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THE SYNTHESIS OF SCLERIN[1]

T. TOKOROYAMA, S. MAEDA, T. NISHIKAWA and T. KUBOTA
Faculty of Science, Osaka City University, Sugimoto-cho, Sumiyoshi-ku, Osaka, Japan

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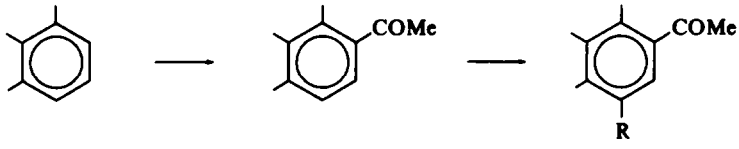
Abstract—The synthesis of sclerin, which confirms the recently proposed formula I, is described.

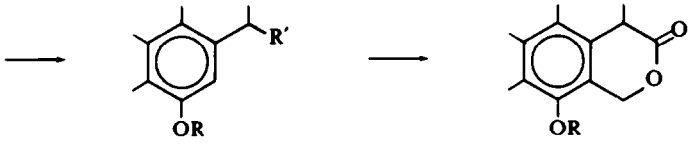
SCLERIN is a metabolite isolated from several *sclerotinia* fungi and has been known to show a growth promoting effect on plants.[2] We have recently established the structure I for this interesting compound[3] and now wish to report its first synthesis,[4] which verify our structure assignment and, at the same time, may serve for wider biological applications.

In the course of the structural study, sclerin was decarboxylated to 1-(5-hydroxy-2,3,4-trimethylphenyl)propionic acid (XIX) which was further degraded to 1-(5-methoxy-2,3,4-trimethylphenyl)ethanol (XIII).[3] Our synthesis took a sequence to



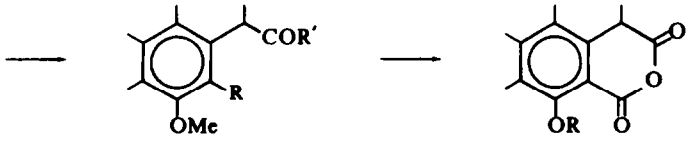
II

IV: R = NO_2
IX: R = NH_2
XI: R = OH
XII: R = OMe



XIII: R = Me, R′ = OH
XIV: R = Me, R′ = Cl
XVI: R = Me, R′ = CN
XVII: R = Me, R′ = CO_2H
XVIII: R = Me, R′ = $CONH_2$
XIX: R = H, R′ = CO_2H
XX: R = H, R′ = CO_2Me
XXI: R = Me, R′ = CO_2Me

XXIV: R = Me
XXV: R = H

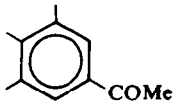


XXVI: R = CH_2OH, R′ = OMe
XXVIII: R = CH_2OH, R′ = NMe_2
XXIX: R = CO_2H, R′ = OH

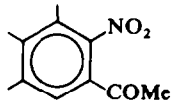
XXXI: R = Me
I: R = H

proceed by way of XIII and XIX as intermediates. Friedel–Crafts acetylation of hemimellitene with acetyl chloride in ethylene dichloride solution at 0° gave a mixture of 2,3,4- (II) and 3,4,5-trimethylacetophenone (III) in the ratios of 65:35–54:46, the former predominating in every case. Marino and Brown[5] have obtained the isomer ratio (II:III) of 21:79 in the same reaction at 25°, in a contrast to that of 65·2:34·8, calculated on the basis of the partial rate factors of toluene. They ascribed this discrepancy to the steric hindrance at *ortho* positions by the strongly buttressed assembly of three methyl groups. Our result is interesting in this connection, although the factors, which influence the isomer ratio, have not been defined.

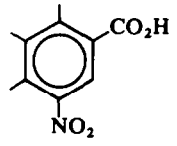
The acetylation mixture was separable by one of three methods: (a) chromatography on an alumina column; (b) fractional recrystallization of the nitrated mixture;



