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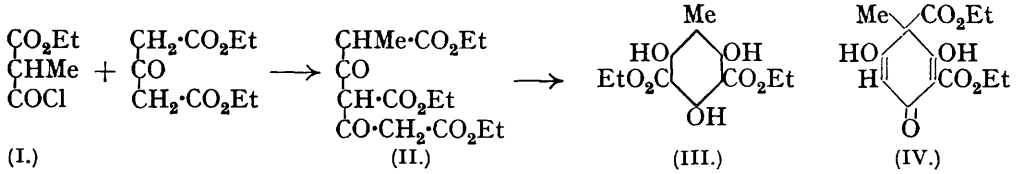
114. *Usnic Acid. Part I. Derivatives of Methylphloroglucinol.*

By Frank H. Curd and Alexander Robertson.

In a comprehensive analytical investigation of usnic acid, Schöpf and Heuck (*Annalen*, 1927, **459**, 233) have shown that this important lichen product and its derivatives contain a methylphloroglucinol nucleus. The experiments described in the present communication were carried out as an essential preliminary step in a synthetical investigation of this substance and its main degradation products and had in view three main objectives: (1) to explore methods for the preparation of methylphloroglucinol in quantity which avoid the use of trinitrotoluene, (2) to orient the methyl ethers of this phenol, and (3) to study the alkylation of its derivatives by the potassium carbonate–acetone method.

(A) *Synthesis of Methylphloroglucinol.*—This phenol may be considered to be formed by the interaction of methylmalonic acid and acetone with the elimination of two molecules of water, and in consequence we were led to attempt the preparation of the compound from two such simple and readily accessible substances. Unfortunately the condensation of ethyl methylmalonate and ethyl acetonedicarboxylate (used in place of the less reactive acetone) in the presence of sodium ethoxide resulted in only a small yield of the *ester* (III). A better yield was obtained, however, when this synthesis was carried out in two stages: The *dione* (II) obtained by the interaction of the acid chloride (I) and ethyl sodioacetonedicarboxylate gave on ring closure with sodium ethoxide an ester which on hydrolysis and



(I.) (II.) (III.) (IV.)

(V.) $CH_3{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH_3$

simultaneous decarboxylation of the resulting acid furnished methylphloroglucinol. This ester we consider to be represented by formula (III), because on general grounds the ring closure of (II) would be expected to proceed in this direction. The structure (III) is supported by the fact that on acetylation in the ordinary manner the compound yields a derivative

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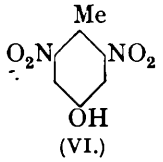
which appears to be a *triacetate*. Nevertheless, in the absence of more direct experimental evidence the alternative structure (IV), which would also be consistent with the formation of methylphloroglucinol by hydrolysis, is not entirely excluded.

On attempting to use ethyl acetoacetate in place of ethyl acetonedicarboxylate it was found that, though the condensation of (I) and ethyl sodioacetoacetate readily yielded ethyl hexane-3 : 5-dione-2 : 4-dicarboxylate (V), the latter dione could not be converted into ethyl methylphloroglucinolcarboxylate.

(B) *Ethers of Methylphloroglucinol.*—The two isomeric monomethyl ethers α-(IX) and β-(X) have been prepared from methylphloroglucinol by Weidel (*Monatsh.*, 1898, **19**, 223) and by Herzig and Wenzel (*ibid.*, 1902, **23**, 112) respectively. The proofs of the orientation of these ethers as well as that of the α-dimethyl ether (XIV) (Weidel, *loc. cit.*) depend on somewhat extensive and involved evidence and cannot be considered to be entirely rigid (cf. Herzig and Eisenstein, *Monatsh.*, 1902, **23**, 563; Herzig and Wenzel, *loc. cit.*; Konya, *ibid.*, 1900, **21**, 422; Pollak and Solomonica, *ibid.*, 1901, **22**, 1002; Weidel and Pollak, *ibid.*, 1897, **18**, 347; 1900, **21**, 15; Karrer, *Helv. Chim. Acta*, 1919, **2**, 466; 1920, **3**, 392).

The preparation of the α-ether (IX) from 2 : 6-dinitro-*p*-toluidine through the stages (VI), (VII), and (VIII) now serves to establish conclusively the orientation of this compound. Hence the isomeric β-monomethyl ether (Herzig and Wenzel, *loc. cit.*) has formula (X).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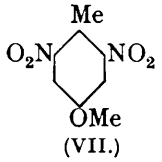
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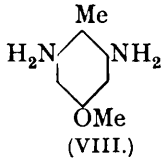
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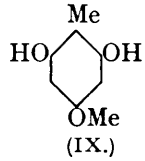
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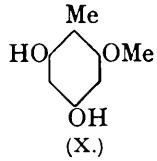
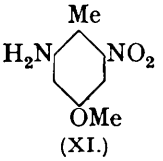

(X.)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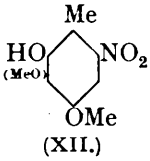
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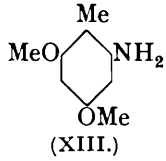
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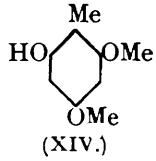
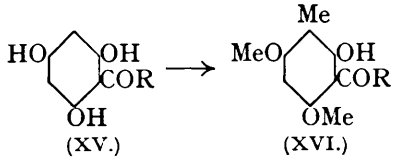
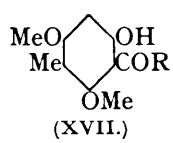

(XIV.)

