373. *The Chemistry of Fungi. Part XXXV.* A Preliminary Investigation of Ergoflavin.*

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Ergoflavin, one of the colouring matters of ergot, has probably the molecular formula $C_{30}H_{26}O_{14}$, and not $C_{15}H_{14}O_7$ as previously suggested. The pigment contains four phenolic hydroxyl groups, two alcoholic hydroxyl groups, two carbonyl groups, and two γ-lactone rings. Degradation of the tetra-*O*-methyl ether with barium hydroxide furnishes a dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl, the structure of which has been substantiated by conversion into 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl, identical with a synthetic specimen.

In addition to the well-known alkaloids,[1] ergot, the sclerotia produced by the fungus *Claviceps purpurea* when grown on rye, contains 1—2% of colouring matter; although the bulk of the latter is amorphous the isolation of a number of pigments has been described, but in general the compounds have been inadequately characterised. Since the isolation [2] of the first crystalline yellow pigment in 1877 but little progress has been reported on the structural chemistry of the group.

A violet substance sclererythrin, the occurrence of which is limited to the walls of the cortical hyphæ, was isolated by Dragendorff and Podwyssotski [2] and the characteristic ultraviolet absorption spectrum of this pigment has been frequently utilised for the detection of ergot.[3,4,5] These authors [2] also obtained a brown amorphous substance, which according to Tschirch,[6] is impure sclererythrin, and described the isolation of the first crystalline yellow pigment, sclerocristallin, $C_{10}H_{10}O_4$, which was supposed to be reversibly convertible into another yellow pigment, scleroxanthin. Tschirch [7] claimed the isolation of crystalline scleroxanthin, but these pigments have not been further characterised and nothing is known concerning their chemistry; the uncharacterised amorphous, yellow pigment, Wenzell's ergoxanthin,[8] has been tentatively identified as scleroxanthin by Barger.[9] In 1897, Jacobj [10] isolated a neutral yellow crystalline pigment, ergochrysin, to which he allocated the formula, $C_{21}H_{22}O_9$. This substance was probably a lactone since it could be converted into an acidic hydrate, $C_{21}H_{24}O_{10}$.

By extraction of ergot with chloroform Kraft [11] in 1906 obtained a pigment, secalonic acid, $C_{14}H_{14}O_6$, in lemon-yellow needles, m. p. 244°, which dissolved readily in aqueous sodium carbonate with effervescence and gave a red-brown ferric reaction. Whilst the pigment could be recovered by the acidification of a freshly prepared solution in alkali, prolonged contact with alkaline reagents caused deep-seated decomposition. On being heated in a vacuum secalonic acid was converted into a non-acidic compound which however dissolved in warm alkali. From the alkaline solution an acidic product was precipitated by acid and Kraft suggested that both secalonic acid and the non-acidic transformation product were lactones. By purification of the yellow precipitate obtained by dilution of an ethereal extract of ergot with light petroleum, Barger [9] in 1931 isolated

* Part XXXIV, preceding paper.

[1] Barger, "Ergot and Ergotism," Gurney and Jackson, London, 1931.
[2] Dragendorff and Podwyssotski, *Arch. exp. Pathol. Pharmakol.*, 1877, **6**, 174.
[3] Tschirch, *Schweiz. Apoth.-Ztg.*, 1922, **60**, 1.
[4] *Idem, Pharm. Acta Helv.*, 1926, **1**, 89.
[5] *Idem*, "Handbuch der Pharmakognosie," Leipzig, 1923, Vol. III, p. 139.
[6] *Idem, Schweiz. Apoth.-Ztg.*, 1917, **65**, 345.
[7] Ref. 5, p. 156.
[8] Wenzell, *Amer. J. Pharm.*, 1910, **82**, 410.
[9] Ref. 1, p. 139.
[10] Jacobj, *Arch. exp. Pathol. Pharmakol.*, 1897, **39**, 104.
[11] Kraft, *Arch. Pharm.*, 1906, **244**, 336.

ergochrysin, and suggested that this compound, scleroxanthin, and secalonic acid were identical, a claim which was supported by molecular-weight determinations on a sample of secalonic acid provided by Kraft.

In 1932 Bergmann [12] isolated ergochrysin from the residues obtained during the commercial production of ergot alkaloids. After removal of the ether-soluble impurities this compound was isolated by extraction with chloroform from which it separated in golden leaflets, m. p. 266°. Crystallised from alcohol–pyridine, the product, m. p. 242—244°, was solvated, and was transformed into the variety of m. p. 266° by recrystallisation from chloroform. Like Barger,[9] Bergmann [12] considered that his material, which was changed by dissolution in alkali into an amorphous material, was identical with secalonic acid and, on the basis of molecular-weight determinations by the Rast method, Kraft's C_{14} formula for secalonic acid was doubled to $C_{28}H_{28}O_{12}$. Acetylation of ergochrysin with acetic anhydride–pyridine gave a low yield of a crystalline substance believed to be a deca-acetate, $C_{48}H_{48}O_{22}$, m. p. 240°; methylation failed to give a crystallisable product. Bergmann's major contribution to the chemistry of ergochrysin was the isolation of oxalic, acetic, and 3-hydroxy-5-methylbenzoic acid, resorcinol, and 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl from a potassium hydroxide fusion of the pigment at 250—260°. This author, who concluded that the tetrahydroxydiphenyl was not an artefact derived from the resorcinol, also found that ergochrysin gave a crystalline nitro-compound, $C_{16}H_{15}O_9N$, m. p. 260°, by the action of nitric acid.

The next important contribution was by Stoll, Renz, and Brack, in 1952,[13] who isolated from Hungarian ergot a yellow crystalline acid which closely resembled secalonic acid, together with a second, closely associated acid, chrysergonic acid. These authors, who consider that their secalonic acid and Kraft's secalonic acid may not be identical with each other or with ergochrysin, showed that their secalonic acid and chrysergonic acid contained methoxyl groups and on the basis of methoxyl estimations revised the formula of secalonic acid to $C_{31}H_{30-32}O_{14}$, and allocated the formula $C_{32}H_{30-32}O_{14}$ to chrysergonic acid. Both compounds gave normal optical rotations in chloroform or acetone but in pyridine the rotation gradually changed to a constant value and the original pigment could not then be recovered. The same phenomenon occurred more rapidly in alkali. Both pigments gave colourless crystalline derivatives with acetic anhydride–pyridine, but analyses and molecular-weight estimations indicate that these were degradation products devoid of acetyl residues. The products from secalonic acid and chrysergonic acid, which were provisionally formulated as $C_{17}H_{16}O_7$ and $C_{15}H_{16}O_7$ respectively, still retained methoxyl groups, but were insoluble in alkali. On fusion with alkali the pigments furnished the same degradation products. The phenolic fraction contained 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl, and the acid fraction succinic and methylsuccinic acid which were not obtained in the degradation of ergochrysin recorded by Bergmann.[12] Under milder conditions, *e.g.*, 50% alkali at 125°, the pigments gave only methylsuccinic acid. From these experiments Stoll *et al.*[13] concluded that secalonic and chrysergonic acid were closely related.

