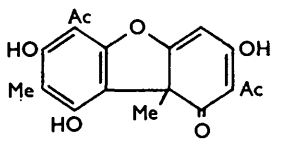
303. *Usnic Acid. Part XIII.* The Orientation and Synthesis of Usnolic Acid.*

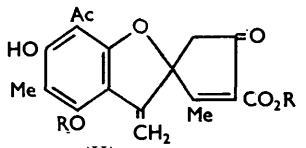
By F. M. Dean, C. A. Evans, Thomas Francis, and Alexander Robertson.

In an extension of earlier work,[1] di-*O*-methylpyrousnic acid has been acylated to give 5-*O*-methylusnetic acid, the acetate of which furnished 7-acetyl-6-hydroxy-4-methoxy-3′-methoxycarbonyl-5 : 2′-dimethyl-3-methylene-4′-oxo*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran identical with methyl *O*-methylusnolate, thus proving that usnolic acid has the same pattern of aromatic substitution as has usnic acid. Usnetic acid from the demethylation of 4-*O*-methylusnetic acid was converted by the standard method into methyl usnolate, the hydrolysis of which gave usnolic acid identical with the isomerisation product of usnic acid.

In Part IX [1] it was shown that the isomerisation of usnic acid (I) by sulphuric acid involved a ring contraction which, on the assumption that the aromatic rings of the isomers were identical, led to the development of structure (II; R = H) for usnolic acid. However, the heterocyclic system in structure (II) is a modified allyl ether grouping, and as such might well have been cleaved by the reagent with subsequent re-cyclisation involving the alternative hydroxyl group, whereupon structure (III) would be correct for usnolic acid. The synthesis of the *spiro*coumaran (II; R = Me), identical with methyl *O*-methylusnolate formed from usnolic acid, has now provided proof that the structure (II; R = H) suggested originally for usnolic acid is correct; in parallel work usnolic acid itself has been synthesised.



(I)



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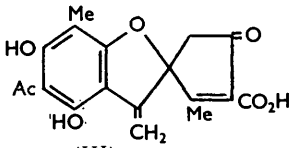

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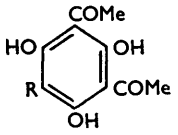

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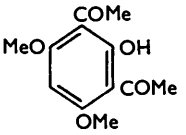

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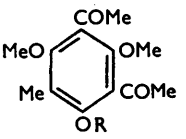

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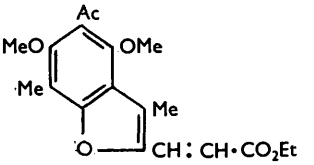


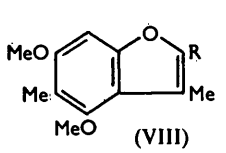
(VII)

In preliminary investigation, 2 : 4-diacetyl-6-methylphloroglucinol (IV; R = Me) appeared to offer advantages as a starting material for the synthesis of compounds of types (II) and (III) because it already contained all the necessary aromatic substituents and because its lower homologue (IV; R = H) could be selectively methylated [2] to the phenol (V) containing an *o*-hydroxycarbonyl grouping necessary for elaboration of the *spiro*-coumaran system by well-established methods.[1] Unfortunately, phenol (IV; R = Me) gave only mixtures of mono- and tri-methyl ethers when selective alkylation was attempted. Further, the dimethyl ether (VI; R = H), available indirectly from (IV; R = Me), failed to react with ethyl bromoacetate, except at relatively high temperatures where a very small quantity of the desired phenoxyacetic ester (VI; R = CH_2·CO_2Et) resulted. On the other hand, the dimethyl ether (VI; R = H) reacted readily with allyl bromide giving (VI; R = CH_2·$CH{:}CH_2$) which was a typical allyl ether in that hydrogenation

* Part XII, *J.*, 1956, 2322.

