336. *Usnic Acid. Part VII. Analogues of Usnolic Acid.*

By Reginald T. Foster, Alexander Robertson, and (in part) Thomas V. Healy.

A brief review of the structures recently proposed for usnic acid leads to the adoption of the expression (I, R = H), first suggested for this compound in Part V (*loc. cit.*) and supported by the work of Schöpf and Ross (*loc. cit.*). A new structure (III, R = CO_2H) for usnolic acid, based on the formula (III, R = H) which was advanced for decarbousnol in Part V, is deduced and its formation from usnic acid is discussed. The synthesis of the two acids (XVII; R = H, R_1 = H) and (XVII; R = Me, R_1 = H) by way of the stages (XI), (XII), (XIII), (XIV), (XV), and (XVI) is described and a detailed comparison of these acids with usnolic acid clearly indicates that the latter compound and its synthetical analogues are similarly constituted, thus affording independent evidence in support of the expression (III, R = CO_2H).

In Part V (J., 1937, 894) Curd and one of us (A. R.) advanced cogent reasons for adopting the view that usnic acid is not a lactone and suggested that the > CO group, which appears as the carboxyl group in the isomeride usnolic acid and is eliminated in the conversion of usnic acid into decarbousnic acid (IV, R = H), was originally present as a ketonic group. To accommodate this conclusion two expressions were proposed for usnic acid at that time, of which (I, R = H) was considered to be the more feasible, and a re-examination of the experimental work on usnic acid described in the literature has led us to regard usnic acid as being best represented by this formula.* It seems reasonable to assume that in a structure of the type (I, R = H) the asymmetric carbon atom (marked +) carrying the angular methyl group is a centre of weakness in the molecule, which in part may be ascribed to the tendency of the system to assume the coumarone type of structure, thus accounting for the behaviour of usnic acid towards hydrolytic agents. In addition, the expression (I, R = H) for usnic acid satisfies the criteria outlined in Part V (*loc. cit.*) and affords a satisfactory basis for the rational formulation of its functional derivatives.

The view that usnic acid can no longer be regarded as a ketonic lactone has been adopted by Asahina and Yanagita (*Ber.*, 1938, **71**, 2260), who accordingly have modified the lactone formula (II), proposed in an earlier communication (*Ber.*, 1937, **70**, 2462), to the expression (V).† These authors consider that the structure (V) affords a satisfactory explanation of the behaviour of usnic acid on hydrolysis and of dihydrousnic acid on thermal decomposition and permits the formulation of usnonic acid and the existence of ethyl *d-iso*oxyacetusnetate. This expression (V) or Haworth's modification of it (VII) (*loc. cit.*), however, does not accord with the results of Schöpf and Ross (*Naturwiss.*, 1938, **26**, 772). The latter authors found that ozonolysis of usnic acid diacetate and alcoholysis of the resulting ozonide gave rise to the *O*-diacetyl-α-coumaranone (VIII) and ethyl αγ-diketovalerate, a result which clearly implies that the molecule undergoes oxidative scission at the position marked by the dotted line in formula (I, R = Ac) or at the corresponding position in formula (V). For several reasons, *e.g.*, an α-coumarone derived from a diacetate of (V) would be a mono- and not a di-acetate, it seems clear that the simultaneous formation of these degradation products cannot be explained on the basis of formula (V) or on the modification (VII). On the other hand, as Schöpf and Ross have indicated, formulæ (I, R = H) and (I, R = Ac) for usnic acid and its diacetate are in entire agreement with these results and allow a conventional explanation of the ozonolysis.

On dehydration with warm concentrated sulphuric acid decarbousnic acid (IV, R = H)

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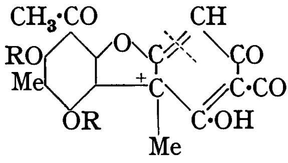
* This structure has been employed in lectures on several occasions in Liverpool during the past two years and at the University of Utrecht in November, 1938.—A. R.

† Haworth (*Ann. Reports*, 1938, **35**, 315) writes Asahina and Yanagita's type of formula as (VII), in which the large ring is a ten-membered one, but as far as we are aware there is no record that the Japanese authors implied or favoured this type of structure. In their memoir of 1938 the latter authors write a part of their chinol formula (II) of 1937 without completing the large ring and indicate that they now adopt the modification (V), which they write in a similar manner as a partial formula, leaving the large ring incomplete. In the chinol formula (1937) the large ring is a nine-membered one and hence presumably in their modification of 1938 this ring is an eight-membered one.

