250. *Usnic Acid. Part IX.* A Revised Structure for Usnolic Acid and the Resolution of (±)-Usnic Acid.*

By F. M. Dean, P. Halewood, S. Mongkolsuk, Alexander Robertson, and W. B. Whalley.

From 3 : 4 : 6-trimethylcoumarone (VIII; R = H) by the general method (Part VII, *J.*, 1939, 1594) an analogue (XI; R = CO_2H) of usnolic acid has been synthesised which on hydrogenation gave di- and tetra-hydro-derivatives and on ozonolysis furnished formaldehyde and a compound shown to be 3 : 4′-diketo-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid (XII; R = H). The structure of this spiran was confirmed by its conversion into 4 : 6-dimethylsalicylic acid (CO_2H = 1) on oxidation or hydrolytic fission. The position of the exocyclic methylene group attacked by ozone in the conversion of (XI; R = CO_2H) into (XII; R = H) was established by the synthesis of a homologue (XV; R = H) from 3-ethyl-4 : 6-dimethylcoumarone with subsequent ozonolysis of this homologue into acetaldehyde and the same *spiro*coumaran (XII; R = H). Similarly, methyl *O*-methylusnolate gave formaldehyde and a triketonic ester (V; R = Me, R′ = CO_2Me). On the basis of these results the structures of type (IV) have been developed for usnolic acid and its synthetical analogues described in the present work and in Part VII.

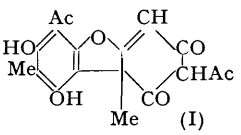
Resolution of (±)-usnic acid and a partial resolution of usnolic acid are described.

With concentrated sulphuric acid usnic acid (I) is converted into usnolic acid, an isomeric carboxylic acid, which on decarboxylation yields decarbousnol, also formed by treatment of decarbousnic acid (II; R = H) by the same reagent (Part V, *J.*, 1937, 894). After a review of the then available evidence in support of structure (I) for usnic acid, Foster, Healy, and one of us (A. R.) (Part VII, *J.*, 1939, 1594) proposed that, of the alternatives possible on the basis of formula (I) for usnic acid, usnolic acid was best represented by (III; R = CO_2H) in agreement with the structure (III; R = H) suggested for decarbousnol (Part V, *loc. cit.*), with the assumption that (III; R = CO_2H) is formed from (I) by way of (II; R = CO_2H). The synthesis of two analogues of usnolic acid, formulated as (VI; R = H, Me respectively), from intermediates of type (II; R = CO_2Et) appeared to support the furano(2′ : 3′-1 : 2)*cyclo*hexa-3 : 6-dien-5-one structure (III; R = CO_2H), especially since the synthetic compounds closely resembled usnolic acid and gave the characteristic blue colour with Ehrlich's reagent exhibited by decarbousnol but not by usnic acid or its degradation products (Part VII, *loc. cit.*). It seemed reasonably certain, therefore, that usnolic acid and its synthetic analogues were similarly constituted but experimental evidence on the nature of the ring system formed by cyclisation of substances of type (II) was lacking. In this connection it may be noted that Asahina and Okazaki (*J. Pharm. Soc. Japan*, 1943, **63**, 618; *Chem. Abs.*, 1951, **45**, 5146; † cf. *Proc. Imp. Acad. Tokyo*, 1943, **19**, 303; *Chem. Abs.*, 1947, **41**, 6235) have substantiated the work of Schöpf and Ross (*Annalen*, 1940, **546**, 1) on the ozonolysis of diacetylusnic acid supporting the structure (I) for usnic acid and by the same procedure found that decarbousnol and its diacetate gave formaldehyde and a triketone $C_{16}H_{14}O_6$. On the basis of these results and of the pyrolytic decomposition of tetrahydrodecarbousnol and the hydrogenated triketone, the Japanese workers concluded that (IV; R = R′ = H) was a possible structure for decarbousnol, apparently retaining (III; R = R′ = H) for usnolic acid and assuming (*a*) that the cyclisation of decarbousnic acid takes a different course from that occurring in the rearrangement of usnic acid to usnolic acid and (*b*) that the conversion of tetrahydrousnolic acid into tetrahydrodecarbousnol involves rearrangement in addition to de-

* Part VIII, preceding paper.

† The only account of this work available to us is the above abstract which came to hand after the greater part of the present work had been completed and the consequent conclusions developed. A. R.

carboxylation; this would presumably apply to the conversion of usnolic acid into decarbousnol.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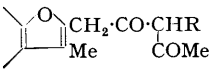
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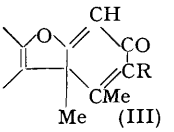
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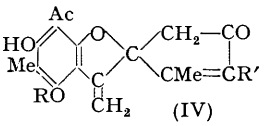
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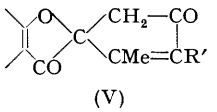
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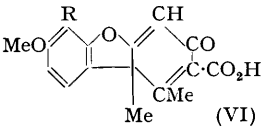
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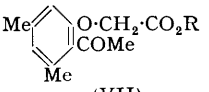
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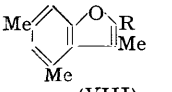
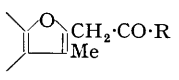

(VIII)

As in the case of usnolic acid the synthetic compounds (Part VII) were available to us only in small quantities and attempts have been made at various times in these laboratories (unpublished work) to provide another analogue in sufficient amount for analytical studies. In the present work, employing 3 : 4 : 6-trimethylcoumarone and effecting improved yields at several stages, we prepared the corresponding usnolic acid analogue by the general method in sufficient quantity for a detailed examination of its properties.

Prepared from 2-hydroxy-4 : 6-dimethylacetophenone, 2-acetyl-3 : 5-dimethylphenoxyacetic acid (VII; R = H) was converted into 3 : 4 : 6-trimethylcoumarone (VIII; R = H) which by Gattermann's method gave 2-formyl-3 : 4 : 6-trimethylcoumarone (VIII; R = CHO), the orientation of which was confirmed by oxidation to the carboxylic acid (VIII; R = CO_2H), identical with a specimen formed by the cyclisation of (VII; R = Et) and subsequent hydrolysis of the resulting ester (VIII; R = CO_2Et). From (VIII; R = CHO) 3 : 4 : 6-trimethylcoumarone-2-acetic acid (IX; R = OH) was prepared by the standard azlactone synthesis and converted into the acid chloride (IX; R = Cl) which reacted with the sodio- or (better) ethoxymagnesio-derivative of ethyl acetoacetate to give the diketo-ester (X). Treatment of (X) with concentrated sulphuric acid at −5° for 3 days gave the ethyl ester of the usnolic acid analogue along with a little of the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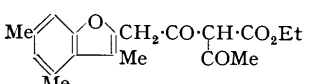
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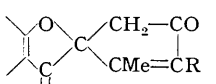
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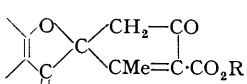
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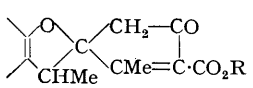
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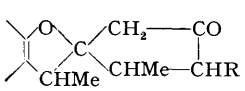
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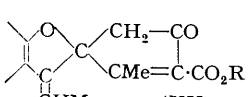
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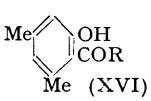
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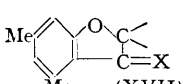
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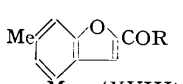
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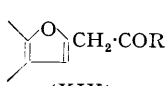
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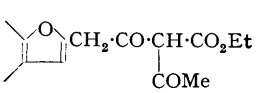
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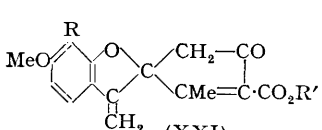
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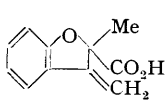
(XXII)

