CLXXX.—*The Alkaloids of Ergot. Part I.*

By Sydney Smith and Geoffrey Millward Timmis.

It is probably true that no drug of vegetable origin has been more often investigated than ergot and this is not surprising in view of the importance of the drug in medical practice. The earlier researches, which extend backward for more than a century, dealt with undoubtedly impure preparations and the first important advance was made by Tanret (*Compt. rend.*, 1875, **81**, 896), who isolated a pure crystalline alkaloid, ergotinine, which he regarded

as the physiologically active principle. This view of ergotinine was not generally accepted, and for knowledge of the physiologically active alkaloid of ergot we are indebted to the researches of Barger, Carr, and Dale, who at the British Association meeting in 1906 announced the isolation of an amorphous alkaloid, ergotoxine, having the pharmacological effects characteristic of ergot, and to Kraft (*Arch. Pharm.*, 1906, **244**, 336), who independently and almost simultaneously described the same alkaloid under the name hydroergotinine. Barger and Carr (J., 1907, **91**, 337) subsequently gave a detailed description of the chemical characteristics of ergotoxine and its salts, and the physiological effects of the alkaloid were fully described by Dale (*Biochem. J.*, 1907, **2**, 240 and elsewhere).

It was shown by Kraft and by Barger and Carr that ergotoxine and ergotinine are interconvertible and by Dale that ergotoxine has an intense physiological activity whereas ergotinine is comparatively inactive. It therefore created considerable interest when Spiro and Stoll (*Verh. Schweiz. Nat. Ges.*, 1920, abstracted in *Ber. ges. Physiol.*, 1921, **8**, 349 and *Chem. Zentr.*, 1921, III, 889—890) described two alkaloids, ergotamine and ergotaminine, which were also interconvertible and one of which, ergotamine, had a much greater biological activity than the other. Moreover, the methods which effected the interconversion of ergotoxine and ergotinine were the same as those which caused the interconversion of ergotamine and ergotaminine. It seemed probable, therefore, that ergotoxine and ergotamine, if not identical, must be closely related, a view which received support when it was shown by Dale and Spiro (*Arch. exp. Path. Pharmacol.*, 1922, **95**, 377) that ergotoxine and ergotamine had the same physiological action not only qualitatively but quantitatively. The identity of pharmacological action was fully confirmed by the subsequent work of Rothlin (*ibid.*, 1928, **138**, 115), Burn and Ellis (*Pharm. J.*, 1927, **64**, 384), and others.

Similarly, some years ago we began an investigation with the object of establishing the chemical identity of ergotoxine and ergotamine or alternatively of more clearly distinguishing the two alkaloids, since the recorded differences were not striking and might possibly be due to variations in the purity of the material used by the respective workers, particularly as ergotoxine had hitherto been obtained only in an amorphous condition.

Ergotoxine can now be obtained in beautifully crystalline form as an additive compound with benzene or its simple homologues (Wellcome Foundation Ltd., and G. M. Timmis, B.P. 286,400), or by crystallisation from carbon disulphide. Crystallisation from such solvents takes place very readily and affords an easy method of purification. The sharp definition of the crystals and the constant

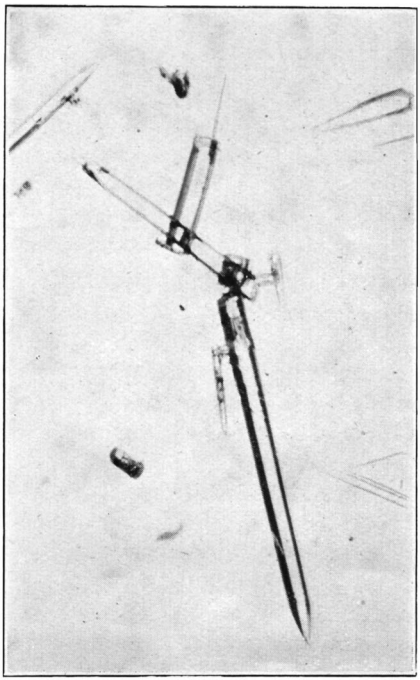
specific rotation leave no doubt concerning the purity of the substance. Ergotoxine cannot according to our experience be crystallised from other solvents and in this respect shows a pronounced difference from ergotamine, which crystallises with great ease from a number of solvents. For the purpose of comparison we have prepared all four alkaloids in a state of purity. The evidence afforded by the crystalline form, specific rotation, solubilities and melting points shows quite clearly that the four alkaloids are definite and distinct substances.

Spiro and Stoll in their publications lay stress on the "protective" methods of extraction devised by Stoll (D.R.-P. 257,272), who suggests (*Naturwiss.*, 1923, **33**, 705) that the failure of other workers to obtain ergotamine may have been due to the use of commercial ergots containing little or no ergotamine either because they were old and deteriorated or because they were originally poor therein, but that the chief cause appeared to have been the use of insufficiently protective methods of extraction.