gives rise to decarbousnol and, of the possible formulæ suggested for the latter compound in Part V (*loc. cit.*), the expression (III, R = H) is now considered to be the most feasible. Further, since usnolic acid, a true carboxylic acid, which is formed by isomerisation of usnic acid under the conditions employed for the conversion of (IV, R = H) into (III, R = H), has been shown to yield (III, R = H) on decarboxylation (Part V, *loc. cit.*), it is represented by the structure (III, R = CO_2H) and is in all probability formed from (I, R = H) by way of the intermediate (IV, R = CO_2H). On the other hand, Asahina and Yanagita (*loc. cit.*) consider that the formation of decarbousnol from decarbousnic acid (IV, R = H) involves the 7-acetyl group in the coumarone residue of the latter compound and accordingly propose structures of the type (VI) for decarbousnol.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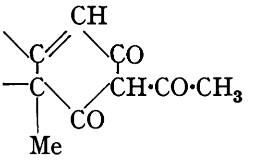
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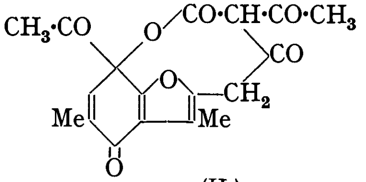
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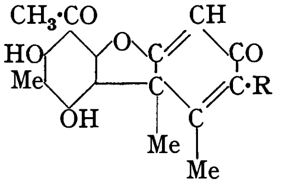
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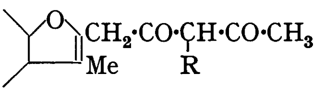
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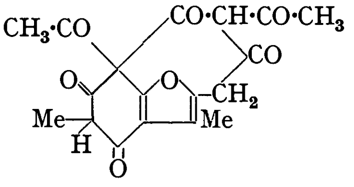
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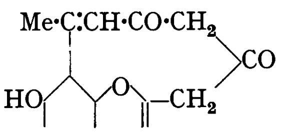
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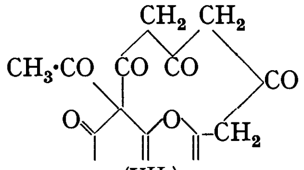
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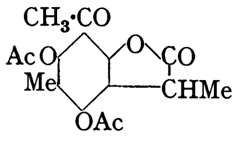
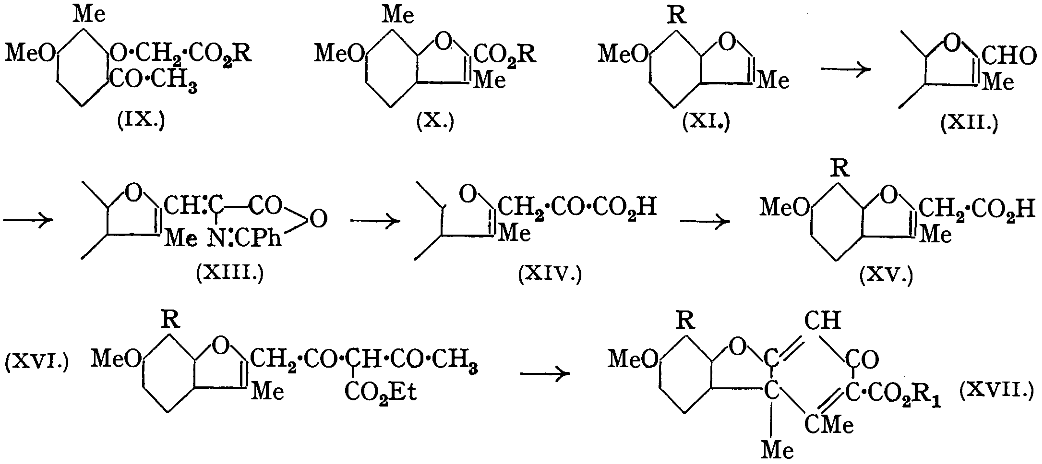

(VIII.)

The formulæ (III, R = H) and (III, R = CO_2H), now regarded as representing decarbousnol and usnolic acid respectively, imply that compounds of the type (IV) undergo a somewhat novel type of cyclisation when treated with warm concentrated sulphuric acid, for which we have been unable to find an analogy in the literature, and it therefore seemed highly desirable that independent synthetical evidence in support of this view should be obtained. On account of the difficulties involved in preparing sufficient starting material for an immediate attempt on the synthesis of usnolic acid we therefore undertook the synthesis of the analogues (XVII; R = H, R_1 = H) and (XVII; R = Me, R_1 = H) and have achieved this objective by a procedure which seems capable of being applied ultimately to the synthesis of usnolic acid or its dimethyl ether. Further, it appeared essential to test the cyclisation of a compound of the type (IV) which did not contain a *C*-acetyl group in the 7-position of the coumarone ring and thus exclude the possibility of the formation of a large-ring type (VI) as envisaged by Asahina and Yanagita (*loc. cit.*).

