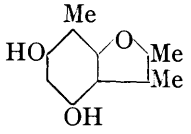
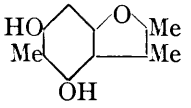
180. *Usnic Acid. Part II. Usneol.*

By Frank H. Curd and Alexander Robertson.

By somewhat different routes Paterno (*Gazzetta*, 1876, **6**, 127) and Schöpf and Heuck (*Annalen*, 1927, **459**, 233) have shown that the removal of the elements of two molecules of acetoacetic acid from usnic acid on hydrolysis and thermal decomposition leaves a phenolic residue usneol, $C_{11}H_{12}O_3$. The latter authors observed that, though this phenol readily formed diacetyl and dibenzoyl derivatives, it did not react with diazomethane to give a dimethyl ether. Further, by degrading usneol with ozone, Schöpf and Heuck isolated a compound, considered to be a mono-acetate of *C*-methylphloracetophenone, which on hydrolysis with sodium hydroxide yielded *C*-methylphloroglucinol, and hence they concluded that usneol was a coumarone (I) or (II) derived from methylphloroglucinol; the experimental results appeared to exclude a structure of the type (III) or (IV).



(I.)



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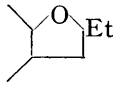
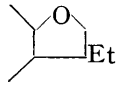


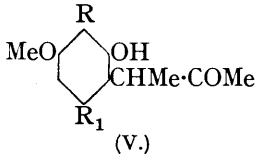
(III.)



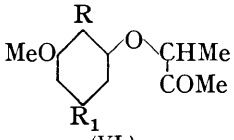
(IV.)

As usneol may be regarded as forming the kernel of the usnic acid molecule, the establishment of its constitution is of great importance. Because of difficulties which might arise in the synthesis of hydroxycoumarones of the types (I), (II), (III), and (IV) we in the first instance confined our attention to the methyl ethers of these compounds. The achievement of our immediate object, *viz.*, the constitution of usneol, was rendered feasible when we succeeded in preparing its O-*dimethyl* and O-*diethyl* ethers by the alkyl iodide–potassium carbonate method.

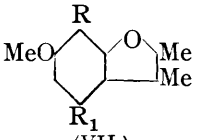
For the synthesis of hydroxy-2 : 3-dimethylcoumarones and their ethers, ring closure of ketones of the type (V) or (VI) appeared to be the most promising method. For practical reasons the second alternative was finally adopted.



(V.)



(VI.)



(VII.)

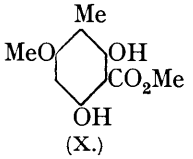
$MeO{\cdot}C_6H_4{\cdot}O{\cdot}CMe{\cdot}CO_2Et$
COMe
(VIII.)

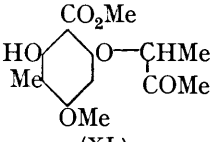
$MeO{\cdot}C_6H_4{\cdot}O{\cdot}CHMe{\cdot}CO_2Et$
(IX.)

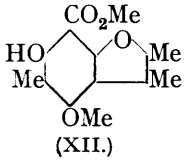
In attempts to obtain the ester (VIII) (for the preparation of VI; R = H, R_1 = H) by the interaction of the sodium salt of resorcinol monomethyl ether and ethyl α-chloro-α-methylacetoacetate in absolute alcohol, the acetyl group was lost and the *phenoxy*-ester (IX) formed. Replacing the chloro-ester by 3-chlorobutan-2-one, we isolated (VI; R = H, R_1 = H) in good yield, and on cyclisation with cold concentrated sulphuric acid this sub-

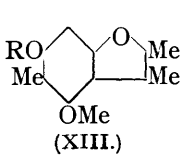
stance gave rise to the *coumarone* (VII; R = H, R_1 = H). In a similar manner the *coumarone* (VII; R = H, R_1 = OMe) was prepared from phloroglucinol dimethyl ether by way of the *ketone* (VI; R = H, R_1 = OMe). The phenoxy-ketones (VI; R = H, R_1 = H) and (VI; R = H, R_1 = OMe) were subsequently prepared more conveniently by the condensation of 3-chlorobutan-2-one and the respective phenols with anhydrous potassium carbonate in boiling acetone: the *phenoxy-ketone* (VI; R = Me, R_1 = OMe), thus obtained from methylphloroglucinol α-dimethyl ether, on ring closure gave 4 : 6-*dimethoxy*-2 : 3 : 7-*trimethylcoumarone* (VII; R = Me, R_1 = OMe) as a crystalline solid which was not identical with usneol dimethyl ether.