[1] Dean, Halewood, Mongkolsuk, Robertson, and Whalley, *J.*, 1953, 1250.
[2] Dean and Robertson, *J.*, 1953, 1241.

resulted in a mixture of the parent phenol (VI; R = H) and the propyl ether (VI; R = Pr) identical with material formed by direct propylation. Although ethyl γ-bromocrotonate behaved like allyl bromide rather than ethyl bromoacetate and gave the phenoxycrotonate (VI; R = CH_2·CH:CH·CO_2Et), this resinified both when hydrolysis of the ester grouping was attempted and when efforts were made to induce dehydration to the coumarone (VII) which might have been a useful intermediate.



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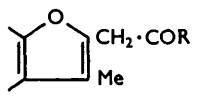

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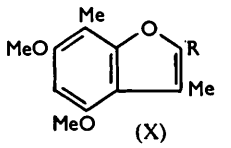

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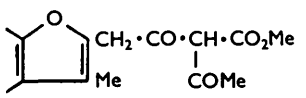

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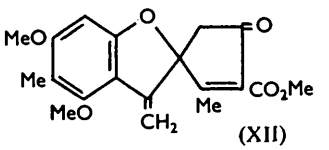

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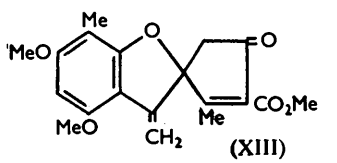
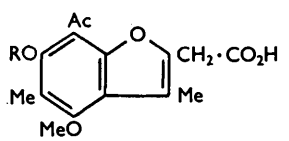


(XIII)

A relatively convenient preparation of 4 : 6-dimethoxy-3 : 5-dimethylcoumarilic acid (VIII; R = CO_2H) has been described.[3]. Catalysed by copper carbonate, decarboxylation of this acid furnished the coumarone (VIII; R = H) from which the aldehyde (VIII; R = CHO) and thence the pyruvic acid (IX; R = CO_2H) were made by the method of Birch and Robertson.[4] When modified, the oxidation of this pyruvic acid to the acetic acid (di-*O*-methylpyrousnic acid) (IX; R = OH) gave satisfactory results, whereupon application of the same sequence of reactions to the coumarilic acid (X; R = CO_2H) gave the corresponding acetic acid (X; R = CH_2·CO_2H). The acids (IX; R = OH)



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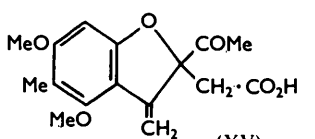

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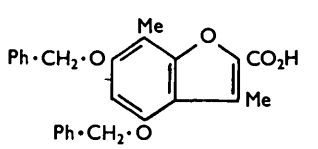

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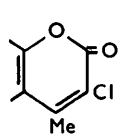
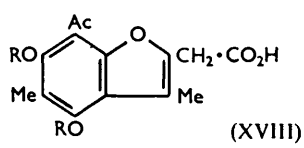


(XVII)



(XVIII)

and (X; R = CH_2·CO_2H) were transformed into the acid chlorides which, with the methoxymagnesio-derivative of methyl acetoacetate, gave diketo-esters type (XI) cyclised by sulphuric acid to the closely similar *spiro*coumarans (XII) and (XIII). It was not expected that insertion of an acetyl group into the free aromatic position of (XII) would be satisfactory because of the many reactive centres in the molecule, and, in practice, only gums resulted when this spiran was treated with acetic anhydride and boron fluoride. Attention was therefore directed to introduction of this acetyl group at an earlier stage in the synthesis.