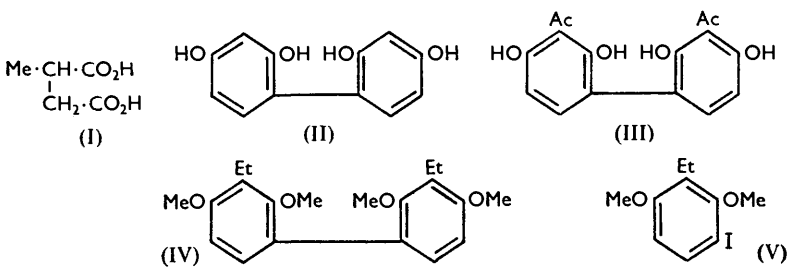
A comprehensive investigation on the ergot pigments is in progress in these laboratories. The present paper deals with our preliminary examination of ergoflavin. This was isolated in 1912 as yellow needles, m. p. 338° (decomp.), by Freeborn [14] who found that it was devoid of methoxyl groups and after intensive drying gave analytical and molecular-weight (Barger's vapour-pressure method [15]) values in agreement with the formula, $C_{15}H_{14}O_7$. Acetylation furnished what appeared to be a tetra-acetate, m. p. 231°, whence hydrolysis regenerated ergoflavin; fusion with alkali gave unidentified phenolic material. Forst [16] and Barger [1] repeated the isolation of ergoflavin, and Bergmann,[12] in his investigation of secalonic acid, obtained ergoflavin, m. p. 344°, and confirmed the C_{15} formula.

[12] Bergmann, *Ber.*, 1932, **65**, 1486, 1489.
[13] Stoll, Renz, and Brack, *Helv. Chim. Acta*, 1952, **35**, 2022.
[14] Freeborn, *Pharm. J.*, 1912, **88**, 568.
[15] Barger, *J.*, 1904, **85**, 286.
[16] Forst, *Arch. exp. Pathol. Pharmakol.*, 1926, **114**, 125.

The Zerewitinoff method indicated the presence of five active hydrogen atoms and acetylation furnished a colourless tetra- or penta-acetate, m. p. 244°, probably identical with Freeborn's acetate, m. p. 231°. Though he failed to isolate crystalline methylation products with diazomethane or dimethyl sulphate Bergmann established that with dilute alkali ergoflavin gave a hydroxy-acid, ergoflavinic acid, $C_{15}H_{16}O_8$, which regenerated ergoflavin on being heated in water, indicating that ergoflavin was a lactone.

In the present work ergoflavin has been isolated from commercial fat residues together with a considerable quantity of a semi-crystalline material, concerning which we shall report later. Ergoflavin forms optically active, yellow needles, m. p. 350° (decomp.), which tenaciously retain solvent of crystallisation, give an intense green ferric reaction in alcohol, are devoid of methoxyl groups, do not furnish derivatives with the usual carbonly reagents, and are not hydrogenated under standard conditions. Most derivatives of ergoflavin retain solvent and do not readily give consistent analytical results. According to the Kuhn–Roth method ergoflavin appears to contain at least two *C*-methyl residues, and a determination of the molecular weight by the ebullioscopic method,[17] in acetone, indicates conclusively that the C_{15} formula of Bergmann [12] and Freeborn [14] must be approximately doubled. Though from the several closely associated formulæ it is not possible at this stage to reach a final conclusion it appears that the formula $C_{30}H_{26}O_{14}$ for ergoflavin is in best accord with the analytical figures of the metabolite and its derivatives and will be used provisionally in the present paper. The accuracy of the molecular-weight estimations was checked against parallel determinations with 2 : 4 : 6 : 2′ : 4′-pentahydroxybenzophenone and is supported by the molecular-weights obtained for various derivatives of ergoflavin. The possibility that the green ferric reaction of ergoflavin is due to the presence of the catechol residue was investigated by using the characteristic pH change from 5 to 2 which occurs when a catechol is added to an aqueous solution of boric acid. Since the pH of a standard solution of boric acid was not influenced by the addition of ergoflavin it seems likely that this system is not present in ergoflavin and hence the characteristic ferric reaction may well be due to an *o*-hydroxycarbonyl moiety.

On oxidation with potassium permanganate ergoflavin gave methylsuccinic acid (I), and fusion with potassium hydroxide yielded acetic and methylsuccinic acid together with 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (II), the isolation of which in conjunction with the general properties of ergoflavin, indicates the presence of an aromatic kernel and a close structural affinity with ergochrysin and secalonic acid. Since resorcinol is not converted into the diphenyl (II) under the conditions of the alkaline fusion it is unlikely that this derivative is an artefact, a conclusion which is substantiated by work described below. The aromatic nature of ergoflavin is also inferred from its ready nitration to a dinitroergoflavin, $C_{30}H_{24}O_{14}(NO_2)_2$ whilst the resistance of the pigment to reduction with sodium and alcohol indicates the absence of a naphthalene system.



