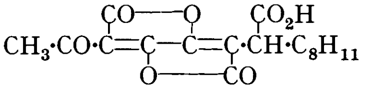
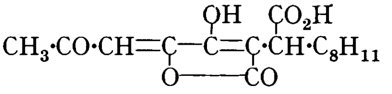
277. *Usnic Acid. Part III. Usnetol, Usnetic Acid, and Pyrousnic Acid.*

By Frank H. Curd and Alexander Robertson.

The optically active yellow lichen compound usnic acid, $C_{18}H_{16}O_7$, was discovered by Rochleder and Heldt (*Annalen*, 1843, **48**, 11) in *Ramalina fraxinea* and in *Usnea barbata*, and its distribution has been subsequently studied by Zopf, Hesse, Knop, and Salkowski, who have found that it occurs in some 75 species of lichen (for the numerous references see Zopf, "Die Flechtenstoffe," 1907, p. 101; Perkin and Everest, "Natural Organic Colouring Matters," 1918, pp. 530—542). Both the *d*- and the *l*-form have been isolated by Salkowski. Our knowledge of the chemistry of this substance is due mainly to the analytical investigations of Salkowski (*Ber.*, 1875, **8**, 1461), Paterno (*Gazzetta*, 1876, **6**, 113; 1882, **12**, 231; 1900, **30**, 109), Widman (*Annalen*, 1900, **310**, 230, 265; 1902, **324**, 139), and Schöpf and Heuck (with Kraus) (*ibid.*, 1927, **459**, 233). From his own experiments and those of previous workers, Widman concluded that usnic acid was a ketonic acid containing an acetoacetic acid residue, and was represented by formula (I). Decarbousnic acid, which is formed from usnic acid by simultaneous addition of the elements of water and loss of a molecule of carbon dioxide, he considered to have formula (II).

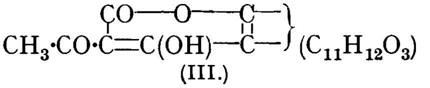
(I.) 

$$CH_3\cdot CO\cdot\overset{CO-}{C}=\overset{O}{\underset{O-}{C}}-C=\overset{CO_2H}{\underset{CO}{C}}\cdot CH\cdot C_8H_{11}$$

 (II.)

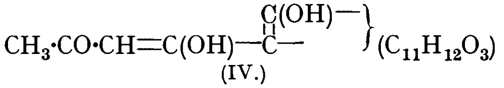
$$CH_3\cdot CO\cdot CH=\overset{OH}{\underset{O-}{C}}-C=\overset{CO_2H}{\underset{CO}{C}}\cdot CH\cdot C_8H_{11}$$

That formula (I) for usnic acid is untenable was shown by Schöpf and Heuck (with Kraus) (*loc. cit.*), who found by the Zerewitinoff method that the compound contains three active hydrogen atoms, whereas (I) allows only for two. These authors obtained tri- and tetra-acetyl derivatives of decarbousnic acid, neither of which possessed acidic properties, thus excluding the structure (II) for this compound, and concluded that neither decarbousnic acid nor usnic acid, which is a comparatively strong acid liberating carbon dioxide from sodium hydrogen carbonate and acetic acid from sodium acetate, possesses a carboxyl group. They proposed the modifications (III) and (IV) of Widman's formulæ for usnic acid and decarbousnic acid respectively, which are also in agreement with the experimental observations of previous workers.



$$CH_3\cdot CO\cdot\overset{CO-O-}{C}=C(OH)-\overset{\overset{C-}{\|}}{C}-\Big\}(C_{11}H_{12}O_3)$$

(III.)



$$CH_3\cdot CO\cdot CH=C(OH)-\overset{\overset{C(OH)-}{\|}}{C}-\Big\}(C_{11}H_{12}O_3)$$

(IV.)

