409. *Usnic Acid. Part IV. The Synthesis of* 4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumarone*-2-*acetic Acid.*

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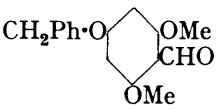
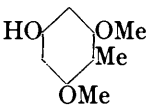
From the evidence discussed in Part III (J., 1933, 1173) it appeared reasonably certain that pyrousnic acid and its dimethyl ether may be represented by formulæ of the type (V) or (VI), and consequently that usnetic acid is the 7-acetyl derivative (V or VI; R = H, R_1 = Ac). Although, by a re-interpretation of the then existing analytical evidence, possible structures for decarbousnic acid and usnic acid, which obviously follow from the alternate formulæ possible for usnetic acid, might have been developed (compare Part III), it was deemed highly desirable to reserve this discussion until irrefutable synthetical evidence on the structure of pyrousnic acid was forthcoming. Accordingly, we have concentrated our efforts on the synthesis of the acids (V; R = Me, R_1 = H) and (VI; R = Me, R_1 = H) and the present communication deals with the preparation of the former compound by a general method.

The starting material for this synthesis was the unknown C-*methylphloroglucinol* β-*dimethyl ether* (II), which, after several unsuccessful efforts in other directions, we ultimately obtained by the catalytic reduction and simultaneous debenzylation of 4-*benzyloxy*-2 : 6-*dimethoxybenzaldehyde* (I), a convenient procedure now employed in these laboratories for the preparation of *C*-methyl- and *C*-dimethyl-phloroglucinol and their

derivatives. The orientation of the β-dimethyl ether follows from that of 2-hydroxy-4-benzyloxy-6-methoxybenzaldehyde (J., 1931, 2676), from which (I) was prepared, and from the fact that it is isomeric and not identical with the *C*-methylphloroglucinol α-dimethyl ether.

α-3 : 5-*Dimethoxy*-4-*methylphenoxypropionic acid* (III) was prepared from the β-dimethyl ether by the potassium carbonate method and on cyclisation according to the method


(I.)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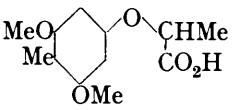
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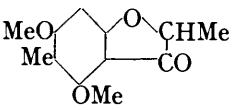
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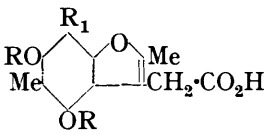
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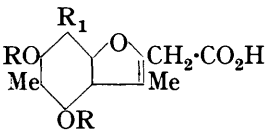
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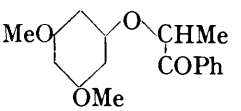
(VII.)

of Stephen and his co-workers (J., 1931, 896) gave rise to the *coumaranone* (IV), which, since it did not appear to be readily soluble in cold aqueous sodium hydroxide, was in all probability largely present as the keto-form. Condensation of this substance with ethyl bromoacetate by the Reformatsky method was accompanied by loss of the elements of water and furnished the *acid* (V; R = Me, R_1 = H).

The fact that the acid (V; R = Me, R_1 = H) is isomeric and not identical with *O*-dimethylpyrousnic acid leads to the conclusion that the latter compound has the structure (VI; R = Me, R_1 = H), and hence that pyrousnic acid and usnetic acid have formulæ (VI; R = H, R_1 = H) and (VI; R = H, R_1 = Ac) respectively, a conclusion in agreement with the analytical evidence described by Asahina and Yanagita (*Ber.*, 1936, **69**, 1646),* whose memoir appeared after the completion of this synthesis.

On account of the inaccessibility of the phenol (II) when this investigation was initiated and in order to test the method, we studied, in the first instance, the synthesis of 6-*methoxy*- and 4 : 6-*dimethoxy*-2-*methylcoumarone*-3-*acetic acid*. The only abnormality encountered was the formation of a considerable amount of a neutral by-product in the conversion of α-3 : 5-*dimethoxyphenoxypropionic acid* into 4 : 6-*dimethoxy*-2-*methylcoumaranone*, which rendered the purification of the latter compound somewhat tedious. This product, which was shown to be 4 : 6-*dimethoxy*-3-*phenyl*-2-*methylcoumarone*, identical with a specimen obtained by the condensation of the coumaranone with phenylmagnesium bromide, must arise by the interaction of α-3 : 5-dimethoxyphenoxypropionyl chloride and the benzene used as a diluent with the formation of the intermediate ketone (VII), which then undergoes cyclisation, giving the coumarone. As the 3-phenylcoumarone was not attacked by the Reformatsky reagents, its complete separation from the coumaranone, which was somewhat tedious, was not essential for the final step in the synthesis.