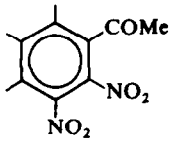
III



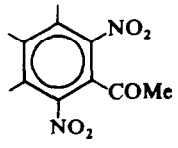
V



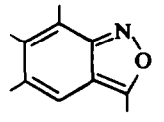
VI



VII



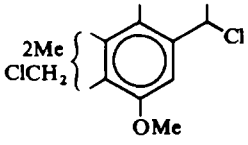
VIII



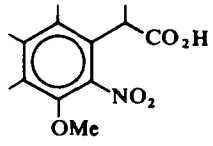
X

(c) rectification on spinning band column, the last one being most convenient. Thus, 2,3,4-trimethylacetophenone (II) was obtained about in 40% yield. Compound II was converted to 5-hydroxy-2,3,4-trimethylacetophenone (XI) in the conventional manner. Nitration of II with the acid mixture (HNO_3—H_2SO_4) gave 5-nitro-2,3,4-trimethylacetophenone (IV), m.p. 64–66° in 68% yield. Small amounts of 5-nitro-2,3,4-trimethylbenzoic acid (VI), m.p. 176–177° was isolated as an acidic product. 5,6-dinitro-2,3,4-trimethylacetophenone (VII), m.p. 138–140° was also obtained, when a larger excess (2 molar equiv.) of the reagent was used. There was a possibility that VII could be 2,6-dinitro-3,4,5-trimethylacetophenone (VIII), derived from III, which admixed in II. However, this was rejected by comparison of VII with VIII, prepared unambigously from III. The nitroacetophenone (IV) was transformed to 5-hydroxy-2,3,4-trimethylacetophenone (XI) by reduction with stannous chloride and following diazotization and hydrolysis of the resulted 5-amino-2,3,4-trimethylacetophenone (IX), m.p. 124–127°. When impure IV was used in this sequence of the reactions, a crystalline byproduct, m.p. 106° was isolated from the mother liquor of XI after chromatographic separation. This compound was found to be an anthranil X derived from V, which was contaminated in the starting material. The structure X was secured (cf. Experimental for spectroscopic evidence) by derivation from V and conversion to 2-amino-3,4,5-trimethylacetophenone. The methyl ether (XII), m.p. 66° of XI, prepared by methylation with dimethyl sulphate, was reduced with lithium aluminium hydride to afford 1-(5-methoxy-2,3,4-trimethylphenyl)ethanol (XIII), m.p. 68–69°.

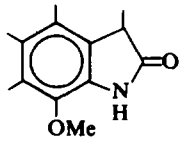
This product (XIII) was shown to be identical with the compound derived from natural sclerin[3] (mixed m.p. and IR).



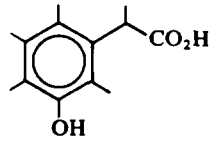
XV



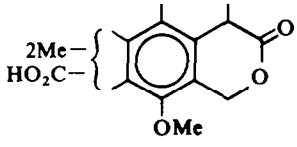
XXII



XXIII



XXX



XXVII

The next stage of the synthesis was the conversion of the alcohol (XIII) to 1-(5-hydroxy-2,3,4-trimethylphenyl)propionic acid (XIX). For this purpose XIII was treated with thionyl chloride smoothly to produce an oily chloride (XIV). However, when XIII was chlorinated with phosphorous pentachloride in chloroform solution, an unexpected crystalline dichloride (XV), m.p. 68–69° was obtained in nearly quantative yield. XV exhibited no absorption due to hydroxyl group, but bands due to C—Cl bonds at 700–670 cm^{-1} instead. The substitution of one of the aromatic methyl groups (but not at nuclear position) by an additional Cl atom was revealed by the NMR spectrum, which showed signals at 2·99 (1H, q, ArH), 4·59 (1H, q, J = 7 c/s, —CHClMe), 5·44 (2H, s, $ArCH_2Cl$), 7·60, 7·70 (each 3H, s, ArMe), 8·17 τ (3H, d, J = 7 c/s, —CHClMe). The reaction of 1-(5-methoxy-2,3,4-trimethylphenyl) ethyl chloride (XIV) with sodium cyanide in DMSO solution at 120° furnished the nitril (XVI). XVI was hydrolysed by heating with mixture of 20% KOHaq and ethylene glycol to give 1-(5-methoxy-2,3,4-trimethylphenyl)propionic acid (XVII), m.p. 126–128°. Overall yield of XVII from XIII was 59%. Corresponding amide (XVIII), m.p. 126–128° was obtained on the hydrolysis in milder condition. Demethylation of XVII with hydroiodic acid yielded 1-(5-hydroxy-2,3,4-trimethylphenyl)propionic acid (XIX), m.p. 128–130°. Identity of XVII and XIX with the corresponding acids obtained from sclerin was ascertained from the mixed m.p. determinations and comparison of their IR spectra.

Our second objective had thus been reached and it remains to elaborate the introduction of one extra carbon atom to XIX, for the completion of sclerin synthesis.

A number of attempts to introduce directly a carboxyl or an aldehyde group on nuclear position by the use of metal halide catalyst[6] were made about the methyl ester (XX) and the methyl ether methyl ester (XXI), but resulted merely in essentially quantitative recovery of the starting material in every case. It is presumable that the rather bulky reaction intermediate inherent in these reactions[7] would hardly be accessible to the nuclear position, which is seriously hindered by the *ortho*-substituents on both sides. The application of Kolbe–Schmidt procedure was also found to be ineffective.