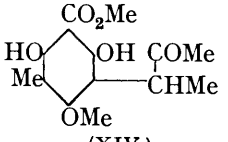
As it now seemed certain that usneol dimethyl ether had the alternative structure (XIII, R = Me), this substance was synthesised by the following indirect method, since the simple procedure used for (VII; R = Me, R_1 = OMe) was inapplicable owing to our failure to prepare methylphloroglucinol β-dimethyl ether:

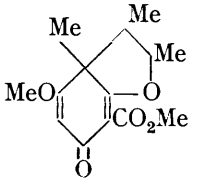

(X.)

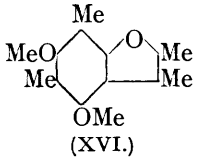

(XI.)


(XII.)


(XIII.)


(XIV.)


(XV.)


(XVI.)

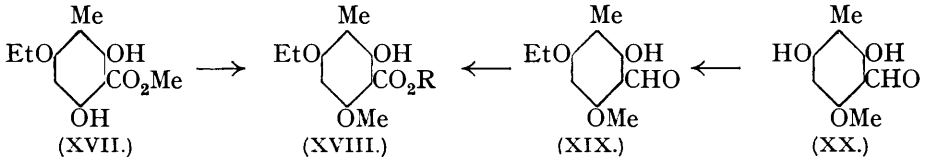
The condensation of the ester (X) and 3-chlorobutan-2-one by the potassium carbonate method was unexpectedly accompanied by simultaneous coumarone cyclisation, yielding *methyl* 6-*hydroxy*-4-*methoxy*-2 : 3 : 5-*trimethylcoumarone*-7-*carboxylate* (XII), which, after hydrolysis and decarboxylation of the resulting *acid*, gave rise to the *hydroxycoumarone* (XIII, R = H). Methylation of (XIII, R = H) furnished usneol dimethyl ether, identified by comparison of the natural and the synthetic picrate.

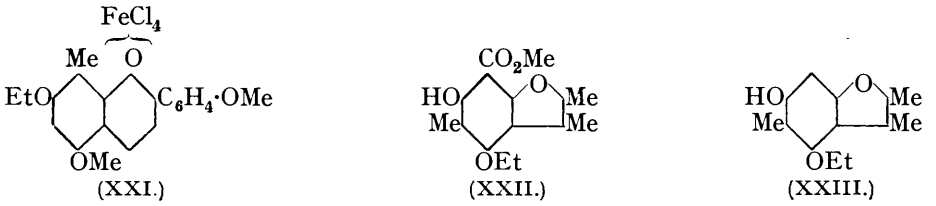
That the coumarone obtained from the ester (X) has the formula (XII) and not an alternative hemi-quinonoid structure (XV) is established by the ultimate success of the synthesis of the dimethyl ether (XIII, R = Me), since a compound having formula (XV) would be expected on hydrolysis and decarboxylation to give a hemi-quinone and not a hydroxy-coumarone.

Regarding the formation of (XII) it is difficult to say whether the first stage is the production of the phenoxy-ketone (XI) or the phenylacetone (XIV), but in support of the former alternative is the fact that, under the conditions employed, compounds of the type (X) yield only ethers and do not undergo further nuclear alkylation (Part I; this vol., p. 437). In this instance, however, both routes lead to the formation of a 2 : 3-dimethylcoumarone.

Although the foregoing synthesis made it reasonably certain that usneol dimethyl ether has formula (XIII, R = Me), and hence usneol itself formula (II), the theoretical analytical values for C, H, and OMe of the ether (XIII, R = Me) are sufficiently close to those of the *C*-methyl derivative (XVI) to render it impossible experimentally to distinguish with certainty between the two compounds without making a direct comparison. While it was not considered likely that usneol or its synthetic monomethyl ether would undergo nuclear methylation by the potassium carbonate method (cf. Part I), nevertheless it was not inconceivable that both compounds might have given rise to the *C*-methyl derivative (XVI), in which case the foregoing orientation of usneol would be completely invalidated. On this account the synthesis of the diethyl ether was undertaken.

Treatment of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate with a molecular proportion of ethereal diazoethane gave the *monoethyl* ether (XVII), which on methylation by the potassium carbonate method furnished the mixed *ether* (XVIII, R = Me). Ethylation of the *aldehyde* (XX) yielded the *ethyl* ether; and this substance must have formula (XIX), since on condensation with acetylanisole by Robinson's procedure it gave rise to the *flavylium ferrichloride* (XXI). On oxidation the *acetate* of (XIX) gave, after the hydrolysis of the product, the *acid* (XVIII, R = H), identical with the acid obtained by the hydrolysis of (XVIII, R = Me), thus clearly establishing the orientation of the latter compound and hence that of (XVII).