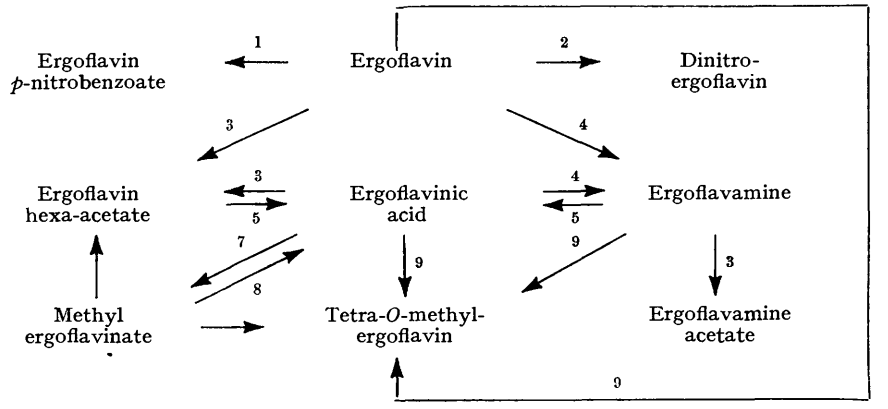
Ergoflavin exhibits the properties of a di-γ-lactone. Thus the infrared spectrum has an absorption band at 1790 cm.$^{-1}$ attributable to this system, and warm dilute potassium hydroxide solution converts the metabolite into a dibasic acid, ergoflavinic acid

[17] Glasstone, " A Textbook of Physical Chemistry," Macmillan, London, 1940, p. 629.

$C_{28}H_{28}O_{12}(CO_2H)_2$ (cf. Bergmann [12]), which is easily soluble in aqueous sodium hydrogen carbonate, readily regnerates ergoflavin in hot dilute acid, is devoid of the infrared band at 1790 cm.$^{-1}$, and exhibits absorption in the carbonyl region at 1740, 1660, 1620, and 1580 and in the acid region at 3600—3300 cm.$^{-1}$. With diazomethane ergoflavinic acid gives methyl ergoflavinate, $C_{28}H_{28}O_{12}(CO_2Me)_2$ [infrared bands at 3570, 3300, 3100, 1735 (aliphatic ester), 1670, 1620, and 1580 cm.$^{-1}$], which on hydrolysis with alkali regenerates ergoflavinic acid and on acetylation furnishes hexa-acetylergoflavin $C_{30}H_{20}O_8(OAc)_6$, identical with the acetylation product of ergoflavin (cf. Bergmann [12] and Freeborn [14]); deacetylation of this acetate with alkali regenerates ergoflavinic acid. Whilst ergoflavin readily furnishes a fully acetylated derivative (devoid of infrared absorption in the hydroxyl region) and a non-crystalline fully substituted *p*-nitrobenzoate (no hydroxyl absorption), it yields only a tetratoluene-*p*-sulphonate, $C_{58}H_{50}O_{22}S_4$, indicating that two of the hydroxylic functions may be subject to steric hindrance.

With methyl sulphate or iodide in acetone with potassium carbonate ergoflavin readily forms tetra-*O*-methylergoflavin, $C_{30}H_{22}O_{10}(OMe)_4$, which exhibits infrared absorption at 3525 (hydroxyl), 1800 (γ-lactone), 1690, 1600, and 1580 cm.$^{-1}$, is not readily soluble in aqueous alkali, has a negative ferric reaction, does not form carbonyl derivatives under the usual conditions, and by the Rast method in camphor and the micromolecular-distillation method [18] has a molecular weight in the region of 600. Consequently it seems likely that the four hydroxyl groups methylated by this process are phenolic (or enolic) and the remaining free hydroxyl groups are alcoholic. That two alcoholic groups are unmethylated is established by the formation of a di-*O*-acetate, $C_{30}H_{20}O_8(OMe)_4(OAc)_2$, and a di-*p*-nitrobenzoate, $C_{44}H_{28}O_{16}N_2(OMe)_4$, from tetra-*O*-methylergoflavin; both derivatives are devoid of hydroxyl absorption in the infrared spectrum. Tetra-*O*-methylergoflavin, which is also formed when methyl ergoflavinate is methylated with methyl sulphate–potassium carbonate in acetone, is unchanged by the prolonged action of diazomethane or by Purdie's reagents. In accordance with the formation from ergoflavin of only a tetratoluene-*p*-sulphonate, tetra-*O*-methylergoflavin does not react with toluene-*p*-sulphonyl chloride. Further, since tetra-*O*-methylergoflavin is not affected by polyphosphoric acid at 170° it is highly probable that the two alcoholic hydroxyl groups are not tertiary. These reactions are summarised in Chart 1.

CHART 1. *Reactions of ergoflavin.*



Reagents: 1, *p*-$NO_2{\cdot}C_6H_4{\cdot}COCl$–$C_5H_5N$. 2, Conc. HNO_3. 3, Ac_2O–C_5H_5N. 4, Aq. NH_3 (*d* 0·88). 5, Hydrolysis. 6, Hot H_2O. 7, CH_2N_2. 8, Aq. KOH. 9, Me_2SO_4–K_2CO_3.

On demethylation with hydriodic acid tetra-*O*-methylergoflavin regenerates ergoflavin, whilst hydrobromic acid gives rise to a di-*O*-methylergoflavin, $C_{30}H_{24}O_{12}(OMe)_2$, which is

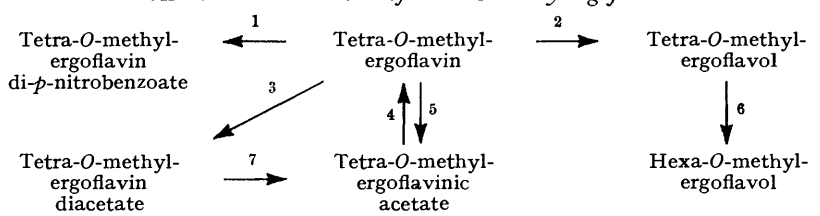
[18] Niederl, Kasanof, Kisch, and Subba Rao, *Mikrochem. Mikrochim. Acta*, 1949, **34**, 132.

identical (infrared spectrum) with the methylation product from ergoflavin with methyl sulphate and sodium hydrogen carbonate in boiling acetone and exhibits infrared bands at 1792 (γ-lactone) and 1603 cm.$^{-1}$ (*o*-hydroxycarbonyl). Methylation of ergoflavin with diazomethane furnished a mixture of tetra-*O*-methylergoflavin and tri-*O*-methylergoflavin, $C_{30}H_{23}O_{11}(OMe)_3$, having an intense green ferric reaction in alcohol and infrared absorption at 1808 (γ-lactone), 1632 (chelated carbonyl), and 1693 cm.$^{-1}$ (isolated carbonyl). These results indicate that ergoflavin contains two *o*-hydroxycarbonyl systems.