Nitration of XVII in acetic anhydride solution at $-30°$ furnished 1-(5-methoxy-6-nitro-2,3,4-trimethylphenyl)propionic acid (XXII), m.p. 208–209°. Catalytic hydrogenation of XXII at the presence of palladized carbon yielded the five-membered lactam (XXIII), m.p. 211–213°, ν_{max} 3180, 1636 cm^{-1}, even after the carboxyl group was protected as methyl ester. This prevented the further transformation by way of Sandmeyer reaction. After all the introduction of a carbon atom to the aromatic position was achieved by the chloromethylation of methyl 1-(5-methoxy-2,3,4-trimethylphenyl)propionate (XXI), which afforded, with concomitant lactonization, 8-methoxy-4,5,6,7-tetramethyl-3-oxoisochromane (XXIV), m.p. 115–116° in high yield (92%). The six-membered lactone formulation for XXIV was well substantiated by the IR peak at 1735 cm^{-1} and signals at 4·44 and 4·66 τ (AB quartet, $J = 14$ c/s) in the NMR spectrum.

The oxidation of the methylene group in XXIV was at first tried for the compounds in which lactone ring is opened. On exposure to alkaline permanganate, XXIV gave small amounts of crystalline acid (XXVII), m.p. 206–210°, the NMR spectrum of which indicated the oxidation of one of the nuclear Me groups instead of the methylene group. When an alkaline solution of XXIV was cautiously acidified and the ether extract was methylated with slight excess of diazomethane, the corresponding hydroxy acid methyl ester (XXVI) was obtained as crystalline solid, ν_{max} 3340, 1735 cm^{-1}. However, XXVI had a tendency to recyclize so easily that the reaction starting from it made meaningless. Jones' oxidation of the amido-alcohol (XXVIII), obtained by aminolysis of XXIV, led to the formation of the desired dicarboxylic acid (XXIX) in poor yield with the reversion of most of the material to the lactone (XXIV). A better result was obtained by the oxidation of XXIV itself.[8] On exposure to Jones' reagent at room temperature for 72 hr, XXIV furnished the dicarboxylic acid (XXIX) in 41% yield with much amount of the recovery. The recycliing of the recovered material raised the yield of XXIX up to 79%. Treatment of XXIX with acetic anhydride gave 8-methoxy-4,5,6,7-tetramethyl-1,3-dioxoisochromane (XXXI), m.p. 104–105°, which was identical with sclerin methyl ether (mixed m.p. and IR). Finally the demethylation of XXXI with boron tribromide[9,10] afforded racemic sclerin, m.p. 121°, which was indistinguishable in mixed melting point determination, IR, UV, NMR spectra and the biological test.*

EXPERIMENTAL

M.ps were uncorrected. The IR spectra were measured, unless specified, as Nujol mull on a Nippon Bunko IR-S spectrometer and the UV spectra were determined in EtOH soln on a Hitachi EPS-2 recording spectrometer. The NMR spectra were taken in $CDCl_3$ soln on a JNMC-60 spectrometer. Chemical shifts are reported in τ-values, using TMS as internal references. Mallinkrodt silicic acid was used for column

* The authors are indebted to Prof. Y. Satomura for this test.

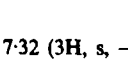
chromatography. Microanalyses were carried out at Microanalytical Laboratory, Faculty of Science, Osaka City University.

2,3,4-*Trimethylacetophenone* (II). To a suspension of powdered anhyd $AlCl_3$ (57·6 g, 0·42 mole) in ethylene dichloride soln, a mixture of hemimellitene (distilled on Na, 50 g, 0·42 mole) and AcCl (65·2 g, 0·83 mole) was added dropwise under stirring and exclusion of moisture at the temp below 5° (40–60 min). After stirring at room temp for further 4 hr, the reaction mixture was poured onto a mixture of ice and conc HCl (5:1) and the product was extracted with ether. Distillation of the neutral extract at reduced press yielded a mixture of the acetylated product, b.p. 95–100°/2 mm, 65·6 g (97·8% of theory), of which gas chromatographic analyses indicated mixing of II and III in the ratios of 65:35–54:46. During the reaction sudden polymerization of the product was sometimes observed from undefined reason. Although the total yield of volatile product lowered in this case (38%), it consisted mostly of II (a selective polymerization!). II was most conveniently separated from III by fractional distillation on a spinning band column: II, 27·1 g (40% yield), b.p. 81°/0·2 mm, ν_{max}^{liq} 1690, 820 cm^{-1}; III, 14·5 g (21·5% yield), b.p. 89°/0·3 mm, ν_{max}^{liq} 1680, 887, 870 cm^{-1}. The separation of II and III was also effected by following two methods: (a) when the acetylation mixture was chromatographed on a column of alumina (activity I) and eluted with pet. ether–benzene (1:1), II was obtained as earlier fractions. (b) The nitrated mixture of the acetylation product was recrystallized from ether and, after removal of 2-*nitro*-3,4,5-*trimethylacetophenone* (V), m.p. 118–120°; ν_{max} 1695, 1535 cm^{-1}; (Found: C, 63·62; H, 6·33; N, 6·88. $C_{11}H_{13}O_3N$ requires: C, 63·75; H, 6·32; N, 6·77%) as the more insoluble component, 5-nitro-2,3,4-trimethylacetophenone (IV) was obtained from the mother liquor.