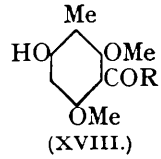
Similarly the structure previously assigned to the α-dimethyl ether (XIV) is confirmed by its production from (VII) through the stages (XI), (XII), and (XIII).

2 : 6-Dinitro-*p*-toluidine has been found to be a convenient substitute for trinitrotoluene as a starting material in the preparation of methylphloroglucinol in quantity.

(C) *Conversion of Phloroglucinol into Derivatives of Methylphloroglucinol.*—In the course of unsuccessful attempts to prepare 4-*O*-methylphloracetophenone (required for an independent investigation) by the partial alkylation of phloracetophenone, we observed that, when the latter ketone was treated with methyl iodide (1 mol. or excess) and potassium carbonate in boiling acetone, nuclear alkylation occurred and a dimethyl ether of a *C*-methylphloracetophenone was formed. Since this appeared to be a feasible method for converting phloroglucinol into derivatives of *C*-methylphloroglucinol, we have examined the reaction in detail and have found that compounds of the type (XV, where R = H, Me, or OMe) are readily converted into derivatives of the type (XVI). Only methyl phloroglucinolcarboxylate gave rise to its trimethyl ether in addition to (XVI, R = OMe).


(XV.) (XVI.)


(XVII.)


(XVIII.)

The orientations of the compounds (XVI, where R = H, Me, or OMe) have been established as follows: in the case of the *ketone* (XVI, R = Me), since the same compound

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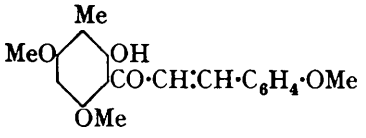
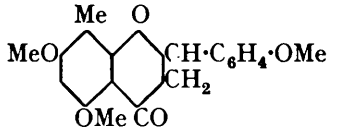
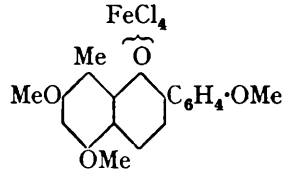
was formed by the condensation of methylphloroglucinol α-dimethyl ether and acetonitrile according to the procedure of Hoesch, the hydroxyl group must be in the *o*-position to the *C*-methyl group and therefore of the three possible formulæ, types (XVI), (XVII), and (XVIII), for this compound formula (XVII, R = Me) is definitely excluded. The ketone gives an intense ferric chloride reaction, indicating that the hydroxyl group is also in the *o*-position to the carbonyl group and thus excluding structure (XVIII). In any case a compound of the latter type, if formed in the reaction mixture, would be expected to undergo further alkylation and yield a trimethyl ether. That the hydroxyl group is in the *o*-position to the carbonyl group is confirmed by the fact that on condensation with anisaldehyde the compound gave rise to the *chalkone* (XIX), which on ring closure yielded the *flavanone* (XX). Hence the ketone must have formula (XVI, R = Me).



(XIX.)



(XX.)



(XXI.)

Similarly the *aldehyde* derived from phloroglucinaldehyde is represented by formula (XVI, R = H). In this case the formation of the same compound from methylphloroglucinol α-dimethyl ether by Gattermann's method and its condensation with acetylanisole yielding 5 : 7 : 4′-*trimethoxy*-8-*methylflavylium ferrichloride* (XXI) by Robinson's procedure serve to establish the relative positions of the methyl, hydroxyl, and aldehyde groups.

The structure of the *ester* (XVI, R = OMe) follows from the fact that on hydrolysis it furnished an *acid*, which on decarboxylation gave rise to methylphloroglucinol α-dimethyl ether and was identical with the acid formed by the oxidation of the *acetate* of the aldehyde (XVI, R = H) and subsequent hydrolysis of the product.

The alkylation of phloroglucinol and its derivatives with alkyl halides and alkalis or alkoxides has been the subject of numerous investigations (Herzig and his collaborators, *Monatsh.*, 1888, **9**, 217, 882; 1889, **10**, 735; 1893, **14**, 376; 1900, **21**, 852, 866; 1901, **22**, 215; 1902, **23**, 81; Margulies, *ibid.*, 1888, **9**, 1045; 1889, **10**, 459; Pollak, *ibid.*, 1897, **18**, 745; Will, *Ber.*, 1884, **17**, 2107). In general the results previously described show that on etherification by such methods phloroglucinol and its derivatives with the exception of the dialkyl ethers, which yield only the corresponding trialkyl ethers, indicating a stable enolic form, tend to undergo nuclear alkylation. Moreover, under these conditions nuclear alkylation is difficult to control and the formation of *C*-polyalkyl derivatives is prone to occur. By means of the methyl iodide–potassium carbonate method, however, only one *C*-methyl group is introduced. This observation is in agreement with the behaviour of methylphloroglucinaldehyde, *methylphloracetophenone*, and methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate, which even on prolonged treatment with the methylating mixture do not undergo further nuclear alkylation, but yield ethers of the type (XVI); in addition the ester also gives rise to its O-*trimethyl* ether.

