructive distillation, both ergotoxine and ergotinine yield a small quantity of a crystalline substance, and this we have been able to identify as *iso*butyrylformamide, $CHMe_2{\cdot}CO{\cdot}CO{\cdot}NH_2$. The yield of this substance is only 5 per cent. of the (very costly) alkaloid employed; as we had only a few decigrams of the substance at our disposal, its identification was somewhat troublesome, but was finally rendered certain by direct comparison with a specimen of *iso*butyrylformamide synthesised for the purpose.

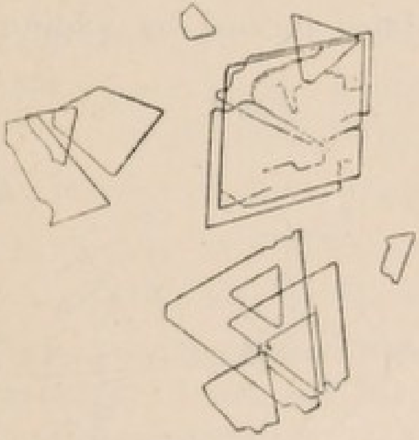
A ketonic amide of this type does not appear to have been previously obtained from a natural substance, and we are unable to suggest the mechanism of its formation from the ergot alkaloids. We do not think, however, that either of the oxygen atoms of the amide belongs to the carboxyl group which we have shown to be present in ergotoxine. If this be admitted, we have accounted for four out of the six oxygen atoms of that alkaloid (or three out of the five present in ergotinine). The two remaining oxygen atoms are not present as phenolic hydroxy- or methoxy-groups, because ergotinine is insoluble in sodium hydroxide, and when examined by Zeisel's method yields a negative result. One of the nitrogen atoms probably has a methyl group attached to it, because something like one equivalent of methyl iodide is set free when ergotinine is examined by Herzig and Meyer's method. At least one of the five nitrogen atoms is tertiary, for a methiodide is slowly formed. It is remarkable that, in spite of having five nitrogen atoms, the ergot alkaloids are only very feeble mono-acid bases.

EXPERIMENTAL.

Phosphate of Ergotoxine Ethyl Ester, $C_{34}H_{40}O_4N_5\cdot CO_2\cdot C_2H_5,H_3PO_4$.

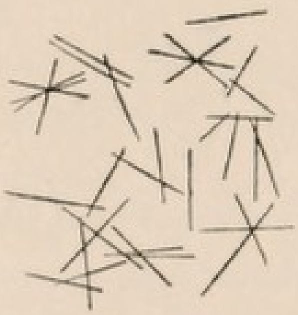
One gram of crystalline ergotinine was suspended in 10 c.c. of absolute ethyl alcohol, and 1·1 equivalent of phosphoric acid dissolved in 5 c.c. of alcohol was added. On warming on the water-bath for fifteen to thirty minutes, the ergotinine gradually dissolved; on cooling, an amorphous solid separated, which was collected and crystallised from 90—95 per cent. ethyl alcohol. In this way about 0·3 gram of a grey product was obtained, which on recrystallisation from 12 c.c. of 95 per cent. alcohol separated in almost white leaflets (Fig. 2), melting at 187—188° (bath previously heated to 180°). For the sake of comparison the crystalline form of ergotoxine phosphate is shown in Fig. 2. These and the other figures were drawn from micro-photographs:

FIG. 1.



Phosphate of ergotoxine ethyl ester.
× 65 diameters.

FIG. 2.



Ergotoxine phosphate.
× 65 diameters.

0·1353 gave 0·2922 CO_2 and 0·0812 H_2O. C = 58·9; H = 6·4.

$C_{37}H_{45}O_6N_5,H_3PO_4$ requires C = 58·9; H = 6·4 per cent.

$C_{35}H_{41}O_6N_5,H_3PO_4$ „ C = 57·9; H = 6·1 „

As the phosphate of an ethyl ester of ergotoxine contains only 1 per cent. more carbon than that of the corresponding ergotoxine salt, a direct determination of the ethoxy-group was made by Zeisel's method:

0·3503 gave 0·1064 AgI. OEt = 5·82.

$C_{34}H_{40}O_4N_5\cdot CO_2Et,H_3PO_4$ requires OEt = 5·97 per cent.