Experimental.

α-3-*Methoxyphenoxypropionic Acid*.—A solution of resorcinol monomethyl ether (15 g.) and ethyl α-bromopropionate (14 g.) in acetone (45 c.c.) containing potassium carbonate (22 g.) was refluxed for 2 hours. After the addition of more acetone the solution was filtered and evaporated, and an ethereal solution of the residue was washed with 2% aqueous sodium hydroxide to remove unchanged phenol, dried, and distilled; the residual ester was obtained as a colourless oil (15—16 g.), b. p. 167—170°/23 mm. Hydrolysis of this compound (5 g.) was effected with 6% alcoholic potassium hydroxide (50 c.c.) (agitate) at room temperature for 65

* The formulæ for usnic acid and decarbousnic acid suggested by the Japanese workers have, along with alternative structures, been employed in discussions at colloquia in Liverpool and elsewhere at various times during the past three years. The results described in the present paper form the successful issue of part of the work on the constitution of usnic acid which has been continued in these laboratories for the past three years, a topic which we have never intended to abandon.—A. R.

minutes and, after the addition of excess of dilute hydrochloric acid, the *acid* was isolated with ether and crystallised from carbon tetrachloride, forming colourless rods (4·5 g.), m. p. 93—94°, soluble in alcohol, ethyl acetate, or chloroform and insoluble in light petroleum (Found : C, 61·1; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

Treatment of this acid (8 g.) with phosphorus pentachloride (9 g.) first at room temperature and, after the initial reaction had ceased, at 40° for 5 minutes gave rise to the acid chloride, which, on removal of the phosphoryl chloride in a vacuum, remained as a pale yellow oil. Addition of concentrated aqueous ammonia to a specimen of this product afforded a good yield of the *amide*, which separated from benzene in colourless prisms, m. p. 102° after sintering at 100° (Found : C, 61·8; H, 6·9; N, 7·1. $C_{10}H_{13}O_3N$ requires C, 61·6; H, 6·7; N, 7·2%).

6-*Methoxy*-2-*methyl*-3-*coumaranone*.—Aluminium chloride (5·2 g.; 1·1 mols.) was added in several portions to a solution of the aforementioned acid chloride (from 8 g. of the acid) in thiophen-free benzene (50 c.c.) maintained at 0° (agitate). After having been kept at room temperature for 16 hours, the mixture was treated with ice and water and extracted several times with ether, the combined extracts were washed with 4% aqueous sodium hydroxide to remove acidic material and then with water, dried, and evaporated, and the residual coumaranone (yellow oil, 4·5 g.) was purified by distillation in a high vacuum, being finally obtained as an almost colourless oil, b. p. 120—125°/1 mm., which solidified (Found : C, 67·0; H, 5·6. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·6%) (compare Auwers and Müller, *Ber.*, 1917, **50**, 1173). With concentrated sulphuric acid it formed a pale yellow solution which, on being warmed, became cherry-red and then dark red. When a solution of 2 : 4-dinitrophenylhydrazine in hot alcohol (25 c.c.) containing concentrated hydrochloric acid (2 c.c.) was added to a solution of the coumaranone (1 g.) in the same solvent (15 c.c.), and the mixture boiled for 2 minutes, an almost theoretical yield of the 2 : 4-*dinitrophenylhydrazone* separated instantaneously; it formed slender, bright red needles, m. p. 206°, from ethyl acetate (Found : C, 53·7; H, 3·9; N, 16·2. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·7%).