Experimental.

Methylmalonic Acid Monoethyl Ester.—This ester was prepared by the following modification of Marguery's method (*Bull. Soc. chim.*, 1905, **33**, 541): KOH (16·1 g.), dissolved in EtOH (250 c.c.), was gradually added to a solution of ethyl methylmalonate (50 g.) in EtOH (200 c.c.), and the mixture warmed on the steam-bath until it became neutral. After the separation of a small amount of potassium methylmalonate the greater part of the EtOH was evaporated, the potassium salt of the half ester pptd. with Et_2O, collected, and decomposed with ice-cold aq. HCl, and the acid-ester isolated with Et_2O and distilled in a vac., b. p. 144—145°/25 mm. [Found: CO_2H, 30·1. Calc. for $C_5H_8O_2(CO_2H)$: CO_2H, 30·8%]. Prepared by Marguery's method, methylmalonyl chloride monoethyl ester had b. p. 80—81°/21 mm.

Ethyl Hexane-2 : 4-dione-1 : 3 : 5-tricarboxylate (II).—The aforementioned acid chloride

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(4 g.) was added to a solution of ethyl sodioacetonedicarboxylate (from 5 g. of ester and 0·6 g. of powdered Na) in Et_2O (50 c.c.) and after the vigorous reaction had ceased the mixture was refluxed for 1 hr. Sufficient H_2O was added to dissolve the NaCl, the ethereal layer was separated, dried, and evaporated, and the residue was distilled in a high vac. Redistillation of the main fraction, b. p. 135—180°/1 mm., finally gave the *ester* (3 g.) as a colourless oil, b. p. 165—168°/1 mm. (Found: C, 54·2; H, 6·5. $C_{15}H_{22}O_8$ requires C, 54·5; H, 6·7%).

Ethyl Methylphloroglucinoldicarboxylate (III).—(A) When the vigorous reaction between the foregoing ester (3 g.) and NaOEt (from 0·3 g. of Na) in Et_2O (30 c.c.) had subsided, the solvent was distilled and the residue kept at 100° for 1 hr. A solution of the product in H_2O (100 c.c.), on being saturated with CO_2, gradually deposited *ethyl methylphloroglucinoldicarboxylate*, which crystallised from EtOH in clusters of colourless flat prisms (1 g.), m. p. 92—93°, and gave a red-brown coloration with alc. $FeCl_3$ [Found: C, 54·9; H, 5·8; OEt, 31·3. $C_9H_6O_5(OEt)_2$ requires C, 54·9; H, 5·6; OEt, 31·7%]. Acidification of the aq. liquor gave a small amount (about 0·1 g.) of an oily acid which was not investigated. Treatment of the ester (0·2 g.) with Ac_2O (4 c.c.) and AcONa (0·4 g.) at 100° for 3 hr. gave the *triacetate*, which crystallised from dil. EtOH or C_6H_6–ligroin in rhombic prisms, m. p. 99°, and did not give a $FeCl_3$ reaction [Found: C, 55·3; H, 5·5; OEt, 21·4. $C_{15}H_{12}O_8(OEt)_2$ requires C, 55·6; H, 5·4; OEt, 22·0%. Di-acetate, $C_{13}H_{10}O_7(OEt)_2$ requires C, 55·4; H, 5·4; OEt, 24·5%].

(B) An intimate mixture of ethyl acetonedicarboxylate (10 g.), ethyl methylmalonate (8·6 g.), and NaOEt (from 2·25 g. of Na) was heated (oil-bath) at 160° for 1 hr. A solution of the product in H_2O (150 c.c.) was extracted with Et_2O to remove unchanged material and saturated with CO_2, and in the course of several hr. a small amount of cryst. ethyl methylphloroglucinoldicarboxylate separated, m. p. and mixed m. p. 92—93° after recrystn. from EtOH (Found: C, 54·9; H, 5·6%).

Acidification of the aq. liquor with mineral acid pptd. a solid, which crystallised from C_6H_6 and then from AcOEt in colourless microscopic needles, m. p. 182—183° (decomp.) (Found: C, 54·4; H, 4·1; OEt, 16·9. Calc. for $C_{12}H_{10}O_7$: C, 54·1; H, 3·8; OEt, 16·9%). This substance, which gave a purple-black $FeCl_3$ reaction, appears to be identical with the compound obtained by Jerdan (J., 1897, **71**, 1111) by the condensation of 2 mols. of ethyl acetonedicarboxylate with the aid of Na in C_6H_6 and shown by Sonn (*Ber.*, 1917, **50**, 138) to be ethyl 4 : 5 : 7-trihydroxycoumarin-6 (or 8)-carboxylate.