corresponding acid, also formed by hydrolysis of the ester; regeneration of the ester from the acid served to establish the identity of their structures. From an examination of the hydrogenation and oxidation products of this keto-acid and its ester, which give the characteristic Ehrlich reaction, it is now clear that the latter compounds do not contain the *cyclo*hexadienone system of (III) but are spirans with an exocyclic methylene group, *viz.*, 4′-keto-4 : 6 : 2′-trimethyl-3-methylene*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid (XI; R = CO_2H) and its ethyl ester. Thus, the ester, which formed a 2 : 4-dinitro-

phenylhydrazone, contained two double bonds as estimated by the perbenzoic acid method, and on hydrogenation at a palladium–charcoal catalyst gave a dihydro-derivative (XIII; R = CO_2Et) containing one double bond (perbenzoic acid method) and forming a 2 : 4-dinitrophenylhydrazone. On hydrolysis, (XIII; R = Et) gave the dihydro-acid (XIII; R = H), identical with the product formed by the hydrogenation of (XI; R = CO_2H) with the palladium catalyst. With Adams' platinum catalyst the esters (XI; R = CO_2Et) and (XIII; R = Et) gave the same tetrahydro-derivative (XIV; R = CO_2Et). Unlike the parent ester (XI; R = CO_2Et) or its dihydro-derivative (XIII; R = Et), the tetrahydro-ester (XIV; R = CO_2Et) formed an unstable dinitrophenylhydrazone and, in agreement with the keto-enolic system possible on the basis of the formula proposed, it gave a positive ferric reaction. On being kept, this compound appeared to revert completely to the keto-form since it did not then give a ferric reaction, but when heated above its melting point the resulting material again gave the ferric reaction. As expected, hydrogenation of (XI; R = CO_2H) at a platinum catalyst gave an unstable acid (XIV; R = CO_2H), having a positive ferric reaction and decomposing on recrystallisation, with the evolution of carbon dioxide, to a neutral product, undoubtedly the analogue (XIV; R = H) of tetrahydrodecarbousnol. An examination of this ketone, which was only obtained in small amounts, is reserved for a future communication.

On ozonolysis the acid (XI; R = CO_2H) and its ester (XI; R = CO_2Et) gave formaldehyde and the spirans (XII; R = H and Et respectively), which were characterised by the formation of oximes; their relationship was confirmed by esterification of (XII; R = H) with ethereal diazoethane to give a product from which the oxime of (XII; R = Et) was obtained. The product (XII; R = H) was readily oxidised by warm Fehling's solution, yielding 4 : 6-dimethylsalicylic acid (XVI; R = OH), a reaction characteristic of coumaran-3-ones; the acid (XVI; R = OH) was also formed by hydrolytic fission of (XII; R = H) with hot alkali. Clearly the conditions which lead to degradation of (XI; R = CO_2H) to (XVI; R = OH) indicate that the exocyclic methylene group in (XI; R = CO_2H) has been removed as in (XII; R = H), otherwise the ketone (XVI; R = Me), and not the acid (XVI; R = OH), would have been formed. The ultra-violet absorption curve of (XII; R = CO_2Et) are very similar to that of (XI; R = CO_2Et), apart from subsidiary variations of the latter, and suggest that the compounds contain the same fundamental system (XVII; where X = C or O). On the other hand, in agreement with the formulæ (XIII) ascribed to it and its parent acid, the dihydro-derivative does not give rise to appreciable amounts of formaldehyde on ozonolysis and does not possess the ultra-violet absorption spectrum characteristic of the system (XVII).

From the foregoing results it is evident that in the cyclisation to a spiran the 3-methyl group of the coumarone (X) becomes the methylene group of the cyclisation product (XI; R = CO_2Et). To confirm this the homologue (XV; R = Et) was synthesised by the general method. 4 : 6-Dimethylpropiophenone was converted by way of 3 : 5-dimethyl-2-propionylphenoxyacetic acid into 3-ethyl-4 : 6-dimethylcoumarone, the formyl derivative of which furnished 3-ethyl-4 : 6-dimethylcoumarone-2-acetic acid by the azlactone route. Interaction of 3-ethyl-4 : 6-dimethylcoumarone-2-acetyl chloride with the ethoxymagnesio-derivative of ethyl acetoacetate and subsequent cyclisation of the product with concentrated sulphuric acid gave a mixture of the spiran (XV; R = H) and its ethyl ester. As expected the ultra-violet absorption spectrum of this ester (XV; R = Et) was very similar to that of (XI; R = CO_2Et) and, in agreement with the view that the group >CH– in the 3-position of the furan residue is essential to spiran formation, ozonolysis of (XV; R = H or Et) gave acetaldehyde and the spiran (XII; R = H or Et respectively). In corroboration of this a small amount of the diketonic ester (XX) was synthesised by the stages (XVIII; R = OH $\longrightarrow$ Cl $\longrightarrow$ CHN_2) $\longrightarrow$ (XIX; R = $Ph{\cdot}CH_2{\cdot}O$ $\longrightarrow$ OH $\longrightarrow$ Cl). On treatment with sulphuric acid under the usual conditions, this ester (XX) gave a neutral substance in pale yellow needles, the properties of which, including the ultra-violet absorption spectrum and negative Ehrlich reaction, differed entirely from those of (XI; R = CO_2Et) and (XV; R = H). In connection with the cyclisation of esters of type (X) it may be noted that the formation of a spiran depends on the ethylenic nature of the double bond in the furan residue (*i.e.*, its lack of aromaticity),

and the production of 2-methyl-3-methylenecoumaran-2-carboxylic acid (XXII) by carboxylation of 2-methyl-3-coumaronylmethylmagnesium chloride (Gaertner, *J. Amer. Chem. Soc.*, 1952, **74**, 5319) offers a close analogy.

From the foregoing results it is now clear that the synthetic compounds, which were formulated in Part VII as *cyclo*hexadienones of type (VI), and whose properties closely resemble those of the spirans (XI) and (XV), are the spirans (XXI; R = R′ = H, and R = Me, R′ = H) and their ethyl esters. Further, from its close similarity to the synthetic analogues usnolic acid clearly has the spiran structure (IV; R = H, R′ = CO_2H). Although, owing to its lack of solubility in suitable solvents, usnolic acid could not be oxidised with ozone, methylation with diazomethane gave the more soluble derivative, methyl O^4-methylusnolate (IV; R = Me, R′ = CO_2Me), which on ozonolysis furnished formaldehyde and a triketone. This compound, which forms a dioxime, has an ultra-violet absorption spectrum corresponding to that of a typical *C*-methylphlorodiacetophenone (Part VIII, preceding paper), and is clearly represented by formula (V; R = Me, R′ = CO_2Me). With regard to the position of the methoxyl group in (IV; R = Me, R′ = CO_2Me)

FIG. 1. FIG. 2.

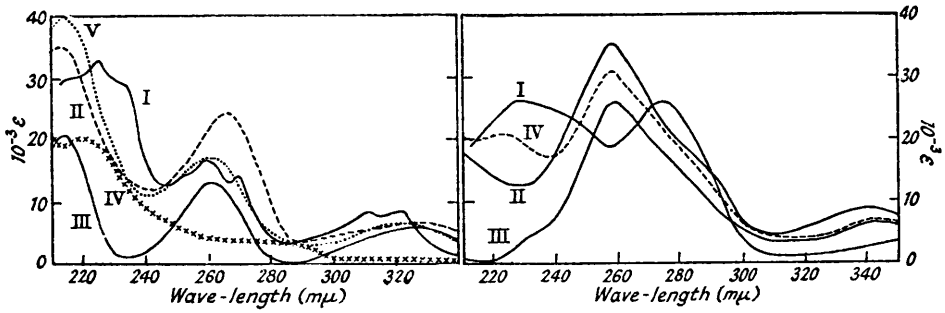

FIG. 1. I, *Ethyl 4′-keto-4 : 6 : 2′-trimethyl-3-methylene*cyclo*pent-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylate* (XI; R = CO_2Me).
II, 3 : 4′-*Diketo-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylic acid* (XII; R = H).
III, 4 : 6-*Dimethylcoumaran-3-one.*
IV, 4′-*Keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylic acid.*
V, *Curve obtained by addition of* III *to* IV. (*All in ethanol.*)

FIG. 2. I, *Methyl* O-*methylusnolate* (IV; R = Me, R′ = CO_2Me).
II, *Methyl 7-acetyl-6-hydroxy-3 : 4′-diketo-5 : 2′-dimethyl-4-methoxy*cyclo*pent-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylate* (V; R = Me, R′ = CO_2Me).
III, 2 : 4-*Diacetyl-6-methylphloroglucinol* 1-*methyl ether.*
IV, *Curve obtained by addition of* III *to* IV *of Fig.* 1. (*All in ethanol.*)

and its ozonolysis product it is reasonable to assume on general grounds that the phenolic hydroxyl group of usnolic acid which undergoes methylation is that in the 4-position of the coumaran residue.