On the removal of the elements of acetoacetic acid from usnic acid by hydrolytic decomposition with alkali, Salkowski, Paterno, and Widman (*locc. cit.*) each obtained a yellow compound, usnetic acid, $C_{14}H_{14}O_6$, which is a carboxylic acid yielding on decarboxylation a yellow phenolic product, usnetol, $C_{13}H_{14}O_4$ (Hesse, *loc. cit.*, appears to have prepared the same derivatives which he termed usnidic acid and usnidol). By loss of an acetyl group on treatment with warm concentrated alkali, usnetol gives rise to usneol,* which we have shown by synthesis of its dimethyl and diethyl ethers to be 4 : 6-dihydroxy-2 : 3 : 5-trimethylcoumarone (this vol., p. 714). Schöpf and Heuck confirmed the observations of previous workers regarding usnetic acid and usnetol, and showed that the latter substance was a hydroxy-ketone which gave a yellow monoacetate and monomethyl ether and a colourless diacetate; a dimethyl ether was not obtained. By successive degradation with ozone and alkali, they converted usnetol into *C*-methylphloroglucinol, and, in view

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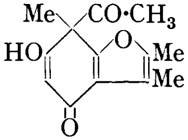
* For convenience we have retained this name, first suggested by Paterno (*loc. cit.*) for the decarboxylation product of pyrousnic acid, which is here shown to be identical with Schöpf and Heuck's deacetylated usnetol. The latter authors were unable to decide whether the compound was a 2 : 3 : 5- or a 2 : 3 : 7-trimethylcoumarone, and accordingly they proposed alternative formulæ for usnic acid and its degradation products. Only one set of formulæ is dealt with in the present communication, but the arguments apply equally to the alternative structures.

of its relationship to usneol, proposed the hemiquinonoid structures of types (V) and (VI) for usnetol and usnetic acid respectively. On the basis of these formulæ, supported by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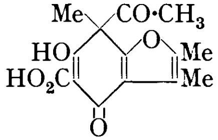
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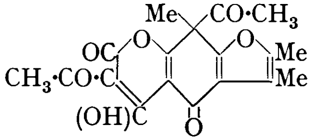
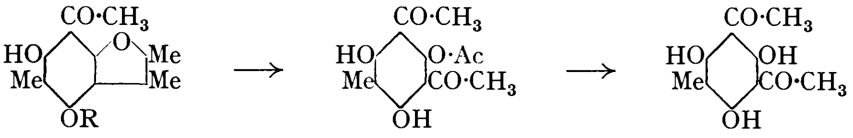
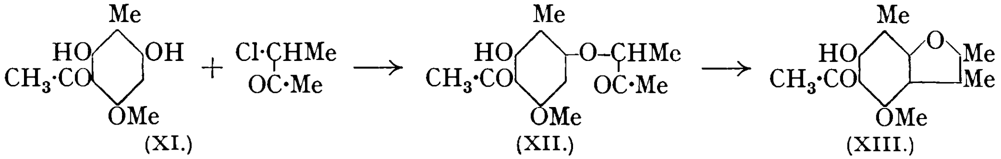

(VII.)

an examination of numerous derivatives of usnic acid and of decarbousnic acid, Schöpf and Heuck concluded that usnic acid is represented by a structure of the type (VII), an extension of formula (III).

O-*Methylusnetol.*—Despite the arguments of Schöpf and Heuck in support of their formula (V) for usnetol, we were of the opinion that a hemiquinonoid structure of this type was most unlikely, and considered that in all probability the substance was a normal *C*-acetyl derivative of usneol (VIII; R = H), believing that the intense yellow colour was in some measure due to the auxochromic effect of the furan nucleus. In this connexion, it may be noted that several simpler phenolic ketones are coloured; *e.g.*, 2 : 6-dihydroxy-4-methoxy-3-methylacetophenone, 2 : 6-dihydroxy-4-methoxy-3-methyl-*n*-butyrophenone (aspidinol) (Robertson and Sandrock, this vol., p. 819), and 2 : 4-dihydroxy-3-methylacetophenone (Jones and Robertson, J., 1932, 1689) are pale yellow, while the *p*-monomethyl ether of the last ketone and 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone are yellow. Though, as we have now shown, prolonged treatment of usnetol with methyl iodide and potassium carbonate in boiling acetone yields only the monomethyl ether (VIII; R = Me), we have observed in the course of numerous alkylation experiments on ketones of the *C*-methylphloroglucinol series (this vol., pp. 437, 819) that the hydroxyl group in the *o*-position to the carbonyl and the *C*-methyl group cannot be alkylated by this method or by means of diazomethane.