For the reason already advanced in the case of methyl 6-hydroxy-4-methoxy-2 : 3 : 5-trimethylcoumarone-7-carboxylate, the product obtained by the condensation of the ester (XVII) and 3-chlorobutan-2-one must be the *coumaronecarboxylic ester* (XXII). Decarboxylation of the *acid* derived from (XXII) gave the *hydroxy-coumarone* (XXIII), which on ethylation furnished an ether identical in every respect with natural *O*-diethylusneol.

As a result of the formula (II) now established for usneol, the ketone obtained by the hydrolysis of usneol ozonide must be 2 : 4-dihydroxy-6-acetoxy- and not 4 : 6-dihydroxy-2-acetoxy-3-methylacetophenone as suggested by Schöpf and Heuck (*loc. cit.*).

Experimental.

O-Dimethyl- and *O-Diethyl-usneol.*—To a boiling solution of usneol (Schöpf and Heuck, *loc. cit.*) (1 g.) in acetone (20 c.c.) and MeI (5 c.c.), K_2CO_3 (5·0 g.) was added in 5 portions during 6 hr., and the mixture then refluxed for a further 12 hr. After the removal of the potassium salts by filtration (wash with hot acetone) the solvent was distilled and a solution of the product in Et_2O was washed with 5% aq. NaOH and then with H_2O, dried, and evaporated. Distillation of the residue in a vac. gave the *dimethyl* ether as a colourless viscous oil, b. p. 168—172°/5 mm., which solidified in a freezing mixture to a mass of needles, remelting below 10° [Found : OMe, 25·4. $C_{11}H_{10}O(OMe)_2$ requires OMe, 28·2%]. Treatment of the compound with warm alc. picric acid gave the *picrate*, which separated from warm EtOH in elongated, dark red, rectangular prisms, m. p. 87—88° (Found : N, 9·5. $C_{19}H_{19}O_{10}N_3$ requires N, 9·4%).

The *diethyl* ether was prepared from usneol (1 g.) with K_2CO_3 (3 g.), EtI (4 c.c.), and acetone (15 c.c.) in the same manner and on distillation in a vac. was obtained as a colourless solid, b. p. 164—175°/20 mm. Recryst. from dil. EtOH, it formed rhombic plates, m. p. 82—83°, readily sol. in the usual org. solvents [Found : C, 72·2; H, 7·9; OEt, 36·3. $C_{11}H_{10}O(OEt)_2$ requires C, 72·6; H, 8·1; OEt, 36·3%]. The *picrate* crystallised from EtOH, containing a little picric acid, in red needles, m. p. 82—83° (Found : N, 9·2. $C_{21}H_{23}O_{10}N_3$ requires N, 8·8%). Crystn. from EtOH in the absence of picric acid caused partial decomp. into the diethyl ether.

Both ethers dissolve in conc. H_2SO_4, forming yellow solutions which on warming become red and then purple; addition of H_2O to the cooled mixture throws down a flocculent purple ppt.

Ethyl α-3-Methoxyphenoxypropionate (IX).—A mixture of resorcinol monomethyl ether (10 g.), ethyl α-chloro-α-methylacetoacetate (Roubleff, *Annalen*, 1890, **259**, 254) (11·5 g.), NaOEt (from 1·85 g. of Na), and anhyd. EtOH (40 c.c.) was refluxed for 5 hr. The greater part of the EtOH was evaporated, excess of H_2O added, the mixture extracted several times with Et_2O, and the combined residual oil distilled in a vac., a main fraction being collected, b. p. 160—

170°/21 mm., which consisted of almost pure *ester*. Redistilled, it had b. p. 164—167°/21 mm. (Found: C, 64·2; H, 7·4. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%).

3-Chlorobutan-2-one.—For the prepn. of this ketone free from isomerides the following method was found to be superior to those described by Roubleff (*loc. cit.*), Korschun (*Ber.*, 1905, **38**, 1128), and Kling (*Compt. rend.*, 1905, **140**, 313): Ethyl α-chloro-α-methylacetoacetate (40 g.) was hydrolysed with boiling EtOH (100 c.c.) containing conc. H_2SO_4 (20 c.c.) and H_2O (10 c.c.) during 4 hr., and, after the addition of excess H_2O, the mixture was extracted several times with Et_2O. The combined ethereal extracts were mixed with H_2O (100 c.c.), the Et_2O distilled with the aid of a fractionating column, the ketone and unchanged ester separated from the residual aq. mixture and dissolved in Et_2O, and the ethereal solution dried with anhyd. Na_2SO_4. After the removal of the solvent (fractionating column) the chloro-ketone was isolated from the residue by fractional distillation, b. p. 114—115°/749·3 mm. On mixing an aq. solution of equimolecular parts of $NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$,HCl and AcONa with an alc. solution of the ketone the *semicarbazone* separated almost instantly and was immediately collected, washed with H_2O, and dried. Cryst. from AcOEt, it formed flat needles, which became red at 130° and melted at 138—139° (decomp.) (Found: Cl, 21·7. $C_5H_{10}ON_3Cl$ requires Cl, 21·7%). The crude product rapidly decomposes if kept in the reaction mixture for more than a few min. The pure substance gradually decomposes.