The structures proposed for usnolic acid and its analogues can now be correlated with their ultra-violet absorption characteristics. In the absence of data for the unsaturated keto-acid system, the absorption of 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid has been taken as an approximation to it. Addition of this absorption (Fig. 1) to that of 4 : 6-dimethylcoumaran-3-one (Fig. 1) or to that of 2 : 4-diacetyl-6-methylphloroglucinol 1-methyl ether (Fig. 2) (Part VIII) gives curves which resemble closely those of 3 : 4′-diketo-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′-*spiro*-coumaran-3′-carboxylic acid (Fig. 1) and methyl 7-acetyl-6-hydroxy-3 : 4′-diketo-4-methoxy-5 : 2′-methyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (Fig. 2) respectively. In appropriate circumstances, usnic acid can be converted into compounds containing phloracetophenone or resorcinol nuclei; therefore, the absorption curves of representative derivatives of phloracetophenone, the diacetylresorcinols, and diacetylphloroglucinol are included for comparison (see Fig. 3).

As expected on the basis of the mechanism involved for conversion (+)- or (−)-usnic

acid into usnolic acid the last compound is invariably obtained in an optically inactive state, but from the structures allocated to usnolic acid and the synthetic analogues these compounds should be resolvable. Attempts to resolve the analogue (XI; R = CO_2H) were unsuccessful but by means of the (−)-brucine salt a partial separation of usnolic acid into (+)- and (−)-fractions was effected.

Resolution of (±)-Usnic Acid.—The (+)-, (−)- and (±)-forms of usnic acid occur naturally and the comparatively ready racemisation of (+)- or (−)-usnic acid with hot

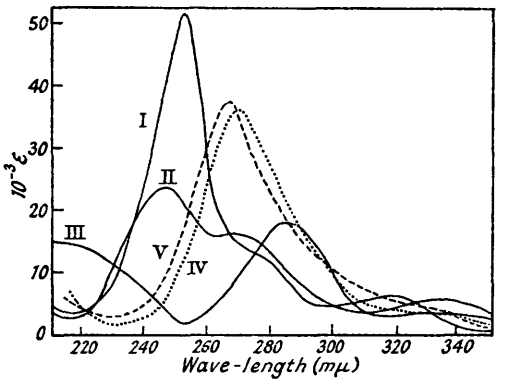

FIG. 3. I, 4 : 6-*Diacetylresorcinol.*
II, 2 : 4-*Diacetylresorcinol.*
III, 2 : 6-*Dihydroxy-4-methoxy-5-methylacetophenone.*
IV, 2 : 4-*Diacetylphloroglucinol.*
V, 2 : 4-*Diacetylphloroglucinol* 1-*methyl ether.* (*All in ethanol.*)

solvents has long been known (cf. Schöpf and Heuck, *Annalen*, 1927, **459**, 264), a result which has not yet been explained on the basis of formula (I) (cf. Mackenzie, *J. Amer. Chem. Soc.*, 1952, **74**, 4067). The resolution of (±)-usnic acid, which as far as we are aware has not been reported, has now been achieved by means of the (−)-brucine salt.

EXPERIMENTAL

Ethyl 2-Acetyl-3 : 5-dimethylphenoxyacetate (VII; R = Et).—2-Hydroxy-4 : 6-dimethylacetophenone (22·5 g.) was prepared in consistent yields by heating *m*-5-xylyl acetate (30 g.) with powdered aluminium chloride (30 g.) at 100° for 5 hours, followed by isolation in the usual manner (cf. Smith and Opie, *J. Org. Chem.*, 1941, **6**, 429; also von Auwers, *Ber.*, 1915, **48**, 90, and von Auwers and Borsche, *ibid.*, p. 1708).

A mixture of this ketone (5 g.), ethyl bromoacetate (5·5 g.), and potassium carbonate (4·7 g.) was heated in boiling acetone (50 ml.) for 20 hours. Evaporation of the filtered solution left *ethyl 2-acetyl-3 : 5-dimethylphenoxyacetate* which formed colourless needles (7·3 g.), m. p. 62°, from aqueous alcohol, readily soluble in ether or benzene, sparingly soluble in light petroleum, and having a negative ferric reaction (Found: C, 66·9; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). A mixture of this ester (146 g.), sodium hydroxide (60 g.), and 50% alcohol (600 g.) was heated on the steam-bath for 1 hour, the greater part of the solvent was distilled in a vacuum, and the residue was cooled to 0° and acidified with hydrochloric acid, giving *2-acetyl-3 : 5-dimethylphenoxyacetic acid*, which separated from dilute alcohol in needles (128 g.), m. p. 166—167° (Found: C, 64·8; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

2-Formyl-3 : 4 : 6-trimethylcoumarone (VIII; R = CHO).—A mixture of 2-acetyl-3 : 5-dimethylphenoxyacetic acid (13·5 g.), sodium acetate (25 g.), and acetic anhydride (50 ml.) was heated under reflux for 1 hour, cooled, and treated with water (300 ml.). After isolation with ether and removal of traces of acidic material with aqueous sodium hydrogen carbonate, the resulting *3 : 4 : 6-trimethylcoumarone* (VIII; R = H) formed colourless needles (8·5 g.), b. p. 128°/20 mm., m. p. 31°, from dilute acetic acid (Found: C, 80·0; H, 7·6. $C_{11}H_{12}O_2$ requires C, 80·3; H, 7·5%). When heated, the orange-red solution of this compound in concentrated sulphuric acid became in turn dark red, violet, and blue.

Condensation of 3 : 4 : 6-trimethylcoumarone (30 g.) and hydrogen cyanide (15 ml.) with aluminium chloride (28 g.) and excess of hydrogen chloride in ether (100 ml.) for 24 hours gave a crystalline product which was hydrolysed with water (2 l.) on the steam-bath for 2 hours. On being kept, the cooled hydrolysate deposited *2-formyl-3 : 4 : 6-trimethylcoumarone* (VIII; R = CHO) (30 g.) which crystallised from benzene in colourless prisms, m. p. 130—131° (Found: C, 76·6; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·5; H, 6·4%), and gave a *2 : 4-dinitrophenylhydrazone*

in small red prisms, m. p. 273°, from ethyl acetate (Found : N, 15·1. $C_{18}H_{16}O_5N_4$ requires N, 15·2%).