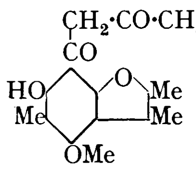

(VIII.) (IX.) (X.)

Because of practical difficulties encountered in our first attempts to synthesise *O*-methylusnetol (VIII; R = Me), we turned our attention to the synthesis of the isomeric keto-coumarone (XIII), which we have termed O-*methyl*iso*usnetol.* According to the general procedure (this vol., p. 714), the interaction of 2 : 4-*dihydroxy*-6-*methoxy*-3-*methylacetophenone* (XI) and 3-chlorobutan-2-one in the presence of potassium carbonate in boiling acetone gave rise directly to (XIII), probably by way of the stage (XII).


(XI.) (XII.) (XIII.)

This isomeride closely resembles usnetol methyl ether, having the same intense yellow colour, and the same ferric chloride and sulphuric acid reactions, and thus afforded evidence of the correctness of our formula (VIII; R = H) for usnetol. Further evidence in support of the structure (VIII; R = H) was obtained in the transformation of (VIII; R = Me) into the *furanochromone* (XV), which was accomplished by condensation with ethyl acetate by means of sodium, and subsequent cyclisation of the resulting *diketone* (XIV) with boiling acetic acid containing a little hydrochloric acid.

Although it is possible that the methyl ether of a compound having either of Schöpf and Heuck's formulæ for usnetol would give rise to a diketone of the type (XVI), yet it is most unlikely that under the conditions employed this derivative would undergo cyclisation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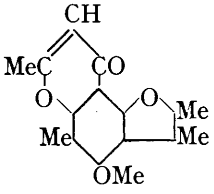
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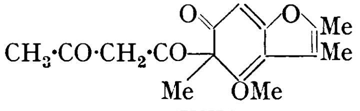
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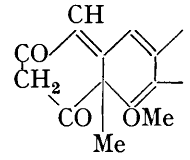
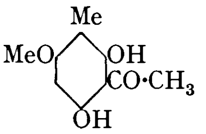

(XVII.)

yielding a product of the type (XVII). The indirect method of chromone formation is to be preferred to ring closure with acetic anhydride and sodium acetate in the case of an acetophenone, where, as Wittig (*Annalen*, 1925, **446**, 155) has shown, a mixed product is liable to be formed.

For the synthesis of *O*-methylusnetol two routes appeared to be possible: (a) the synthesis of usnetol monomethyl ether and subsequent application of the Hoesch reaction, and (b) the general method used for the synthesis of the isomeride (XIII). In the first instance the latter was adopted. The condensation of *C*-methylphloroglucinol β-monomethyl ether and acetonitrile according to the method of Hoesch gave rise to only one *ketone* which must have formula (XVIII), since, on methylation by the methyl iodide–potassium carbonate method, it gave rise to 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone.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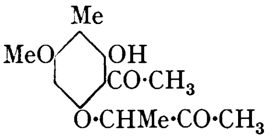
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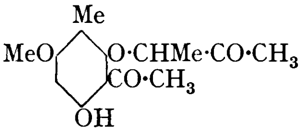
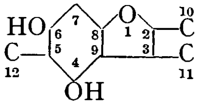

(XX.)

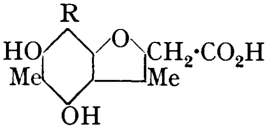
The interaction of (XVIII) and 3-chlorobutan-2-one in boiling acetone in the presence of potassium carbonate furnished a *phenoxy-ketone* which has formula (XIX) and not (XX) (which would have ultimately resulted in a hemiquinone), since we have already shown that on alkylation compounds of type (XVIII) yield only 6-*O*-alkyl derivatives (*loc. cit.*). In attempts to effect the cyclisation of (XIX) under the usual conditions with concentrated or alcoholic sulphuric acid, the substance was either recovered unchanged or converted into intractable resinous products. Ultimately, by means of a large excess of zinc chloride in warm alcohol, (XIX) was converted into a compound which appeared to be a polymeride and on distillation in a high vacuum gave rise to *O*-methylusnetol (VIII; R = Me), identical in every way with the natural substance.