Methyl α-3-Methoxyphenoxyethyl Ketone (VI; R = H, R_1 = H).—(A) A mixture of the anhyd. sodium salt of resorcinol monomethyl ether (prepared by the interaction of 4 g. of the phenol and 0·6 g. of Na in 40 c.c. of dry Et_2O and subsequent removal of the solvent) and 3-chlorobutan-2-one (3 g.) was kept for 10 min. and then heated on the steam-bath for ½ hr. After the addition of H_2O the mixture was basified with aq. NaOH. The *phenoxy-ketone*, distilled in steam, isolated by means of Et_2O, and distilled in vac., was a colourless, unpleasant-smelling liquid (1·8 g.), b. p. 157—158°/24 mm. [Found: C, 68·0; H, 7·5; OMe, 15·3. $C_{10}H_{11}O_2(OMe)$ requires C, 68·1; H, 7·2; OMe, 15·9%].

(B) The phenol (5 g.) and the chloro-ketone (6 g.) were allowed to react in boiling acetone (20 c.c.) in the presence of K_2CO_3 (10 g.) during 2 hr. Addition of an excess of dil. aq. NaOH then pptd. the phenoxy-ketone (5 g.), which was isolated with Et_2O and distilled in vac.; b. p. 153°/19 mm. The *semicarbazone* separated from warm MeOH in stellate clusters of needles, m. p. 126—127° (Found: C, 57·3; H, 7·2. $C_{12}H_{17}O_3N_3$ requires C, 57·4; H, 6·8%).

6-Methoxy-2: 3-dimethylcoumarone (VII; R = H, R_1 = H).—The foregoing phenoxy-ketone (4 g.) was gradually added to conc. H_2SO_4 (10 c.c.) kept at 0° (agitate). 10 Min. later, the deep red mixture was diluted with ice-water, the H_2SO_4 neutralised with aq. NaOH, and the product distilled in steam, isolated by means of Et_2O, and distilled in vac. (twice), the *coumarone* being obtained as a colourless oil (2 g.), b. p. 145°/21 mm. (Found: C, 74·9; H, 7·2. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). The red solution in conc. H_2SO_4 becomes colourless on dilution with H_2O. Addition of H_2O to a solution of the compound in warm alc. picric acid pptd. the *picrate*, which crystallised from warm EtOH, containing a little picric acid, in red needles, m. p. 76—77° (Found: N, 10·7. $C_{17}H_{15}O_9N_3$ requires N, 10·4%).

Methyl α-3: 5-Dimethoxyphenoxyethyl Ketone.—After the vigorous reaction between the anhyd. sodium salt of phloroglucinol dimethyl ether (from 5 g. of the ether and 0·74 g. of Na) and 3-chlorobutan-2-one (4 g.) had subsided, the mixture was heated on the steam-bath for ½ hr. and then kept at room temp. for 1 hr. Addition of an excess of dil. aq. NaOH pptd. an oil, which was isolated with Et_2O and on distillation gave a main fraction, b. p. 165—180°/13 mm., consisting of almost pure *phenoxy-ketone*. The redistilled compound was a colourless oil (2·7 g.), b. p. 167°/13 mm. [Found: C, 63·9; H, 7·4; OMe, 28·4. $C_{10}H_{10}O_2(OMe)_2$ requires C, 64·3; H, 7·1; OMe, 27·7%]. The *semicarbazone* separated from warm EtOH in rhombic plates, m. p. 167—168°, sparingly sol. in hot MeOH or EtOH (Found: C, 55·6; H, 7·1. $C_{13}H_{19}O_4N_3$ requires C, 55·5; H, 6·8%).