This aldehyde (0·5 g.), in acetone (20 ml.), was oxidised with potassium permanganate (1 g.) in water (20 ml.) for 2 hours and the solution was cleared at 0° with sulphur dioxide and diluted with water. Crystallisation of the precipitate from dilute alcohol gave 3 : 4 : 6-trimethylcoumarone-2-carboxylic acid (VIII; R = CO_2H) in colourless prisms (0·25 g.), m. p. 266—269° (decomp.) (Found : C, 70·6; H, 6·2. Calc. for $C_{12}H_{12}O_3$: C, 70·6; H, 5·9%). A mixture of this acid and its ethyl ester was formed by the cyclisation of ethyl 2-acetyl-3 : 5-dimethylphenoxyacetate (6 g.) with alcoholic sodium ethoxide (from 0·1 g. of sodium and 10 ml. of alcohol) and separated by aqueous sodium hydrogen carbonate. The acid (2·5 g.) had m. p. and mixed m. p. 266—269° (decomp.) (cf. Thorpe and Jordan, *J.*, 1915, **107**, 389, who record m. p. 149°). *Ethyl* 3 : 4 : 6-*trimethylcoumarone*-2-*carboxylate* (VIII; R = CO_2Et) formed colourless needles (2 g.), m. p. 94—95°, from dilute alcohol (Found : C, 72·3; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

3 : 4 : 6-*Trimethylcoumarone*-2-*acetic Acid* (IX; R = OH).—A mixture of 2-formyl-3 : 4 : 6-trimethylcoumarone (8 g.), hippuric acid (14 g.), sodium acetate (8 g.), and acetic anhydride (50 ml.) was heated on the steam-bath for 1½ hours and diluted with alcohol (150 ml.). Next day the crystalline *azlactone* was collected and recrystallised from acetic acid, forming orange needles (11·3 g.), m. p. 200° (Found : N, 4·3. $C_{21}H_{17}O_3N$ requires N, 4·2%). This compound (30 g.) was hydrolysed with boiling 20% aqueous potassium hydroxide (300 ml.) for 1½ hours, and the solution diluted with water (750 ml.), mixed with diatomite (5 g.), filtered, cooled, and acidified with concentrated hydrochloric acid, giving a precipitate of 3 : 4 : 5-*trimethylcoumarone*-2-*pyruvic acid* (IX; R = CO_2H) mixed with benzoic acid. When the mixture was heated to 60° on the steam-bath the benzoic acid dissolved, leaving the pyruvic acid which on isolation separated from dilute alcohol (charcoal) in pale yellow needles (17 g.), m. p. 224° (Found : C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). In the present instance this procedure for the separation of the acids was superior to the standard sulphur dioxide method.

A solution of the crude pyruvic acid (17 g.) in 10% aqueous potassium hydroxide (50 ml.) at 0° was mixed with hydrogen peroxide (20 ml. of 100 vol.), warmed until effervescence began, cooled to 0°, diluted with ice-water (1000 g.), and acidified with concentrated hydrochloric acid. Thus precipitated, 3 : 4 : 6-*trimethylcoumarone*-2-*acetic acid* (IX; R = OH) (14 g.) crystallised from dilute methanol or acetic acid in colourless plates, m. p. 186°, having a red sulphuric acid reaction (Found : C, 71·5; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

Ethyl α-*Acetyl*-γ-(3 : 4 : 6-*trimethyl*-2-*coumaronyl*)*acetoacetate* (X)—When the vigorous reaction between 3 : 4 : 6-trimethylcoumarone-2-acetic acid (5 g.) and phosphorus pentachloride (5 g.) in chloroform (50 ml.) had subsided (*ca.* 15 min.) the mixture was heated on the steam-bath for ½ hour and the solvent and phosphorus oxychloride were then removed in a vacuum, leaving the crystalline acid chloride (IX; R = Cl). With concentrated ammonia this compound gave 3 : 4 : 6-*trimethylcoumarone*-2-*acetamide* (IX; R = NH_2) which formed colourless plates, m. p. 175°, from benzene (Found : N, 6·4. $C_{13}H_{15}O_2N$ requires N, 6·5%).

Carbon tetrachloride (2 drops) was added to a hot mixture of ethyl acetoacetate (3·3 g.) and alcohol (1·2 g.) containing magnesium turnings (0·6 g.) and, after the vigorous reaction had somewhat subsided, ether (30 ml.) was introduced. The mixture was then heated under reflux until the magnesium was converted into the ethoxymagnesio-derivative of ethyl acetoacetate. This was mixed with a solution of 3 : 4 : 6-trimethylcoumarone-2-acetyl chloride (from 5 g. of acid) in ether (150 ml.) and heated for a further 6 hours, cooled, and treated with slight excess of dilute acetic acid to decompose the magnesium complex. The ethereal solution was isolated, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving ethyl α-acetyl-γ-(3 : 4 : 6-trimethyl-2-coumaronyl)acetoacetate as a pale red, viscous oil (6·7 g.) with a cherry-red ferric reaction in alcohol. The same compound was prepared by the interaction of molecular proportions of the acid chloride and ethyl sodioacetoacetate in boiling ether for 24 hours. On agitation of an ethereal solution of the compound with aqueous copper acetate the green copper derivative separated.

Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—The foregoing keto-ester (5 g.) was cyclised with concentrated sulphuric acid (13 ml.) at 0° for 3 days and the dark brown mixture then poured into ice-water (50 g.). On isolation with ether the product was separated into the spiran-ester (XI; R = CO_2Et) (3 g.) and the corresponding acid (XI; R = CO_2H) (0·1 g.). The proportion of acid increased and that of its ester decreased when the reaction was carried out at higher temperatures. Similar results were obtained when the keto-ester was replaced by its sodium or

copper derivative. Purified from aqueous alcohol (charcoal) and then from light petroleum (b. p. 40—60°), the *ester* (XI; R = CO_2Et) formed colourless needles, m. p. 95—96°), moderately soluble in the usual organic solvents and giving a deep blue colour with Ehrlich's reagent and a blue colour in the Legal test (Found: C, 72·8; H, 6·2. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%). Perbenzoic acid titrations indicated the presence of 2·05 double bonds. The 2 : 4-*dinitrophenylhydrazone* separated from benzene–light petroleum (b. p. 60—80°) in orange needles, m. p. 200° (Found: N, 11·2. $C_{25}H_{24}O_7N_4$ requires N, 11·4%).

A hot solution of the ester (0·5 g.) in alcohol (8 ml.) was diluted with water to a faint turbidity at 80°, and then treated with 8% aqueous sodium hydroxide (2 ml.). 5 Minutes later the mixture was acidified with dilute hydrochloric acid and the acid was isolated with ether and purified from benzene–light petroleum (b. p. 60—80°) and then chloroform–light petroleum (b. p. 40—60°), forming pale yellow needles (0·3 g.), m. p. 166—166·5°, which give a blue Ehrlich and a red Legal test (Found: C, 71·6; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). This *acid* was identical with the product formed in the cyclisation experiments and on esterification with diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 94—95°.

During numerous attempts to resolve this acid the (+)-N-*methylamphetamine* salt was prepared by mixing solutions of the acid (3 g.) and the base (1·6 g.) in benzene. The volume of the benzene solution was reduced to about 10 ml. and, on addition of ether, the salt separated in colourless needles, m. p. 150° (Found: C, 74·7; H, 7·3; N, 3·4. $C_{17}H_{16}O_4$,$C_{10}H_{15}N$ requires C, 74·8; H, 7·2; N, 3·2%).

4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran* (XI; R = H).—A solution of the aforementioned acid (0·5 g.) in quinoline, containing copper bronze (0·1 g.), was kept at 190° for 10 minutes, cooled, diluted with ether (50 ml.), filtered, washed with dilute hydrochloric acid to remove the quinoline and then with aqueous sodium hydrogen carbonate, dried, and evaporated. Crystallised from light petroleum (b. p. 40—60°), the residue gave the spiro*coumaran* in almost colourless plates (0·1 g.), m. p. 80°, soluble in the usual organic solvents and giving a deep blue Ehrlich reaction (Found: C, 80·2; H, 6·8. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

Hydrogenation of Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—This ester (1 g.), in ethyl acetate (100 ml.), was hydrogenated with a palladium–charcoal catalyst (from 0·5 g. of charcoal and 2·5 ml. of 2% aqueous palladium chloride) and hydrogen at atmospheric pressure; absorption (1 mol.) was complete after ½ hour. On isolation the 3 : 4 : 6 : 2′-*tetramethyl* compound (XIII; R = Et) separated from dilute acetic acid or from light petroleum (b. p. 60—80°) in long needles (0·7 g.), m. p. 85—86°, giving a blue Ehrlich reaction (Found: C, 72·7; H, 7·1. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%); titration with perbenzoic acid indicated the presence of one double bond. The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 193—194°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·2. $C_{25}H_{26}O_7N_4$ requires N, 11·3%). An improved yield of tetramethyl compound (2·75 g. from 3 g. of ester) was subsequently obtained when the hydrogenation was effected in acetic acid, and the catalyst prepared *in situ*.

