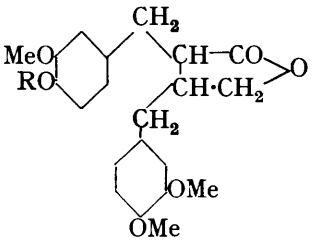
220. *The Constituents of Natural Phenolic Resins. Part VII. Arctigenin.*

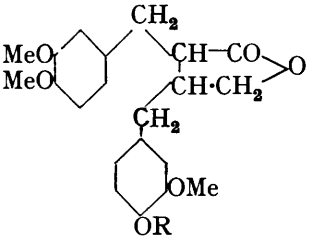
By Robert D. Haworth and William Kelly.

The seeds of the burdock (*Arctium Lappa*, L.) contain the glucoside arctiin, which was isolated by Shinoda and Kawagoe (*J. Pharm. Soc. Japan*, 1929, **49**, 565, 1165). Hydrolysis with 30% sulphuric acid yielded glucose and a lævorotatory lactone, arctigenin, $C_{22}H_{26}O_6$, containing three methoxyl groups, and the formation of 3-methoxy-4-ethoxybenzoic acid and veratric acid by the oxidation of *l*-arctigenin ethyl ether indicated the presence of both guaiacol and veratrole residues. Omaki (*ibid.*, 1935, **55**, 159 and private communication)

modified the molecular formula to $C_{21}H_{24}O_6$ and limited the structural formula to (I; R = H) or (II; R = H) by identifying *l*-arctigenin methyl ether with *l*-matairesinol



(I.)



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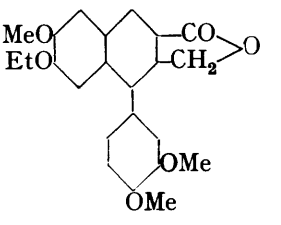
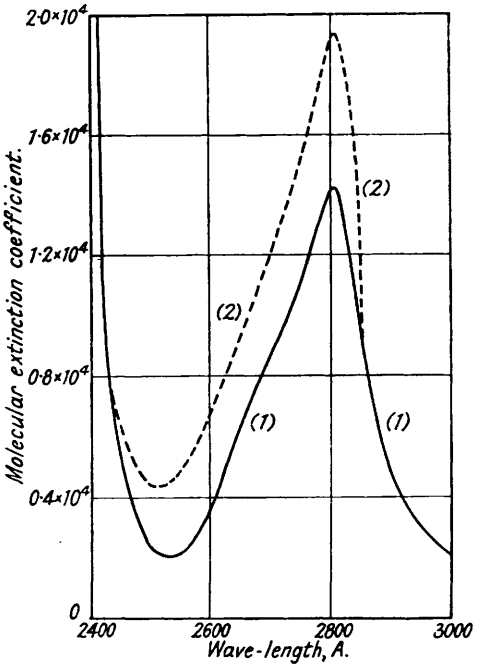


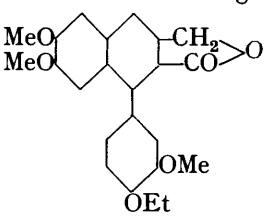
(III.)

dimethyl ether. The present communication describes experiments which enable a decision to be made between those two alternative formulæ. The Japanese chemists were unable to obtain *l*-arctigenin ethyl ether in the crystalline form. We have been equally unsuccessful in this respect, but crystalline *dinitro-* and *dibromo*-derivatives have been prepared. By reactions similar to those described in Part V (this vol., p. 725), racemic forms of the lactones (I; R = Et) and (II; R = Et) have been synthesised. These lactones are crystalline and yield crystalline dinitro- and dibromo-derivatives. The ultra-violet absorption spectra of *l*-arctigenin ethyl ether and the synthetic lactone (I; R = Et) were identical (Fig.); the lactone (II; R = Et) exhibited a maximum at the same wave-length, but the intensity of absorption was appreciably greater than in the case of *l*-arctigenin ethyl ether.