4: 6-Dimethoxy-2: 3-dimethylcoumarone.—The preceding phenoxy-ketone (2 g.) was carefully added with stirring to conc. H_2SO_4 (5 c.c.) at 0°. After 4 min. the dark red solution on dilution with H_2O (100 c.c.) became colourless and deposited the cryst. *coumarone* in the course of 2 hr. Recryst. from dil. EtOH or dil. AcOH, it formed colourless plates (1·5 g.), m. p. 55°, easily sol. in the usual org. solvents (Found: C, 69·9; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). With conc. H_2SO_4 the substance forms a deep orange solution, which darkens on heating and finally becomes brownish-purple; addition of H_2O to the cooled acid mixture then forms a blue-green solution, which deposits a blue-green flocculent ppt. The *picrate* separated from warm EtOH in dark red needles, m. p. 129—130° (Found: N, 9·9. $C_{18}H_{17}O_{10}N_3$ requires N, 9·7%).

Methyl α-3 : 5-Dimethoxy-2-methylphenoxyethyl Ketone (VI; R = Me, R_1 = OMe).—A mixture of methylphloroglucinol α-dimethyl ether (Part I, *loc. cit.*) (6 g.), 3-chlorobutan-2-one (7·6 g.), acetone (25 c.c.), and K_2CO_3 (10 g.) was refluxed for 2·5 hr. After the addition of an excess of dil. aq. NaOH to the reaction mixture, the *ketone* was isolated with Et_2O, distilled in a high vac., and obtained as a colourless oil (5 g.), b. p. 151—152°/1 mm. [Found : OMe, 25·9. $C_{11}H_{12}O_2(OMe)_2$ requires OMe, 26·1%]. The *semicarbazone* crystallised from EtOH in needles, m. p. 172—173° (Found : C, 56·7; H, 7·4. $C_{14}H_{21}O_4N_3$ requires C, 57·0; H, 7·1%).

4 : 6-Dimethoxy-2 : 3 : 7-trimethylcoumarone (VII; R = Me, R_1 = OMe).—The ring closure of the foregoing ketone (3 g.) was effected with cold conc. H_2SO_4 (15 c.c.) during 3 min. at 0°, and, on isolation, the *coumarone* separated from warm dil. EtOH in colourless plates (2·3 g.), m. p. 68°, readily sol. in the usual org. solvents [Found : C, 70·5; H, 7·2; OMe, 28·2; *M* (Rast), 222, 232. $C_{11}H_{10}O(OMe)_2$ requires C, 70·9; H, 7·3; OMe, 28·2%; *M*, 220]. It dissolved in conc. H_2SO_4, forming an orange solution which on warming changed to red and then to brilliant purple; addition of H_2O formed a green ppt. The *picrate* crystallised from hot EtOH in green needles, m. p. 110—111° (Found : C, 57·6; H, 4·8; N, 6·1, 6·5. $2C_{13}H_{16}O_3,C_6H_3O_7N_3$ requires C, 57·4; H, 5·2; N, 6·3%. $C_{13}H_{16}O_3,C_6H_3O_7N_3$ requires C, 51·0; H, 4·2; N, 9·4%).

Methyl 6-Hydroxy-4-methoxy-2 : 3 : 5-trimethylcoumarone-7-carboxylate (XII).—A solution of methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (Herzig and Wenzel, *Monatsh.*, 1902, **23**, 81) (5 g.) and 3-chlorobutan-2-one (6 g.) in acetone (50 c.c.) was refluxed with K_2CO_3 (8 g.) for 12 hr., the mixture diluted with H_2O (150 c.c.), the acetone and unchanged ketone removed in a vac., and the residual mixture extracted several times with Et_2O. Evaporation of the combined, dried ethereal extracts left a residue which, on crystn. from dil. EtOH, gave the *ester* in clusters of colourless slender needles (3 g.), m. p. 123—124° [Found : C, 63·2; H, 6·4; OMe, 23·6. $C_{12}H_{10}O_3(OMe)_2$ requires C, 63·6; H, 6·1; OMe, 23·5%]. With alc. $FeCl_3$ the compound gives a dark green coloration. It dissolves in conc. H_2SO_4, forming a pale yellow solution which on warming becomes red and then purple; addition of H_2O then gives a purple ppt.

A solution of the ester (1 g.) in 5% aq. KOH (20 c.c.) and EtOH (15 c.c.) was heated on the water-bath for 1 hr., cooled, diluted with H_2O, and acidified with aq. HCl. *6-Hydroxy-4-methoxy-2 : 3 : 5-trimethylcoumarone-7-carboxylic acid* thus obtained separated from warm EtOH in colourless needles, m. p. 214—215° (decomp.) (Found : C, 62·8; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). The $FeCl_3$ reaction is green in EtOH and blue-green in aq. EtOH. The behaviour of the acid with H_2SO_4 is identical with that of the ester.