With alkali tetra-*O*-methylergoflavin gave a small yield of tetra-*O*-methylergoflavinic acid, $C_{28}H_{24}O_8(OMe)_4(CO_2H)_2$, which is more conveniently obtained by hydrolysis of di-*O*-acetyltetra-*O*-methylergoflavin. This acid [infrared absorption at 3600—3100 (acid), 1740, 1700, and 1600 cm.$^{-1}$] is very readily re-lactonised by heat, boiling water or acid, or attempted further methylation. Barium hydroxide degrades tetra-*O*-methylergoflavin to a dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (III) having the characteristic green ferric reaction of ergoflavin. The constitution of this product was established by reduction and subsequent methylation of the product to 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl (IV), the synthesis of which was achieved by the Ullmann condensation of 3-ethyl-1-iodo-2 : 4-dimethoxybenzene (V). The production of the diphenyl derivative (III) under comparatively mild conditions conclusively indicates that the 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl obtained from the fusion of ergoflavin with alkali is not an artefact and hence that ergoflavin contains this diphenyl system. Moreover, the isolation of this C_{16} fragment provides collateral evidence in favour of the new molecular formula for ergoflavin proposed in this communication.

Reduction of tetra-*O*-methylergoflavin with excess of lithium aluminium hydride gives rise to tetra-*O*-methylergoflavol, $C_{30}H_{34}O_{10}(OMe)_4$, which exhibits strong hydroxyl absorption (3390 cm.$^{-1}$) but is devoid of lactone and carbonyl absorption and dissolves readily in cold 2N-aqueous sodium hydroxide. Methylation of this product gave hexa-*O*-methylergoflavol, $C_{30}H_{28}O_4(OMe)_6(OH)_4$. These reactions are summarised in Chart 2.

CHART 2. *Reactions of tetra-O-methylergoflavin.*



Reagents: 1, p-$NO_2{\cdot}C_6H_4{\cdot}COCl$–$C_5H_5N$. 2, $LiAlH_4$. 3, Ac_2O–C_5H_5N. 4, Heat. 5, Aq. KOH. 6, Me_2SO_4–K_2CO_3. 7, Hydrolysis.

Ergoflavin in aqueous ammonia slowly furnishes a red crystalline product, provisionally called ergoflavamide, which is readily soluble in cold 2N-aqueous sodium hydroxide without evolution of ammonia, although on boiling ammonia was evolved and the solution then contained ergoflavinic acid. The infrared spectrum of this product exhibits absorption at 3550—3200 (OH and NH?), 1780, 1650, and 1600 cm.$^{-1}$. On methylation with methyl sulphate–potassium carbonate in boiling acetone ergoflavamide yields tetra-*O*-methylergoflavin, with the evolution of ammonia, and on acetylation a nitrogen-containing acetate.

Thus ergoflavin contains a diphenyl nucleus and has four phenolic and two alcoholic hydroxyl groups, two γ-lactone groups, and two carbonyl groups; the remaining oxygen atoms are probably present in ether linkages. Further, it seems highly likely that the molecule of ergoflavin is symmetrical, produced in Nature by oxidative coupling of identical C_{15} fragments (cf. the similar dracorubin [19]).

[19] Robertson, Whalley, and Yates, *J.*, 1950, 3117.

Experimental

Ergoflavin.—The alkaloid-free oil (1 part) obtained by extraction of ergot with ether, was diluted with light petroleum (b. p. 60—80°) (5 parts). The resulting gelatinous precipitate separated more readily on addition of small amounts of methanol. It was collected by filtration (filter-aid) or by centrifugation (without a filter-aid) and on being dried at room temperature was a yellow-brown solid; 50 gallons of oil furnished 0·5—1 kg. of solid. This product (100 g.) was added to acetone (200 ml.) containing hydrochloric acid (10 ml.) and 24 hr. later the solution was filtered (undissolved solid was discarded) and concentrated to *ca.* 40 ml. The thick, black viscous residue was extracted with ether (3 × 350 ml.) and on being kept for 24 hr. the extract deposited crude ergoflavin (7 g.). On being concentrated to 500 ml. the ethereal solution deposited more crude ergoflavin (1—2 g.) during 24 hr.; in the course of 2—3 weeks the residual liquors deposited an amorphous, bright yellow solid (5—10 g.).

When a solution of the crude ergoflavin (8 g.) in the minimum amount of hot acetone (*ca.* 50 ml.) was concentrated to *ca.* 20 ml. and diluted with warm methanol (200 ml.) the resulting dark green solution deposited ergoflavin (5—6 g.) which on repeated crystallisation from methanol, aqueous methanol, dioxan, or aqueous dioxan formed yellow needles, m. p. 350° (decomp.), $[\alpha]_D^{21}$ +37·5° (*c* 1·236 in acetone), $\lambda_{max.}$ 240, 260, 381 mμ ($E_{1\,cm.}^{1\%}$ 350, 346, 130 respectively) [Found: C, 58·8, 59·3, 58·6, 58·6, 58·7; H, 4·8, 4·9, 4·4, 4·7, 4·4; *C*-Me, 3·7; OMe, 0. $C_{30}H_{30}O_{14}$ requires C, 58·6; H, 4·9. $C_{30}H_{26}O_{14}$ requires C, 59·0; H, 4·3; (2) *C*-Me, 5·0%]. Vicininal hydroxyl test: a concentrated solution of boric acid had pH 5 and addition of catechol or di*iso*propyl catechol to this gave a solution of pH 2. With quinol or ergoflavin the boric acid solution had an unchanged pH of 5.

Molecular weight. This was determined ebullioscopically in acetone solution by Lansberger's method,[17] using the formula: rise in b. p. = (Mass of solute × 100*K*)/(vol. of solution × Mol. wt. of solute), *K* being taken as 22·2° for acetone.

The acetone was previously dried over potassium carbonate and distilled and the ergoflavin was dried at 100°/15 mm. or over phosphoric oxide. The following results were obtained:

(*A*) Wt. of ergoflavin, 0·5 g. B. p. of acetone, 56·38°. *M* (mean of three determinations), 642.

(*B*) Wt. of ergoflavin, 0·5 g. B. p. of acetone, 56·25°. *M* (mean of six determinations), 660.

With the same apparatus and solvent the molecular weight of 2 : 4 : 6 : 3′ : 4′-pentahydroxybenzophenone (*M*, 262) was determined: Wt. of ketone, 0·3 g. B. p. of acetone, 56·37°. *M* (mean of six determinations), 279.

Ergoflavin is readily soluble in acetone or pyridine, moderately soluble in methanol, alcohol, ethyl acetate, or dioxan, sparingly soluble in ether or benzene, and insoluble in 2N-aqueous sodium hydrogen carbonate. In alcohol it exhibits an intense green ferric reaction and forms a deep yellow solution in 2N-aqueous sodium carbonate or sodium hydroxide.