Pyrousnic Acid and Usnetic Acid.—The new formula for usnetol entails a revised structure for usnetic acid, and though direct experimental evidence is not available, an examination of the properties of this compound, together with those of pyrousnic acid, has enabled us to limit the choice to one of two formulæ. Pyrousnic acid was first obtained by Paterno (*loc. cit.*), who found that on decarboxylation it gave rise to usneol, which Schöpf and Heuck (*loc. cit.*) suggested was identical with the coumarone obtained by *C*-deacetylation of usnetol. We have confirmed the results of Paterno, and have also found that pyrousnic acid is formed along with a new acid, which we have termed *usnetinic acid*, in the course of the preparation of usnetic acid according to the directions of Schöpf and Heuck.

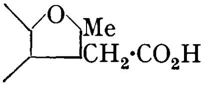
The behaviour of pyrousnic acid towards methylating agents closely resembles that of usneol. With diazomethane only the *methyl* ester is formed, but on prolonged methylation by the methyl iodide–potassium carbonate method, *methyl* O-*dimethylpyrousnate* is obtained, which on hydrolysis yields O-*dimethylpyrousnic acid*. Unlike usnetol, pyrousnic acid cannot be preferentially methylated to yield a monomethyl ether, and does not give a coloration with alcoholic ferric chloride, hence it is reasonably certain that the carboxyl group is not attached at position 7 of the skeleton formula (XXI). This conclusion is in agreement with the fact that methyl 6-hydroxy-4-methoxy-2 : 3 : 5-trimethylcoumarone-7-carboxylate (this vol., p. 714), which gives an intense ferric chloride reaction, is not methylated by the potassium carbonate–methyl iodide method even on prolonged treatment with a large excess of the reagents. Further, pyrousnic acid is not a phenylacetic acid having the carboxyl group at position 12, because on being heated above its melting point it is quantitatively decarboxylated and does not form an anhydro (coumaranone) derivative, and because it does not give a coloration with aqueous ferric chloride, a property which is common to *o*-hydroxyphenylacetic acids. Finally, the attachment of the carboxyl group at either the 2-, 3-, 4-, 5-, 6-, 8-, or 9-position would necessitate a hemiquinonoid structure, which is excluded by the existence of the *O*-dimethyl ether. We consider, therefore, that pyrousnic acid is a furylacetic acid having the carboxyl group at either the 10- or the 11-position, and thus has formula (XXII; R = H) or (XXIII; R = H).



(XXI.)



(XXII.)



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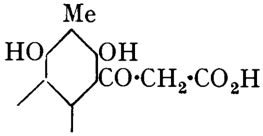

(XXIV.)

We have now shown that, by the removal of the *C*-acetyl group with hot concentrated potassium hydroxide, usnetic acid is converted into pyrousnic acid, and therefore, in view of the following established relationships between usnetic acid, pyrousnic acid, usnetol,

$$\begin{tikzcd} \begin{array}{c}\text{Usnetic acid}\\ C_{14}H_{14}O_6\end{array} \arrow[r, "-CH_2\cdot CO_2H\ +H_2O"'] \arrow[d, "-CO_2"] & \begin{array}{c}\text{Pyrousnic acid}\\ C_{12}H_{12}O_5\end{array} \arrow[d, "-CO_2"] \\ \begin{array}{c}\text{Usnetol}\\ C_{13}H_{14}O_4\end{array} \arrow[r, "-CH_2\cdot CO_2H\ +H_2O"'] & \begin{array}{c}\text{Usneol}\\ C_{11}H_{12}O_3\end{array} \end{tikzcd}$$

and usneol, usnetic acid must be a *C*-acetyl derivative of pyrousnic acid having either formula (XXII; R = Ac) or (XXIII; R = Ac). That usnetic acid is not an *o*-hydroxybenzoylacetic acid (XXIV), since, as we have found, it does not undergo ring closure on treatment with warm mineral acids to give a 4-hydroxycoumarin, is in agreement with the conclusion that pyrousnic acid is not an *o*-hydroxybenzoic acid, which alone would arise by the hydrolytic decomposition of (XXIV).