By means of Gattermann's method the *aldehyde* (XII, R = H), unaccompanied by isomerides, was obtained in excellent yield from the coumarone (XI, R = H) (compare this vol., p. 921) and its orientation was established by the fact that on oxidation with potassium permanganate in aqueous acetone it furnished 6-methoxy-4-methylcoumarone-2-carboxylic acid. Hydrolysis of the *azlactone* (XIII, R = H), prepared from this aldehyde in the usual manner, and oxidation of the resulting *pyruvic acid* (XIV, R = H) with alkaline hydrogen peroxide gave rise to the *coumarone-2-acetic acid* (XV, R = H), which on treatment with phosphorus pentachloride in chloroform yielded the acid chloride, characterised by the formation of the *amide*. Interaction of this chloride with ethyl sodioacetoacetate in absolute ether gave a very viscous, oily product, which could not be purified but undoubtedly consisted of the almost pure keto-ester (XVI, R = H) and gave a strong ferric reaction (compare Robinson and co-workers, J., 1925, **127**, 166; 1926, 1713). On being warmed with concentrated sulphuric acid under the conditions whereby usnic acid is converted into usnolic acid and decarbousnic acid is dehydrated to decarbousnol (Paterno, *Gazzetta*, 1900, **30**, 109; Widman, *Annalen*, 1902, **324**, 184), this ketonic ester (XVI, R = H) gave rise to a mixture of an acid and its *ethyl* ester for which we consider the expressions (XVII; R = H, R_1 = H) and (XVII; R = H, R_1 = Et) respectively to be the most feasible. Though the acid (XVII; R = H, R_1 = H) was obtained as a *hydrate* which could not be completely dehydrated, its relationship to the ester (XVII; R = H, R_1 = Et) was established by conversion into the latter with diazoethane. Hydrolysis of the ethyl ester with concentrated sulphuric acid regenerated the parent acid, which was also characterised by the formation of the *methyl* ester with diazomethane.


(IX.) (X.) (XI.) (XII.) (XIII.) (XIV.) (XV.) (XVI.) (XVII.)

In order to exclude the possibility that the cyclisation of the ketonic ester (XVI, R = H) to the anhydro-compound might have involved the interaction of the δ-carbonyl group of the side chain with the carbon atom in the 7-position of the coumarone residue it was decided to test the cyclisation of the homologue (XVI, R = Me) in which the 7-position is blocked by a methyl group. Accordingly this ester was synthesised from the *acid* (IX, R = H) by way of the stages (XI, R = Me), (XII, R = Me), (XIII, R = Me), (XIV, R = Me) and (XV, R = Me) and the properties of the crude compound closely resembled those of (XVI, R = H). On treatment with sulphuric acid in the same manner it underwent cyclisation, yielding a mixture of the *acid* (XVII; R = Me, R_1 = H) and its *ethyl* ester (XVII; R = Me, R_1 = Et).

In their general properties the synthetic analogues closely resemble usnolic acid and in certain respects decarbousnol. Unlike the ketonic esters type (XVI) and in agreement with the structure type (XVII), neither the synthetic acids nor their esters give a reaction with alcoholic ferric chloride or *o*-phenylenediamine (compare Asahina and Yanagita, *loc. cit.*). In this connexion it may be noted that, though usnolic acid and decarbousnol do not react with *o*-phenylenediamine, they give blue-green ferric reactions, a property due to the presence of the hydroxyl and carbonyl groups of the usnetol residue; the latter invariably behaves in this manner except in usnic acid and decarbousnic acid, where this coloration is masked by the effect of the 1 : 3-diketonic system. The synthetic acids or their esters do not give the bright colorations on being gently warmed with sulphuric acid which are characteristic of the benzofuran nucleus, but both compounds give the intense brilliant blue Ehrlich reaction which in agreement with Asahina and Yanagita (*Ber.*, 1937, **70**, 1500) we have found to be characteristic of usnolic acid and decarbousnol and is not given by usnic acid or any of its degradation products. The only other derivative of usnic acid which we have found to give an Ehrlich reaction is the anilide of decarbousnic acid, but in this case the colour is yellowish-green, becoming greenish-yellow on dilution with much water. The synthetic acids or their esters do not appear to react readily with carbonyl reagents, *e.g.*, 2 : 4-dinitrophenylhydrazine, a result which is in keeping with the structure type (XVII) where the ethylenic linkages are in the αβ- and α′β′-positions to the carbonyl group. Though Widman (*Annalen*, 1902, **324**, 171) has shown that the methyl and ethyl esters of usnolic acid yield normal mono-oximes, these derivatives are almost certainly formed by reaction with the carbonyl group of the acetyl residue in the 7-position of the potential coumarone system in (III, $R = CO_2Me$, or $R = CO_2Et$). On being warmed with aniline, usnolic acid is converted into the anilide of decarbousnic acid with the elimination of carbon dioxide and it has been found that the acids (XVII; $R = H$, $R_1 = H$) and (XVII; $R = Me$, $R_1 = H$) behave in a similar manner, but the amorphous neutral products which give the same Ehrlich reaction as decarbousnic acid anilide have not yet been crystallised. Owing to lack of material the crystalline product obtained in small yield by the decarboxylation of the acid (XVII; $R = Me$, $R_1 = H$) has not been completely investigated, but it is clearly analogous to decarbousnol (compare Part V, *loc. cit.*) and gives the same blue Ehrlich reaction.