Interaction of di-*O*-methylpyrousnic acid (IX; R = OH) and acetic anhydride in the presence of boron fluoride might have given, not only 4-*O*-methylusnetic acid (XIV; R = H) arising from the usual aromatic acylation accompanied by demethylation, but also an exomethylenecoumaran (XV) resulting from a reaction with acetylium formally parallel

[3] Dean, Evans, and Robertson, *J.*, 1954, 4565.
[4] Birch and Robertson, *J.*, 1938, 306.

to the acid-catalysed cyclisation of compounds of type (XI) to *spiro*coumarans. However, only the usnetic acid derivative (XIV; R = H) was isolated. The acid chloride from the corresponding acetate (XIV; R = Ac) was condensed with the methoxymagnesio-derivative of methyl acetoacetate and when treated with sulphuric acid the product was simultaneously cyclised and deacetylated, giving methyl *O*-methylusnolate (II; R = Me) identical with the ester obtained by alkylation of usnolic acid with diazomethane.[1]

Demethylation of methyl *O*-methylusnolate to usnolic acid was found to be impracticable; further, the use of the benzyl group for protection of the hydroxyl group was discounted because the dibenzyloxycoumarilic acid (XVI), though readily obtainable from the chlorocoumarin (XVII), could not be decarboxylated or converted into the homologous acetic acid by the Arndt–Eistert reaction. Fortunately, dealkylation of 4-*O*-methylusnetic acid with magnesium iodide gave a fair yield of usnetic acid (XVIII; R = H) identical with a sample from alkaline degradation of usnic acid, and, when subjected to the standard sequence of reactions, the corresponding diacetate (XVIII; R = Ac) furnished methyl usnolate identical with a sample prepared from usnolic acid.[1] At first, hydrolysis of methyl usnolate proved troublesome, but eventually conditions were found in which this ester was smoothly converted into usnolic acid (II; R = H) indistinguishable from an authentic specimen.

Experimental

2 : 4-*Diacetyl*-6-*methylphloroglucinol* (IV; R = Me).—Acetic acid (20 ml.), containing *C*-methylphloroglucinol triacetate (5·0 g.) was saturated with boron fluoride at −10° and 10 min. later the brown viscous mass was stirred into water (150 ml.), giving a yellow solid which was decomposed by dissolution in hot 50% alcohol. The resulting 2 : 4-diacetyl-6-methylphloroglucinol separated from the cooled solution, forming needles (4·0 g.), m. p. 170°, from dilute alcohol (Found: C, 58·8; H, 5·6. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%).

Attempted dimethylation of this phenol (1·0 g.) in boiling acetone (50 ml.) with methyl sulphate (1·2 g., 2·2 mols.) and potassium carbonate (2·0 g.) during 4 hr. followed by removal of insoluble matter and solvent gave an orange gum partly soluble in 2N-aqueous sodium hydroxide. Crystallised from light petroleum (b. p. 60—80°), the insoluble fraction furnished 2 : 4-diacetyl-6-methylphloroglucinol trimethyl ether in prisms (0·4 g.), m. p. and mixed m. p. 66—67°. Regained by acidification of the alkaline solution, the soluble fraction crystallised from dilute alcohol, giving 2 : 4-diacetyl-6-methylphloroglucinol 1-methyl ether in needles (0·2 g.), m. p. and mixed m. p. 97°. The use of methyl iodide as the alkylating agent gave a similar result.

2 : 4-*Diacetyl*-6-*methylphloroglucinol* 1 : 3-*Dimethyl Ether* (VI; R = H).—Warmed on the steam-bath with N-aqueous sodium hydroxide (20 ml.), 2 : 4-diacetyl-6-methylphloroglucinol 5-acetate 1 : 3-dimethyl ether [2] (1·0 g.; m. p. 80°) dissolved in about 25 min. Liberated by hydrochloric acid and isolated with ether, the resulting 2 : 4-*diacetyl*-6-*methylphloroglucinol* 1 : 3-*dimethyl ether* separated from dilute alcohol in fine, pale yellow needles (0·6 g.), m. p. 64°, having a dark red ferric reaction in alcohol [Found: C, 61·6; H, 6·4; OMe, 24·5. $C_{11}H_{10}O_3(OMe)_2$ requires C, 61·9; H, 6·4; OMe, 24·6%]. The acetate used in this preparation formed platelets, m. p. 80°, but sometimes a second form was encountered which existed as cubes, m. p. 92° [Found: C, 61·2; H, 6·2; OMe, 20·9. Calc. for $C_{13}H_{12}O_4(OMe)_2$: C, 61·2; H, 6·2; OMe, 21·1%]. Acetylation of the phenol (VI) regenerated the acetate which could again be obtained in either form, but definite conditions for their interconversion could not be established.