Prepared by the interaction of ergoflavin (1 g.), pyridine (3 ml.), and acetic anhydride (25 ml.) on the steam-bath during 30 min., the *hexa-acetate* separated from chloroform–light petroleum (b. p. 60—80°) in prisms (1·3 g.), m. p. 248—249° (decomp.), $[\alpha]_D^{20}$ +61·2° (*c* 0·62 in dioxan), $\lambda_{max.}$ 340, 338 mμ ($E_{1\,cm.}^{1\%}$ 343, 61 respectively) [Found: C, 57·5, 57·9, 56·9, 57·1, 57·1, 56·8, H, 4·7, 4·7, 5·0, 4·6, 4·7, 4·7. $C_{30}H_{20}O_8(OAc)_6$ requires C, 58·6; H, 4·4. $C_{30}H_{20}O_8(OAc)_6,H_2O$ requires C, 57·3; H, 4·5%]. The same acetate (310 mg.) was formed (*a*) when a mixture of ergoflavin (0·5 g.), sodium acetate (3 g.), and acetic anhydride (5 ml.) was heated in a sealed tube at 200—230° for 1 hr., (*b*) when ergoflavin (100 mg.), acetic anhydride (5 ml.), and sodium acetate (500 mg.) were heated under reflux for 1½ hr., or (*c*) when ergoflavin (1 g.), acetic anhydride (23 ml.), and pyridine (1 ml.) were refluxed for 5 hr. On being boiled with methanol (15 ml.) and 2N-aqueous sodium hydroxide (15 ml.) for 6 hr. this acetate (250 mg.) was hydrolysed and after removal of the alcohol in a vacuum the aqueous liquor was extracted once with ether and acidified. Purified from aqueous methanol the precipitate gave ergoflavinic acid (110 mg.) having m. p. and mixed m. p. 340° (decomp.) and the requisite infrared spectrum.

Prepared from ergoflavin (1 g.) and toluene-*p*-sulphonyl chloride (1·3 g.) in pyridine (10 ml.) at 0° for 2 days, *ergoflavin tetratoluene*-p-*sulphonate* separated from alcohol (sparingly soluble) in needles (0·7 g.), m. p. 231° (decomp.) (Found: C, 56·5; H, 4·6. $C_{58}H_{50}O_{22}S_4$ requires C. 56·8; H, 4·1%).

Dinitroergoflavin.—Ergoflavin (1 g.) dissolved in concentrated nitric acid (25 ml.) at 20° in 15 min. The red solution was added to ice (50 g.) and on purification from methanol the precipitate gave *dinitroergoflavin* in prisms (1·1 g.), m. p. 260° (decomp.), $[\alpha]_D^{20}$ +66·5° (in EtOH) [Found (specimen dried at 15°): C, 48·4, 48·7; H, 4·2, 3·6; N, 3·8. Found (specimen dried at 120°/1 mm. for 5 hr.): C, 51·5; H, 3·5. $C_{30}H_{24}O_{14}(NO_2)_2$ requires C, 51·4; H, 3·4; N, 4·0. $C_{30}H_{24}O_{14}(NO_2)_2,2H_2O$ requires C, 48·9; H, 3·8; N, 3·8%].

Ergoflavinic Acid.—A mixture of ergoflavin (3 g.) and 2N-aqueous potassium hydroxide (100 ml.) was warmed on the steam-bath for 10 min. and the bright yellow solution cooled and acidified (Congo) with 5N-hydrochloric acid. The gelatinous precipitate was extracted with ethyl acetate (3 × 40 ml.), and the product purified from aqueous methanol, giving ergoflavinic acid in yellow needles (2·7 g.) m. p. *ca.*, 340° (decomp.), $[\alpha]_D^{15}$ +542·6° (*c* 2·0 in alcohol), $\lambda_{max.}$ 355, 370 mμ ($E_{1\,cm.}^{1\%}$ 351, 105 respectively) (Found, on specimen dried at 100°/1 mm.: C, 55·6; H, 4·8. Calc. for $C_{30}H_{30}O_{16}$: C, 55·8; H, 4·7%). Bergmann [12] records m. p. 340° (decomp.). This acid, which is readily soluble in 2N-aqueous sodium hydrogen carbonate, has an intense green ferric reaction in alcohol, and on recrystallisation from acetic acid regenerates ergoflavin. It is readily soluble in dioxan, but very sparingly soluble in benzene, ethyl acetate, ether, or chloroform.

Excess of ethereal diazomethane was added to a solution of ergoflavinic acid (1·5 g.) in acetone (50 ml.) followed 30 min. later by excess of light petroleum (b. p. 40—60°): a crystalline solid separated. Purified from methanol, this furnished *methyl ergoflavinate* in very pale yellow needles (1·23 g.), m. p. 300—315° (decomp.) [Found: C, 56·2, 56·4; H, 5·1, 5·1; OMe, 9·5, 9·6. $C_{30}H_{28}O_{14}(OMe)_2$ requires C, 56·9; H, 5·0; OMe, 9·2%].

Methylation of methyl ergoflavinate (1·56 g.) in boiling acetone (70 ml.) with potassium carbonate (6 g.) and methyl sulphate (3·5 ml.) for 6 hr. gave tetra-*O*-methylergoflavin (1·16 g.) [m. p. and mixed m. p.; infrared spectrum (see below)]. Treated with excess of diazomethane in dioxan (25 ml.) for 10 days, methyl ergoflavinate (0·7 g.) furnished tetra-*O*-methylergoflavin (0·1 g.) accompanied by much non-crystallisable material.

Methyl ergoflavinate (0·35 g.) with boiling acetic anhydride (15 ml.) and pyridine (1·5 ml.) for 25 min. furnished hexa-*O*-acetylergoflavin (0·35 g.), m. p. and mixed m. p. 248—249°, with the requisite infrared spectrum. A high yield of the same derivative was obtained with hot sodium acetate–acetic anhydride in 1 hr.

Methyl ergoflavinate (0·2 g.) was heated in boiling acetone (15 ml.) containing potassium carbonate (0·2 g.) for 6 hr. and the solvent removed in a vacuum. The residue was triturated with N-aqueous sodium hydrogen carbonate, leaving ergoflavin (0·1 g.) having the requisite m. p., mixed m. p., and infrared spectrum.