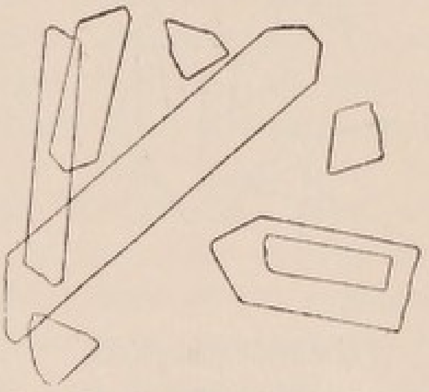
The rotation of this salt was also determined in 75 per cent. alcohol. $l = 1$ dcm.; $c = 2·03$; α_D $+1·58°$; $[\alpha]_D$ $+77·8°$. From the phosphate obtained in the manner described, the base was set free by sodium carbonate, dissolved in ether, and dried with sodium sulphate. From the ethereal solution of the base obtained in this way, the hydrochloride and the oxalate were precipitated by adding alcoholic hydrochloric acid and ethereal oxalic acid solutions respectively.

Hydrochloride of Ergotoxine Ethyl Ester, $C_{37}H_{45}O_6N_5,HCl$.

The precipitated salt crystallised from 90 per cent. alcohol in large plates (Fig. 3), which melted at 206—207° (bath previously heated to 190°). For the sake of comparison, crystals of ergotoxine hydrochloride (m. p. 205°) are shown in Fig. 4.*

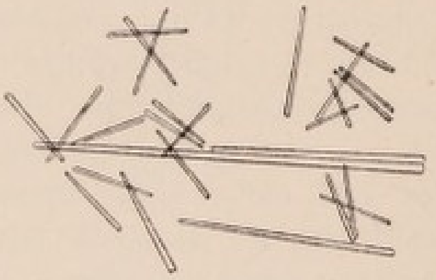
The difference in crystalline form existing between salts of ergotoxine and the corresponding salts of the ethyl ester is also clearly shown in the case of the oxalates formed by adding an ethereal solution of oxalic acid to the bases dissolved in ether. Both salts melt at 179—180°, but whereas the ergotoxine oxalate forms elongated, rectangular prisms, the salt of the ester crystallises in hexagonal leaflets.

FIG. 3.



Hydrochloride of ergotoxine ethyl ester.
× 65 diameters.

FIG. 4.



Ergotoxine hydrochloride.
× 65 diameters.

By warming ergotinine with a solution of phosphoric acid in methyl alcohol, crystalline salts of ergotoxine methyl ester are readily obtainable. As in the case of the ethyl ester, this base is amorphous, thus resembling ergotoxine; the ester bases differ, however, from ergotoxine in being insoluble in dilute sodium hydroxide.

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* In the previous paper (Trans., 1907, **81**, 350) it was stated that ergotoxine hydrochloride forms "diamond-shaped plates and very thin and very long, square-ended needles." The plates, however, were an admixture of the hydrochloride of ergotoxine ethyl ester.

Salts of Ergotoxine.

In addition to the phosphate, the hydrochloride, and the two oxalates of ergotoxine, which were described in the earlier paper, several other salts have been obtained crystalline. They were prepared in each case by adding a dilute ethereal or alcoholic solution of the acid to a solution of ergotoxine in ether, until no further precipitate was formed. The precipitated salt was dried in a vacuum, and crystallised from warm 90 to 95 per cent. alcohol. Not infrequently the salt separates as a jelly on cooling; in such cases it is best to dilute the solution, so that nothing separates on cooling, and then to add a few drops of dry ether at intervals.

Ergotoxine picrate forms pale yellow, acicular prisms, melting at 214—215° (bath first heated to 210°):

0·1536 gave 17·2 c.c. N_2 (moist) at 10·5° and 757 mm. N=13·2.

$C_{35}H_{41}O_6N_5,C_6H_3O_7N_3$ requires N=13·1 per cent.

Ergotoxine hydrobromide, acicular prisms, melting at 208°:

0·1042 gave 0·0260 AgBr. Br=10·6.

$C_{35}H_{41}O_6N_5,HBr$ requires Br=11·3 per cent.

Ergotoxine sulphate, prisms, melting at 197°:

0·1192 gave 0·0358 $BaSO_4$. H_2SO_4=12·6.

$C_{35}H_{41}O_6N_5,H_2SO_4$ requires H_2SO_4=13·5 per cent.

This appears to be a somewhat impure acid sulphate; that prepared by Kraft was the normal one.

Ergotoxine nitrate forms short, broad prisms, melting at 193—194°.

Action of Methyl Iodide on Ergotinine, Ergotoxine, and Ergotoxine Esters.