5-*Nitro*-2,3,4-*trimethylacetophenone* (IV). Compound II (41 g) was dissolved in conc H_2SO_4 (86·5 ml) by adding dropwise under mechanical stirring at the temp below 5°. To this soln a mixture of conc HNO_3 (S.G. 1·42, 18·2 ml) and conc H_2SO_4 (27·4 ml) was added as rapidly as possible under vigorous stirring and cooling with ice–salt bath in order to keep the reaction temp below 0°. The mixture was allowed to react for further 10 min after the completion of the addition and, then, poured on ice–water. Ether extract was washed with $NaHCO_3$aq and water, and dried. The crystalline residue left after the evaporation of the solvent was recrystallized from EtOH to give 5-*nitro*-2,3,4-*trimethylacetophenone* (IV) as pale yellow needles (34·5 g, 68% yield), m.p. 64–65°; ν_{max} 1695, 1525, 1360 cm^{-1}; NMR 2·19 (1H, s, ArH), 7·32 (3H, s, MeCO—), 7·54 (6H, s, 2ArMe), 7·64 (3H, s, ArMe). (Found: C, 63·78; H, 6·45; N, 6·85. $C_{11}H_{13}O_3N$ requires: C, 63·75; H, 6·32; N, 6·77%). The acidic product obtained by the acidification of the $NaHCO_3$ washings was recrystallized from benzene to give 5-*nitro*-2,3,4-*trimethylbenzoic acid* (VI) as yellow needles (2·4 g), m.p. 176–177°; ν_{max} 3380–2100, 1710, 1525, 1360 cm^{-1}, λ_{max} 224 (ε 8100), 269 mμ (2070). (Found: C, 57·52; H, 5·40; N, 6·73. $C_{10}H_{11}O_4N$ requires: C, 57·41; H, 5·30; N, 6·90%).

Methylation of VI with CH_2N_2 and recrystallization of the product from pet. ether gave *methyl* 5-*nitro*-2,3,4-*trimethylbenzoate* as yellow crystals, m.p. 66°; ν_{max} 1720, 1525, 1360, 1178 cm^{-1}. (Found: C, 59·47; H, 5·92; N, 6·37. $C_{11}H_{13}O_4N$ requires: C, 59·18; H, 5·82; N, 6·28%). When the nitration was carried out by using an excess (2 molar equiv) of the reagent, the recrystallization of the neutral product from EtOH gave in 8% yield, as hardly soluble crystals, 5,6-*dinitro*-2,3,4-*trimethylacetophenone* (VII), m.p. 138–140°; ν_{max} 1705, 1550, 1365 cm^{-1}; NMR: 7·38 (3H, s, MeCO—), 7·62 (3H, s, ArMe), 7·70 (6H, s, 2ArMe). (Found: C, 52·44; H, 4·93; N, 11·04. $C_{11}H_{12}O_5N_2$ requires: C, 52·38; H, 4·80; N, 11·11%). Nitration of V in the same way as above produced 2,4-*dinitro*-3,4,5-*trimethylacetophenone* (VIII), m.p. 152–155°; ν_{max} 1710, 1530, 1360 cm^{-1}. (Found: C, 52·62; H, 4·92; N, 11·15. $C_{11}H_{12}O_5N_2$ requires: C, 52·38; H, 4·80; N, 11·11%). This compound was found to be different from VII by mixed m.p. determination and comparison of IR spectra.