In our opinion the close similarity of the properties of usnolic acid with those of the synthetic analogues, type (XVII), affords clear evidence that the former compound and decarbousnol have the corresponding structures (III, $R = CO_2H$) and (III, $R = H$), thus affording collateral evidence in favour of the expression (I, $R = H$) for usnic acid. It must be noted in this connexion that the expression (III, $R = CO_2H$) for usnolic acid can also be derived on the basis of formula (V) for usnic acid and further that from formula (VII) a structure analogous to (III, $R = CO_2H$) for usnolic acid is possible in which the methyl group in juxtaposition to the angular methyl is replaced by the residue $\cdot CH_2 \cdot CO_2H$. The formulæ (V) and (VII) for usnic acid, however, are clearly excluded by the results of Schöpf and Ross (*loc. cit.*) and the former structure is also open to objections of a stereochemical nature. With regard to usnonic acid and dihydrousnic acid, for which Asahina and Yanagita (*loc. cit.*) have advanced structures based on their formulation of usnic acid, we hope to deal with this topic in a future communication, but it may be noted in the meantime that in view of the well-known tautomeric properties of the phloroglucinol nucleus, the suggestions of the Japanese authors may be equally well applied to formula (I, $R = H$). In any case evidence of the structure of dihydrousnic acid based on the results of its thermal degradation must be accepted with considerable reserve.

EXPERIMENTAL.

6-Methoxy-2-formyl-3-methylcoumarone (XII, $R = H$).—Ethyl 3-methoxy-6-acetylphenoxyacetate was prepared from 2-hydroxy-4-methoxyacetophenone by the potassium carbonate–acetone method in almost theoretical yield and the acid formed by hydrolysis was converted into 6-methoxy-3-methylcoumarone (XI, $R = H$) (Kostanecki and Tambor's method, *Ber.*, 1909, **42**, 901), which was also prepared by the following route: An ethereal solution of the product obtained by the interaction of resorcinol monomethyl ether (15 g.), chloroacetone (14·5 g.), and potassium carbonate (45 g.) in boiling acetone (250 c.c.) during 4 hours was extracted with excess of 5% aqueous sodium hydroxide to remove unchanged monomethyl ether (6 g.), washed with water, and dried. Distillation of the residue left on removal of the solvent yielded 3-methoxyphenoxyacetone as a colourless oil (10·2 g.), b. p. 150—153°/20 mm., which gave a *2 : 4-dinitrophenylhydrazone*, forming pale yellow needles, m. p. 146°, from ethyl acetate (Found: C, 53·5; H, 4·7; N, 15·7. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·5; N, 15·6%). The phenoxy-ketone (4 g.) was dissolved in concentrated sulphuric acid (16 c.c.), maintained at 0°, and 5 minutes later the brown solution was poured into ice-water, giving a precipitate of 6-methoxy-3-methylcoumarone (0·33 g.) in plates, which was isolated with ether and purified by distillation, b. p. 79—82°/0·4 mm., m. p. 58°, and gave a violet, blue, and finally green sulphuric acid reaction.

Interaction of 6-methoxy-3-methylcoumarone (10 g.) and hydrogen cyanide (10 c.c.) in ether (100 c.c.) saturated with hydrogen chloride during 24 hours gave a crystalline aldimine hydrochloride, which on hydrolysis with water (100 c.c.) on the steam-bath for 15 minutes furnished the *aldehyde* (10 g.), forming colourless prisms, m. p. 105°, from alcohol (Found: C, 69·3; H, 5·3. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). The *2 : 4-dinitrophenylhydrazone* separated from ethyl acetate in small red prisms, m. p. 262° (Found : N, 15·3. $C_{17}H_{14}O_6N_4$ requires N, 15·1%); the semicarbazone had m. p. 248°.

The aldehyde (0·5 g.), dissolved in acetone (15 c.c.) at 45°, was oxidised with a solution of potassium permanganate (0·9 g.) in water (20 c.c.) at the same temperature and after 1 hour the solution was cleared with sulphur dioxide, diluted with water, and extracted several times with ether. Evaporation of the combined extracts left 6-methoxy-3-methylcoumarone-2-carboxylic acid mixed with a little unchanged aldehyde. The latter was removed by means of aqueous sodium bicarbonate and, on crystallisation from alcohol, the acid formed needles, m. p. 190° (decomp.), identical with an authentic specimen (Kostanecki and Lampe, *Ber.*, 1908, **41**, 1330) and giving an intense brown coloration with alcoholic ferric chloride (Found : C, 64·0; H, 5·1. Calc. for $C_{11}H_{10}O_4$: C, 64·1; H, 4·9%).

6-*Methoxy*-3-*methylcoumarone*-2-*pyruvic Acid* (XIV, R = H).—Condensation of the foregoing aldehyde (8 g.) with hippuric acid (14 g.) by means of acetic anhydride (50 c.c.) and sodium acetate (8 g.) on the steam-bath in the course of 1½ hours gave the *azlactone* (XIII, R = H), which separated on the addition of 50% alcohol (140 c.c.) to the reaction mixture and then formed orange-red rectangular prisms (12 g.), m. p. 194°, from alcohol (Found : C, 72·0; H, 4·6; N, 4·4. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%). Hydrolysis of this compound (8 g.) was effected with boiling 10% aqueous sodium hydroxide (120 c.c.) for 8 hours and after the addition of water (100 c.c.) the solution was saturated with sulphur dioxide, the benzoic acid removed with ether, and the aqueous liquor digested on the steam-bath with concentrated hydrochloric acid (30 c.c.) for 1½ hours, giving a yellow crystalline precipitate of the *pyruvic acid* (XIV, R = H). Recrystallised from dilute methyl alcohol, this compound formed pale yellow needles (3 g.), m. p. 196°, which, on being warmed with concentrated sulphuric acid, became reddish-brown and then green (Found : C, 62·8; H, 4·9. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%). The *oxime* separated from ethyl acetate–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 166° (Found : N, 5·3. $C_{13}H_{13}O_5N$ requires N, 5·3%).