Ergotinine and allied bases appear to have one tertiary nitrogen atom. Ergotinine dissolves readily in methyl iodide, but when the solution is left at the laboratory temperature for some days, it is gradually transformed into a white jelly, readily soluble in alcohol; this jelly doubtless represents the methiodide. Ergotoxine and its esters behave in a similar way, except that the reaction is more rapid. In no case, however, could a crystalline product be isolated. We give as an example the analysis of the precipitate formed in a solution of ergotoxine methyl ester in methyl iodide; the substance, presumably the methiodide, was washed with dry ether and dried at 100°:

0·1300 gave 0·0365 AgI. I=15·2.

$C_{36}H_{42}O_6N_5,CH_3I$ requires I=16·2 per cent.

Action of Absolute Alcohol on Ergotinine.

A solution of 0·24 gram of crystalline ergotinine in 100 c.c. of absolute ethyl alcohol was divided into two portions. A 2·2-dcm. polarimeter tube was filled with one portion of the solution, and kept in the dark at the laboratory temperature for some months. During this time the rotation gradually decreased, as shown by the following table:

	α_D.	l.	$[\alpha]_D$.
June 11th	+1·76°	2·2 dcm.	+333°
June 12th	+1·71	2·2 ,,	+324
June 14th	+1·66	2·2 ,,	+314
June 17th	+1·61	2·2 ,,	+305
June 28th	+1·61	2·2 ,,	+305
July 19th	+1·52	2·2 ,,	+290
Sept. 13th	+0·62	1 ,,	+258

The other portion was heated under a reflux condenser on the water-bath; here the change was more rapid:

Time in hours.	α_D.	l.	$[\alpha]_D$.
0	+1·76°	2·2 dcm.	+333°
1	+1·59	2 ,,	+331
4	+1·41	2 ,,	+294
8½	+0·67	2 ,,	+275
15½	+0·61	1 ,,	+254
23	+0·59	1 ,,	+246
30	+0·48	1 ,,	+200
37	+0·37	1 ,,	+154

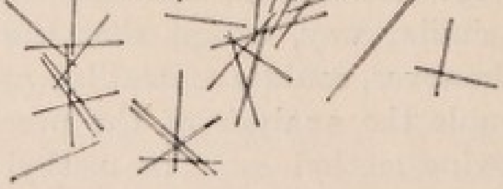
In boiling alcoholic solution the change is even more rapid. A saturated solution prepared by shaking at 10° gave:

$$l=2{\cdot}2 \text{ dcm.};\ c=0{\cdot}2566;\ \alpha_D+1{\cdot}91°;\ [\alpha]_D+338°.$$

After boiling for five minutes, $[\alpha]_D$ fell to 327°, after one hour to 300°, after three hours to 242°.

Crystals of ergotinine, obtained by rapidly cooling a boiling alcoholic solution, are shown below:

FIG. 5.



Ergotinine. × 65 diameters.

Isolation of iso*Butyrylformamide on Destructive Distillation of the Ergot Alkaloids.*

The formation of a crystalline sublimate can be observed by carefully heating a few milligrams of ergotinine or ergotoxine in a small tube. The alkaloids melt and decompose, and a minute quantity of a colourless liquid appears in the cold part of the tube; this soon crystallises, and if the operation is carried out under diminished pressure the substance appears at once in glistening leaflets.

It was soon found that the substance, once set free, sublimes at 100°, and cannot be recrystallised from organic solvents without great loss. Its purification was therefore carried out by sublimation under diminished pressure.

Ergotinine (in some cases ergotoxine) was heated in quantities of 0·5 gram at a time in a flask of 5—10 c.c. capacity, which was provided with a neck 25 cm. long and 1 cm. wide. Almost the whole of the bulb could be immersed in a metal-bath at 220—240°; the lower part of the neck, adjoining the bulb, was jacketed with steam, and the flask was evacuated to 2 mm. pressure. By this means the crystalline sublimate collected only on the upper part of the neck, above the steam-jacket. It was contaminated with a little yellow oil, and was purified as follows. The region of the tube where the sublimate had condensed was cut off, placed in a test-tube, and the substance re-sublimed in a boiling water-bath under a pressure of 15 to 20 mm.; it condensed on the upper portion of the test-tube, from which it was removed by means of a glass rod. In this way 0·09 gram of pure sublimate was obtained from the base from 3 grams of somewhat impure exgotoxine phosphate; in another experiment, 0·5 gram of pure ergotinine yielded 0·021 gram of sublimate, or 4·2 per cent.

As thus obtained, the substance formed thin, large, glistening leaflets, melting in a sealed tube at 109°, readily soluble in cold alcohol, but only sparingly so in cold water and in benzene:

0·0467 gave 0·0881 CO_2 and 0·0325 H_2O. $C=51·1$; $H=7·4$.
0·1034 „ 0·1946 CO_2 „ 0·0756 H_2O. $C=51·3$; $H=8·1$.
0·0860 „ 8·8 c.c. N_2 (moist) at 19° and 767 mm. $N=12·0$.
$C_5H_9O_2N$ requires $C=52·1$; $H=7·8$; $N=12·2$ per cent.