6-*Methoxy*-2-*methylcoumarone*-3-*acetic Acid*.—Ethyl bromoacetate (5 g.) was gradually added to a boiling solution of the foregoing coumaranone (5 g.) in benzene (30 c.c.) containing zinc filings (3 g., free from oxide) and a crystal of iodine, and the mixture refluxed for 5 hours. After the addition of ice and water to the cooled reaction mixture the product was isolated with ether and hydrolysed by being boiled with a solution of potassium hydroxide (2·5 g.) in methyl alcohol (40 c.c.) and water (9 c.c.) for 2 hours. On isolation with ether the *acid* was separated from neutral material by means of aqueous sodium bicarbonate and purified by crystallisation from a little ethyl acetate and then from ethyl acetate–light petroleum (b. p. 60—80°), forming colourless diamond-shaped plates (1·7 g.), m. p. 115—116° (Found : C, 65·4; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). On being warmed, the yellow solution of this compound in concentrated sulphuric acid becomes red and then puce.

α-3 : 5-*Dimethoxyphenoxypropionic Acid*.—Interaction of phloroglucinol dimethyl ether (7 g.), ethyl α-bromopropionate (10 c.c.), and potassium carbonate (14 g.) in boiling acetone (35 c.c.) during 3 hours gave rise to the *ethyl* ester (10 g.) as a colourless oil, b. p. 188—190°/16 mm. (Found : C, 61·2; H, 7·0. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%). The clear solution obtained by agitating a mixture of the ester (10 g.) and aqueous alcoholic potassium hydroxide (from 6 g. of hydroxide, 47 g. of alcohol, and 47 c.c. of water) for 5 minutes was kept at room temperature for 1 hour, and acidified with excess of dilute hydrochloric acid. The resulting *phenoxy-acid* formed slender needles (8·5 g.), m. p. 115—116°, from dilute alcohol [Found : C, 58·4; H, 6·3; OMe, 27·2. $C_9H_8O_3(OMe)_2$ requires C, 58·4; H, 6·2; OMe, 27·5%].

The acid chloride was prepared by means of phosphorus pentachloride, and a specimen converted into the amide, m. p. 92° after crystallisation from benzene.

4 : 6-*Dimethoxy*-2-*methyl*-3-*coumaranone*.—On distillation the viscous product obtained by the interaction of a mixture of the aforementioned acid chloride (from 6 g. of the acid) and aluminium chloride (4 g.) in benzene (50 c.c.) at 0° for 3—4 hours yielded an almost colourless main fraction, b. p. 162—170°/0·5 mm., which partly solidified on being kept. On redistillation a quantity of this material (24 g.) obtained from several experiments gave three main fractions : b. p. 120—140°/0·15 mm. (1 g.), b. p. 157—159°/0·15 mm. (15·6 g.), and b. p. 160—180°/0·15 mm. (4 g.). Each fraction was dissolved in warm methyl alcohol and after cooling the product (A) which had crystallised was separated; further small quantities of this solid were obtained by concentrating and cooling the alcoholic liquors. The combined alcoholic solutions were then evaporated, and the residue distilled, giving a main fraction consisting of the pure *coumaranone* (7·8 g.), b. p. 150—151°/0·35 mm., which crystallised in the course of several weeks and then separated from a small volume of ether in colourless prisms, m. p. 74—75° [Found : C, 63·5;

H, 5·7; OMe, 28·7. $C_9H_6O_2(OMe)_2$ requires C, 63·5; H, 5·8; OMe, 29·8%]. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright red, prismatic needles, m. p. 240° (Found : C, 52·6; H, 4·0; N, 14·4. $C_{17}H_{16}O_7N_4$ requires C, 52·8; H, 4·1; N, 14·4%).

The solid by-product (A) (3·2 g.), which was insoluble in aqueous sodium hydroxide and did not contain a carbonyl group, formed colourless irregular prisms, m. p. 125°, from methyl alcohol, and was identical with an authentic specimen of 4 : 6-*dimethoxy*-3-*phenyl*-2-*methylcoumarone* (Found : C, 76·0; H, 6·1. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). The authentic specimen was prepared by the interaction of 4 : 6-dimethoxy-2-methyl-3-coumaranone (3 g.) with a slight excess of phenylmagnesium bromide in 35 c.c. of ether at room temperature for 24 hours and on isolation in the usual manner had m. p. 125° after recrystallisation from methyl alcohol.