5-*Amino*-2,3,4-*trimethylacetophenone* (IX). Compound IV (39·1 g, 0·187 mole) was added in one portion to a vigorously stirred soln of $SnCl_2 \cdot 2H_2O$ (29 g) in conc HCl (168 ml). After an abrupt reaction subsided, the reaction mixture was heated for further 15 min at 100° and then poured into 40% NaOHaq. Extraction of the product with $CHCl_3$ afforded 5-*amino*-2,3,4-*trimethylacetophenone* (IX, 31·3 g, 92% yield), m.p. 124–127°; ν_{max} 3460, 3370, 1680 cm^{-1}. When impure IV was used in the series of the reactions from IV to XI, 3,5,6,7-*tetramethylanthranil* (X) was isolated from the mother liquor of XI by chromatography. Compound X was obtained, after recrystallization from pet. ether, as leaflets, m.p. 105–106°; ν_{max} 1650, 1445, 1230, 883, 868, 850, 825 cm^{-1}; λ_{max} 268 (ε 1300), 279 (2040), 294 (2770), 321 mμ (5600); NMR 3·00 (1H, s, ArH),



7·32 (3H, s, —C=C—O—), 7·56, 7·76, 7·82 (each 3H, s, 3ArMe). (Found: C, 75·48; H, 7·43; N, 8·05. $C_{11}H_{13}ON$ requires: C, 75·40; H, 7·48; N, 7·99%).

The identification was made by comparison with the authentic sample obtained through reduction of V with $SnCl_2$. Further treatment of X with $SnCl_2$ under more vigorous condition (reflux for 2 hr) gave *2-amino-3,4,5-trimethylacetophenone*; needles (from pet. ether), m.p. 115–117°; ν_{max} 3450, 3310, 1620, 1695, 1540, 1250 cm^{-1}; λ_{max} 270 (ε 5970), 376 mμ (2660); NMR: 2·62 (1H, s, ArH), 3·90 (2H, br. s, —NH_2), 7·47 (3H, s, —COMe), 7·80 (6H, s, 2ArMe), 7·82 (3H, s, ArMe). (Found: C, 74·81; H, 8·63; N, 8·12. $C_{11}H_{15}ON$ requires: C, 74·54; H, 8·53; N, 7·90%).

5-Hydroxy-2,3,4-trimethylacetophenone (XI). Compound IX (32·5 g, 0·207 mole) was diazotized by stirring with 6N H_2SO_4 (70 ml) for 30 min and following addition of $NaNO_2$ (15 g) soln in water (30 ml). The diazotized soln was added to boiling 10% H_2SO_4 for hydrolysis. Extraction of the product with $CHCl_3$ and recrystallization from benzene furnished *5-hydroxy-2,3,4-trimethylacetophenone* (XI) as colourless needles (21·3 g, 68% yield), m.p. 168°; ν_{max} 3340, 1680, 1080 cm^{-1}. (Found: C, 74·26; H, 8·05. $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92%).

5-Methoxy-2,3,4-trimethylacetophenone (XII). Compound XI (21·4 g) was methylated by boiling with Me_2SO_4 (83 g), anhyd K_2CO_3 (90 g) and anhyd acetone (234 ml) under reflux for 8 hr. Recrystallization of the product from pet. ether afforded *5-methoxy-2,3,4-trimethylacetophenone* (XII, 17·9 g, 78% yield), m.p. 66°; ν_{max} 1685, 1110 cm^{-1}. (Found: C, 74·90; H, 8·40. $C_{12}H_{16}O_2$ requires: C, 74·97; H, 8·39%).

1-(5-Methoxy-2,3,4-trimethylphenyl)ethanol (XIII). A soln of XII (13·6 g, 0·071 mole) in abs ether (115 ml) was mixed with a suspension of LAH (1·4 g, 0·037 mole) and the mixture was refluxed for 2·5 hr. After addition of EtOAc and 10% H_2SO_4 aq, the product was extracted with ether to give *1-(5-methoxy-2,3,4-trimethylphenyl)ethanol* (XIII) as prisms (from pet. ether, 12·2 g, 90% yield), m.p. 68–69°; $\nu_{max}^{CHCl_3}$ 3800, 3480, 1600, 1470, 1305, 1130 cm^{-1}. (Found: C, 74·25; H, 9·30. $C_{12}H_{18}O_2$ requires: C, 74·19; H, 9·34%). The IR spectrum of XIII was superimposable with that of XIII derived from sclerin.[3]

Reaction of compound XIII *with phosphorus pentachloride.* A soln of XIII (3.2 g, 0·016 mole) in $CHCl_3$ (EtOH free, 150 ml) was treated with PCl_5 (freshly sublimed, 12·6 g, 0·06 mole) and $CaCO_3$ (7·0 g). The mixture was stirred for 1·5 hr at 0° and for 24 hr at room temp. Usual working up and recrystallization of the product from pet. ether yielded crystalline XV (3·7 g), m.p. 75–77° (from pet. ether); ν_{max} 700–670 cm^{-1}; NMR: 2·99 (1H, s, ArH), 4·59 (1H, q, J = 7 c/s, —C<u>H</u>ClMe), 5·44 (2H, s, $ArCH_2Cl$), 7·60, 7·70 (each 3H, s, ArMe), 8·17 (3H, d, J = 7 c/s, —CHCl<u>Me</u>). (Found: C, 58·67; H, 6·64. $C_{12}H_{16}OCl_2$ requires: C, 58·24; H, 6·47%).