The vapour-density was determined by Victor Meyer's method:

0·0913 gave 22·05 c.c. moist air at 17° and 762 mm. V.D. = 53.
$C_5H_9O_2N=115$ requires V.D. = 57·5.

Although the percentage of carbon found is rather low, the formula $C_5H_9O_2N$ is established with certainty. At first we found several per cent. too much nitrogen, until we employed cuprous chloride (compare Haas, Trans., 1906, **89**, 570). The same difficulty was experienced by Barger and Carr in determining the nitrogen in ergotinine (Trans., 1907, **91**, 343, footnote), and is apparently due to the presence of a *gem*-dimethyl group, resulting in the formation of methane. We have now actually located this dimethyl group in *iso*butyrylformamide, where, on analysis by Dumas's method, unless cuprous chloride or lead chromate is used, it produces a much larger error than when accompanied by the rest of the molecule in ergotinine. Some of this methane probably also escaped combustion in the carbon and hydrogen estimations quoted.

The melting point of our substance corresponded closely with three substances of the formula $C_5H_9O_2N$ described in the literature, namely, butyrylformamide, *iso*butyrylformamide, and lævulinamide.

We first prepared butyrylformamide by the method given below. This substance was found to have a striking resemblance to the sublimate from the ergot alkaloids, and melted at 108°, but on mixing with this substance the melting point was 89—90°. We next prepared *iso*butyrylformamide, which again was quite similar in its properties. It melted at 107—108°, and this time the melting point remained unchanged, when the synthetic was mixed with the natural substance. The melting points may be tabulated thus:

1. Butyrylformamide, 108°. Mixture of 1 and 2, 88—89°.
2. *iso*Butyrylformamide, 107—108°. Mixture of 1 and 3, 89—90°.
3. Substance from ergot alkaloids, 109°. Mixture of 2 and 3, 107—108°.

In addition, the vapours of 2 and 3 readily gave, on gentle warming, the pyrrole reaction with a pinewood splint moistened with hydrochloric acid, but 1 gave only a doubtful coloration on strongly heating.

The sublimate from the ergot alkaloids is therefore *iso*butyrylformamide, $CHMe_2\cdot CO\cdot CO\cdot NH_2$.

In addition to this substance we obtained, on destructive distillation of the alkaloids under 2 mm. pressure, a small quantity of a base boiling at 88—89°, which was condensed in a tube cooled by carbon dioxide and acetone, and had an odour like pyrrolidine. The substance left in the flask was somewhat volatile under 2 mm. pressure, and crept up the sides of the flask as an amber-coloured, viscid liquid, but could not be distilled.

Synthesis of Butyryl and iso*Butyrylformamide.*

Moritz (Trans., 1881, **39**, 14) prepared butyryl and *iso*butyrylcyanide from the corresponding chlorides and silver cyanide. We found the yield to be very unsatisfactory, and therefore adopted Claisen's method (*Ber.*, 1898, **31**, 1023), using anhydrous hydrogen cyanide. 12·5 Grams of butyryl chloride were added to a solution of 3·2 grams of hydrogen cyanide in 46 c.c. of dry ether, and to the well-cooled solution 10 c.c. of pyridine were slowly added. After standing overnight, the pyridine hydrochloride, which had separated, was removed by filtration. The ethereal filtrate was washed with 5 per cent. sulphuric acid to remove the pyridine, and then with water to remove the acid. After drying, the ethereal solution was evaporated, and the residue distilled, when 1 gram of butyrylcyanide was obtained; the rest of the reaction product consisted mostly of the bimolecular polymeride. By hydrolysis with 85 per cent. sulphuric acid, 0·4 gram of butyrylformamide was obtained. It was purified by sublimation from a boiling-water bath under diminished pressure, and melted in a sealed tube at 108° (Moritz found 105—106°). *iso*Butyrylformamide was prepared in the same way, and melted at 107—108°. As stated above, this substance, unlike the normal amide, on heating, readily gives the pyrrole reaction with pinewood. Its melting point is given by Moritz (erroneously) as 125—126°, by Brunner (*Monatsh.*, 1894, **15**, 758) as 106—107°, and by Fränke and Kohn (*Monatsh.*, 1899, **20**, 887) as 110°.

We desire to acknowledge our indebtedness to Messrs. E. T. Thompson and S. M. Pettet, who have respectively made the microphotographs and drawings, from which the figures of crystals have been prepared.

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