6-Hydroxy-4-methoxy-2 : 3 : 5-trimethylcoumarone (XIII, R = H).—The foregoing acid (1·4 g.) was decarboxylated by being kept at 220° for 3—4 min., and the resulting *coumarone* distilled in a high vac., b. p. 120—130°/1 mm., and then crystallised from dil. EtOH; it formed colourless plates (0·8 g.), m. p. 133° [Found : C, 69·8; H, 6·8; OMe, 15·6. $C_{11}H_{11}O_2(OMe)$ requires C, 69·9; H, 6·8; OMe, 15·1%]. The compound is sol. in aq. NaOH, but does not give a $FeCl_3$ reaction.

4 : 6-Dimethoxy-2 : 3 : 6-trimethylcoumarone (*O-Dimethylusneol*) (XIII, R = Me).—The monomethyl ether (1 g.) was methylated with MeI (3 c.c.) and K_2CO_3 (2·5 g.) in boiling acetone (10 c.c.) during 3 hr. and an ethereal solution of the crude product was washed with 5% aq. NaOH and then with H_2O, dried, and evaporated. Distillation of the residue in a high vac. gave *O*-dimethylusneol as a colourless oil, b. p. 140—145°/1 mm. (Found : OMe, 27·1%). The sulphuric acid reaction was identical with that given by the natural ether. Cryst. from warm EtOH, the picrate formed dark red, rectangular prisms, m. p. 87—88°, and was identical in every respect with a specimen prepared from the natural compound (Found : C, 50·9; H, 4·5; N, 9·7. Calc. for $C_{19}H_{19}O_{10}N_3$: C, 50·8; H, 4·2; N, 9·4%).

Methyl 2 : 6-Dihydroxy-4-ethoxy-3-methylbenzoate (XVII).—Methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (2·5 g.) was dissolved in Et_2O (25 c.c.) and treated with an ethereal solution (75 c.c.) of diazoethane (from 3·5 c.c. of nitroso-*N*-ethylurethane). 12 Hr. later, the solvent was distilled and, on crystn. from MeOH, the residual *ester* formed short thick prisms (1·5 g.), m. p. 108—109° [Found : C, 58·0; H, 6·4; OAlk., 13·9. $C_8H_6O_3(OMe)(OEt)$ requires C, 58·4; H, 6·2; OAlk., 14·2%]. This compound is readily sol. in EtOH or acetone and with alc. $FeCl_3$ gives a dark green coloration which changes to brownish-green on dilution with H_2O.

Methylation of Methyl 2 : 6-Dihydroxy-4-ethoxy-3-methylbenzoate.—Methylation of this ester (1 g.) with MeI (2 c.c.) and K_2CO_3 (3 g.) in boiling acetone (10 c.c.) during 3 hr. gave a mixture of its mono- and di-methyl ethers, which were separated by fractional crystn. from aq. MeOH. The less sol. compound, *methyl 2-hydroxy-6-methoxy-4-ethoxy-3-methylbenzoate* (XVIII), separated from 80% MeOH in clusters of needles (0·5 g.), m. p. 134° [Found : C, 60·1; H, 6·7; OAlk.,

19·7. $C_8H_5O_2(OEt)(OMe)_2$ requires C, 60·0; H, 6·7; OAlk., 20·0%]. With alc. $FeCl_3$ it gives a greenish-brown coloration.

Cryst. from dil. MeOH, the second product, *methyl* 2 : 6-*dimethoxy*-4-*ethoxy*-3-*methylbenzoate*, formed rectangular plates, m. p. 93° [Found : C, 61·3; H, 7·1; OAlk., 24·8. $C_8H_4O(OEt)(OMe)_3$ requires C, 61·4; H, 7·1; OAlk., 25·2%]. This compound is much more sol. in all org. solvents than the previous hydroxy-ester. It is insol. in aq. NaOH, and does not give a $FeCl_3$ reaction.

2 : 4-*Dihydroxy*-6-*methoxy*-3-*methylbenzaldehyde* (XX).—An ethereal solution of methylphloroglucinol α-methyl ether (Part I, *loc. cit.*) (4 g.) containing HCN (4 c.c.) and $Zn(CN)_2$ (1·6 g.) was saturated with HCl and 4 hr. later the aldimine double compound was collected, washed with Et_2O, and hydrolysed with H_2O (100 c.c.) on the steam-bath during 20 min. The resulting *aldehyde* separated from EtOH in golden-yellow needles (3·5 g.), m. p. 243—244° (slight decomp.) (Found : C, 59·5; H, 5·7. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). In EtOH the $FeCl_3$ reaction is purple.