1-(5-Methoxy-2,3,4-trimethylphenyl)propionic acid (XVII). A soln of XIII (14 g, 0·072 mole) in anhyd benzene (10 ml) was stirred with $SOCl_2$ (5·083 g, 0·262 mole) for 1 hr at 30°. Excess of the reagent was removed by distilling *in vacuo* several times with benzene to give *1-(5-methoxy-2,3,4-trimethylphenyl)ethyl chloride* (XIV, 5·551 g), ν_{max}^{liq} 1603, 1490, 1470, 1130, 675 cm^{-1}; NMR: 3·06 (1H, s, ArH), 4·56 (1H, q, J = 7 c/s, —C<u>H</u>ClMe), 6·10 (3H, s, —OMe), 7·72, 7·77, 7·82 (each 3H, s, 3ArMe), 8·15 (3H, d, J = 7 c/s, —CHCl<u>Me</u>). A soln of XIV (5·551 g) in DMSO (15 ml) was added dropwise to the soln of NaCN (2·57 g, 0·524 mole) in DMSO (26 ml) maintained at 60°. Treatment in the usual manner gave *1-(5-methoxy-2,3,4-trimethylphenyl)propionitrile* (XVI) as an oil (5·705 g), ν_{max} 2250 cm^{-1}. The hydrolysis of XVI (5·705 g) was performed by heating with water (0·95 ml), KOH (5·66 g) and ethylene glycol (22 ml) under reflux for 12 hr. Recrystallization of the acidic product (3·977 g) from benzene–pet. ether gave XVII as colourless prisms (3·415 g, 59% yield from XIII), m.p. 131–132°; $\nu_{max}^{CCl_4}$ 3560–2240, 1708, 1600, 1470, 1418, 1295, 1240, 1125, 859 cm^{-1}. (Found: C, 70·43; H, 8·36. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%). This product was indistinguishable with XVII obtained from sclerin in m.p., mixed m.p., IR and chromatographic behaviour. The neutral product (1·447 g) was recrystallized from benzene to afford *1-(5-methoxy-2,3,4-trimethylphenyl)propionamide* (XVIII), m.p. 126–128°; ν_{max} 3480, 3180, 1700, 1650 cm^{-1}. (Found: C, 70·91; H, 8·84. $C_{13}H_{20}O_2N$ requires: C, 70·59; H, 8·59%).

1-(5-Hydroxy-2,3,4-trimethylphenyl)propionic acid (XIX). The methyl ether acid XVII (500 mg) was heated with a mixture of HI soln (S.G., 1·7, 4 ml) and Ac_2O (2·7 ml) at 110° for 1·5 hr. After usual working up, the product was recrystallized from benzene–$CHCl_3$ to give *1-(5-hydroxy-2,3,4-trimethylphenyl)propionic acid* (XIX) as prisms, m.p. 128–130°; ν_{max} 3680–2460, 1705, 1600, 1645, 1285, 1220, 1190, 1070, 870 cm^{-1}. (Found: C, 69·18; H, 7·78. $C_{12}H_{16}O_3$ requires: C, 69·21; H, 7·74%). This product was identical with XIX obtained from sclerin (mixed m.p. and IR).

1-(5-Methoxy-6-nitro-2,3,4-trimethylphenyl)propionic acid (XXII). A soln of XVII (2·1 g, 9·45 mmoles) in Ac_2O (50 ml) was added dropwise with a mixture of fuming HNO_3 (4 ml) and Ac_2O (4 ml) at −30° during 10 min. The mixture was stirred further 10 min at this temp and poured on ice–water. Recrystallization of the product from benzene furnished *1-(5-methoxy-6-nitro-2,3,4-trimethylphenylpropionic acid* (XXII, 1·34 g, 53% yield), m.p. 210–212°; ν_{max} 3250–2240, 1710, 1537 cm^{-1}. (Found: C, 58·65; H, 6·48; N, 5·43.

$C_{13}H_{17}O_5N$ requires: C, 58·42; H, 6·41; N, 5·24%). The reaction at higher temp (−5°) using the acid mixture (HNO_3—H_2SO_4) resulted in the formation of an amorphous product presumably because of partial cleavage of the ether linkage (IR).