Attempts to condense ethyl methylmalonate and ethyl acetonedicarboxylate with Na gave unsatisfactory results.

Methylphloroglucinol.—Ethyl methylphloroglucinoldicarboxylate (0·5 g.) was hydrolysed with 5% aq. KOH (10 c.c.) in an atm. of H on the steam-bath for 3 hr. After acidification methylphloroglucinol was isolated with Et_2O and purified by sublimation in a high vac. and then by crystn. from AcOEt–light petroleum (b. p. 60—80°) forming clusters of colourless needles, m. p. 210—212°, identical with an authentic specimen (Found: C, 60·4; H, 6·1. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·7%). The triacetate separated from light petroleum in needles, m. p. and mixed m. p. 58°.

2 : 6-*Dinitro*-p-*cresol* (VI).—A solution of 2 : 6-dinitro-*p*-toluidine (15 g.) in conc. H_2SO_4 (110 c.c.) and H_2O (110 c.c.) was diazotised at below 0° with $NaNO_2$ (8 g.) dissolved in H_2O (15 c.c.). After ½ hr. the slight excess of HNO_2 was destroyed with urea, and the diazonium solution gradually added to a boiling solution of $CuSO_4$ (350 g.) in H_2O (350 c.c.). Isolated by means of Et_2O, the *cresol* was obtained as a reddish-coloured solid, which crystallised from hot toluene in pale yellow needles (8 g.), m. p. 154—155° (Found: N, 14·6. $C_7H_6O_5N_2$ requires N, 14·1%). With aq. NaOH or $NaHCO_3$ this compound forms an orange-coloured solution.

Methylation of the cresol with Me_2SO_4 and aq. KOH gave rise to the *methyl* ether (VII), which crystallised from 75% AcOH in long straw-coloured needles, m. p. 103—104° [Found: OMe, 14·9. $C_7H_5O_4N_2(OMe)$ requires OMe, 14·6%].

Methylphloroglucinol α-Methyl Ether (IX).—Granulated Sn (35 g.) was added in portions to a mixture of the foregoing cresol ether (10 g.) and conc. HCl (60 c.c.) maintained at 70—80° for 2 hr. The filtered solution was evaporated in a vac., and the residue heated at 100° to remove the last traces of HCl and then dissolved in H_2O (600 c.c. at 70°). After the removal of the Sn by means of H_2S the liquor was evaporated in an atmosphere of CO_2 and a solution of the residue in air-free H_2O (800 c.c.) was refluxed in an atm. of CO_2 for 30 hr. The greater part of the H_2O was then distilled in a vac., the residual liquor (100 c.c.) extracted several times with Et_2O, and the combined extracts dried and evaporated. A warm xylene extract of the crude product, on cooling, deposited methylphloroglucinol α-methyl ether in needles, m. p. 124° after recrystn. The residue insol. in hot xylene consisted of almost pure methylphloroglucinol,

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which probably resulted from a small amount of 2 : 6-diamino-*p*-cresol formed by demethylation of the methyl ether during the concn. of the acid solution of the tin double salt.

2 : 6-Dinitro-*p*-toluidine (7 g.) was reduced with Sn (23 g.) and HCl aq. (47 c.c.) to 2 : 4 : 6-triaminotoluene, and the latter converted into methylphloroglucinol by Weidel's method (*Monatsh.*, 1898, **19**, 223). A specimen of the monomethyl ether obtained directly from methylphloroglucinol was identical with the methyl ether of methylphloroglucinol described above, m. p. and mixed m. p. 124°.

In the etherification of methylphloroglucinol with MeOH and HCl it was noted that the success of the expt. depended entirely on the following conditions, the saturation of a solution of methylphloroglucinol in MeOH with dry HCl without cooling, and then subsequently cooling to induce crystn. of the methyl ether–HCl double compound. If, on the other hand, the mixture was cooled to below 0° during the passage of HCl as indicated by Weidel (*loc. cit.*), a cryst. double compound separated almost immediately which on decomp., however, re-formed the original phenol. It was also found that on treatment with aq. $NaHCO_3$ the cryst. α-methyl ether–HCl double compound gave conveniently a theo. yield of the α-ether (isolated with Et_2O).