Hydrogenation of the acid (4 g.) by the same procedure gave the corresponding *acid* (XIII; R = CO_2H) which separated from dilute alcohol and then light petroleum (b. p. 60—80°) in straw-coloured, irregular plates, m. p. 139° (decomp.), having a positive Ehrlich and alkaline nitroprusside reaction and a negative ferric reaction (Found: C, 71·4; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The same acid was obtained by the hydrolysis of ethyl 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate by the procedure employed for the 3-methylene analogue.

With hydrogen (1 mol. absorbed) and a platinum catalyst (from 0·1 g. of platinum oxide) in ethyl acetate (50 ml.) ethyl 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (1 g.) gave *ethyl* 4′-*keto*-3 : 4 : 6 : 2′-*tetramethyl*cyclo*pentane*-1′-spiro-2-*coumaran*-3′-*carboxylate*, forming colourless needles (0·75 g.), m. p. 91—92°, from light petroleum (b. p. 60—80°), which had a blue Ehrlich reaction and a transient ferric reaction in alcohol (freshly prepared solution) (Found: C, 72·4; H, 7·5. $C_{19}H_{24}O_4$ requires C, 72·2; H, 7·6%). It formed an unstable 2 : 4-dinitrophenylhydrazone, m. p. 99—100°, which could not be recrystallised. Hydrogenation (2 mol. of hydrogen absorbed) of the 3-methylene compound (XI; R = CO_2Et) with a platinum catalyst gave the same derivative, m. p. and mixed m. p. 91—92°.

Ozonolysis of Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—A stream of ozone and oxygen was led into a solution of the ester (1 g.) in carbon tetrachloride (30 ml.) until a faint turbidity appeared (35—40 min.).

After the removal of excess of ozone with a stream of oxygen the filtered solution was evaporated in a vacuum and the residual ozonide treated with water (50 ml.) for 24 hours. Distillation of the decanted aqueous liquor gave aqueous formaldehyde, identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 165°, which was purified by chromatography on aluminium oxide, and in a second experiment as the dimedone derivative (0·22 g.), m. p. 191°, identical with an authentic specimen.

The gummy residue left from the aqueous liquor was dissolved in the minimum amount of methanol and treated with 50% aqueous potassium hydroxide (15 ml.) at 0°, giving a crystalline solid (0·1—0·4 g.) which was isolated immediately, and washed with water and ether. This salt (1 g.), which had a blue ferric reaction in alcohol, was decomposed with concentrated hydrochloric acid (2 ml.) in the least quantity of 50% methanol and the resulting *ethyl* 3 : 4′-*diketo*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* was isolated with ether and crystallised from methanol or light petroleum, forming colourless prisms which had m. p. 91—92°, and a negative ferric and a deep green alkaline nitroprusside reaction, and reduced Fehling's solution (Found: C, 68·7; H, 6·1; OEt, 14·4. $C_{16}H_{13}O_4$·OEt requires C, 68·8; H, 5·7; OEt, 14·2%). The *oxime* separated from alcohol in flat parallelograms, m. p. 226° (decomp.), readily soluble in 2N-sodium hydroxide (yield, almost theoretical) (Found: C, 65·5; H, 5·8; OEt, 14·1. $C_{16}H_{14}O_4N$·OEt requires C, 65·7; H, 5·5; OEt, 13·7%). The same oxime was obtained from the crude resinous ozonolysis product before conversion into the potassium salt.

Similarly, ozonolysis of the acid (XI; R = CO_2H) (1 g.) in carbon tetrachloride (30 ml.) furnished formaldehyde and 3 : 4′-*diketo*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylic acid* which was extracted by sodium hydrogen carbonate solution from a solution of the crude ozonolysis product in ether and crystallised from benzene–light petroleum (b. p. 60—80°), forming cream-coloured hexagonal prisms (0·35 g.), m. p. 158—159° (decomp.) (Found: C, 66·6; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The *oxime* separated from dilute alcohol in cream-coloured prisms, m. p. 215° (decomp.) (Found: N, 8·8. $C_{10}H_{16}O_5N_2$ requires N, 8·9%). Esterification of the acidic ozonolysis product with ethereal diazoethane gave a gum which on oximation yielded the oxime of ethyl 3 : 4′-diketo-4 : 6 : 2′-trimethyl-*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate [m. p. and mixed m. p. 226° (decomp.)].

4 : 6-*Dimethylsalicylic Acid* (XVI; R = OH).—(*a*) Ethyl 3 : 4′-diketo-4 : 6 : 2′-trimethyl-*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (0·4 g.) was heated with Fehling's reagent (30 ml.) on the steam-bath for 20 minutes and the resulting solution acidified and extracted with ether. By means of 2N-sodium hydroxide 4 : 6-dimethylsalicylic acid (0·16 g.) was isolated from the extract and on purification from aqueous alcohol (charcoal) had m. p. 166°, identical with an authentic specimen synthesised by the following route. Prepared from 2-hydroxy-4 : 6-dimethylbenzaldoxime by the standard method, 2-hydroxy-4 : 6-dimethylbenzonitrile (1 g.) separated from water in colourless plates, m. p. 178—179°, and on hydrolysis with 90% sulphuric acid at 70° for 4 hours was converted into 2-*hydroxy*-4 : 6-*dimethylbenzamide* which separated from hot water in irregular plates (0·3 g.), m. p. 197° (Found: N, 8·8. $C_9H_{11}O_2N$ requires N, 8·5%). On treatment with 80% sulphuric acid (15 ml.) at 70° for 40 hours this compound (0·5 g.) gave 2-hydroxy-4 : 6-dimethylbenzoic acid which was isolated from the diluted reaction mixture with ether and purified by means of aqueous sodium hydrogen carbonate and then aqueous methanol, forming irregular prisms, m. p. 166° (cf. Stollé and Kuebel, *Ber.*, 1921, **54**, 1213).

(*b*) The potassium derivative (0·5 g.) of the last-mentioned spiran was heated with 2N-sodium hydroxide (10 ml.) on the steam-bath for ½ hour, cooled, and acidified with dilute sulphuric acid. On isolation with ether followed by purification by means of aqueous sodium hydrogen carbonate and then alcohol, 4 : 6-dimethylsalicylic acid (0·13 g.) had m. p. and mixed m. p. 166°.

2-*Hydroxy*-4 : 6-*dimethylpropiophenone*.—Propionic anhydride (500 g.) was added gradually to a well-stirred solution of *m*-xylen-5-ol (460 g.) in water (3 l.) containing sodium hydroxide (160 g.) during 1 hour, and an hour later m-5-*xylyl propionate*, a colourless oil (625 g.), b. p. 167°/56 mm., was isolated (Found: C, 75·0; H, 7·8. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). A mixture of this compound (100 g.) and powdered aluminium chloride (100 g.) was kept at 100° for 5 hours and the complex decomposed in the usual manner. The resulting 2-*hydroxy*-4 : 6-*dimethylpropiophenone* (83 g.) formed long slender needles, m. p. 76°, from dilute alcohol, having a weak purple ferric reaction in alcohol (Found: C, 73·7; H, 7·8. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). The *oxime* separated from dilute methanol in prisms, m. p. 136° (Found: N, 6·9. $C_{11}H_{15}O_2N$ requires N, 7·3%).