7-Methoxy-3,4,5,6-tetramethyl-2-oxodihydroindol (XXIII). The nitro acid XXII (1 g) in a soln of AcOH (5 ml) was hydrogenated at the presence of 10% Pd–C (550 mg). After treatment in the usual way, the product (790 mg) was recrystallized from benzene to yield *7-methoxy-3,4,5,6-tetramethyl-2-oxodihydroindol* (XXIII), m.p. 211–213°; ν_{max} 3190, 1697, 1633 cm^{-1}. (Found: C, 71·38; H, 7·94; N, 6·40. $C_{13}H_{17}O_2N$ requires: C, 71·20; H, 7·82; N, 6·39%).

8-Methoxy-4,5,6,7-tetramethyl-3-oxoisochroman (XXIV). HCl gas was introduced into a stirred mixture of XXI (7 g),* formalin (37%, 21·5 g) and conc HCl (26 g) for 1 hr at room temp and for 5 hr at 60°. Dilution with water and subsequent extraction with ether furnished a crystalline product, which was recrystallized from pet. ether. Compound XXIV was obtained as plates (6·34 g, 91·5% yield), m.p. 115–118°; ν_{max} 1735, 1330, 1255, 1205, 1012, 1097, 1052, 1010, 950, 880, 745, 725 cm^{-1}; NMR: 4·16, 4·36 (2H, AB quartet, J = 14 c/s, $ArCH_2OCO$—), 5·72 (1H, q, J = 8 c/s, —C<u>H</u>Me), 6·21 (3H, s, —OMe), 7·52 (6H, s, 2ArMe), 7·56 (3H, s, ArMe), 8·32 (3H, d, J = 8 c/s, —CH<u>Me</u>). (Found: C, 71·83; H, 7·66. $C_{14}H_{18}O_3$ requires: C, 71·77; H, 7·76%). XXIV was dissolved in 5% NaOH aq by warming at 60° and the resulted soln was, after cooling, acidified to pH 4–5 with dil AcOH. The ether extract was immediately methylated with ethereal CH_2N_2 to afford XXVI as a crystalline solid; ν_{max} 3340, 1735 cm^{-1}. However XXVI reverted to XXIV during recrystallization.

8-Hydroxy-4,5,6,7-tetramethyl-3-oxoisochroman (XXV). The lactone XXIV (50 mg) was heated with AcOH (1 ml) and HBr soln (48%, 1 ml) under refluxing for 5 hr. Extraction with $CHCl_3$ and subsequent recrystallization of the product from pet. ether–benzene yielded *8-hydroxy-4,5,6,7-tetramethyl-3-oxoisochroman* (XXV, 27 mg), m.p. 166–167·5°; ν_{max} 3330, 1705 cm^{-1}. (Found: C, 71·02; H, 7·40. $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32%). Demethylation of XXIV with BBr_3 in the same manner as that of XXXI gave XXV in a better yield. When treated with HI soln (S.G. 1·7, 1·6 ml) and Ac_2O (1·1 ml) at 120° for 4 hr, XXIV (200 mg) gave XXX as colourless crystals (129 mg), m.p. 153°; ν_{max} 3560–2200, 1695 cm^{-1}. NMR: 2·60 (1H, s, —OH), 6·82 (1H, q, J = 8 c/s, MeC<u>H</u>), 7·82 (12H, s, 4ArMe), 8·65 (3H, d, J = 8 c/s, —CH<u>Me</u>). (Found: C, 70·49; H, 8·31. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%). Jones' oxidation of XXV gave small amounts of an undefined crystalline product, m.p. 197–199°, ν_{max} 3385, 1710, 1673, 1587, 1295 cm^{-1}.

Potassium permanganate oxidation of compound XXIV. A soln of XXIV (200 mg, 0·86 mmole) was oxidized with $KMnO_4$ soln (206 mg, 1·3 mmole in 5 ml water) at 5° for 3 hr. The reaction mixture was acidified and treated with $NaHSO_3$ to dissolve precipitated MnO_2. Ether extract was divided into neutral (71 mg) and acidic (71 mg) fractions. Recrystallization of the acidic fraction from benzene gave a crystalline acid (11 mg), m.p. 206–210°; ν_{max} 3700–2240, 1740, 1695 cm^{-1}; NMR: AB quartet centred at 4·38 (2H, $ArCH_2OCO$—), 6·02 (3H, s, —OMe), 5·50 (1H, q, J = 7 c/s, —C<u>H</u>Me), 7·68 (6H, s, 2ArMe), 8·38 (3H, d, J = 7 c/s, —CH<u>Me</u>). From the data above, this acid is considered to have the structure XXVII, which derived from XXIV by oxidation of one of the nuclear Me groups in place of the hydroxylmethylene group. The neutral part exhibited OH absorption (3480 cm^{-1}) in the IR spectrum and, on oxidation with Jones' reagent transformed to the mixture of acids, which mainly consisted of XXVII. Therefore the neutral product is presumed to have the structure in which one of the aromatic Me groups is oxidized to the hydroxymethylene stage.