(1) l-*Arctigenin ethyl ether* or *synthetic lactone* (I; R = Et).
(2) *Synthetic lactone* (II; R = Et).

Conclusive evidence in favour of (I; R = H) has been obtained by studying the cyclo-dehydrogenation of *l*-arctigenin ethyl ether under conditions similar to those employed previously in the case of *l*-matairesinol dimethyl ether (J., 1935, 633). When *l*-arctigenin ethyl ether was treated with lead tetra-acetate, it was converted into a mixture of two isomeric lactones, $C_{23}H_{22}O_6$, melting at 224° and 248°, which have been identified as (III) and (IV) respectively, by comparison with synthetic specimens obtained by methods described in the experimental section. Of the two alternative formulæ for *l*-arctigenin, only (I; R = H) accounts for its conversion into the lactones (III) and (IV). The lactones (V) and (VI), which are the anticipated cyclo-dehydrogenation products of (II; R = Et), have also been synthesised, and the difference between (V) and (VI) and the products obtained from *l*-arctigenin ethyl ether exclude formula (II; R = H) for arctigenin.



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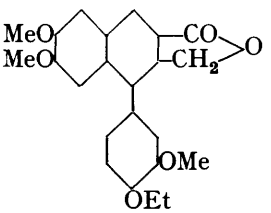
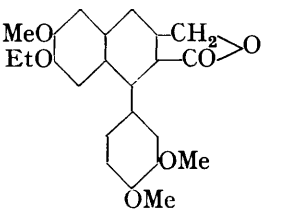


(V.)



(VI.)

Experimental.

l-*Arctigenin Ethyl Ether* (I; R = Et).—*l*-Arctigenin (0·5 g. kindly supplied by Dr. T. Omaki) was dissolved in alcohol (5 c.c.) containing potassium hydroxide (0·2 g.). Ethyl sulphate (0·5 g.) was added and after 12 hours the solution was heated for 1 hour on the water-bath. Most of the alcohol was removed by distillation and the residue was acidified and lactonised by heating at 100° for ½ hour. The product was extracted with ether, washed with dilute sodium hydroxide solution, and dried, and the solvent removed. The residual oil (0·5 g.) did not crystallise. The *dibromo*-derivative, prepared by the addition of bromine (2 mols.) to a solution of the ether in acetic acid (10 parts), crystallised from methyl alcohol in colourless slender prisms, m. p. 128—129° (Found : C, 49·4; H, 4·6. $C_{23}H_{26}O_6Br_2$ requires C, 49·5; H, 4·7%). The *dinitro*-compound, prepared by the action of nitric acid in cold acetic acid solution, crystallised from chloroform–methyl alcohol in pale yellow needles, m. p. 166—167° (Found : C, 56·5; H, 5·5. $C_{23}H_{26}O_{10}N_2$ requires C, 56·3; H, 5·3%).

Cyclo-dehydrogenation of l-*Arctigenin Ethyl Ether.*—*l*-Arctigenin ethyl ether (0·25 g.) and lead tetra-acetate (0·75 g.) were heated in acetic acid (3 c.c.) for ½ hour at 80°. After addition of water, the mixture was extracted with chloroform and the extract was washed with aqueous sodium bicarbonate, the solvent removed, and the residue dissolved in a little methyl alcohol. The solid (25 mg., m. p. 190—220°), which gradually separated, was collected after 3 hours and fractionally crystallised from chloroform–methyl alcohol. The sparingly soluble fractions eventually yielded cream-coloured stout prisms, m. p. 247—248° (Found : C, 70·0; H, 5·7. $C_{23}H_{22}O_6$ requires C, 70·1; H, 5·6%). The tail fractions yielded colourless slender needles, m. p. 223—224° (Found : C, 69·9; H, 5·7%). The lower-melting compound dissolves more rapidly than the isomer in chloroform–methyl alcohol and this fact is of considerable use in effecting the separation.