As a result of the new formula established for usnetol, all the formulæ proposed by Schöpf and Heuck (*loc. cit.*) for usnic, usnolic, and decarbousnic acids and their numerous derivatives are completely invalidated. A discussion of new structures for these compounds is reserved until we have completed our examination of usnolic and decarbousnic acids.

Ozonisation of Usnetol.—The product obtained by treatment of the ozonide of usnetol (VIII; R = H) with water must have formula (IX) and not the hemiquinonoid structure proposed by Schöpf and Heuck (*loc. cit.*), and hence the removal of the *O*-acetyl group of this product with warm alcoholic hydrochloric acid yields a *C*-diacetyl derivative of methylphloroglucinol (X).

EXPERIMENTAL.

Pyrousnic Acid.—The *d*-usnic acid, m. p. 203—204°, used in the subsequent experiments was obtained from *Usnea barbata* (Robertson and Stephenson, J., 1932, 1678) and from *Cladonia alpestris* collected at Røros, Norway, by Dr. B. Lynge of the University of Oslo. The racemic acid was prepared by refluxing a xylene solution of *d*-usnic acid for 6 hours.

(A). A mixture of usnic acid (5 g.) and 50% aqueous potassium hydroxide (15 g.) was heated to 210° (oil-bath) in an atmosphere of hydrogen; at 170—180° the solution effervesced and acetone was evolved (identified as its 2 : 4-dinitrophenylhydrazone). The mixture was then kept at 210° for 10 minutes, cooled, poured into dilute sulphuric acid, filtered (to remove a little tar), and extracted 3 times with ether. Evaporation of the dried extracts left pyrousnic acid as an oil which gradually crystallised. Recrystallised by slow evaporation of an aqueous solution in a vacuum and then from ethyl acetate–light petroleum (b. p. 60—80°), it formed colourless needles, m. p. 199—200° (decomp.) after sintering at 195° (Found : C, 60·8; H, 5·3. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). This compound is easily soluble in alcohol, ethyl acetate, and hot water, does not give a coloration with aqueous or alcoholic ferric chloride, and liberates carbon dioxide from aqueous sodium hydrogen carbonate.

After the removal of the pyrousnic acid, the liquor was found to contain acetic acid, which was converted into the silver salt by way of the potassium salt (Found : Ag, 64·4. Calc. for $C_2H_3O_2Ag$: Ag, 64·7%).

Pyrousnic acid was decarboxylated by heating in a high vacuum at 200°, and the resulting usneol obtained as a yellow sublimate, m. p. 178—179°, after crystallisation from chloroform–light petroleum, identical with an authentic specimen (Found : C, 68·5; H, 6·4. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·3%).

Treatment of pyrousnic acid (1·5 g.) in ether (25 c.c.) with an excess of ethereal diazomethane (from 5 c.c. of nitrosomethylurethane) (80 c.c.) during 1 hour gave rise to the *methyl* ester, which crystallised from ethyl acetate–light petroleum (charcoal) and then from dilute methyl alcohol in colourless slender needles, m. p. 186° (slight decomp.) [Found : C, 62·2; H, 5·8; OMe, 12·1. $C_{12}H_{11}O_4(OMe)$ requires C, 62·4; H, 5·6; OMe, 12·4%]. This derivative, which does not give a ferric chloride reaction, is readily soluble in the usual organic solvents and in aqueous sodium hydroxide, but insoluble in aqueous sodium carbonate. On being kept, the solution in aqueous sodium hydroxide becomes blue and then green.

(B). Usnetic acid (3 g.) was heated with 50% aqueous potassium hydroxide (10 g.) at 205° for ¼ hour in an atmosphere of hydrogen, and the cooled melt acidified with dilute sulphuric acid. Pyrousnic acid (1·2 g.) was isolated from the filtered solution with ether, and on crystallisation from water and then from ethyl acetate–light petroleum formed needles, m. p. and mixed m. p. 200—201° (Found : C, 60·7; H, 5·5%). Acetic acid was isolated from the aqueous liquor left after the separation of the pyrousnic acid, and identified by conversion into the silver salt (Found : Ag, 64·0%).