3-*Ethyl*-4 : 6-*dimethylcoumarone*.—A mixture of 2-hydroxy-4 : 6-dimethylpropiophenone (100 g.), potassium carbonate (85 g.), ethyl bromoacetate (96 g.), and acetone (500 ml.) was heated under reflux for 20 hours. On isolation the resulting *ethyl* 3 : 5-*dimethyl*-2-*propionylphenoxyacetate* was obtained as a colourless liquid (146 g.), b. p. 316°/748 mm. (Found : OEt, 17·1. $C_{13}H_{15}O_3$·OEt requires OEt, 17·0%) which by hydrolysis with boiling 10% aqueous-alcoholic sodium hydroxide (400 ml.) for 1 hour gave 3 : 5-*dimethyl*-2-*propionylphenoxyacetic acid*, forming colourless needles (121 g.), m. p. 124°, from benzene (Found : C, 65·8; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

A mixture of this acid (100 g.), sodium acetate (100 g.), and acetic anhydride (300 ml.) was heated (oil-bath) under reflux for 1 hour, cooled, and poured into water. 24 Hours later the resulting colourless liquid 3-*ethyl*-4 : 6-*dimethylcoumarone* (63 g.) was isolated with ether and purified by distillation (b. p. 176°/56 mm.) (Found : C, 83·2; H, 7·6. $C_{12}H_{14}O$ requires C, 82·8; H, 8·1%). A solution of this coumarone (40 g.) in ether (150 ml.) containing hydrogen cyanide (25 ml.) and aluminium chloride (34 g.) was saturated at 0° with hydrogen chloride, kept for 24 hours, and evaporated in a current of air. Hydrolysis of the residue with water (1500 g.) at 0° and then on the steam-bath for 2 hours gave an almost theoretical yield of 3-*ethyl*-2-*formyl*-4 : 6-*dimethylcoumarone* which was distilled (b. p. 120°/2 mm.) and then crystallised from dilute alcohol, forming colourless plates, m. p. 73° (Found : C, 77·0; H, 6·6. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%), and giving a 2 : 4-*dinitrophenylhydrazone* in deep red prisms, m. p. 253°, from benzene–light petroleum (Found : N, 15·0. $C_{19}H_{18}O_5N_4$ requires N, 14·7%).

Oxidation of this aldehyde (1 g.) in acetone (30 ml.) with potassium permanganate (0·6 g.), dissolved in water (20 ml.), yielded 3-*ethyl*-4 : 6-*dimethylcoumarone*-2-*carboxylic acid* (0·6 g.), forming colourless prisms, m. p. 230°, from acetic acid, identical with the acid (0·7 g.) formed by the cyclisation of ethyl 3 : 5-dimethyl-2-propionylphenoxyacetate (1 g.) with sodium ethoxide (from 0·2 g. of sodium) in alcohol (10 ml.) on the steam-bath for 15 min. (Found : C, 71·8; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

3-*Ethyl*-4 : 6-*dimethylcoumarone*-2-*acetic Acid*.—A mixture of 3-ethyl-2-formyl-4 : 6-dimethylcoumarone (40 g.), hippuric acid (70 g.), sodium acetate (40 g.), and acetic anhydride (250 ml.) was heated on the steam-bath for 2 hours, cooled, and diluted with 50% alcohol (700 ml.). 24 Hours later the *azlactone* was isolated and purified from acetic acid, forming deep yellow needles (61 g.), m. p. 187° (Found : N, 4·3. $C_{22}H_{19}O_3N$ requires N, 4·1%). Hydrolysed by the procedure employed for the azlactone from 2-formyl-3 : 4 : 6-trimethylcoumarone, this compound (30 g.) gave 3-*ethyl*-4 : 6-*dimethyl*-2-*coumaronepyruvic acid* which separated from dilute alcohol in yellow irregular prisms (17·4 g.), m. p. 203° (Found : C, 69·7; H, 6·0. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). The *oxime* separated from alcohol in fawn-coloured prisms, m. p. 171° (decomp.) (Found : N, 5·2. $C_{15}H_{17}O_4N$ requires N, 5·1%).

Oxidation of the pyruvic acid (17·4 g.) in 5% aqueous potassium hydroxide (100 ml.) with hydrogen peroxide (20 ml. of 100-vol.) at 0° gave 3-*ethyl*-4 : 6-*dimethylcoumarone*-2-*acetic acid* which crystallised from 50% acetic acid in colourless slender needles (14 g.), m. p. 141° (Found : C, 72·6; H, 6·8. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). Treatment of this acid with excess of boiling thionyl chloride for 30 minutes yielded the chloride which with concentrated ammonia furnished the amide, forming colourless needles, m. p. 172°, from dilute alcohol.

3-*Ethylidene*-4′-*keto*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylic Acid* (XV; R = H).—3-Ethyl-4 : 6-dimethylcoumarone-2-acetic acid (10 g.) in chloroform (50 ml.) was converted into the acid chloride with phosphorus pentachloride (10 g.) on the steam-bath for ½ hour. A solution of the resulting crude chloride in ether (150 ml.) was added to a suspension of the ethoxymagnesio-derivative of ethyl acetoacetate (from 6·5 g. of ester, 2·4 g. of alcohol, and 1·15 g. of magnesium) in ether (60 ml.), and the mixture heated under reflux for 6 hours, cooled, and treated with dilute acetic acid. After having been washed with 2N-sodium hydrogen carbonate, 2N-hydrochloric acid, and then water, the ethereal solution was dried and evaporated, leaving a red viscous oil, a solution of which in concentrated sulphuric acid (40 ml.) was kept at −5° for 5 days, poured into ice-water (1 kg.), and extracted with ether (2 × 200 ml.). The combined extracts were washed with water and then 2N-sodium hydrogen carbonate (2 × 25 ml.), dried, and evaporated, leaving a yellow oil which slowly solidified and on crystallisation from light petroleum (b. p. 40—60°) gave *ethyl* 3-*ethylidene*-4′-*keto*-4 : 6 : 2′-*trimethyl*cyclo*penten*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* in almost colourless prisms (5—6 g.), m. p. 80°, with a negative ferric and Ehrlich reaction and a positive alkaline nitroprusside reaction (Found : C, 73·6; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). Acidification of the aqueous sodium hydrogen carbonate washings gave only a trace of gum.

A mixture of the red viscous oil (5 g.) and sulphuric acid monohydrate (40 ml.) was heated on the steam-bath for 1 hour, cooled, poured into ice-water (500 ml.), and extracted with ether. The 3-*ethylidene-acid* (XV; R = H) was isolated from the ethereal extracts with 2N-sodium hydrogen carbonate and crystallised from dilute methanol in pale yellow plates (1·1 g.), m. p. 137°, giving the colour reactions of the ethyl ester (Found: C, 72·2; H, 6·1. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). The same acid was formed by hydrolysis of the aforementioned ethyl ester (1 g.) with 50% alcohol (60 ml.), containing 8% aqueous sodium hydroxide (4 ml.), at 80° for 10 minutes. On isolation it was purified by means of 2N-sodium hydrogen carbonate and then dilute methanol, forming pale yellow plates, m. p. 136°. Esterification of the acid with ethereal diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 80°.

Ozonolysis of the 3-*Ethylidene-ester* (XV; R = Et).—This ester (1 g.), in carbon tetrachloride (30 ml.), was oxidised with ozone according to the method employed for the analogous 3-methylenecoumaran. From the aqueous hydrolysate of the ozonide acetaldehyde was removed by a stream of nitrogen and converted into the dimedone derivative (20 mg.), m. p. 140°, identical with an authentic specimen. The same product (30 mg.), m. p. 140°, was also obtained directly from the filtered hydrolysate in another experiment.