6-*Methoxy*-3-*methylcoumarone*-2-*acetic Acid* (XV, R = H).—30% Hydrogen peroxide (4 c.c.) was slowly added to the foregoing pyruvic acid (2 g.), dissolved in 5% aqueous sodium hydroxide, and 1 hour later the solution was warmed at 50° for 15 minutes, cooled, and saturated with sulphur dioxide. The resulting *coumarone*-2-*acetic acid* separated from methyl alcohol in colourless leaflets (1·6 g.), m. p. 145°, which gave a brown, then red, and finally purple sulphuric acid reaction (Found : C, 65·4; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

Phosphorus pentachloride (5 g.) was added in three portions to a solution of the acid (5 g.) in absolute chloroform (50 c.c.) in the course of 10 minutes, the mixture warmed at 40° for 5 minutes to ensure that the reaction was complete, and the solvent and phosphoryl chloride removed in a vacuum. To ensure the removal of the last traces of phosphoryl chloride the residue was twice dissolved in benzene and the solvent again evaporated in a vacuum, finally leaving the acid chloride as a pale greenish oil, a specimen of which gave the *amide* on treatment with excess of concentrated aqueous ammonia. The latter substance formed colourless plates, m. p. 162°, from benzene (Found : N, 6·6. $C_{12}H_{13}O_3N$ requires N, 6·4%).

6′-*Methoxy*-3′ : 3-*dimethyl*-2′ : 3′-*dihydrobenzofurano*-(2′ : 3′ : 5 : 4)-$\Delta^{2:5}$-cyclo*hexadienone*-2-*carboxylic Acid* (XVII; R = H, R_1 = H).—A solution of the aforementioned acid chloride (from 5 g. of acid) in absolute ether (40 c.c.) was added to ethyl sodioacetoacetate (from 3 g. of ester and 0·6 g. of sodium) in ether (65 c.c.) (agitate), maintained at about — 5°, in the course of 10 minutes and, after having been kept at room temperature for 18 hours, the mixture was refluxed for 1 hour. More ether was then added to the cooled mixture, followed by sufficient water to dissolve the sodium chloride, the aqueous layer was separated and twice extracted with ether, and the combined ethereal solutions washed several times with aqueous sodium bicarbonate to remove 6-methoxy-3-methylcoumarone-2-acetic acid (0·75 g.), dried, and evaporated, leaving the keto-ester (XVI, R = H) mixed with a little ethyl acetoacetate. The latter impurity was removed by distillation in a high vacuum, 0·1 mm. (oil bath at 80°), and the residual product obtained as a very viscous, pale orange-yellow liquid which did not solidify and decomposed in the course of attempts to purify it by distillation. With alcoholic ferric chloride this material gave an intense orange-red coloration.

A solution of the crude keto-ester (XVI, R = H) (5 g.) in concentrated sulphuric acid (25 g.) was kept at 60° for 1¾ hours and then poured into ice-water (250 g.), giving a dark brown, viscous precipitate. The mixture was extracted several times with ether, and the combined extracts washed twice with saturated aqueous sodium bicarbonate. Acidification of the latter washings with hydrochloric acid precipitated the acid (XVII; R = H, R_1 = H), which was purified by repeated crystallisation from aqueous alcohol (charcoal) and was obtained as a *hydrate* in yellow or pale yellow (depending on the size of crystal), diamond-shaped plates (0·8 g.), m. p. 147°, readily soluble in aqueous sodium bicarbonate and having a negative ferric reaction in alcohol and a negative sulphuric acid reaction, alone or in the presence of a drop of ferric chloride [Found : C, 63·3; H, 5·2; OMe, 10·5. $C_{15}H_{11}O_4(OMe),H_2O$ requires C, 63·2; H, 5·3; OMe, 10·2%. Found in a specimen dried in a high vacuum at 100° : C, 66·1, 65·9; H, 5·1, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%]. Admixed with 6-methoxy-3-methylcoumarone-2-acetic acid, m. p. 145°, this compound melted at about 110°. Treatment of the well-powdered hydrate with an excess of ethereal diazomethane gave rise to the *methyl* ester, which separated from aqueous methyl alcohol and then from light petroleum (b. p. 60—80°) containing a little benzene in almost colourless, squat prisms, m. p. 101° [Found : C, 67·9; H, 5·4; OMe, 20·5. $C_{15}H_{10}O_3(OMe)_2$ requires C, 68·0; H, 5·3; OMe, 20·7%].