Oxidation of Ergoflavin with Potassium Permanganate.—Potassium permanganate (20 g.) in water (500 ml.) was added with cooling during 6 hr. to ergoflavin (4 g.), dissolved in acetone (250 ml.), and next day the solution was clarified with 2N-sulphuric acid (15 ml.) and the acetone removed in a vacuum. Exhaustive extraction of the aqueous liquors with ether gave a brown semi-crystalline acidic product (1·88 g.) which was esterified with ethanolic hydrogen chloride at 60° for 6 hr. The resulting mixed esters distilled at 2 mm., furnishing a pale yellow neutral oil (1·5 g.). Prepared from this product (0·2 g.) and phenylhydrazine (0·5 g.) at 100° for 5 min., the bisphenylhydrazide of oxalic acid formed needles, m. p. 259°, from alcohol (Found: C, 62·0; H, 5·4. Calc. for $C_{14}H_{14}O_2N_4$: C, 62·2; H, 5·2%).

The mixed esters were converted in the *p*-phenylphenacyl derivative in the usual manner and gave the bis-*p*-phenylphenacyl derivative of methylsuccinic acid, m. p. and mixed m. p. 181° (Found: C, 75·8; H, 5·2. Calc. for $C_{33}H_{28}O_6$: C, 76·1; H, 5·4%).

Fusion of Ergoflavin with Alkali.—Ergoflavin (2 g.) was added during 5 min. to molten potassium hydroxide (15 g.) at 190° in a nickel crucible in nitrogen. The frothing melt was kept at 190—200° for 10 min., cooled, dissolved in water (100 ml.), acidified (Congo-red) with hydrochloric acid, and exhaustively extracted with ether. After being washed with N-aqueous sodium hydrogen carbonate the extract was evaporated, leaving a phenol (0·3 g.) which could not be satisfactorily purified but on methylation in boiling acetone by methyl sulphate–potassium carbonate followed by distillation of the product at 1 mm. gave a neutral, viscous resin; crystallisation from ether then furnished 2 : 4 : 2′ : 4′-tetramethoxydiphenyl in prisms (0·1 g.), m. p. and mixed m. p. 97° [Found: C, 70·0; H, 6·5; OMe, 45·5. Calc. for $C_{12}H_6(OMe)_4$: C, 70·1; H, 6·6; OMe, 45·3%].

The solution from the alkali fusion was acidified (Congo-red) with sulphuric acid and distilled

with steam until the distillate was neutral. The solid remaining after the evaporation of the neutralised distillate was converted into the *p*-phenylphenacyl derivative and on purification from methanol this furnished the derivative of acetic acid, m. p. and mixed m. p. 112° (Found: C, 75·3; H, 5·5. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·6%).

The acid fraction from the alkaline fusion of ergoflavin (6 g.) was esterified with boiling 5% alcoholic hydrogen chloride for 2 hr. and the resultant ester distilled at 105°/18 mm. (1·5 g.). Further purification by distillation gave ethyl methylsuccinate, n_D^{20} 1·4208 (Found: C, 56·6; H, 8·4. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%; n_D^{20} 1·4233). The identity of this ester was further confirmed by the preparation of the *p*-phenylphenacyl derivative, m. p. and mixed m. p. 180°. Variations of these fusion conditions gave inferior yields.

Methylation of Ergoflavin.—(*a*) Methylation of ergoflavin (5 g.) in boiling acetone (60 ml.) with potassium carbonate (15 g.) and methyl sulphate (10 ml.) was complete in 3½ hr. The filtered solution was evaporated in a vacuum and the residue treated with water (100 ml.). Next day the buff precipitate was purified from acetone–methanol and then from benzene–light petroleum (b. p. 60—80°), giving *tetra*-O-*methylergoflavin* in needles (4·8 g.), m. p. 282° (decomp.), $[\alpha]_D^{22}$ +28·6° (*c* 1·5 in $CHCl_3$), $\lambda_{max.}$ 252, 348 mμ ($E_{1\,cm.}^{1\%}$ 442, 85 respectively) [Found: C, 62·6, 61·6, 62·5, 62·4, 62·9, 63·0; H, 5·5, 5·3, 5·7, 5·3, 5·6; OMe, 18·5, 18·1, 18·4, 18·1. *M* (Rast), 605, 641 (by the micromolecular distillation method [18]) 635. Found (for specimen dried at 100°/4 mm. for 5 hr. and then at 140°/4 mm. for 1 hr.): C, 61·8, 61·8; H, 5·2, 5·3; OMe, 17·8, 17·9, 18·1. $C_{30}H_{22}O_{10}(OMe)_4$ requires C, 61·3; H, 5·1; OMe, 18·7%; *M*, 666]. Methylation of ergoflavin in acetone with methyl iodide–potassium carbonate at 20° for 12 days gave a 40% yield of tetra-*O*-methylergoflavin. Tetra-*O*-methylergoflavin has a negative ferric reaction in alcohol and does not react with the usual carbonyl reagents. Prepared quantitatively by the pyridine–acetic anhydride method at room temperature for 24 hr., *di*-O-*acetyltetra*-O-*methylergoflavin* separated from light petroleum (b. p. 60—80°)–chloroform in plates, m. p. 340° (decomp.) [Found: C, 60·5, 60·2, 60·0; H, 5·5, 5·4, 5·3; OMe, 16·9. $C_{34}H_{26}O_{12}(OMe)_4$ requires C, 60·8; H, 5·1; OMe, 16·5%]. The *di*-p-*nitrobenzoate* of tetra-*O*-methylergoflavin separated from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 192° (decomp.) [Found: C, 59·5; H, 4·5; N, 2·9, 2·9; OMe, 12·2. $C_{44}H_{28}O_{16}N_2(OMe)_4$ requires C, 59·8; H, 4·2; N, 2·9; OMe, 12·9%].