2-*Hydroxy*-6-*methoxy*-4-*ethoxy*-3-*methylbenzaldehyde* (XIX).—Ethylation of the foregoing aldehyde (2·5 g.) was effected with EtI (5 c.c.) and K_2CO_3 (6 g.) in boiling acetone (25 c.c.) during 5 hr. and on isolation the *ethyl* ether crystallised from warm EtOH in colourless needles (1·6 g.), m. p. 126—127° [Found : C, 62·5; H, 6·9; OAlk., 14·1. $C_8H_6O_2(OEt)(OMe)$ requires C, 62·9; H, 6·7; OAlk., 15·2%]. The compound is readily sol. in warm MeOH or EtOH and in cold AcOEt and with alc. $FeCl_3$ gives a purple-brown coloration. Acetylation with Ac_2O and pyridine at 100° for 3 hr. furnished the *acetate*, which separated from dil. EtOH in needles or plates, m. p. 116—117° (Found : C, 61·8; H, 6·7. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

A solution of the aldehyde (0·35 g.) and acetylanisole (0·6 g.) in dry AcOEt (10 c.c.) was saturated with HCl and 2 days later 5 : 4′-dimethoxy-7-ethoxy-8-methylflavylium chloride was pptd. with Et_2O and converted into the *ferrichloride* (XXI) in the usual manner. This derivative separated from AcOH in clusters of red needles, m. p. 169—170° (Found : C, 45·8; H, 4·1. $C_{20}H_{21}O_4Cl_4Fe$ requires C, 45·9; H, 4·0%).

2-*Hydroxy*-6-*methoxy*-4-*ethoxy*-3-*methylbenzoic Acid*.—(A) 2-Acetoxy-6-methoxy-4-ethoxy-3-methylbenzaldehyde (1·2 g.) in warm acetone (75 c.c. at 50—55°) was oxidised by the gradual addition of a solution of $KMnO_4$ (1·5 g.) in H_2O (35 c.c. at 50—55°) containing $MgSO_4$ (1·5 g.). ½ Hr. later, the solution was cleared with SO_2, the acetone allowed to evaporate, the aq. liquor extracted with $CHCl_3$, and the acetate of the acid (0·6 g.) isolated from the extract by means of aq. $NaHCO_3$ and hydrolysed with 10% aq. KOH (10 c.c.) at room temp. for 2 hr. On isolation, the *product* crystallised from MeOH in clusters of needles, m. p. 167—168° (Found : C, 58·1; H, 6·6. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). It is readily sol. in hot EtOH or AcOEt, and insol. in warm light petroleum, and with alc. $FeCl_3$ gives a brown coloration. This acid (0·3 g.) was decarboxylated by being heated at 200° in the presence of a trace of Cu powder for 10 min., and the product extracted with warm light petroleum (50—60°). On cooling, the extract deposited 4-*methoxy*-6-*ethoxy*-o-*cresol* in needles, m. p. 79—80° after sublimation in a high vac. [Found : C, 65·9; H, 7·8; OAlk., 17·5. $C_7H_6O(OMe)(OEt)$ requires C, 65·9; H, 7·7; OAlk., 17·5%]. This phenol does not give a $FeCl_3$ reaction.

(B) Hydrolysis of the methyl ester (0·2 g.) with 20% aq. KOH (2·5 c.c.) and EtOH (2·5 c.c.) on the water-bath for 1 hr. gave the acid, which separated from warm MeOH in clusters of needles, m. p. and mixed m. p. 167—168°, having a $FeCl_3$ reaction and solubilities identical with a specimen prepared by method (A) [Found : OAlk., 14·1. Calc. for $C_8H_6O_3(OMe)(OEt)$: OAlk., 14·2%]. Decarboxylated, it gave 4-methoxy-6-ethoxy-*o*-cresol, m. p. and mixed m. p. 79—80°.

Methyl 6-*Hydroxy*-4-*ethoxy*-2 : 3 : 5-*trimethylcoumarone*-7-*carboxylate* (XXII).—Methyl 2 : 6-dihydroxy-4-ethoxy-3-methylbenzoate (2·5 g.) was allowed to react with 3-chlorobutan-2-one (2·5 g.) in the presence of K_2CO_3 (4 g.) in boiling acetone (25 c.c.) during 3 hr. and, after the addition of H_2O, the mixture was extracted several times with Et_2O. Evaporation of the dried extracts left an oil, which was dissolved in warm dil. EtOH and, on cooling, the *ester* separated in colourless needles, m. p. 100—101° (Found : C, 64·4; H, 6·6. $C_{15}H_{18}O_5$ requires C, 64·8; H, 6·5%). With alc. $FeCl_3$ the compound gives a green coloration.