3-*Methoxy*-4-*ethoxybenzoic Acid.*—3-Methoxy-4-ethoxybenzaldehyde (10 g.) was suspended in a boiling solution of sodium bicarbonate (5 g.) in water (50 c.c.), and a solution of potassium permanganate (9 g.) in water (200 c.c.) gradually added. The manganese dioxide was removed and washed with hot water, the combined washings and filtrate were acidified and cooled, and the 3-methoxy-4-ethoxybenzoic acid (10 g.), m. p. 195°, collected. The acid chloride, prepared in 90% yield by the action of thionyl chloride, boiled at 158—160°/0·2 mm. and crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 73° (Vanzetti and Dreyfuss, *Gazzetta*, 1934, **66**, 381, give m. p. 73°).

O-*Ethyleugenol Oxide.*—*O*-Ethyleugenol (25 g.) was shaken for 24 hours with a suspension of iodine (40 g.) and mercuric oxide (18 g.) in moist ether (100 c.c., containing 6 c.c. of water). The dried filtrate was shaken with powdered potassium hydroxide (50 g.) for 48 hours, filtered, washed with water, and dried, the solvent removed, and the residue distilled. O-*Ethyleugenol oxide* (14 g.), b. p. 137—138°/0·2 mm., was obtained as a colourless liquid which rapidly solidified and crystallised from ether–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 37—38° (Found : C, 68·9; H, 7·5. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

α-*Cyano*-β-3-*methoxy*-4-*ethoxyphenylacrylic Acid.*—3-Methoxy-4-ethoxybenzaldehyde (10 g.) in alcohol (15 c.c.) was mixed with a 25% solution of sodium cyanoacetate (30 c.c.) : 10% sodium hydroxide solution (5 c.c.) was added, the solution shaken and kept for 1 hour, and neutral impurities removed in ether. Acidification of the filtrate precipitated the *acid*, which separated from methylated spirits in lemon-yellow needles (9·2 g.), m. p. 212—213° (Found : equiv., 247. $C_{13}H_{13}O_4N$ requires equiv., 247).

α-*Cyano*-β-3-*methoxy*-4-*ethoxyphenylpropionic acid* was prepared by adding, with rapid stirring, an ice-cold suspension of the above acid (10 g.) in water (250 c.c.) to 2% sodium amalgam (350 g.). The temperature was kept at 0° and a continuous stream of carbon dioxide was passed until the amalgam was exhausted. Acidification yielded the *acid* (9 g.), which crystallised from benzene in colourless prisms, m. p. 152—153° (Found : equiv., 251. $C_{13}H_{15}O_4N$ requires equiv., 249). The *methyl* ester, prepared by boiling the acid (8 g.) with 4% methyl-alcoholic hydrogen chloride (90 c.c.), crystallised from methyl alcohol in colourless plates (7 g.), m. p. 61—62° (Found : C, 63·6; H, 6·4. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5%).

Ethyl 3-*Methoxy*-4-*ethoxybenzoylacetate.*—Solutions of sodium (4·6 g.) in alcohol (75 c.c.) and 3-methoxy-4-ethoxybenzoyl chloride (10·7 g.) in ether (75 c.c.) were added to ethyl acetoacetate (13·5 g.) in ether (75 c.c.), the additions being made in three portions as described by Perkin and Weizmann (J., 1906, **89**, 1659) for a similar case. After 60 hours, the precipitate (X) was collected, suspended in water, and acidified, and the solid product was collected, dissolved in a solution of ammonium chloride (9 g.) in 15% aqueous ammonia (50 c.c.) and water (200 c.c.),

and shaken for ½ hour. The precipitate was collected and crystallised from methyl alcohol; jagged prisms (4·2 g.), m. p. 79—80°, were obtained, giving a brown ferric test (Found : C, 63·2; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). A further yield (1·8 g.) was obtained from the filtrate from (X). Water was added, neutral impurities removed in benzene, and the alkaline liquor acidified and extracted with ether. Removal of the ether left an oil, which was shaken with ammonia and ammonium chloride as described above.