Demethylation of tetra-*O*-methylergoflavin (0·5 g.) with boiling hydriodic acid (8 ml.; *d* 1·7) and acetic acid (from 6 ml. of anhydride) for 1 hr. gave ergoflavin (0·32 g.), identical with an authentic specimen. When the demethylation of tetra-*O*-methylergoflavin (0·5 g.) was effected with boiling hydrobromic acid (5 ml.) and acetic acid (from 10 ml. of anhydride) for 1 hr., crystals rapidly separated from the initially clear solution. Purified from acetone–methanol, these gave *di*-O-*methylergoflavin* in yellow prisms (0·3 g.), m. p. 338° (decomp.), with an intense green ferric reaction in alcohol [Found: C, 59·9; H, 4·9; OMe, 7·7. $C_{30}H_{24}O_{12}(OMe)_2$ requires C, 60·0; H, 5·0; OMe, 9·7%]. Methylated by the methyl sulphate–potassium carbonate–acetone method this ether regenerated, in high yield, tetra-*O*-methylergoflavin, having the requisite m. p., mixed m. p. and infrared spectrum.

(*b*) A solution of ergoflavin (0·6 g.) in acetone (20 ml.) containing sodium hydrogen carbonate (2 g.) and methyl sulphate (2 ml.) was heated under reflux for 48 hr. On isolation in the usual manner the product was purified from acetone–methanol, giving (A) a substance (0·15 g.), m. p. 295° (decomp.), with a negative ferric reaction (possibly impure tetra-*O*-methylergoflavin), and (B) di-*O*-methylergoflavin in yellow prisms, m. p. 320—330° (decomp.), which has an intense green ferric reaction in alcohol and is identical with the product prepared by partial demethylation of tetra-*O*-methylergoflavin [Found: C, 59·0, 59·0; H, 5·2, 5·2; OMe, 10·6. Calc. for $C_{30}H_{24}O_{12}(OMe)_2$: C, 60·0; H, 5·0; OMe, 9·7%].

(*c*) A solution of ergoflavin (0·12 g.) in methanol (15 ml.) was treated with excess of ethereal diazomethane at 5° for 6 days. Purification of the product from acetone–methanol gave tetra-*O*-methylergoflavin (0·04 g.), m. p. and mixed m. p. 282° (decomp.), and *tri*-O-*methylergoflavin* in yellow needles (0·05 g.), m. p. 248—252° (decomp.), with an intense green ferric reaction in in alcohol [Found: C, 59·8; H, 5·3; OMe, 14·6. $C_{30}H_{23}O_{11}(OMe)_3$ requires C, 60·7; H, 5·0; OMe, 14·4%].

Tetra-O-*methylergoflavinic Acid.*—(*a*) A suspension of di-*O*-acetyltetra-*O*-methylergoflavin (5 g.) in methanol (100 ml.) and water (100 ml.) containing potassium hydroxide (10 g.) was heated under reflux for 6 hr.; a clear solution was formed after 45 min. The alcohol was removed in a vacuum and the residual solution acidified (Congo) with 5N-hydrochloric acid and

extracted with ethyl acetate. The ethyl acetate extract soon deposited crystals which on purification from methanol gave *tetra-O-methylergoflavinic acid* in rods (2·2 g.), m. p. 237—238° (decomp.) [Found: C, 54·1; H, 6·5; OMe, 17·2, 17·5. $C_{30}H_{26}O_{12}(OMe)_4$ requires C, 58·1; H, 5·4; OMe, 17·7. $C_{30}H_{26}O_{12}(OMe)_4,3H_2O$ requires C, 54·0; H, 5·9; OMe, 16·4%].

(*b*) A mixture of tetra-*O*-methylergoflavin (0·5 g.), methanol (30 ml.), water (30 ml.), and sodium hydroxide (2 g.) was boiled for 6 hr. and the alcohol was removed in a vacuum. The acidified solution was then extracted with ethyl acetate, and the product purified from methanol–ethyl acetate, giving slightly impure tetra-*O*-methylergoflavinic acid (0·1 g.).

Tetra-*O*-methylergoflavinic acid is readily soluble in 2N-aqueous sodium hydrogen carbonate, has a negative ferric reaction in alcohol, does not yield a 2 : 4-dinitrophenylhydrazone, and on being heated above its m. p. rapidly resolidifies by conversion into tetra-*O*-methylergoflavin which then melts at 280°. Re-lactonisation also occurs when tetra-*O*-methylergoflavinic acid is boiled in water or when a suspension of the acid (0·2 g.) in 5N-hydrochloric acid (25 ml.) was boiled for 1 hr. On isolation the crystalline product, m. p. 260—270° (0·17 g.), gave tetra-*O*-methylergoflavin, m. p. and mixed m. p. 282—283° with the requisite infrared spectrum, on purification.

Alkaline Degradation of Tetra-O-methylergoflavin.—A suspension of tetra-*O*-methylergoflavin (2 g.) in water (50 ml.), containing barium hydroxide octahydrate (25 g.), was heated under reflux for 5 hr., a clear orange solution being formed. The cooled, acidified hydrolysate was exhaustively extracted with ether, and the extract washed successively with 2N-aqueous sodium carbonate and 2N-aqueous sodium hydroxide, after which the ethereal solution did not contain a neutral fraction. Acidification of the carbonate washings gave an intractable precipitate (0·86 g.), but on being acidified the sodium hydroxide extract gave a product which was isolated with benzene and chromatographed from this solvent on silica gel. The benzene eluate furnished a *dimethyl ether* of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl. This ether separated from light petroleum (b. p. 60—80°) in pale yellow plates (50 mg.), m. p. 168° [Found: C, 65·6; H, 5·6; OMe, 18·5; *C*-Me, 8·7; *M* (Rast), 333. $C_{14}H_6O_4(Me)_2(OMe)_2$ requires C, 65·4; H, 5·5; OMe, 18·8; *C*-Me, 9·1%; *M*, 330]. It has an intense green ferric reaction in alcohol. Extensive modification of the reaction conditions did not improve the yield of this phenol. The *dipiperonylidene derivative* separated from alcohol (sparingly soluble) in orange-red needles, m. p. 235° [Found: OMe, 10·3. $C_{32}H_{20}O_8(OMe)_2$ requires OMe, 10·4%].

With methyl sulphate–potassium carbonate in boiling acetone for 7 hr. this phenol furnished a quantitative yield of 3 : 3′-*diacetyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl* which separated from light petroleum (b. p. 60—80°) in needles, m. p. 138° [Found: C, 67·4; H, 6·2; OMe, 34·6. $C_{16}H_{10}O_2(OMe)_4$ requires C, 67·0; H, 6·2; OMe, 34·6%].