Ethyl 2 : 4-*Diacetyl*-3 : 5-*dimethoxy*-6-*methylphenoxyacetate* (VI; R = $CH_2{\cdot}CO_2Et$).—The interaction of 2 : 4-diacetyl-6-methylphloroglucinol 1 : 3-dimethyl ether (1·0 g.) and ethyl bromoacetate (0·8 g.) in boiling diethyl ketone (25 ml.), containing potassium carbonate (1·0 g.), for 2 hr. gave a brown gummy product which was freed from phenolic material by means of 2N-aqueous sodium hydroxide and purified from benzene by use of an aluminium oxide column. Evaporation of the fawn eluate left a solid which furnished the *phenoxyacetate* in needles (50 mg.), m. p. 139—140°, after several recrystallisations fom light petroleum (b. p. 40—60°) [Found: C, 60·5; H, 6·2; alkoxyl (as OMe) 27·8. $C_{13}H_{11}O_4(OMe)_2{\cdot}OEt$ requires C, 60·3; H, 6·5; alkoxyl (as OMe) 27·5%]. When diethyl ketone was replaced by acetone, ethyl methyl ketone, or benzene, there was no reaction.

2 : 4-*Diacetyl*-6-*methylphloroglucinol* 5-*Allyl* 1 : 3-*Dimethyl Ether* (VI; R = CH_2·CH:CH_2).—Formed by the interaction of 2 : 4-diacetyl-6-methylphloroglucinol 1 : 3-dimethyl ether (1·0 g.), allyl bromide (1·0 g.), and potassium carbonate (2 g.) in boiling acetone (15 ml.) during 8 hr., the oil gave on distillation the *allyl ether* (VI; R = CH_2·CH:CH_2) (0·8 g.), b. p. 170° (bath)/0·05 mm., with a negative ferric reaction (Found : C, 65·2; H, 6·7. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9%).

A solution of this allyl ether (1·0 g.) in methanol (150 ml.) containing 1% palladium–charcoal (1 g.) was shaken in hydrogen at ordinary pressure until absorption ceased. The oil left when the catalyst and solvent were removed was partly soluble in 2N-aqueous sodium hydroxide; the alkaline washings of this contained 2 : 4-diacetyl-6-methylphloroglucinol 1 : 3-dimethyl ether (0·4 g.), m. p. and mixed m. p. 64°, and the non-phenolic material supplied 2 : 4-*diacetyl*-6-*methylphloroglucinol* 1 : 3-*dimethyl* 5-n-*propyl ether* (0·5 g.), b. p. 120° (bath)/0·05 mm. (Found : C, 65·6; H, 7·6. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). Comparison of infrared spectra identified this propyl ether with the product obtained by the action of propyl iodide on 2 : 4-diacetyl-6-methylphloroglucinol 1 : 3-dimethyl ether in the potassium carbonate–acetone method.

Ethyl γ - (2 : 4 - *Diacetyl* - 3 : 5 - *dimethoxy* - 6 - *methylphenoxy*)*crotonate* (VI; R = CH_2·CH:CH·CO_2Et).—In 6 hr., the purple colour of a mixture of 2 : 4-diacetyl-6-methylphloroglucinol 1 : 3-dimethyl ether (1·0 g.), ethyl γ-bromocrotonate (1·5 g.) and potassium carbonate (2·0 g.) in boiling acetone had faded to yellow. The alkali-insoluble product crystallised from light petroleum (b. p. 40—60°), giving the *phenoxycrotonate* in needles (1·3 g.), m. p. 94°, having a negative ferric reaction (Found : C, 62·9; H, 6·6. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·6%). In hot alcoholic sodium ethoxide or dilute sodium hydroxide this ester rapidly resinified.