β-3-*Methoxy*-4-*ethoxybenzoylpropionic Acid.*—The above benzoylacetate (5·8 g.) and ethyl bromoacetate (4·1 g.) were added to a solution of sodium (0·56 g.) in alcohol (50 c.c.). After boiling for 16 hours, the solution was diluted, acidified, and extracted with ether. Removal of the ether gave an oil, which was hydrolysed by boiling first for 48 hours with 20% sulphuric acid (80 c.c.) and then for 2 hours with a small excess of 5% methyl-alcoholic potassium hydroxide. The alcohol was removed, water added, and neutral products removed in ether; acidification yielded the *acid*, which crystallised from benzene in colourless needles (4·0 g.), m. p. 136—137° (Found : equiv., 248. $C_{13}H_{16}O_5$ requires equiv., 252).

β-3 : 4-*Dimethoxybenzyl*-α-3-*methoxy*-4-*ethoxybenzylbutyrolactone* (dl-*Arctigenin Ethyl Ether*) (I; R = Et).—Methyl sodio-α-cyano-β-3-methoxy-4-ethoxyphenylpropionate [prepared from the methyl ester (2 g.) and sodium (0·2 g.)] in alcohol (20 c.c.) and *O*-methyleugenol oxide (1·6 g.) were allowed to react at room temperature for 4 days. The solution was diluted with water, and neutral impurities removed in ether; the alkaline liquor was acidified with dilute hydrochloric acid and heated on the water-bath for 15 minutes. The oil, isolated with ether, was boiled for 3 hours with concentrated hydrochloric acid (10 c.c.). The *product* was extracted with chloroform and washed with dilute sodium hydroxide solution, and the solvent removed; the residue crystallised from methyl alcohol in colourless hexagonal plates (0·7 g.), m. p. 105—106° (Found : C, 68·8; H, 6·9. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·0%). The *dibromo*-derivative, prepared in cold acetic acid solution, separated from methyl alcohol in slender needles, m. p. 88—89° (Found : C, 49·3; H, 4·9. $C_{23}H_{26}O_6Br_2$ requires C, 49·5; H, 4·7%). The *dinitro*-compound, prepared by the action of concentrated nitric acid (2·2 mols.) in acetic acid solution, crystallised from chloroform–ethyl alcohol in pale yellow, felted needles, m. p. 159° (Found : C, 56·2; H, 5·6. $C_{23}H_{26}O_{10}N_2$ requires C, 56·3; H, 5·3%).

α-3 : 4-*Dimethoxybenzyl*-β-3-*methoxy*-4-*ethoxybenzylbutyrolactone* (II; R = Et), prepared from methyl sodio-α-cyano-β-3 : 4-dimethoxyphenylpropionate (from 2 g. of ester) (this vol., p. 728) and *O*-ethyleugenol oxide (1·6 g.) as described above in the preparation of the isomer (I; R = Et), crystallised from methyl alcohol in hexagonal prisms (0·7 g.), m. p. 95—96° (Found : C, 69·1; H, 7·1. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·0%). The *dibromo*-derivative separated from methyl alcohol in slender needles, m. p. 99—100° (Found : C, 49·3; H, 4·6. $C_{23}H_{26}O_6Br_2$ requires C, 49·5; H, 4·7%). The *dinitro*-compound was obtained in pale yellow, felted needles, m. p. 172—173°, from chloroform–ethyl alcohol (Found : C, 56·1; H, 5·2. $C_{23}H_{26}O_{10}N_2$ requires C, 56·3; H, 5·3%).

Synthesis of cyclo-*Dehydro-lactones with* CO *in Position* 2.—α-*Acetyl*-β-3-*methoxy*-4-*ethoxybenzylbutyrolactone.* A mixture of *O*-ethyleugenol oxide (10 g.) and ethyl sodioacetoacetate (prepared from the ester, 10 g.) in alcohol (25 c.c.) was kept for 7 days at room temperature. Water was added, neutral impurities removed in ether, and the alkaline liquor acidified. The *butyrolactone*, isolated with benzene, crystallised from benzene–ether in colourless slender needles (7·6 g.), m. p. 87—88°, which gave a purple ferric test (Found : C, 66·0; H, 6·9. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·9%).