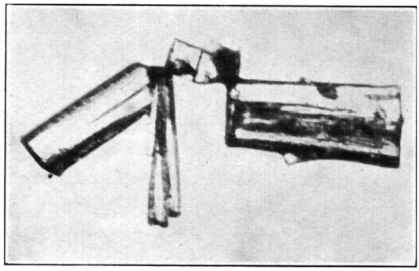
Our experience, on the contrary, has been that the isolation of the alkaloids may be effected satisfactorily by ordinary methods of alkaloid extraction such as that of Kraft (*loc. cit.*). Stoll's process consists essentially in treating the drug with a solution of a weakly acidic substance such as aluminium sulphate, ferrous sulphate, ferric chloride or copper sulphate. The acid material is freed from extractive matter by treatment with a solvent such as benzene or ether. The alkaloid is then set free by treatment with an alkali and extracted with ether or benzene or similar solvent. It is difficult to agree that such a process is less likely to cause decomposition of the alkaloids than the process of Kraft, which consists in extracting the drug with ether, extracting the alkaloids from the ethereal solution with a weak acid such as citric acid, and precipitating the alkaloids from the slightly acid extract by means of a base. In our experience it is immaterial as far as the nature of the alkaloid is concerned whether the alkaloids are prepared by the method of Kraft or by the processes described by Stoll.

During the past few years we have examined many commercial specimens of ergot from Spain, Portugal, Russia, Poland, Scandinavia, Hungary, and Czecho-Slovakia, all of which gave ergotoxine and ergotinine and these alkaloids only. These ergots were all obtained from rye which is the variety used traditionally in medicine and is officially specified by the pharmacopœias.

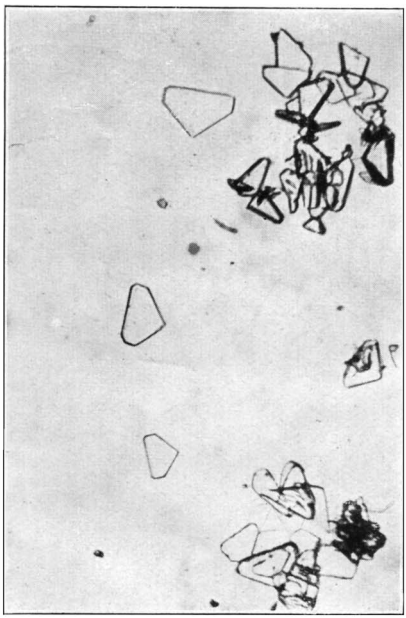
Ergot grows on other *Gramineæ* besides rye and we therefore examined some of the unofficial ergots. This part of the investigation is at present incomplete, as these varieties of ergot are difficult to procure. We have, however, been able to obtain three specimens



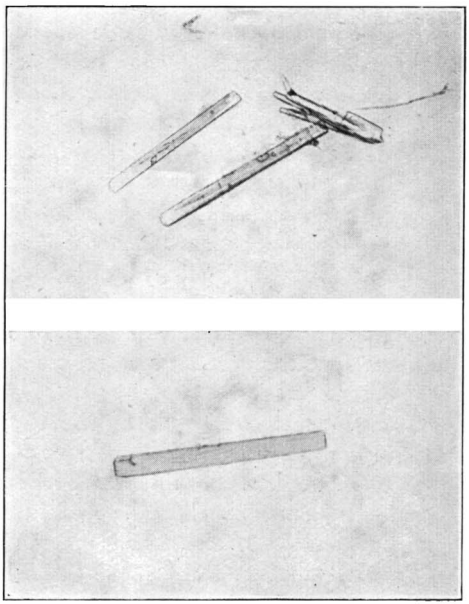
Ergotinine.



Ergotoxine.



Ergotaminine.



Ergotamine.

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of the ergot growing on tall fescue (*Festuca*), which were collected in New Zealand in 1927, 1928 and 1929. Two of them gave excellent yields of ergotamine, but the third contained comparatively little alkaloid. These ergots were extracted by the method of Kraft.

These results suggest that the isolation of ergotamine and ergotaminine depends not on the special methods of extraction upon which Stoll lays so much stress but upon the nature of the ergot.

In our experience ergot of rye gives ergotoxine and ergotinine only and in this we confirm the results of Tanret, who isolated ergotinine, and of Barger and Carr and of Kraft, who isolated both alkaloids.

Barger and Carr suggested the formulæ $C_{35}H_{41}O_6N_5$ and $C_{35}H_{39}O_5N_5$ for ergotoxine and ergotinine, and Spiro and Stoll assigned the formula $C_{33}H_{35}O_5N_5$ to ergotamine and ergotaminine. Although we have made many analyses of these alkaloids and their salts, we have not succeeded in finding conditions which give completely satisfactory results. Previous workers have experienced this difficulty also and we prefer to reserve a discussion of the composition and inter-relationship of the four alkaloids until these difficulties have been overcome or until we have been able to prepare degradation products which will throw light upon this question.

EXPERIMENTAL.

Isolation of Ergotoxine and Ergotinine.—The mixed crude alkaloids were prepared from ergot by the method of Kraft (*loc. cit.*), the average yield being 0·1 to 0·15%. The crude alkaloid is treated with methyl alcohol, which dissolves ergotoxine and leaves most of the ergotinine undissolved. The solution of ergotoxine with some ergotinine may then be purified by taking advantage of the different solubilities of the sulphates (Kraft), or purification may be effected by preparing the phosphate (Barger and Carr, *loc. cit.*). The ergotinine residue is readily purified by crystallisation from dilute alcohol.