6-*Nitro*-4-*methoxy*-o-*toluidine* (XI).—(A) A slow stream of H_2S was led into a mixture of 2 : 6-dinitro-4-methoxytoluene (5 g.), aq. NH_3 (3 c.c., *d* 0·880), and EtOH (20 c.c.) for 2 hr.; the mixture was occasionally heated on the steam-bath. After the addition of an excess of H_2O the ppt. of the crude base and S was collected, washed, and extracted with hot 10% HCl aq. On basification the extract deposited the *amine* (1·8 g.), which separated from warm H_2O in pale yellow needles, m. p. 82—83°, readily sol. in EtOH or AcOEt and sparingly sol. in light petroleum (Found: C, 52·5; H, 6·0. $C_8H_{10}O_3N_2$ requires C, 52·8; H, 5·6%). The *acetyl* derivative crystallised from EtOH in colourless needles, m. p. 171—172° (Found: C, 53·4; H, 6·0. $C_{10}H_{12}O_4N_2$ requires C, 53·7; H, 5·4%).

(B) A mixture of the dinitro-compound (5 g.), acetone (25 c.c.), and aq. Na_2S_2 (20·5 c.c. of a solution prepared from 30 g. of $Na_2S,9H_2O$, 4 g. of S, and 110 c.c. of H_2O) was refluxed for 5 hr., cooled, and diluted with H_2O. The amine (1·7 g.) was isolated with dil. HCl aq. from the ppt. thus obtained, m. p. 81—82° after purification. The residue insol. in HCl aq. consisted of the unchanged dinitro-compound (0·8 g.).

(C) The following was found to be the most successful method and was suitable for the prepn. of the base in quantity: A solution of $SnCl_2,2H_2O$ (15·85 g.) in EtOH (100 c.c.) saturated with HCl was carefully added to a suspension of 2 : 6-dinitro-4-methoxytoluene (5 g.) in EtOH (25 c.c.), and the reaction completed by boiling on the steam-bath for ½ hr. Next day the greater part of the EtOH was removed in a vac. and the amine (2·3 g.) and unchanged dinitro-compound (1 g.) were pptd. with H_2O and separated in the usual manner.

6-*Nitro*-4-*methoxy*-o-*cresol* (XII).—The foregoing nitroamine (5 g.) was dissolved in H_2SO_4 (75 c.c.) and H_2O (15 c.c.) and diazotised at below 0° with $NaNO_2$ (1·8 g.). 2 Hr. later the slight excess of HNO_2 was destroyed with urea, and the diazonium solution gradually added to boiling 20% H_2SO_4 (200 c.c.). On cooling, the *cresol* (4·6 g.) solidified and was collected and purified by crystn. from light petroleum (b. p. 60—80°), forming orange-yellow needles (2·5 g.), m. p. 126° (Found: N, 7·7. $C_8H_9O_4N$ requires N, 7·7%). This compound is extremely sol. in the usual org. solvents except light petroleum. Methylation of the phenol with 15% aq. KOH and Me_2SO_4 furnished 6-*nitro*-2 : 4-*dimethoxytoluene*, which separated from dil. aq. MeOH in plates, m. p. 93° [Found: OMe, 31·8. $C_7H_5O_2N(OMe)_2$ requires OMe, 31·5%].

4 : 6-*Dimethoxy*-o-*toluidine* (XIII).—6-Nitro-2 : 4-dimethoxytoluene (17·5 g.) was reduced with a boiling solution of $Na_2S,9H_2O$ (60 g.) in H_2O (90 c.c.) during 6 hr., and the resulting amine isolated with Et_2O. The addition of H_2SO_4 (23 g.) to the dried ethereal solution of the base pptd. the sulphate, which separated from warm H_2O as a hydrate in colourless needles. Treatment of this salt with Ac_2O and excess of AcONa at room temp. for 12 hr. gave the *acetyl* derivative, which crystallised from AcOEt–light petroleum in clusters of needles, m. p. 146° (Found: C, 63·1; H, 7·3. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2%).

Methylphloroglucinol α-*Dimethyl Ether* (XIV).—A solution of the aforementioned sulphate (7 g.) in 13·5% H_2SO_4 (75 c.c.) was diazotised at below 0° with $NaNO_2$ (1·85 g.), after ½ hr. the excess of HNO_2 was destroyed with urea, the diazonium solution gradually added to boiling 20% H_2SO_4 (200 c.c.), the cooled reaction mixture saturated with $(NH_4)_2SO_4$, and the phenol isolated with Et_2O. Purified by distillation in a high vac. and then by crystn. from light petroleum (b. p. 60—80°), it was obtained in clusters of colourless needles (2·5 g.), b. p. 135°/1 mm., m. p. 67—68° [Found: C, 64·0; H, 7·0; OMe, 36·8. Calc. for $C_7H_6O(OMe)_2$: C, 64·3; H, 7·0; OMe, 36·9%]. The compound is readily sol. in EtOH, AcOEt, or C_6H_6 and insol. in warm H_2O.

A specimen of the α-dimethyl ether was prepared according to the directions of Weidel

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(*loc. cit.*) and found to have m. p. and mixed m. p. 66—67° (Weidel and Pollak and Solomonica, *locc. cit.*, respectively quote m. p. 60—61° and 60°).