α-3 : 4-*Dimethoxybenzoyl*-β-3-*methoxy*-4-*ethoxybenzylbutyrolactone* (a i). 3 : 4-Dimethoxybenzoyl chloride (5·3 g.) was added to the sodio-derivative of the above lactone (prepared from the lactone, 7·5 g., and sodium, 0·6 g.) in benzene (70 c.c.). After 12 hours the mixture was boiled for 1 hour and washed with 1% sodium hydroxide solution, and most of the benzene removed. The residue was mixed with ether (100 c.c.) and shaken with 5% sodium hydroxide solution (80 c.c.) for 7 hours. The alkaline layer was acidified, and the *lactone* (a i) isolated with chloroform and washed with sodium bicarbonate solution; it crystallised from methyl alcohol in colourless lustrous plates (4·2 g.), m. p. 129—130°, which gave a green ferric test (Found : C, 66·8; H, 6·3. $C_{23}H_{26}O_7$ requires C, 66·7; H, 6·3%).

α-3-*Methoxy*-4-*ethoxybenzoyl*-β-3 : 4-*dimethoxybenzylbutyrolactone* (b i), prepared from α-acetyl-β-3 : 4-dimethoxybenzylbutyrolactone (10 g.) (this vol., p. 727) and 3-methoxy-4-ethoxybenzoyl chloride (8 g.) as described above in the preparation of (a i), crystallised from methyl alcohol in colourless plates (7 g.), m. p. 123—124°, which gave a green ferric test (Found : C, 66·9; H, 6·3. $C_{23}H_{26}O_7$ requires C, 66·7; H, 6·3%).

Lactone of 6-*methoxy*-7-*ethoxy*-1-3′ : 4′-*dimethoxyphenyl*-3-*hydroxymethyl*-3 : 4-*dihydronaphthalene*-2-*carboxylic acid* (a ii). The lactone (a i) (1 g.) was warmed for 20 minutes with methyl-alcoholic hydrogen chloride; the product, isolated with ether and washed with dilute sodium hydroxide solution, was dehydrated with potassium hydrogen sulphate (2 g.) at 180° for ¾ hour. The *lactone* (a ii), isolated with chloroform, crystallised from chloroform–methyl alcohol in small cubic crystals (0·6 g.), m. p. 189—190° (Found: C, 69·7; H, 6·3. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1%).

The *lactone* of 6 : 7-*dimethoxy*-1-3′-*methoxy*-4′-*ethoxyphenyl*-3-*hydroxymethyl*-3 : 4-*dihydronaphthalene*-2-*carboxylic acid* (b ii), prepared similarly from (b i), crystallised from chloroform–methyl alcohol in colourless prisms, m. p. 192—193° (Found: C, 69·5; H, 6·0. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1%).

Lactone of 6-*methoxy*-7-*ethoxy*-1-3′ : 4′-*dimethoxyphenyl*-3-*hydroxymethylnaphthalene*-2-*carboxylic acid* (VI). The dihydronaphthalene (a ii) (0·1 g.) was heated for ¼ hour at 80° with lead tetra-acetate (0·2 g.) in acetic acid (2 c.c.). After dilution with water the product was extracted with chloroform and washed with sodium bicarbonate solution, the solvent removed, and the residue crystallised from chloroform–methyl alcohol, forming colourless rectangular prisms (0·08 g.), m. p. 243—244° (Found: C, 69·9; H, 5·8. $C_{23}H_{22}O_6$ requires C, 70·1; H, 5·6%). A depression in m. p. of about 20° was observed when this *lactone* (VI) was mixed with the lactone, m. p. 247—248°, obtained by the action of lead tetra-acetate on *l*-arctigenin ethyl ether.