O-*Dimethylpyrousnic Acid.*—Methyl pyrousnate (1·5 g.) was methylated with methyl iodide (5 c.c.) and potassium carbonate (4·5 g.) in boiling acetone (15 c.c.) during 8 hours. After the addition of more acetone, the potassium salts were removed by filtration, the solvent distilled, and a solution of the residue in ether washed with 5% aqueous sodium hydroxide, dried, and evaporated. The residual *methyl* O-*dimethylpyrousnate* crystallised in contact with a little methyl alcohol and then separated from dilute methyl alcohol in colourless, thick needles, m. p. 63—64° [Found : C, 64·5; H, 6·9; OMe, 33·0. $C_{12}H_9O_2(OMe)_3$ requires C, 64·8; H, 6·5; OMe, 33·5%]. This compound is easily soluble in the usual organic solvents and yields an unstable red picrate. With concentrated sulphuric acid it forms a deep yellow solution which on warming becomes red and then purple; addition of water to the cooled mixture then gives a purple precipitate.

Methylation of pyrousnic acid with methyl iodide and potassium carbonate in boiling acetone also gave rise directly to methyl *O*-dimethylpyrousnate.

A solution of the ester (0·75 g.) in 10% aqueous potassium hydroxide (7·5 c.c.) and methyl alcohol (7·5 c.c.) was refluxed for ¾ hour, cooled, and acidified with hydrochloric acid. The resulting *acid* was purified by means of aqueous sodium hydrogen carbonate and then by crystallisation from ethyl acetate–light petroleum, forming clusters of colourless prisms, m. p. 126—127° [Found: C, 63·6; H, 6·3. $C_{12}H_{10}O_3(OMe)_2$ requires C, 63·6; H, 6·1%]. This compound is easily soluble in alcohol and ethyl acetate, and insoluble in light petroleum. With concentrated sulphuric acid it forms a brilliant yellow solution, which on warming becomes red and then purple; the latter colour is discharged on dilution with water.

Usnetinic Acid.—*d*- or *r*-Usnic acid (30 g.) was hydrolysed with 75% aqueous potassium hydroxide according to the directions of Schöpf and Heuck (*loc. cit.*), and after the separation of the usnetic acid the filtrate was extracted 3 times with ether. The oil left on evaporation of the dried extracts was dissolved in a little water, and the solution filtered from insoluble usnetic acid (0·5 g.) and evaporated in a vacuum at room temperature. Usnetinic acid (1·7 g.), contaminated with oil and a trace of pyrousnic acid, gradually separated. Evaporation of the mother-liquor to dryness then gave almost pure pyrousnic acid (0·8 g.), which separated from ethyl acetate–light petroleum in clusters of needles, m. p. and mixed m. p. 198—199°; the methyl ester crystallised from dilute methyl alcohol in slender needles, m. p. and mixed m. p. 185—186°.

Recrystallised from water and then several times from ethyl acetate–light petroleum (b. p. 60—80°), *usnetinic acid* formed colourless, thick, tubular prisms, m. p. 180—181° (decomp.), readily soluble in warm water and in all the usual organic solvents except light petroleum (Found: C, 59·5, 59·5; H, 5·2, 5·1. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). Addition of ferric chloride to an aqueous solution of the compound gives a red coloration; an alcoholic solution does not give a reaction. On being heated, the orange solution of the substance in concentrated sulphuric acid becomes red and then greenish-purple; addition of water then gives an almost colourless solution.

O-*Methylusnetic Acid.*—Treatment of usnetic acid (2 g.) with an excess of ethereal diazomethane (from 6·8 c.c. of nitrosomethylurethane) gave rise to methyl *O*-methylusnetate, m. p. 117—118°, after crystallisation from methyl alcohol [Found: C, 62·5; H, 6·1; OMe, 20·1. Calc. for $C_{14}H_{12}O_4(OMe)_2$: C, 62·8; H, 5·9; OMe, 20·3%]. Hydrolysis of the ester (1 g.) with 10% aqueous sodium hydroxide and methyl alcohol (10 c.c.) on the steam-bath afforded the *acid*, which was purified by means of aqueous sodium hydrogen carbonate and then by crystallisation from dilute alcohol, forming clusters of yellow needles, m. p. 164—165° [Found: C, 61·3; H, 5·6; OMe, 10·6. $C_{14}H_{13}O_5(OMe)$ requires C, 61·6; H, 5·5; OMe, 10·6%]. The acid is soluble in alcohol, ethyl acetate, acetone, and aqueous sodium acetate, and gives a green coloration with alcoholic ferric chloride.