Evaporation of the dried ethereal solution left on separation of the acid gave the *ethyl* ester (XVII; R = H, R_1 = Et), which formed colourless, elongated, rectangular prisms (0·3 g.), m. p. 122°, from dilute alcohol, insoluble in dilute aqueous sodium hydroxide and having negative ferric and sulphuric acid reactions [Found : C, 68·8; H, 5·7; OAlkyl, 10·0. $C_{15}H_{10}O_3(OMe)(OEt)$ requires C, 68·8; H, 5·7; OAlkyl, 10·2%]. After this ester (0·2 g.) had been heated with concentrated sulphuric acid (2 c.c.) at 60° for 1½ hours, the addition of ice-water to the cooled mixture gave a precipitate of the acid (XVII; R = H, R_1 = H), which on purification from dilute alcohol gave the hydrate, m. p. and mixed m. p. 147°. When the ethyl ester (0·2 g.) was heated on the water-bath for 1 hour with acetic acid (3 c.c.) and concentrated hydrochloric acid (1·5 c.c.), and the mixture diluted with water, an oily precipitate was obtained from which 6-methoxy-3-methylcoumarone-2-acetic acid, m. p. 145°, was isolated by means of aqueous sodium bicarbonate and purified from methyl alcohol.

Esterification of the acid (XVII; R = H, R_1 = H) with excess of ethereal diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 122°, after crystallisation from dilute alcohol and then light petroleum (b. p. 80—100°).

When a small amount of the acid or either of its esters and an equal amount of *p*-dimethylaminobenzaldehyde were gently warmed with 2 drops of hydrochloric acid for a few seconds and the mixture treated with 2—3 c.c. of alcohol, an intense bright blue solution was obtained, identical with that given by decarbousnol or usnolic acid (Ehrlich's reaction). Under the same conditions decarbousnic acid does not give a coloration.

3-*Methoxy*-6-*acetyl*-2-*methylphenoxyacetic Acid* (IX, R = H).—In the preparation of 2-hydroxy-4-methoxy-3-methylacetophenone according to the directions of Robinson and Shah (J., 1934, 1494) the amount of methyl iodide should be 322 g., *i.e.*, 5 mols., and not 225 g. as given by these authors. When 345 g. of iodide were used in this experiment, the yield of ketone obtained was 30 g.

Interaction of this ketone (20 g.), ethyl bromoacetate (35 g.), and potassium carbonate (30 g.) in boiling acetone (200 c.c.) during 48 hours gave rise to the ethyl ester (IX, R = Et) of the phenoxyacetic acid, which on distillation was obtained as a colourless oil (20 g.), b. p. 180—185°/15 mm.; the 2 : 4-*dinitrophenylhydrazone* formed bright orange needles, m. p. 167°, from ethyl acetate (Found : C, 54·0; H, 4·9; N, 12·7. $C_{20}H_{22}O_8N_4$ requires C, 53·8; H, 4·9; N, 12·6%). The crude ester (20 g.) was boiled with aqueous-alcoholic potassium hydroxide (from 250 c.c. of water, 150 c.c. of alcohol, and 20 g. of alkali) on the steam-bath for 1 hour, the greater part of the alcohol distilled in a vacuum, and the residue acidified with dilute hydrochloric acid. The resulting *acid* (IX, R = H) formed colourless, slender rods (12 g.), m. p. 133°, from warm water [Found : C, 60·5; H, 5·8; OMe, 12·9. $C_{11}H_{11}O_4(OMe)$ requires C, 60·5; H, 5·9; OMe, 13·0%].

6-*Methoxy*-3 : 7-*dimethylcoumarone*-2-*carboxylic Acid* (X, R = H).—A solution of ethyl 3-methoxy-6-acetyl-2-methylphenoxyacetate (5 g.) in alcohol (15 c.c.) containing sodium ethoxide (from 0·35 g. of sodium) was refluxed for 1 hour, diluted with water, and extracted several times with ether. Evaporation of the dried extracts left *ethyl* 6-*methoxy*-3 : 7-*dimethylcoumarone*-2-*carboxylate*, which separated from dilute alcohol in colourless plates (1·2 g.), m. p. 75°, giving a blue coloration with warm sulphuric acid (Found : C, 67·8; H, 6·4. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). Acidification of the alkaline liquors left on isolation of the ester with hydrochloric acid yielded 3-methoxy-6-acetyl-2-methylphenoxyacetic acid (2·5 g.), m. p. and mixed m. p. 133°, after purification.

Hydrolysis of the ester (X, R = Et) (0·8 g.) with 5% aqueous-alcoholic potassium hydroxide (25 c.c.) for 1 hour gave rise to the *acid* (X, R = H), which formed colourless plates (0·5 g.), m. p. 225° (decomp.), from ethyl acetate [Found : C, 65·5; H, 5·5; OMe, 14·0. $C_{11}H_9O_3(OMe)$ requires C, 65·5; H, 5·5; OMe, 14·1%].