2-*Hydroxy*-4 : 6-*dimethoxy*-3-*methylbenzaldehyde* (XVI, R = H).—(A) A solution of phloroglucinaldehyde (3 g.) in acetone (30 c.c.) was refluxed with MeI (7·5 c.c.) and powdered K_2CO_3 (8 g.) for 3 hr., filtered, and evaporated. A solution of the residue in hot EtOH, on cooling, deposited the *aldehyde* in plates (0·75 g.), m. p. 168—169° after recrystn. [Found in material dried at 110° : C, 60·8; H, 6·4; OMe, 32·1. $C_8H_6O_2(OMe)_2$ requires C, 61·2; H, 6·1; OMe, 31·6%]. The compound is readily sol. in AcOEt or AcOH and sparingly sol. in warm light petroleum and gives a purple coloration with alc. $FeCl_3$.

Methylation of methylphloroglucinaldehyde (Herzig, Wenzel, and Gehringen, *Monatsh.*, **1903**, **24**, 876) (1·5 g.) with MeI (3 c.c.) and K_2CO_3 (4·5 g.) in boiling acetone (20 c.c.) during 1 hr. gave the dimethyl ether (0·85 g.), m. p. and mixed m. p. 168—169° after purification (Found in specimen dried at 110° : C, 60·5; H, 6·3%).

(B) A mixture of methylphloroglucinol α-dimethyl ether (1·7 g.), HCN (2·5 c.c.), $ZnCl_2$ (1 g.), and dry Et_2O (30 c.c.) was saturated with HCl. Next day the cryst. solid was collected, washed with Et_2O, and hydrolysed with H_2O (50 c.c.) on the steam-bath for 15 min. The resulting aldehyde crystallised from EtOH in plates (1·4 g.), m. p. and mixed m. p. 168—169° (Found: C, 61·3; H, 6·3%). Despite a careful search a second product could not be isolated.

Acetylation of 2-hydroxy-4 : 6-dimethoxy-3-methylbenzaldehyde (1 g.) with Ac_2O (10 c.c.) and pyridine (5 c.c.) on the steam-bath for 3 hr. gave the *acetate*, which separated from aq. EtOH in slender needles, m. p. 123—124° (Found : C, 60·8; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

5 : 7 : 4′-*Trimethoxy*-8-*methylflavylium Ferrichloride* (XXI).—The foregoing aldehyde (0·57 g.) was condensed with acetylanisole (1·2 g.) in AcOEt by means of HCl. After 2 days the flavylium chloride was pptd. with Et_2O and converted into the *ferrichloride* in the usual manner. This salt separated from AcOH in needles or short thick prisms, m. p. 196—197° (Found : C, 44·9; H, 3·9. $C_{19}H_{19}O_4Cl_4Fe$ requires C, 44·8; H, 3·7%).

Methylation of Methyl Phloroglucinolcarboxylate.—A solution of this ester (Herzig and Wenzel, *Monatsh.*, 1902, **23**, 81) (3 g.) in acetone (30 c.c.) was refluxed with MeI (8 c.c.) and K_2CO_3 (8 g.) for 3 hr. and after isolation in the usual manner the product was dissolved in hot MeOH. On cooling, ***methyl* 2-*hydroxy*-4 : 6-*dimethoxy*-3-*methylbenzoate*** separated in elongated rectangular prisms (0·25 g.), m. p. 144—145° (Found : C, 58·3; H, 6·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). This ester is moderately easily sol. in warm EtOH or acetone, and sparingly sol. in ligroin. With alc. $FeCl_3$ it gives a greenish-brown coloration.

Addition of H_2O to the methyl-alc. mother liquors pptd. methyl 2 : 4 : 6-trimethoxybenzoate (2·35 g.), which crystallised from light petroleum in thick prisms, m. p. 66—67° [Found : C, 58·9; H, 6·3; OMe, 54·2. Calc. for $C_7H_2O(OMe)_4$: C, 58·4; H, 6·2; OMe, 54·9%].

Methylation of methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (Herzig and Wenzel, *loc. cit.*) (1 g.) with MeI (2 c.c.) and K_2CO_3 (3 g.) in acetone during 3 hr. gave methyl 2-hydroxy-4 : 6-dimethoxy-3-methylbenzoate (0·5 g.), m. p. 145—146° after purification [Found : C, 58·2; H, 6·4; OMe, 41·5. Calc. for $C_8H_5O_2(OMe)_3$: C, 58·4; H, 6·2; OMe, 41·2%]. A further quantity of the ether (0·2 g.) was isolated from the mother-liquors.

Methylation of Methyl 2 : 4 : 6-*Trihydroxy*-3-*methylbenzoate.*—This ester (Herzig and Wenzel, *loc. cit.*) (1 g.) was methylated with MeI (3 c.c.) and K_2CO_3 (3 g.) in boiling acetone during 3 hr. A solution of the product in the minimum amount of hot MeOH gradually gave methyl 2-hydroxy-4 : 6-dimethoxy-3-methylbenzoate (0·35 g.), m. p. and mixed m. p. 145°. The filtrate from this ester was diluted with H_2O and a solution of the ppt. in hot MeOH on cooling deposited a further quantity of the compound (0·05 g.).