4 : 6-*Dibenzyloxy*-3 : 7-*dimethylcoumarilic Acid* (XVI).—The reaction between 3-chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin [3] (10 g.) and benzyl bromide (15·5 g.) in boiling acetone (200 ml.), containing potassium carbonate (20 g.), gave after 4 hr. the 5 : 7-*dibenzyloxy*-3-*chloro*-4 : 8-*dimethylcoumarin* (XVII) which separated from benzene in needles (15 g.), m. p. 223° (Found : C, 71·5; H, 4·9. $C_{25}H_{21}O_4Cl$ requires C, 71·3; H, 5·0%).

This dibenzyloxycoumarin (2 g.) was added to potassium hydroxide (0·6 g.) in boiling " Carbitol " (50 ml.) and, 10 min. later, the mixture was diluted with an equal volume of water and acidified with hydrochloric acid, liberating crude 4 : 6-*dibenzyloxy*-3 : 7-*dimethylcoumarilic acid*, which, purified from dilute methanol (charcoal), formed biprisms (1·5 g.), m. p. 210° (decomp.) (Found : C, 74·9; H, 5·5. $C_{25}H_{22}O_5$ requires C, 74·6; H, 5·5%). A solution of this acid in warm sulphuric acid had a violet tinge. The *methyl ester* (diazomethane) separated from methanol in white needles, m. p. 116—118° (Found : C, 75·0; H, 5·8. $C_{26}H_{24}O_5$ requires C, 75·0; H, 5·8%).

This coumarilic acid was stable in boiling " Carbitol," glycerol, or quinoline with or without the addition of copper compounds. The acid chloride formed by the action of phosphorus pentachloride on the acid or of thionyl chloride on the sodium salt was a greenish solid which with ethereal diazomethane at −2° during 24 hr. gave a yellow, crude diazo-ketone. No identifiable products were obtained when this diazo-ketone was treated with silver oxide or silver benzoate in methanol, or heated in benzyl alcohol and dimethylaniline.

4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumarone* (VIII; R = H).—Carbon dioxide was rapidly evolved for 10 min. from a mixture of 4 : 6-dimethoxy-3 : 5-dimethylcoumarilic acid (5 g.) and copper carbonate (0·5 g.) at 220°; distillation of the product gave 4 : 6-dimethoxy-3 : 5-dimethylcoumarone, b. p. 125° (bath)/0·05 mm., as a yellow oil (3·0 g.) which gave a purple colour in warm sulphuric acid [Found : C, 69·6; H, 7·0; OMe, 29·6. Calc. for $C_{10}H_8O(OMe)_2$: C, 69·9; H, 6·8; OMe, 30·1%].

4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumaron*-2-*ylacetic Acid* (*Di*-O-*methylpyrousnic Acid*) (IX; R = OH).[4]—4 : 6-Dimethoxy-3 : 5-dimethylcoumaron-2-ylpyruvic acid (1·5 g.), dissolved in 2N-aqueous sodium hydroxide (15 ml.) at −5°, was oxidised with hydrogen peroxide (100-vol.; 1 ml.). Five min. later, slow acidification of the mixture precipitated the crude product which was isolated with ether and purified from benzene on aluminium oxide. The eluate furnished di-*O*-methylpyrousnic acid as prisms (0·9 g.), m. p. 127°, from benzene and then from dilute methanol [Found : C, 63·4; H, 6·2; OMe, 23·6. Calc. for $C_{12}H_{10}O_3(OMe)_2$: C, 63·6; H, 6·1; OMe, 23·5%].