6-*Methoxy*-3 : 7-*dimethylcoumarone* (XI, R = Me).—A mixture of 3-methoxy-6-acetyl-2-methylphenoxyacetic acid (20 g.), sodium acetate (50 g.), and acetic anhydride (150 c.c.) was refluxed for ½ hour and after the decomposition of the anhydride with an excess of water the mixture was neutralised with sodium carbonate, and the product isolated with ether. On distillation in a vacuum the *coumarone* was obtained as a colourless oil (12 g.), b. p. 92—93°/0·1 mm., giving a pale green and then blue sulphuric acid reaction (Found : C, 74·7; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). The *picrate* of this substance formed bright red, rectangular prisms, m. p. 92°, from alcohol (Found : C, 50·5; H, 3·8; N, 10·4. $C_{11}H_{12}O_2,C_6H_3O_7N_3$ requires C, 50·4; H, 3·7; N, 10·4%).

6-*Methoxy*-2-*formyl*-3 : 7-*dimethylcoumarone* (XII, R = Me).—Interaction of the foregoing coumarone (10 g.), hydrogen cyanide (10 c.c.), and excess of hydrogen chloride in ether (100 c.c.), followed by hydrolysis of the resulting greenish-yellow aldimine hydrochloride with water (100 c.c.) on the steam-bath, gave the *aldehyde*, which separated from alcohol in clusters of tetrahedral prisms (10 g.), m. p. 102° [Found : C, 70·6; H, 6·0; OMe, 15·0. $C_{11}H_9O_2(OMe)$ requires C, 70·6; H, 5·9; OMe, 15·2%]. The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 284°, from ethyl acetate (Found : N, 14·5. $C_{18}H_{16}O_6N_4$ requires N, 14·6%).

Oxidation of the aldehyde (0·5 g.), dissolved in acetone (15 c.c.), with a solution of potassium permanganate (0·9 g.) in water (20 c.c.) gave rise to 6-methoxy-3 : 7-dimethylcoumarone-2-carboxylic acid, which was separated from a little unchanged aldehyde by means of aqueous sodium bicarbonate and then crystallised from ethyl acetate, forming colourless prisms (0·2 g.), m. p. 225° (decomp.), identical with an authentic specimen.

6-*Methoxy*-3 : 7-*dimethylcoumarone*-2-*pyruvic Acid* (XIV, R = Me).—Condensation of the aforementioned aldehyde (8 g.) with hippuric acid (14 g.) by means of acetic anhydride (50 c.c.) and sodium acetate (8 g.) on the steam-bath for 1½ hours and subsequent addition of 50% alcohol (140 c.c.) yielded the *azlactone* (XIII, R = Me), which was digested with warm alcohol and then crystallised from ethyl acetate, forming elongated, rectangular, crimson prisms (12 g.), m. p. 218°, sparingly soluble in alcohol (Found : C, 72·6; H, 5·0; N, 4·2. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9; N, 4·0%).

The azlactone (10 g.) was hydrolysed with boiling 10% aqueous sodium hydroxide (150 c.c.) during 8 hours and on isolation by the method employed for the lower homologue (XIV, R = H) the resulting *pyruvic acid* was obtained as a yellow microcrystalline solid (4·5 g.), which separated from alcohol in tiny, pale yellow needles, m. p. 228° (Found : C, 64·2; H, 5·5. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%). The *oxime* formed clusters of colourless rectangular prisms, m. p. 162° (decomp.), from dilute acetic acid (Found : N, 5·1. $C_{14}H_{15}O_5N$ requires N, 5·1%).

During the hydrolysis of the azlactone a small amount of a crystalline solid appeared in the condenser. This material (from several experiments) was distilled in steam and then crystallised from aqueous methyl alcohol, forming clusters of diamond-shaped plates, m. p. 41°, which gave an olive-green and then a blue sulphuric acid reaction [Found : C, 75·7; H, 7·4; OMe, 16·2. $C_{11}H_{11}O(OMe)$ requires C, 75·8; H, 7·4; OMe, 16·3%]. The picrate separated from methyl alcohol in deep crimson needles, m. p. 103° (Found : C, 51·7; H, 4·2; N, 9·9. $C_{12}H_{14}O_2,C_6H_3O_7N_3$ requires C, 51·6; H, 4·1; N, 10·0%). From its analysis and properties this compound is clearly 6-*methoxy*-2 : 3 : 7-*trimethylcoumarone* and is probably formed by decomposition of the pyruvic acid. Hydrogenation of the coumarone, dissolved in acetic acid, with the aid of a palladium–charcoal catalyst gave rise to 6-*methoxy*-2 : 3 : 7-*trimethylcoumaran*, which was obtained as a colourless mobile oil, having a negative sulphuric acid reaction (Found : C, 75·4; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). (A considerable number of analogous azlactones have been hydrolysed in this laboratory but this is the first occasion on which the formation of a product of this type has been observed.—A. R.)