Conversion of compound XXIV *to* XXIX *via* *1-(6-hydroxymethyl-5-methoxy-2,3,4-trimethylphenyl)-N,N-dimethylpropionamide* (XXVIII). A mixture of XXIV (225 mg, 0·96 mmole), EtOH (20 ml) and Me_2NH (40 ml, 0·6 mmole) was stirred at room temp for 48 hr. Removal of the solvent and the excess reagent *in vacuo* yielded a crystalline residue (205 mg), which was chromatographed on a column of silica gel (10 g). Elution with benzene–$CHCl_3$ (3:7) afforded *1-(6-hydroxymethyl-5-methoxy-2,3,4-trimethylphenyl)-N,N-dimethylpropionamide* (XXVIII), after recrystallization from benzene, as crystals, m.p. 144–145°; ν_{max} 3400, 1633, 1618 cm^{-1}. (Found: C, 68·89; H, 9·08; N, 5·11. $C_{16}H_{25}O_3N$ requires: C, 68·78; H, 9·02; N, 5·01%).

* Application of this reaction to the free acid (XVII) gave unsatisfactory results.

A soln of XXVIII (112 mg, 0·4 mmole) in acetone (3 ml) was oxidized with Jones' reagent (0·3 ml, 2·25 equiv) at room temp for 4 hr. The oily product (89 mg) was recrystallized from benzene to afford XXIX as crystals (11 mg). Chromatography of the mother liquor on silica gel column gave XXIV (28 mg), further amounts of XXIX (23 mg) and an undefined crystalline product (13 mg); ν_{max} 3280, 1720, 1710 cm^{-1}.

8-Methoxy-4,5,6,7-tetramethyl-1,3-dioxochroman (XXXI). A soln of XXIV (6·34 g, 0·027 mole) in acetone (165 ml) was added with CrO_3–H_2SO_4 soln* (10 ml, 0·08 equiv) and stirred at room temp for 72 hr. During this time, two additional portions of the reagent (each 10 ml) was added after 8 and 24 hr, respectively. The reaction mixture was diluted with water, extracted with ether and the acidic product was separated by washing with $NaHCO_3$ aq. From the neutral part, 3·0 g (47%) of XXIV was recovered. The $NaHCO_3$ washings afford, after acidification and subsequent ether extraction, *1-(6-carboxy-5-methoxy-2,3,4-trimethylphenyl)propionic acid* (XXIX) as an oil (2·95 g, 41% yield; taking account of the recovery, 79%); $\nu_{max}^{CCl_4}$ 3600–2300, 1750–1705, 1460, 1285, 1217, 1090 cm^{-1}, which was used for following reaction without further purification. The acid XXIX (1·82 g) thus obtained was treated with Ac_2O (14 ml) under refluxing for 1·5 hr. The soln was evaporated *in vacuo* to leave an oily residue which was chromatographed on a column of silica gel. Elution with $CHCl_3$ furnished, after recrystallization from pet. ether–benzene, *8-methoxy-4,5,6,7-tetramethyl-1,3-dioxoisochroman* (XXXI) as prisms (922 mg), m.p. 104–105°; $\nu_{max}^{CCl_4}$ 2910, 1805, 1755, 1295, 1097, 995 cm^{-1}. This product found to be identical with sclerin methyl ether.

Sclerin (I). A soln of XXXI (922 mg) in CH_2Cl_2 (10·2 ml) was added dropwise with BBr_3 (4·1 ml) dissolved in CH_2Cl_2 (6·1 ml) at −70°. The reaction mixture was allowed to warm up to room temp and stirred for further 20 min. The reaction mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried and evaporated to dryness to afford, after crystallization from ether, *8-hydroxy-4,5,6,7-tetramethyl-1,3-dioxochroman* (I) as plates (786 mg), m.p. 121°. (Found: C, 66·83; H, 6·25. $C_{13}H_{14}O_4$ requires: C, 66·65; H, 6·02%). The product I was indistinguishable with sclerin in m.p., mixed m.p., TLC, IR, UV, NMR and biological test.

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* A soln of 2·67 g CrO_3 in 2·30 ml conc H_2SO_4 was diluted to the total volume of 10 ml.[11]