Purified by the procedure employed for the 3-methylenecoumaran product, the gummy solid from the ozonide gave the coumaran-3-one ester (XII; R = Et), m. p. and mixed m. p. 91—92°.

Similarly, ozonolysis of the 3-ethylidene acid gave acetaldehyde and the coumaran-3-one acid (XII; R = H), m. p. and mixed m. p. 158—159°.

4 : 6-*Dimethylcoumarone*-2-*carboxylic Acid* (XVIII; R = OH).—2-Hydroxy-4 : 6-dimethylbenzaldehyde (Duff, *J.*, 1941, 547) gave a 2 : 4-*dinitrophenylhydrazone* in squat red needles, m. p. 253°, from light petroleum (b. p. 60—80°) (Found: N, 17·3. $C_{15}H_{14}O_5N_4$ requires N, 17·0%). Interaction of the aldehyde (4·9 g.) with methyl bromoacetate (5·1 g.) and potassium carbonate (4·8 g.) in boiling acetone (300 ml.) for 8 hours gave *methyl* 2-*formyl*-3 : 5-*dimethylphenoxyacetate* which formed colourless needles, m. p. 98°, from dilute methanol (Found: C, 64·7; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%) and gave a 2 : 4-*dinitrophenylhydrazone* in slender orange needles, m. p. 188°, from dilute alcohol (Found: N, 14·0. $C_{18}H_{18}O_7N_4$ requires N, 13·9%). This ester exhibits phototropy, becoming yellow on exposure to light and then reverting to the colourless form in the dark. On hydrolysis with 2N-aqueous-methanolic sodium hydroxide it gave 2-formyl-3 : 5-dimethylphenoxyacetic acid which separated from dilute acetic acid in needles, m. p. 170°, and yielded a 2 : 4-*dinitrophenylhydrazone* in orange needles, m. p. 192°, from dilute alcohol (Found: N, 14·5. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

A solution of methyl 2-formyl-3 : 5-dimethylphenoxyacetate (5 g.) in methanol (50 ml.), containing sodium methoxide (from 1·1 g. of sodium), was heated on the steam-bath for 15 minutes, diluted with water (50 ml.), and again heated for 15 minutes. The cooled reaction mixture was extracted with ether to remove a little 4 : 6-dimethylcoumarone (0·2 g.), b. p. 219°/760 mm. (picrate, m. p. 61°) (Stoermer, *Annalen*, 1900, **312**, 295) and then acidified, giving a mixture of 4 : 6-*dimethylcoumarone*-2-*carboxylic acid* and 2-formyl-3 : 5-dimethylphenoxyacetic acid. On being cooled a solution of this mixture in hot acetic acid deposited the former acid in irregular prisms (2·4 g.), m. p. 257°, after recrystallisation from dilute alcohol, with a blue sulphuric acid reaction (Found: C, 69·5; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). Prepared with thionyl chloride, the chloride from this acid gave the *amide* which formed plates, m. p. 173°, from dilute alcohol (Found: N, 7·4. $C_{11}H_{11}O_2N$ requires N, 7·4%).

On dilution with water the acetic acid liquor left on the removal of 4 : 6-dimethylcoumarone-2-carboxylic acid gave 2-formyl-3 : 5-dimethylphenoxyacetic acid (1 g.), m. p. and mixed m. p. 170°, after recrystallisation from dilute alcohol.

4 : 6-*Dimethylcoumarone*-2-*acetic Acid* (XIX; R = OH).—Formed when 4 : 6-dimethylcoumarone-2-carboxylic acid (1 g.) was heated with thionyl chloride (2 ml.) under reflux for 45 min., the acid chloride was purified by distillation and obtained as colourless crystals (0·9 g.), b. p. 140°/2 mm., m. p. 75°. A solution of this product in ether (20 ml.) was added to a threefold excess of ethereal diazomethane at 0° and 24 hours later the diazo-ketone (XVIII; R = CHN_2) (0·4 g.) was collected, forming long yellow needles, m. p. 147°, from methanol; a further quantity (0·5 g.) was obtained on evaporation of the ethereal liquor. When this compound was subjected to the Wolff rearrangement with methanol and silver oxide under the usual conditions the yields of the requisite acetic acid were indifferent (50 mg. of crude product from 1 g. of diazo-ketone) and the modified procedure of Wilds and Meader (*J. Org. Chem.*, 1948, **13**, 763) was adopted. A flask containing a mixture of the diazo-ketone (1 g.), benzyl alcohol (5 ml.), and dimethylaniline (5 ml.) was immersed in an oil-bath at 190° and the reaction,

which commenced after 3 minutes, was complete in about 15—20 min. After having been washed with 2N-hydrochloric acid an ethereal solution (100 ml.) of the reaction mixture was evaporated and the residual red oil heated with 40% aqueous potassium hydroxide (5 ml.) on the steam-bath for 2 hours, diluted with water (20 ml.), extracted with ether, treated with charcoal, filtered, and acidified, giving a mixture of 4 : 6-*dimethylcoumarone-2-acetic acid* (XIX; R = OH) (0·3 g.) and 4 : 6-dimethylcoumarone-2-carboxylic acid (0·1 g.) which were separated by fractional crystallisation from dilute methanol. The more soluble 4 : 6-dimethylcoumarone-2-acetic acid formed colourless needles, m. p. 113°, having a violet sulphuric acid reaction (Found: C, 70·2; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

Prepared from 4 : 6-dimethylcoumarone-2-acetic acid (1·6 g.) with phosphorus pentachloride (1·6 g.) in chloroform (50 ml.) at room temperature for ½ hour and then at 40° for 15 minutes, the acid chloride was dissolved in ether (50 ml.) mixed with ethereal ethoxymagnesio-derivative of ethyl acetoacetate (from 1·3 g. of ester), refluxed for 6 hours, and treated with a little dilute hydrochloric acid. On isolation with ether the crude product was dissolved in cooled concentrated sulphuric acid and, after being kept at −5° for 3 days, the solution was poured on ice and extracted with ether. The combined extracts were washed with alkali, dried, and evaporated, leaving a neutral *substance* which separated from light petroleum (b. p. 60—80°) in pale yellow needles (0·15 g.), m. p. 156° (Found: C, 68·1; H, 6·2. $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·3%). This product, which gave a negative Ehrlich reaction and a positive alkaline nitroprusside reaction, had an ultra-violet absorption spectrum totally different from that of usnolic acid and its analogues.

Resolution of Optically Inactive Usnic Acid.—(+)-Usnic acid, m. p. 204°, $[\alpha]_D^{20}$ +495° (*c*, 0·5 in $CHCl_3$) was isolated from *Usnea florida* (Web), *U. florida* (Ach), and *Usnea hirta* (Ach) which had been collected in Wales. (+)-Usnic acid (0·5 g.), dissolved in 8% aqueous sodium hydroxide (20 ml.), was treated with methyl sulphate (1·5 c.c.), added in 3 portions, the solution was acidified, and the precipitate was well washed with water and heated with 75% methanol (20 ml.). On cooling, the filtered solution deposited (+)-O-*methylusnic acid* which crystallised from acetone in bright yellow prisms (0·25 g.), m. p. 136°, $[\alpha]_D^{20}$ +355° (*c*, 2·0 in $CHCl_3$) (Found: C, 63·1; H, 5·0; OMe, 8·6. $C_{18}H_{15}O_6$·OMe requires C, 63·7; H, 5·0; OMe, 9·0%).