6-*Methoxy*-3 : 7-*dimethylcoumarone*-2-*acetic Acid* (XV, R = Me).—Oxidation of the foregoing pyruvic acid (XIV, R = Me) (2 g.), dissolved in 5% aqueous sodium hydroxide (40 c.c.), with 30% hydrogen peroxide (4 c.c.) during 1 hour gave rise to the *coumarone*-2-*acetic acid* as a light brown solid, which separated from dilute alcohol (charcoal) in colourless rectangular prisms (1·6 g.), m. p. 158° [Found : C, 66·7; H, 6·0; OMe, 13·2. $C_{12}H_{11}O_3(OMe)$ requires C, 66·7; H, 5·9; OMe, 13·3%].

By the method employed in the case of 6-methoxy-3-methylcoumarone-2-acetic acid this acid (5 g.) was converted into the chloride with phosphorus pentachloride (5 g.) in chloroform (50 c.c.). The product was obtained as a light brown oil and on treatment with a little concentrated ammonia solution a specimen gave the *amide*, which formed plates, m. p. 179°, from benzene (Found : N, 6·2. $C_{13}H_{15}O_3N$ requires N, 6·0%).

6′-*Methoxy*-3′ : 7′ : 3-*trimethyl*-2′ : 3′-*dihydrobenzofurano*-(2′ : 3′ : 5 : 4)-$\Delta^{2:5}$-cyclo*hexadienone*-

2-*carboxylic Acid* (XVII; $R = Me, R_1 = H$).—A solution of the aforementioned acid chloride (from 5 g. of acid) in absolute ether (40 c.c.) was added to a suspension of ethyl sodioacetoacetate (from 3 g. of ester and 0·6 g. of sodium) in the same solvent (65 c.c.) at below 0° and 18 hours later the mixture was refluxed for 1 hour. The ethereal solution was washed with water and then several times with aqueous sodium bicarbonate to remove 6-methoxy-3 : 7-dimethylcoumarone-2-acetic acid, dried, and evaporated, leaving the product mixed with a small amount of ethyl acetoacetate. Removal of the latter impurity in a high vacuum (oil bath at 80°) left the ester (XVI, $R = Me$) as a pale reddish-brown, viscous, wax-like, semi-solid (5·4 g.), which gave an intense orange-red ferric reaction in alcohol. Cyclisation of this material (5 g.) was effected with concentrated sulphuric acid (25 g.) at 60° for $1\frac{3}{4}$ hours, and the products worked up by the method employed in the case of the lower homologue (XVI; $R = H, R_1 = H$). Crystallisation of the acidic fraction from aqueous acetone (charcoal) gave the *acid* (XVII; $R = Me, R_1 = H$) in clusters of pale straw-coloured needles or plates, m. p. 150°, readily soluble in alcohol, acetic acid, or benzene, sparingly soluble in light petroleum, and having a negative ferric reaction in alcohol [Found in specimen dried in a high vacuum at 70° : C, 68·0; H, 5·3; OMe, 10·2. $C_{16}H_{13}O_4(OMe)$ requires C, 68·0; H, 5·3; OMe, 10·3%]. A mixture of 6-methoxy-3 : 7-dimethylcoumarone-2-acetic acid, m. p. 158°, and this acid melted at about 127°. On being warmed with concentrated sulphuric acid, this substance did not give a coloration alone or in the presence of a drop of ferric chloride.

From the neutral fraction, which was obtained as a brown oil, boiling light petroleum (b. p. 40—60°) extracted a light brown solid, which on crystallisation from aqueous alcohol gave the *ester* (XVII; $R = Me, R = Et$) in small, colourless, squat, hexagonal prisms (0·5 g.), readily soluble in alcohol or benzene, sparingly soluble in cold light petroleum, and having negative sulphuric acid and ferric reactions [Found : C, 69·6; H, 6·3; OAlkyl, 9·8. $C_{16}H_{12}O_3(OMe)(OEt)$ requires C, 69·5; H, 6·1; OAlkyl, 9·8%]. When a solution of the ester (0·2 g.) in concentrated sulphuric acid (2 g.) was kept at 60° for $1\frac{1}{2}$ hours, cooled, and treated with an excess of ice-water, a precipitate of the acid (XVII; $R = Me, R_1 = H$) was obtained. On purification by means of aqueous sodium bicarbonate and crystallisation from aqueous acetone this specimen had m. p. and mixed m. p. 150°. Esterification of the acid with excess of ethereal diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 115° after purification from aqueous alcohol.

Both the acid (XVII; $R = Me, R_1 = H$) and its ethyl ester gave intense bright blue colorations with Ehrlich's reagent, identical with those given by the acid (XVII; $R = H, R_1 = H$), decarbousnol, and usnolic acid. When the acid (0·3 g.) was heated with aniline (1·5 c.c.) on the steam-bath for 2 minutes, carbon dioxide was evolved and after the addition of alcohol (3 c.c.) and then acetic acid (3 c.c.) a light brown amorphous product was precipitated with water which would not crystallise (Found in material reprecipitated from acetic acid and dried : N, 3·5. Calc. for $C_{22}H_{23}O_3N$: N, 4·0%). The Ehrlich reaction given by this product was almost identical with that of the anilide of decarbousnic acid.

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