4-O-*Methylusnetic Acid* (XIV; R = H).—Acetic acid (2 ml.) containing di-*O*-methylpyrousnic acid (0·8 g.) and acetic anhydride (0·6 g.) was saturated with boron fluoride without

cooling. Next day, the mixture was diluted with water, the dark green acidic oil was isolated with ether, and the ethereal solution extracted with aqueous sodium hydrogen carbonate. Acidification of the extract supplied 4-*O*-methylusnetic acid, crystallising from benzene (charcoal) in needles (0·8 g.), m. p. 166°, giving a green ferric reaction in alcohol (Found: C, 61·9; H, 5·6; OMe, 10·5. $C_{14}H_{13}O_5$·OMe requires C, 61·6; H, 5·5; OMe, 10·6%). Obtained from 4-*O*-methylusnetic acid (500 mg.) with acetic anhydride containing a trace of sulphuric acid, the *acetate* separated from benzene in needles (450 mg.), m. p. 134° (Found: C, 61·6; H, 5·8. $C_{17}H_{18}O_7$ requires C, 61·1; H, 5·4%).

Usnetic Acid (XVIII; R = H).—An intimate mixture of 4-*O*-methylusnetic acid (0·4 g.) and magnesium iodide (1·5 g.) was kept in nitrogen for 1 hr. at 190°. The solid remaining when the product was boiled with 2N-sulphuric acid (75 ml. × 2) was dissolved in ether and extracted into aqueous sodium hydrogen carbonate. After clarification of the extract with charcoal, acidification with hydrochloric acid furnished usnetic acid which crystallised in needles (0·1 g.), m. p. and mixed m. p. 198—199°; the identity with a natural specimen was confirmed by comparison of the infrared spectra.

Acetylation of this acid (0·5 g.) was effected by acetic anhydride and a trace of sulphuric acid in 2 hr. Purified by precipitation with light petroleum (b. p. 60—80°) from a solution in ethyl acetate, the *diacetate* then separated from aqueous methanol in needles (0·25 g.), m. p. 173°, having a negative ferric reaction (Found: C, 59·9; H, 5·1. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%).

2-Formyl-4 : 6-dimethoxy-3 : 7-dimethylcoumarone (X; R = CHO).—On decarboxylation by the method used for the 3 : 5-dimethyl isomeride, 4 : 6-dimethoxy-3 : 7-dimethylcoumarilic acid (5 g.) gave 4 : 6-dimethoxy-3 : 7-dimethylcoumarone (3·0 g.), b. p. 140° (bath)/0·05 mm., solidifying to prisms, m. p. 95—96° [Found: C, 69·9; H, 6·8; OMe, 30·2. Calc. for $C_{10}H_8O(OMe)_2$: C, 69·9; H, 6·8; OMe, 30·1%].

A solution of this coumarone (3·0 g.) in ether (75 ml.), containing zinc chloride (0·2 g.) and hydrogen cyanide (3 ml.), was saturated at 0° with hydrogen chloride and 3 days later the resulting green aldimine hydrochloride was collected, washed with ether, and hydrolysed with boiling water for 10 min. The *2-formylcoumarone* (X; R = CHO) separated in small yellow rhombs (3·0 g.) and had the same form, m. p. 158°, when purified from dilute methanol and then benzene [Found: C, 66·6; H, 6·2; OMe, 26·9. $C_{11}H_8O_2(OMe)_2$ requires C, 66·7; H, 6·0; OMe, 26·5%]. On being warmed, the yellow solution of this aldehyde in sulphuric acid became purple. The *rhodanine derivative* crystallised from acetone in dark red needles, m. p. 298° [Found: C, 55·0; H, 4·6; N, 3·8; OMe, 17·6. $C_{14}H_9O_2NS_2(OMe)_2$ requires C, 55·0; H, 4·3; OMe, 17·7%], and gave intractable gums when hydrolysed.