3 : 3′-*Diethyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl.*—(*a*) A mixture of the above dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (170 mg.), 100% hydrazine hydrate (1 ml.), and diethylene glycol (6 ml.) was heated at 140—150° for ½ hr. A solution of potassium hydroxide (1 g.) in water (1 ml.) was then added and the mixture kept at 140—150° for a further ½ hr. and then slowly heated to 200° (without a condenser) and finally maintained at 200—210° for 2 hr. After isolation the crude product was methylated by methyl sulphate–potassium carbonate–acetone and the resulting ether purified from light petroleum (b. p. 40—60°), giving 3 : 3′-*diethyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl* in prisms (75 mg.), m. p. 109° [Found: C, 72·6; H, 8·3; OMe, 37·0. $C_{16}H_{14}(OMe)_4$ requires C, 72·7; H, 7·9; OMe, 37·6%].

(*b*) An agitated solution of 2-ethyl-1 : 3-dimethoxybenzene [20] (5·5 g.) in alcohol (25 ml.) was treated alternately with iodine (9 g.) and yellow mercuric oxide (5 g.), portionwise, and when decolorisation was complete the mixture was filtered into water, the salts were well washed with ether, and the excess of liquor was extracted with ether. Distillation of the combined extracts gave 2-ethyl-1 : 3-dimethoxybenzene (2—3 g.) and 3-*ethyl*-1-*iodo*-2 : 4-*dimethoxybenzene* (4 g.), b. p. 155—157°/13 mm. [Found: C, 41·0; H, 4·5; OMe, 20·8. $C_8H_7I(OMe)_2$ requires C, 41·1; H, 4·5; OMe, 21·2%]. A mixture of the iodo-compound (3·3 g.) and copper bronze (4 g.) was heated at 254° for 1½ hr., giving 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl which was isolated by extraction with light petroleum (b. p. 40—60°) and crystallised from methanol or light petroleum (b. p. 40—60°) as prisms, m. p. and mixed m. p. 109° and having the requisite infrared spectrum, [Found: C, 72·9; H, 8·1; OMe, 37·4. Calc. for $C_{16}H_{14}(OMe)_4$: C, 72·7; H, 7·9; OMe, 37·6%].

[20] Sprenger and Ruoff, *J. Org. Chem.*, 1946, **11**, 189.

Tetra-O-methylergoflavol.—A solution of tetra-*O*-methylergoflavin (3 g.) in dioxan (20 ml.) was added dropwise to a suspension of lithium aluminium hydride (6 g.) in boiling ether (250 ml.), and the mixture then heated under reflux for 4 hr. On isolation in the usual manner the product gave *tetra*-O-*methylergoflavol* which separated from aqueous methanol in needles (1·9 g.), m. p. >320° (decomp.), $\lambda_{max.}$ 214, 260 mμ ($E^{1\%}_{1cm.}$ 840, 275) [Found (on specimen dried at 70°/0·01 mm. for 3 hr.): C, 57·7, 57·3; H, 7·3, 6·8; OMe, 17·8, 17·8. Found (on specimen dried at 140°/0·01 mm. for 21 hr.): C, 58·4, 58·7; H, 6·8, 6·9. $C_{30}H_{34}O_{10}(OMe)_4$ requires C, 60·2; H, 6·8; OMe, 18·5%; *M*, 578. $C_{30}H_{34}O_{10}(OMe)_4,H_2O$ requires C, 58·6; H, 6·9. $C_{30}H_{34}O_{10}(OMe)_4,2H_2O$ requires C, 57·0; H, 7·0; OMe, 17·3%. *M* (by micro-molecular distillation method [18]), 600]. This phenol is readily soluble in 2N-aqueous sodium hydroxide and has a negative ferric reaction in alcohol. Methylation of tetra-*O*-methylergoflavol (0·6 g.) with aqueous-methanolic 3N-potassium hydroxide and methyl sulphate at 60° furnished *hexa*-O-*methylergoflavol* as a semicrystalline solid (0·4 g.), m. p. 190° (decomp.), insoluble in 2N-aqueous sodium hydroxide [Found: C, 61·1, 60·2, 60·6, 60·5, 60·4; H, 7·9, 7·5, 7·4, 7·3, 7·3; OMe, 28·7, 27·1, 27·3, 27·4, 27·4. $C_{30}H_{32}O_8(OMe)_6$ requires C, 61·2; H, 7·1; OMe, 26·3%].

Ergoflavamide.—The yellow colour of a solution of ergoflavin (2 g.) in aqueous ammonia (*d* 0·88; 100 ml.) changed to deep red in 10—15 min., and 12 hr. later the cooled solution was acidified with 5N-aqueous hydrochloric acid. Rapid crystallisation of the gelatinous orange-red precipitate (2·3 g.) from aqueous methanol at 60° containing 2N-aqueous hydrochloric acid (5 drops) furnished *ergoflavamide* in red needles (1·8 g.), m. p. 340°, $[\alpha]_D^{23}$ +113·2° (in EtOH) (Found: C, 52·3, 52·2; H, 5·4, 5·6; N, 3·8, 3·5%). When a solution of ergoflavin (0·5 g.) in alcohol (100 ml.) was saturated with ammonia and the resulting red solution evaporated in a vacuum 48 hr. later, rapid crystallisation of the residual red solid from aqueous methanol gave ergoflavamide in red needles, m. p. and mixed m. p. 340° (Found: C, 51·2; H, 5·4; N, 2·9%).

Prolonged contact of the crude product with the solvent during purification reduces the yield of pure ergoflavamide. The amide is readily soluble in cold 2N-aqueous sodium hydroxide without the liberation of ammonia. When a solution of ergoflavamide (0·1 g.) in 10% aqueous sodium hydroxide (25 ml.) was boiled for 20 min. ammonia was evolved and acidification of the cooled hydrolysate gave ergoflavinic acid which separated from aqueous methanol in yellow plates, m. p. *ca.* 300°, having the requisite infrared spectrum, $[\alpha]_D^{21}$ +227·9° (in EtOH) (Found: C, 51·7; H, 5·0%). Methylation of ergoflavamide (0·3 g.) by methyl sulphate–acetone–potassium carbonate for 5 hr. proceeded with evolution of ammonia to furnish a semi-crystalline solid which was difficult to purify and had the infrared spectrum of tetra-*O*-methylergoflavin. Acetylation of ergoflavamide (0·2 g.) by pyridine–acetic anhydride at room temperature for 24 hr. gave a semi-crystalline *acetate*, m. p. *ca.* 200° (decomp.) [from chloroform–light petroleum (b. p. 60—80°)] (Found: C, 56·9; H, 4·8; N, 2·5%).

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