After the removal of the solid, excess H_2O was added to the filtrate and the ppt. collected, dried and crystallised from light petroleum. ***Methyl* 2 : 4 : 6-*trimethoxy*-3-*methylbenzoate*** (0·55 g.) thus obtained formed colourless plates, m. p. 80—82° [Found : C, 59·8; H, 6·9; OMe, 51·0. $C_8H_4O(OMe)_4$ requires C, 60·0; H, 6·7; OMe, 51·7%]. It is readily sol. in MeOH, EtOH, and in warm light petroleum and does not give a $FeCl_3$ reaction. A mixture of the compound (0·7 g.), EtOH (5 c.c.), and 20% aq. KOH (5 c.c.) was heated on the steam-bath for 1 hr., cooled, acidified, and extracted several times with Et_2O. The combined ethereal extracts were washed with aq. $NaHCO_3$ to remove traces of acid, dried, and evaporated, leaving methylphloroglucinol trimethyl ether. Treatment of this compound with Br in AcOH gave rise to the ***dibromide***, which crystallised from EtOH in clusters of silky needles, m. p. 102—103° [Found : OMe, 27·2. $C_7H_3Br_2(OMe)_3$ requires OMe, 27·4%]. Bromination of an authentic specimen of

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methylphloroglucinol trimethyl ether (Herzig and Theuer, *Monatsh.*, 1900, **21**, 855) in a similar manner gave the same dibromide, m. p. and mixed m. p. 102—103° (Found: OMe, 27·5%).

2-*Hydroxy*-4 : 6-*dimethoxy*-3-*methylbenzoic Acid*.—(A) The methyl ester (0·5 g.) was warmed on the steam-bath with 50% MeOH (10 c.c.) containing KOH (0·5 g.) for 1 hr., cooled, and acidified with dil. HCl. The *acid* was collected, washed, and crystallised from MeOH, forming colourless rectangular prisms, m. p. 182° (Found: C, 56·3; H, 5·9. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). This compound, which is readily sol. in EtOH, gives a greenish-brown $FeCl_3$ reaction. It was decarboxylated by being heated at 210—220° for 10 min., and a solution of the oily product in warm light petroleum (b. p. 60—80°) gradually deposited methylphloroglucinol α-dimethyl ether in needles, m. p. 67—68°, identical with an authentic specimen.

(B) The acetate of 2-hydroxy-4 : 6-dimethoxy-3-methylbenzaldehyde (0·8 g.) was dissolved in warm acetone (50 c.c. at 50—55°) and oxidised by the gradual addition of a solution of $KMnO_4$ (1 g.) and $MgSO_4$ (1 g.) in H_2O (25 c.c.). ½ Hr. later the mixture was cleared with SO_2, the acetone evaporated at room temp., and the aq. liquor extracted with $CHCl_3$. The acetate of the acid was 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., yielding the acid, which separated from MeOH in clusters of rectangular prisms, m. p. and mixed m. p. 182—183° (Found: C, 56·3; H, 6·0%).

***Methylphloracetophenone*.**—Methylphloroglucinol (6·6 g.) was condensed with acetonitrile (2·32 g.) in Et_2O (60 c.c.) by means of powdered anhydrous $ZnCl_2$ (3 g.) and excess of HCl, and 2 days later a solution of the cryst. ketimine double compound in H_2O (100 c.c.) was neutralised with NH_3 aq. and boiled for 15 min. On cooling, *methylphloracetophenone* separated in clusters of colourless needles, m. p. of anhyd. material after recrystn. from H_2O 211—212° (Found in air-dried material: C, 54·4; H, 6·1; H_2O, 9·6. $C_9H_{10}O_4,H_2O$ requires C, 54·0; H, 6·0; H_2O, 9·0%. Found in specimen dried at 130° for 2 hr.: C, 58·9; H, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The compound is readily sol. in EtOH, acetone, or hot H_2O, and gives with alc. $FeCl_3$ a purple-black coloration, which becomes purple on the addition of H_2O. Treatment of the ketone (0·5 g.) with pyridine (1 c.c.) and Ac_2O (2 c.c.) at 37° for 2·5 days gave the *triacetate*, which separated from dil. EtOH in clusters of needles, m. p. 111° (Found: C, 58·7; H, 5·2. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

2-*Hydroxy*-4 : 6-*dimethoxy*-3-*methylacetophenone* (XVI, R = Me).—(A) Methylphloroglucinol α-dimethyl ether (2 g.) was condensed with acetonitrile (0·75 g.) in dry Et_2O (15 c.c.) with HCl, in the presence of $ZnCl_2$ (1 g.). Next day an excess of Et_2O was added, the solvent decanted, and the solid residue hydrolysed by boiling with H_2O (50 c.c.) for 15 min. After cooling, the *ketone*, which had partially separated in the course of the hydrolysis, was collected and recrystallised from EtOH, forming colourless rectangular prisms (1·7 g.), m. p. 141—142° (Found: C, 62·5; H, 6·4. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). This compound gives with alc. $FeCl_3$ a brownish-purple coloration, which is unchanged by the addition of H_2O. Acetylation of the compound (0·25 g.) with Ac_2O and pyridine (1 c.c.) at 37° for 3 days furnished the *acetate*, which crystallised from 50% EtOH and then from 50% AcOH in needles, m. p. 86—87° (Found: C, 62·1; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

A second product could not be isolated either by extraction of the crude solid with 10% aq. Na_2CO_3 or by prolonged hydrolysis of the aq. liquors left after the separation of the cryst. ketone.