A solution of (±)-usnic acid (2 g.) (Schöpf and Heuck, *Annalen*, 1927, **459**, 233) in the minimum amount of acetone was treated with (−)-brucine (2·35 g.), dissolved in methanol (10 ml.), and the greater part of the acetone evaporated on the steam-bath. On cooling, the mixture deposited (−)-brucine (±)-usnate in small colourless plates, m. p. 213° (decomp.) $[\alpha]_D^{20}$ −10° (*c*, 5·0 in $CHCl_3$). This salt (4 g.) was boiled with methanol (100 ml.) for 2 minutes and filtered, giving solid (A) and solution (B). Solid (A) was then extracted with boiling methanol (100 ml.) for 5 min., yielding solid (A_1) and solution (B_1). Repetition of this process with (A_1) and methanol (50 ml.) gave solid (A_2) and solution (B_2). The solutions (B), (B_1), and (B_2) were combined and diluted with water (1 l.), and 24 hours later the solid (C) was collected, leaving the filtrate (D).

The almost colourless residue (A_2) had m. p. 226° (decomp.), $[\alpha]_D^{20}$ +212° (*c*, 2·5 in $CHCl_3$) and was indistinguishable from a specimen of the (−)-brucine salt of authentic (+)-usnic acid which had m. p. 227° (decomp.), $[\alpha]_D^{20}$ +222° (*c*, 5·0 in $CHCl_3$). Decomposition of this salt (A_2) with 2N-sodium hydroxide followed by acidification with 2N-hydrochloric acid gave (+)-usnic acid which was purified from chloroform and alcohol, forming long yellow prisms, m. p. 204°, $[\alpha]_D^{20}$ +467° (*c*, 5·0 in $CHCl_3$), identical with a natural specimen.

Treatment of the filtrate (D) with 2N-hydrochloric acid gave (−)-usnic acid which on purification from chloroform and alcohol had m. p. 203°, $[\alpha]_D^{20}$ −367° (*c*, 5·0 in $CHCl_3$), identical with an authentic specimen. The (−)-brucine salt was prepared from this (−)-acid and had m. p. 222° (decomp.), $[\alpha]_D^{20}$ −240° (*c*, 0·3 g. in $CHCl_3$), whilst the (−)-brucine salt of authentic (−)-usnic acid had m. p. 224° (decomp.), $[\alpha]_D^{20}$ −254° (*c*, 5·0 in $CHCl_3$).

Usnolic Acid.—The following improved method was employed for the preparation of this compound from usnic acid. A solution of usnic acid (1 g.) in sulphuric acid monohydrate (10 ml.) was kept at 40—50° for 1 hour, cooled, and poured on ice (100 g.). The reaction vessel was washed with water (20 ml.) and then ethanol (20 ml.), and the washings were added to the main product. This mixture was heated to about 95—98°, whereupon the original flocculent precipitate of usnolic acid became macrocrystalline. On isolation this product (0·85—0·9 g.) formed yellow plates, m. p. 230—231° (decomp.) (cf. Stenhouse and Groves, *J.*, 1881, **39**, 234, and Curd and Robertson, Part V, *J.*, 1937, 894). Methylation of usnolic acid (1 g.) with methyl sulphate (1·25 g.) and potassium carbonate (1·25 g.) in boiling acetone (50 ml.) for 5 hours gave *methyl* O-*methylusnolate* (IV; R = Me, R′ = CO_2Me) which separated from light petroleum (b. p.

40—60°) and then dilute acetic acid in pale yellow rectangular plates (0·5 g.), m. p. 134° [Found : C, 63·8; H, 5·6; OMe, 17·8. $C_{13}H_{14}O_5(OMe)_2$ requires C, 64·5; H, 5·4; OMe, 16·7%]. This compound gives an emerald-green ferric, a blue Ehrlich, and a violet alkaline nitroprusside reaction. Treatment of usnolic acid in 1 : 1 (vol.) ether–chloroform with ethereal diazomethane for 20 min., followed by decomposition of the excess of diazomethane with acetic and evaporation of the solution, left a residue which crystallised in contact with methanol, giving an almost theoretical yield of methyl *O*-methylusnolate, m. p. and mixed m. p. 134°. Reaction with diazomethane for shorter periods, *e.g.*, 10 min., gave a mixture of methyl usnolate, m. p. 202°, along with a little methyl *O*-methylusnolate (Widmann, *Annalen*, 1902, **324**, 139) whilst prolonged treatment gave a gummy product.

Hydrogenation of usnolic acid (1 g.) in ethyl acetate (250 ml.) with hydrogen (2 mols. absorbed) with a platinum catalyst (0·1 g.) furnished a yellow gummy product which, on purification with aqueous sodium hydrogen carbonate to remove resin and then by crystallisation from dilute methanol, gave *tetrahydrousnolic acid* in pale yellow needles (0·65 g.), m. p. 134° (decomp.) (Found : C, 59·3; H, 5·8. $C_{19}H_{22}O_8$ requires C, 59·0; H, 6·0%).

Ozonolysis of methyl *O*-methylusnolate (0·5 g.) in ethyl acetate (60 ml.), followed by treatment of the product with water for 24 hours, gave an aqueous solution containing formaldehyde which was isolated as the dimedone derivative, m. p. and mixed m. p. 191°, together with a gummy solid. Crystallised from methanol and then benzene–light petroleum (b. p. 60—80°), this gave the *methyl ether* of methyl 7-acetyl-4 : 6-dihydroxy-3 : 4′-diketo-5 : 2′-dimethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (V; R = Me, R′ = CO_2Me) in colourless prisms (0·2 g.), m. p. 137—139°, which reduced Fehling's solution and gave a red ferric and a transient blue alkaline nitroprusside reaction [Found : C, 61·1; H, 4·9; OMe, 15·2. $C_{17}H_{12}O_6(OMe)_2$ requires C, 61·0; H, 4·9; OMe, 16·6%]. Oximation of (V; R = Me, R′ = CO_2Me) by the sodium acetate method for 2 days at room temperature gave a dioxime, which formed pointed plates, m. p. 243° (decomp.), with a reddish-purple ferric reaction and contained methanol of crystallisation [Found : N, 6·2; OMe, 22·9. $C_{17}H_{14}O_6N_2(OMe)_2$,MeOH requires N, 6·4; OMe, 21·3%].

Attempted Resolution of Usnolic Acid.—A solution of the acid (2 g.) in the minimum amount of hot acetone was mixed with (−)-brucine (2·3 g.), dissolved in acetone (20 ml.), and the mixture concentrated; the *brucine* salt of usnolic acid separated in irregular fawn-coloured prisms (4·2 g.), m. p. 190°, $[\alpha]_D^{20}$ −10° (*c*, 4·0 in $CHCl_3$) (Found : N, 4·1. $C_{41}H_{42}O_{11}N_2$ requires N, 3·8%). This salt (4 g.) was digested with hot methanol (50 ml.) for 2 min. and the insoluble residue then repeatedly extracted with boiling methanol (100 ml.) until the weight was reduced to about 1·5 g. This residual solid (0·5 g.), m. p. 209° (decomp.), $[\alpha]_D^{20}$ −30° (*c*, 2·0 in $CHCl_3$), was decomposed with 2N-hydrochloric acid (2 ml.) in methanol (10 ml.), and the precipitated usnolic acid twice recrystallised from dilute methanol containing a drop of dilute hydrochloric acid, forming plates (0·2 g.), m. p. 233°, $[\alpha]_D^{20}$ −19° (*c*, 1·0 in MeOH). Treatment of this product (0·25 g.) with sulphuric acid monohydrate (5 ml.) at 50° for 1 hour gave usnolic acid, m. p. 233°, after purification which had a zero rotation and gave a brucine salt, m. p. 190°, $[\alpha]_D^{20}$ −10° (*c*, 0·25 in $CHCl_3$).

On dilution with water followed by acidification with 2N-hydrochloric acid the initial extract (50 ml.) of the brucine salt gave usnolic acid, m. p. 233°, $[\alpha]_D^{20}$ +31° (*c*, 1·0 in MeOH), after being twice recrystallised from dilute methanol. The brucine salt of this product had m. p. 203° $[\alpha]_D^{20}$ −3·3° (*c*, 0·3 in $CHCl_3$).

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