6-*Hydroxy*-4-*methoxy*-7-*acetoacetyl*-2 : 3 : 5-*trimethylcoumarone* (XIV).—On methylation with methyl iodide (3 c.c.) and potassium carbonate (1·5 g.) in boiling acetone (15 c.c.) during 4 hours, usnetol (1 g., prepared by decarboxylation of usnetic acid) gave rise to the monomethyl ether, which separated from alcohol in yellow, elongated, hexagonal prisms, m. p. 127—128°, and was identical with a specimen prepared from diazomethane [Found: OMe, 12·4. Calc. for $C_{13}H_{13}O_3(OMe)$: OMe, 12·5%]. With cold concentrated sulphuric acid, the compound formed a yellow solution which on warming became red and then purple.

A mixture of *O*-methylusnetol (1·2 g.), ethyl acetate (25 c.c.), and sodium (0·6 g. in small pieces) was heated on the steam-bath for 6 hours, a little alcohol was added to destroy traces of sodium, and the solution diluted with water and acidified with acetic acid. On removal of the unchanged ethyl acetate by means of a current of air, the *diketone* solidified, and on crystallisation from alcohol formed slender yellow needles (0·8 g.), m. p. 126—127° (Found: C, 66·2; H, 6·6. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%). With alcoholic ferric chloride this compound gives a greenish-brown coloration. Mixed with *O*-methylusnetol, it melted at 100—101°.

7-*Methoxy*-2 : 8 : 4′ : 5′-*tetramethyl*-5 : 6-*furano*-(2′ : 3′)-*chromone* (XV).—After the foregoing diketone (0·4 g.) was boiled with acetic acid (8 c.c.) containing 4 drops of concentrated hydrochloric acid for ½ minute, addition of water precipitated the *chromone*, which separated from dilute acetic acid as a hydrate in thick needles, m. p. 192° (Found, in specimen dried at 100° for 1 hour: C, 70·2; H, 6·2. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). The compound is readily soluble in alcohol, acetic acid, or ethyl acetate, and does not give a ferric chloride reaction. The sulphuric acid reaction is identical with that of usnetol methyl ether.

2 : 4-*Dihydroxy*-6-*methoxy*-3-*methylacetophenone* (XI).—Methylphloroglucinol α-monomethyl ether (5·2 g.) was condensed with acetonitrile (1·85 g.) in ether (50 c.c.) by means of zinc chloride (1·5 g.) and excess of hydrogen chloride. The ketimine double compound separated as an oil which gradually crystallised and after 2 days was hydrolysed by boiling with water (100 c.c.) for 20 minutes. Crystallised from dilute alcohol, the resulting *ketone* formed almost colourless needles, m. p. 224° [Found: C, 61·4; H, 6·4; OMe, 16·0. $C_9H_9O_3(OMe)$ requires C, 61·2; H, 6·1; OMe, 15·8%]. This substance, which is almost insoluble in ethyl acetate or benzene, gives a purplish-brown coloration with alcoholic ferric chloride.

6-*Hydroxy*-4-*methoxy*-5-*acetyl*-2 : 3 : 7-*trimethylcoumarone* (O-*Methyl*isousnetol) (XIII).—A mixture of the foregoing ketone (1·5 g.), 3-chlorobutan-2-one (Part II, *loc. cit.*) (1·5 g.), and acetone (15 c.c.) was refluxed for 2·5 hours and diluted with an excess of 1% aqueous sodium hydroxide. Acidification of the filtered solution with hydrochloric acid precipitated the *ketocoumarone* as a yellow solid, which separated from alcohol in elongated, rectangular prisms (1·3 g.), m. p. 109—110° [Found: C, 67·6; H, 6·6; OMe, 12·6. $C_{13}H_{13}O_3(OMe)$ requires C, 67·7; H, 6·5; OMe, 12·5%]. The ferric chloride and the sulphuric acid reaction are identical with those of *O*-methylusnetol; a mixture of the two compounds melted at 90—92°. The *oxime* crystallised from dilute methyl alcohol in colourless rhombic prisms, m. p. 161—162° (Found: C, 63·5; H, 6·9. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5%); it gives a greenish-black coloration with alcoholic ferric chloride.