(B) Methylation of phloracetophenone (3 g.) with MeI (10 c.c.) and K_2CO_3 (9 g.) in acetone (30 c.c.) during 3 hr. gave rise to 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone (1 g.), m. p. and mixed m. p. 141—142° after purification [Found: C, 62·8; H, 7·0; OMe, 29·5. $C_9H_8O_2(OMe)_2$ requires C, 62·8; H, 6·7; OMe, 29·5%]. The same product was obtained when the methylation was continued for 30 hr. and in neither case was a second compound formed.

(C) Treatment of methylphloracetophenone (0·3 g.) with MeI (3 c.c.) and K_2CO_3 (1 g.) in boiling acetone (7 c.c.) for 3 hr. gave rise to 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone, m. p. and mixed m. p. 143—144° after purification.

2-*Hydroxy*-4 : 6 : 4′-*trimethoxy*-3-*methylchalkone* (XIX).—A solution of the foregoing ketone (1·5 g.) and anisaldehyde (1·2 g.) in a mixture of EtOH (24 c.c.) and H_2O (6 c.c.) containing KOH (6 g.) was kept for 12 hr., diluted with H_2O, and acidified with HCl. The *chalkone* thus pptd. was collected and crystallised from EtOH, forming orange-yellow needles (2 g.), m. p. 134—135° [Found: C, 69·5; H, 5·9; OMe, 28·2. $C_{16}H_{11}O_2(OMe)_3$ requires C, 69·5; H, 6·1; OMe, 28·4%]. It is readily sol. in Et_2O, AcOEt, or hot EtOH and gives a brown coloration with alc. $FeCl_3$. Acetylation of the chalkone (0·3 g.) with Ac_2O (5 c.c.) and AcONa (0·3 g.) on the steam-bath for 3 hr. gave the *acetate*, which separated from EtOH in pale straw-coloured, hexagonal plates, m. p. 148° after sintering at 145° (Found: C, 67·7; H, 6·1. $C_{21}H_{22}O_6$ requires C, 68·1; H, 6·0%).

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5 : 7 : 4'-*Trimethoxy*-8-*methylflavanone* (XX).—The foregoing styryl ketone (1 g.) was boiled with a mixture of EtOH (75 c.c.) and H_2SO_4 (15 c.c.) for 15 hr. After the addition of an excess of H_2O the *flavanone* was isolated by means of Et_2O and crystallised from MeOH, forming colourless rhombic plates, m. p. 144°, which do not give a $FeCl_3$ reaction (Found: C, 69·7; H, 6·0. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

2 : 4'-*Dihydroxy*-4 : 6-*dimethoxy*-3-*methylchalkone*.—A mixture of 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone (0·5 g.) and *p*-hydroxybenzaldehyde (0·4 g.) was heated on the water-bath with aq. EtOH (8 c.c.) containing KOH (3 g.) for 6 hr. On isolation the *chalkone* was washed with C_6H_6 to remove traces of unchanged ketone and crystallised from EtOH, forming orange-red flat needles, m. p. 199—200°, which gave a brown $FeCl_3$ reaction (Found: C, 68·5; H, 6·0. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). The *diacetate* separated from EtOH in colourless rectangular prisms, m. p. 135° (Found: C, 66·3; H, 5·6. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·5%).

Ethyl* 2-*Acetyl*-3 : 5-*dimethoxy*-6-*methylphenoxyacetate.—A mixture of 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone (1 g.), ethyl bromoacetate (2 g.), K_2CO_3 (2 g.), and acetone (15 c.c.) was refluxed for 8 hr. After the addition of H_2O the aq. mixture was filtered to remove a small amount of cryst. unchanged ketone and extracted several times with Et_2O. Evaporation of the dried extracts left the *ester* (0·2 g.), which solidified and was purified by repeated crystn. from light petroleum (b. p. 60—80°), forming needles, m. p. 70° (Found: C, 60·6; H, 7·0. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). The compound is readily sol. in MeOH or EtOH and does not give a reaction with alc. $FeCl_3$.

Unlike 4 : 6-*O*-dimethylphloroacetophenone (Kostanecki and Tambor, *Ber.*, 1909, **42**, 909), 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone does not condense with ethyl bromoacetate in an alc. solution of NaOEt.

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