4 : 6-Dimethoxy-3 : 7-dimethylcoumarone-2-acetic Acid (X; R = CH_2·CO_2H).—A mixture of 2-formyl-4 : 6-dimethoxy-3 : 7-dimethylcoumarone (3·0 g.), hippuric acid (5·0 g.), sodium acetate (4·0 g.), and acetic anhydride (20 ml.) was kept on a steam-bath for 1·5 hr. and then macerated with 50% alcohol (100 ml.). Next day the solid was washed with water (300 ml.) and crystallised from acetone, giving the *azlactone* in orange needles, m. p. 238° [Found: C, 69·6; H, 4·8; N, 3·6; OMe, 16·6. $C_{20}H_{13}O_3N(OMe)_2$ requires C, 70·0; H, 5·1; N, 3·7; OMe, 16·4%].

After 10 hours, ammonia was no longer evolved from a boiling mixture of this azlactone (4 g.) and potassium hydroxide (8 g.) in 50% alcohol (40 ml.) which was then cooled, diluted with an equal volume of water, and saturated with sulphur dioxide. Three hours later, the tarry precipitate was removed and the clear solution was warmed with hydrochloric acid (15 ml.) on a steam-bath for 20 min. Thus precipitated, the crude pyruvic acid was purified from benzene, forming needles (1·7 g.), m. p. 196°, which did not give consistent analytical results. A solution of the crude acid (1·7 g.) in 2N-aqueous sodium hydroxide (15 ml.) at −5° was treated with hydrogen peroxide (100-vol.; 1 ml.) as for the 3 : 5-dimethyl isomeride and on purification from dilute methanol (charcoal) and then benzene the product furnished *4 : 6-dimethoxy-3 : 7-dimethylcoumaron-2-ylacetic acid* in needles (1·0 g.), m. p. 158—159°, giving a purple solution in warm sulphuric acid [Found: C, 64·0; H, 6·4; OMe, 23·7. $C_{12}H_{10}O_3(OMe)_2$ requires C, 63·6; H, 6·1; OMe, 23·5%].

4 : 6-Dimethoxy-3′-methoxycarbonyl-5 : 2′-dimethyl-3-methylene-4′-oxocyclopent-2′-ene-1′-spiro-2-coumaran (XII).—A mixture of magnesium powder (0·12 g.), absolute methanol (0·18 g.), methyl acetoacetate (0·6 g.), and a drop of carbon tetrachloride was heated gently under reflux until no further change occurred, diluted with anhydrous ether (10 ml.), boiled for a further 2 hr.,

and treated with an ethereal solution (40 ml.) of 4 : 6-dimethoxy-3 : 5-dimethylcoumaron-2-ylacetyl chloride which was prepared from the coresponding acid (1·0 g.) and phosphorus pentachloride (1·0 g.) in chloroform by the standard method. Next day, the mixture was boiled for 1 hr. and then treated with a slight excess of 2N-acetic acid, whereupon evaporation of the ethereal layer left the crude diketo-ester type (XI) as a reddish oil. On treatment with sulphuric acid (2·5 ml.) at 0° for 2 days followed by the addition of ice, this oil gave a gum which was dissolved in ether, washed with aqueous sodium hydrogen carbonate, and recovered. Triturated with methanol, the gum crystallised and was purified by adsorption of the impurities on aluminium oxide from a benzene solution. Crystallised from dilute methanol, the solid then furnished the 5 : 2′-*dimethyl*-spiro-2-*coumaran* in needles (0·6 g.), m. p. 141° $\lambda_{max.}$ 235, 267, 323 mμ (10^{-3} ε 28·2, 14·8, 11·3), which had blue Ehrlich and Légal reactions [Found : C, 66·0; H, 5·9; OMe, 27·0. $C_{16}H_{11}O_3(OMe)_3$ requires C, 66·3; H, 5·8; OMe, 27·0%].