Hydrolysis of this ester (5 g.) with 50% aq. EtOH (100 c.c.) containing KOH (5 g.) on the steam-bath during 1 hr. gave 6-*hydroxy*-4-*ethoxy*-2 : 3 : 5-*trimethylcoumarone*-7-*carboxylic acid*, which separated from dil. MeOH in thick needles, m. p. 191—192° (decomp.) (Found : C, 63·8; H, 6·5. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). The $FeCl_3$ reaction is identical with that of the ester.

4 : 6-*Diethoxy*-2 : 3 : 5-*trimethylcoumarone* (O-*Diethylusneol*).—The aforementioned acid (1·5 g.), mixed with a little Cu, was kept at 200—220° for 5 min., and the residue distilled in a

high vac., b. p. 135—138°/1 mm., and dissolved in warm dil. EtOH. On cooling, the solution deposited *6-hydroxy-4-ethoxy-2 : 3 : 5-trimethylcoumarone* (XXIII) in plates, m. p. 123—124° after recrystn. from dil. AcOH (Found : C, 70·5; H, 7·6. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). This compound is readily sol. in the usual anhyd. solvents and in aq. NaOH, but does not give a $FeCl_3$ reaction.

A solution of the monoethyl ether (0·5 g.) in acetone (10 c.c.) was refluxed with EtI (3 c.c.) and K_2CO_3 (4·5 g.) for 5 hr., diluted with more acetone, filtered, and evaporated. An ethereal extract of the residue was washed with aq. NaOH and then with H_2O, dried, and distilled, leaving usneol diethyl ether, which on crystn. from dil. EtOH formed colourless plates, m. p. 82—83°, identical in every respect with a natural specimen (Found : C, 72·3; H, 8·0%). The picrate separated from EtOH, containing a little picric acid, in red needles, m. p. 84—85°, undepressed by the addition of the natural derivative.

The Condensation of Methyl 2 : 4 : 6-Trihydroxy-3-methylbenzoate and 3-Chlorobutan-2-one.—The chloro-ketone (1·75 g.) was added in 3 portions to a boiling solution of the ester (2·5 g.) in acetone (15 c.c.) containing K_2CO_3 (3·7 g.) in the course of 2 hr. The solid (A) obtained by the addition of an excess of H_2O to the reaction mixture separated from EtOH in clusters of slender needles, m. p. 130—131° [Found : C, 62·3; H, 5·5; OMe, 12·5; *M* (Rast), 266, 272. $C_{12}H_{11}O_4(OMe)$ requires C, 62·4; H, 5·6; OMe, 12·4%; *M*, 250]. From its method of formation in a manner analogous to the partial alkylation of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate, this product (A) is almost certainly *methyl 4 : 6-dihydroxy-2 : 3 : 7-trimethylcoumarone-5-carboxylate*. With conc. H_2SO_4 it forms an orange solution which on warming becomes red and finally greenish-purple; dilution with H_2O then throws down a blue-green flocculent ppt. Addition of a drop of aq. $FeCl_3$ to 1 c.c. of an alc. solution of the coumarone gives a green coloration; with more $FeCl_3$ a brown colour is produced. On being warmed with alc. picric acid containing a drop of H_2SO_4, the compound formed the *picrate*, which separated from warm EtOH containing picric acid and a drop of H_2SO_4; m. p. 104—105° (Found : N, 8·2. $C_{19}H_{17}O_{12}N_3$ requires N, 8·7%). The presence of H_2SO_4 is essential for the formation and purification of this unstable derivative. On hydrolysis with alkali, methyl 4 : 6-dihydroxy-2 : 3 : 7-trimethylcoumarone-5-carboxylate completely decomposed.

In one expt. the chloro-ketone (3·5 g.) was added in one portion to a boiling solution of the ester (5 g.) in acetone (35 c.c.) containing K_2CO_3 (7·4 g.) and a *compound* (B) isomeric with (A) was obtained which crystallised from EtOH in clusters of short thick prisms, m. p. 98—99° (Found : C, 62·4; H, 6·0; OMe, 11·9%). This substance is unaffected by ethereal diazomethane and gives a green coloration with alc. $FeCl_3$. Mixed with a specimen of (A), it melted at 82—83°. The reaction with H_2SO_4 is similar to that given by (A). The *picrate* of (B) was prepared and purified by the method adopted in the case of (A), m. p. 84—85° (Found : N, 7·9%). A mixture of the two picrates had m. p. 72—73°.

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