Ergotoxine was usually prepared from the phosphate by triturating the salt with water and sodium bicarbonate. The mixture was extracted with ether, and the extract evaporated to dryness. The solid residue was dissolved in hot benzene, from which it readily crystallised on cooling in six-sided prisms containing 21% of benzene and having a specific rotation $[\alpha]^{19°}_{5461} = -179°$ and $[\alpha]^{19°}_{5790} = -156°$ ($c = 1$ in chloroform). Ergotoxine can be crystallised from toluene, the xylenes and mesitylene and separates in each case associated with the solvent, which can be removed by very prolonged drying at 90° in a vacuum. The solvent-free residue has a specific rotation $[\alpha]^{18°}_{5461} = -226°$ and $[\alpha]^{20°}_{5790} = -197°$ ($c = 1$ in chloroform). Ergot-

oxine is sparingly soluble in carbon disulphide and separates in stout prisms on the spontaneous evaporation of a solution in this solvent. It is insoluble in light petroleum, sparingly soluble in ether, and very soluble in methyl and ethyl alcohol, chloroform and acetone and ethyl acetate, but does not crystallise from these solvents. When an acetone solution is diluted with water, the base separates in an amorphous condition (distinction from ergotamine, which crystallises readily under these conditions). The amorphous base is hygroscopic. The dry substance when placed in a bath at 170° and slowly heated begins to soften at 180° (corr.) and melts very indefinitely between 190° and 200°. It is readily soluble in 1—3% aqueous sodium hydroxide solution but insoluble in sodium carbonate solution.

Ergotinine was most readily purified by crystallisation from hot alcohol containing from 10—50% of water. It crystallised in long, thin, glistening, colourless prisms, free from solvent. It has $[\alpha]_{5461}^{19°} = +513°$, $[\alpha]_{5790}^{19°} = +435°$ ($c = 1$ in chloroform). It is insoluble in light petroleum, very sparingly soluble in pure ether, sparingly soluble in acetone and in methyl and ethyl alcohols, easily soluble in benzene and chloroform. The dry substance when placed in a bath at 200° and slowly heated melts and decomposes at 239° (corr.) after preliminary darkening. Barger and Carr (*loc. cit.*) record decomposition points up to 229° (corr.), but, as pointed out by these authors, the decomposition point is not very characteristic. Ergotinine is insoluble in solutions of alkaline hydroxides or carbonates.

Isolation of Ergotamine and Ergotaminine.—The mixed crude alkaloids were prepared from *Festuca* ergot in the same manner as ergotoxine and ergotinine from ergot of rye. The crude alkaloid was treated with three parts of methyl alcohol, which dissolved ergotamine and left a residue of ergotaminine. The methyl-alcoholic extract was diluted with five volumes of ether, and the solution extracted with aqueous citric acid. The acid extracts on basification with sodium carbonate gave a precipitate of ergotamine.

Ergotamine may be purified by preparing the phosphate. The base is dissolved in 10 parts of dry acetone and treated with a solution of phosphoric acid in acetone. The phosphate separates in a semi-crystalline condition and may be recrystallised or converted into the base by treatment with ether and sodium bicarbonate. Ergotamine crystallises readily from aqueous acetone in long rectangular plates containing solvent or less readily from benzene in small needles. It is insoluble in light petroleum, less soluble than ergotoxine in benzene, chloroform and ether, and easily soluble in nitrobenzene and pyridine. The dry substance has specific rotation

$[\alpha]^{20°}_{5461} = -181°$ and $[\alpha]^{20°}_{5790} = -159°$ ($c = 1$ in chloroform). When placed in a bath at 205° and slowly heated, the dry substance melts fairly sharply and decomposes at 213—214° (corr.) after softening and darkening. It is soluble in a dilute solution of sodium hydroxide but insoluble in aqueous sodium carbonate. Ergotamine isolated from commercial ergotamine tartrate crystallised in the same form as the alkaloid isolated from *Festuca* ergot and after recrystallisation had an identical specific rotation and m. p.

Ergotaminine was prepared by the crystallisation of the crude residue obtained as above. It crystallises from alcohol, acetone, nitrobenzene and ether, pyridine and water, chloroform, and light petroleum. It separates from alcohol in the characteristic thin triangular plates free from solvent as described by Spiro and Stoll or in five-sided plates as illustrated. It is practically insoluble in light petroleum, sparingly soluble in benzene, toluene, methyl and ethyl alcohols, acetone and ethyl acetate, fairly readily soluble in chloroform and nitrobenzene, and easily soluble in pyridine. It has specific rotation $[\alpha]^{18°}_{5461} = +450°$ and $[\alpha]^{18°}_{5790} = +385°$ ($c = 0{\cdot}5$ in chloroform). When placed in a bath at 240° and slowly heated, it melts and decomposes at 252° (corr.). It is insoluble in dilute solutions of alkaline hydroxides or carbonates.

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