4 : 6-*Dimethoxy*-3′-*methoxycarbonyl*-7 : 2′-*dimethyl*-3-*methylene*-4′-*oxo*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran* (XIII) was prepared from 4 : 6-dimethoxy-3 : 7-dimethylcoumaron-2-ylacetic acid (1·0 g.) by the method given above for the isomeride (XII) and on crystallisation from methanol, formed yellow cubes (0·8 g.), m. p. 143°, $\lambda_{max.}$ 223, 233, 287 mμ (10^{-3} ε 27·5, 27·5, 19·1), having a deep blue reaction in the Ehrlich and Légal tests [Found : C, 66·0; H, 5·9; OMe, 27·0%].

Methyl 4-O-*Methylusnolate* (II; R = Me).—4-*O*-Methylusnetic acid 6-acetate (1·0 g.), dissolved in chloroform (15 ml.), was converted into the acid chloride by phosphorus pentachloride (0·7 g.) at room temperature for 15 min. and then under reflux for 30 min. After the removal of the solvent and phosphorus oxychloride, a solution of the red product in ether was added to the methoxymagnesio-derivative of methyl acetoacetate (from 0·35 ml. of ester), and the mixture refluxed for 1 hr. before the addition of 2N-acetic acid (10 ml.). Unchanged 4-*O*-methylusnetic acid acetate (0·2 g.) was removed from the ethereal layer by aqueous sodium hydrogen carbonate. Evaporation of the dried (Na_2SO_4) ether solution then left a viscous orange oil which was treated with sulphuric acid (2·5 ml.) at −2° for 2 days. An ethereal solution of the gummy solid, which was precipitated by the addition of ice, was washed with sodium hydrogen carbonate solution to remove acid and then with water, dried (Na_2SO_4), and evaporated. In contact with methanol, the residue crystallised and could then be recrystallised from that solvent, giving methyl *O*-methylusnolate in yellow prisms (0·25 g.), m. p. 131°, undepressed on admixture with a natural specimen, m. p. 134° (Found : C, 64·5; H, 5·7. Calc. for $C_{20}H_{20}O_7$: C, 64·5; H, 5·4%) Confirmation of this identity was obtained from a comparison of infrared spectra of the two specimens.

Usnolic Acid (II; R = H).—An ethereal solution of the acid chloride from usnetic acid diacetate (0·5 g.) and phosphorus pentachloride (0·32 g.) was added to the methoxymagnesio-derivative of methyl acetoacetate (from 0·16 ml. of ester), and the mixture heated under reflux for 1 hr. The resulting diketo-ester type (XI) was kept with sulphuric acid (1·25 ml.) at −2° for 2 days, and an ethereal solution of the sticky product obtained by the addition of ice was washed with aqueous sodium hydrogen carbonate and evaporated. On being kept, the residue crystallised and was then chromatographed on a silica column (10 × 1 cm.) from 2 : 3 chloroform–benzene. The product, readily eluted by the same solvent, was crystallised from methanol and then from benzene, giving methyl usnolate in yellow needles (100 mg.), m. p. and mixed m. p. 202° (Found : C, 63·6; H, 5·2; OMe, 9·0. Calc. for $C_{18}H_{15}O_6{\cdot}OMe$: C, 63·7; H, 5·1; OMe, 8·7%). This ester and an authentic specimen gave identical infrared spectra.

Of the various techniques of hydrolysis and demethylation examined, only the following was satisfactory. Methyl usnolate (0·05 g.) was kept in sulphuric acid dihydrate (2·5 ml.) at 60° for 15 min. The cooled and diluted solution was shaken with ether from which the product was extracted into aqueous sodium hydrogen carbonate. On acidification, the extract supplied usnolic acid, crystallising from aqueous methanol in yellow plates (0·03 g.), m. p. and mixed m. p. 230° (Found : C, 63·1; H, 4·7. Calc. for $C_{18}H_{16}O_7$: C, 62·8; H, 4·7%). This acid and an authentic specimen gave identical infrared spectra.

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates in this Department.

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