2 : 6-*Dihydroxy*-4-*methoxy*-3-*methylacetophenone* (XVIII).—Methylphloroglucinol β-mono-

methyl ether (5 g.) was prepared directly by the simultaneous hydrolysis and decarboxylation of methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (7·5 g.) with 15% aqueous potassium hydroxide (100 c.c.) and methyl alcohol (50 c.c.); m. p. 115—116°, after crystallisation from benzene (compare Herzig and Wenzel, *Monatsh.*, 1902, **23**, 81).

A solution of this compound (5 g.) and acetonitrile (1·85 g.) in ether (50 c.c.) containing zinc chloride (1·5 g.) was saturated with dry hydrogen chloride, and after 2 days the crystalline ketimine double compound was hydrolysed by boiling with water (125 c.c.) for 20 minutes. The solution of the solid product in ether (200 c.c.) was extracted with 10% aqueous sodium carbonate, washed, dried, and evaporated, leaving 2 : 6-*dihydroxy*-4-*methoxy*-3-*methylacetophenone*, which separated from warm xylene and then from benzene in clusters of pale yellow needles (4·7 g.), m. p. 197—198° [Found : C, 61·1; H, 6·1; OMe, 15·6. $C_9H_9O_3(OMe)$ requires C, 61·2; H, 6·1; OMe, 15·8%]. The substance is readily soluble in warm methyl or ethyl alcohol, and with alcoholic ferric chloride gives a green coloration which changes to brownish-purple on dilution with water. Methylation of this ketone (0·3 g.) with methyl iodide (1 c.c.) and potassium carbonate (0·6 g.) in boiling acetone (5 c.c.) for 2 hours afforded 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone, which separated from alcohol in rectangular prisms, m. p. 141—142°, identical in every way with an authentic specimen (this vol., p. 437). Despite a careful search, a second (isomeric) ketone could not be detected in the aqueous sodium carbonate extract or in the benzene liquor.

α-Methyl-α-3-hydroxy-5-methoxy-2-acetyl-4-methylphenoxyacetone (XIX).—A mixture of 2 : 6-dihydroxy-4-methoxy-3-methylacetophenone (1 g.), 3-chlorobutan-2-one (1 g.), potassium carbonate (2 g.), and acetone (10 c.c.) was heated on the steam-bath for 8 hours, diluted with water, and extracted several times with ether. Evaporation of the dried extracts left the *phenoxy-ketone* as an oil, which solidified in contact with a little alcohol, and on recrystallisation from dilute alcohol formed small rectangular plates (0·75 g.), m. p. 151—152° (Found : C, 63·0; H, 7·1. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). This compound is easily soluble in ethyl acetate and insoluble in warm light petroleum, and with alcoholic ferric chloride gives a purple coloration almost identical with that given by 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone.

6-*Hydroxy*-4-*methoxy*-7-*acetyl*-2 : 3 : 5-*trimethylcoumarone* (O-*Methylusnetol*) (VIII; R = Me).—A solution of the foregoing phenoxy-ketone (1 g.) and fused zinc chloride (7·5 g.) in alcohol (15 c.c.) was heated on the water-bath for 5 hours, a further quantity of zinc chloride (7·5 g.) being added after 2 hours. The reaction mixture was poured into water, and the amorphous solid collected, washed, and dried. This product, which could not be crystallised, appeared to be a polymeride of *O*-methylusnetol. On distillation in a high vacuum it gave rise to the latter compound as a yellow oil, which solidified in contact with a little alcohol. Recrystallised from the same solvent, synthetical *O*-methylusnetol formed yellow, elongated, hexagonal prisms, m. p. and mixed m. p. 127—128°, and was identical in every way with a natural specimen (Found: C, 67·6; H, 6·6. Calc. for $C_{14}H_{16}O_4$: C, 67·7; H, 6·5%). The oxime separated from methyl alcohol in colourless prisms which turned green on exposure to light, m. p. and mixed m. p. 184—185°, identical with the natural derivative.

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