4 : 6-*Dimethoxy*-2-*methylcoumarone*-3-*acetic Acid.*—On distillation, the product obtained from the condensation of the foregoing coumaranone (5 g.) and ethyl bromoacetate (5 g.) in benzene (32 c.c.) by means of zinc gave a main fraction (2 g.), b. p. 162—163°/0·73 mm., m. p. 55—57°, consisting of almost pure *ethyl* ester. This compound formed slender needles, m. p. 63°, from dilute alcohol (Found : C, 64·7; H, 6·8. $C_{15}H_{18}O_5$ requires C, 64·8; H, 6·5%)

Hydrolysis of the ester with 5% aqueous-methyl alcoholic potassium hydroxide gave rise to the *acid*, m. p. 141—142°, which separated in colourless needles, m. p. 147—148°, from warm benzene [Found : C, 62·6; H, 5·8; OMe, 24·7. $C_{11}H_8O_3(OMe)_2$ requires C, 62·4; H, 5·6; OMe, 24·8%]. On being warmed, the cherry-red solution of this substance in sulphuric acid became brown-red and then violet.

[With FRANK H. CURD]. 4-*Benzyloxy*-2 : 6-*dimethoxybenzaldehyde*.—Methylation of 2-hydroxy-4-benzyloxy-6-methoxybenzaldehyde (*loc. cit.*) (4·5 g.) with excess of methyl iodide (10 c.c.) and potassium carbonate (8 g.) for 6 hours gave an almost theoretical yield of the *ether*, which formed colourless needles, m. p. 122—123°, from alcohol, having a negative ferric reaction [Found : C, 70·7; H, 5·9; OMe, 21·5. $C_{14}H_{10}O_2(OMe)_2$ requires C, 70·6; H, 5·6; OMe, 22·8%] (the analogous compound, 4-*p*-toluenesulphonoxy-2 : 6-dimethoxybenzaldehyde, gives a correspondingly low methoxyl value; Karrer and Helfenstein, *Helv. Chim. Acta*, 1927, **10**, 789).

Reduction of this compound (1 g.), dissolved in acetic acid (50 c.c.), with hydrogen (approx. 270 c.c. absorbed) and a palladium–charcoal catalyst (from 0·5 g. of charcoal and 0·1 g. of palladium chloride) was complete in about 10 minutes. *C-Methylphloroglucinol β-dimethyl ether* was isolated with ether from the filtered reaction mixture which had been neutralised with aqueous sodium bicarbonate and was crystallised from carbon tetrachloride, forming needles (0·5 g.), m. p. 148—149° (Found : C, 64·4; H, 7·1. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%).

α-3 : 5-*Dimethoxy*-4-*methylphenoxypropionic Acid.*—Condensation of *C*-methylphloroglucinol β-dimethyl ether (4·4 g.) and ethyl α-bromopropionate gave rise to the ethyl ester (5·4 g.) which on hydrolysis furnished the *acid* (4·8 g.). This compound separated from carbon tetrachloride in needles, m. p. 123—123·5° (Found : C, 59·8; H, 6·7. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

4 : 6-*Dimethoxy*-2 : 5-*dimethylcoumaranone*.—Treatment of the acid chloride from the foregoing acid (5·4 g.) with aluminium chloride (5 g.) in benzene (80 c.c.) at 0° for 3 hours gave the *coumaranone*, which, on distillation in a vacuum, solidified, b. p. 123—127°/0·2 mm., m. p. 66—67°, and then formed elongated rectangular prisms (2·8 g.), m. p. 69—70°, from methyl alcohol (Found : C, 64·8; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). On being warmed, the yellow solution of the compound in concentrated sulphuric acid becomes brownish-red.

4 : 6-*Dimethoxy*-2 : 5-*dimethylcoumarone*-3-*acetic Acid.*—Condensation of 4 : 6-dimethoxy-2 : 5-dimethylcoumaranone (1·8 g.) with ethyl bromoacetate (1·7 g.) by means of zinc and hydrolysis of the resulting ester yielded the *acid*, which was purified by means of aqueous sodium bicarbonate and then by crystallisation from ethyl acetate, forming colourless, elongated, rectangular prisms (0·75 g.), m. p. 179—180° [Found : C, 63·7; H, 6·0; OMe, 22·8. $C_{12}H_{10}O_3(OMe)_2$ requires C, 63·6; H, 6·1; OMe, 22·5%]. On being warmed, the yellow solution of the compound in sulphuric acid becomes brown-red and finally indigo-blue (compare behaviour of the isomeric *O*-dimethylpyrousnic acid; J., 1933, 1177).

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