The *lactone* of 6 : 7-*dimethoxy*-1-3′-*methoxy*-4′-*ethoxyphenyl*-3-*hydroxymethylnaphthalene*-2-*carboxylic acid* (IV), prepared similarly from (b ii), crystallised from chloroform–methyl alcohol in cream-coloured prisms, m. p. 247—248° (Found: C, 70·0; H, 5·7. $C_{23}H_{22}O_6$ requires C, 70·1; H, 5·6%), which gave no depression on admixture with the lactone, m. p. 247—248°, obtained from *l*-arctigenin ethyl ether.

Synthesis of cyclo-*Dehydro-lactones with* CO *in Position* 3.—β-3 : 4-*Dimethoxybenzoyl*-α-3-*methoxy*-4-*ethoxybenzylideneпropionic acid* (c i). Dry powdered sodium β-3 : 4-dimethoxybenzoylpropionate (4 g.), 3-methoxy-4-ethoxybenzaldehyde (4 g.), and acetic anhydride (4 c.c.) were heated on the water-bath for 2 hours. Water was added, and the product collected, washed successively with water, methyl alcohol, and ether, and crystallised from chloroform–methyl alcohol. The *γ-lactone* separated in golden-yellow needles (4·6 g.), m. p. 180° (Found: C, 69·2; H, 5·7. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%). The lactone (2·2 g.) was warmed for ½ hour with a solution of sodium methoxide (prepared from sodium, 0·16 g.) in methyl alcohol (10 c.c.). After the addition of water and boiling for ½ hour, the alcohol was removed; the *acid*, liberated by acidification of the filtered solution, crystallised from chloroform–methyl alcohol in colourless felted needles (1·8 g.), m. p. 188—189° (Found: equiv., 397. $C_{23}H_{24}O_7$ requires equiv., 400).

β-3-*Methoxy*-4-*ethoxybenzoyl*-α-3 : 4-*dimethoxybenzylidenepropionic acid* (d i). The *γ-lactone* prepared similarly from β-3-methoxy-4-ethoxybenzoylpropionic acid and veratraldehyde, separated from benzene in yellow needles, m. p. 162—163° (Found: C, 69·1; H, 6·0. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%). The *acid* (d i) crystallised from chloroform–methyl alcohol in colourless prisms, m. p. 189—190° (Found: equiv., 399. $C_{23}H_{24}O_7$ requires equiv., 400).

β-3 : 4-*Dimethoxybenzoyl*-α-3-*methoxy*-4-*ethoxybenzylidene*-β-*methylenepropionic acid* (c ii). The keto-acid (c i) (2·8 g.) in 10% sodium hydroxide solution (14 c.c.) was kept for 22 hours with 20% formalin (7 c.c.). The diluted solution was acidified, and the *product* collected and crystallised from benzene; colourless prisms (2·5 g.), m. p. 180°, were obtained (Found: equiv., 408. $C_{23}H_{24}O_7$ requires equiv., 412).

β-3-*Methoxy*-4-*ethoxybenzoyl*-α-3 : 4-*dimethoxybenzylidene*-β-*methylenepropionic acid* (d ii), prepared similarly by the action of formalin on (d i), crystallised from chloroform–benzene in colourless prisms, m. p. 176—177° (Found: equiv., 409. $C_{23}H_{24}O_7$ requires equiv., 412).

Lactone of 6-*methoxy*-7-*ethoxy*-1-3′ : 4′-*dimethoxyphenyl*-2-*hydroxymethylnaphthalene*-3-*carboxylic acid* (III). The methylene acid (c ii) (2·2 g.), glacial acetic acid (14 c.c.), and concentrated hydrochloric acid (30 c.c.) were allowed to react for 24 hours. After dilution with water, the solid was collected and warmed on the water-bath with 10% sodium hydroxide solution (10 c.c.) for 1 hour. The filtered solution was acidified, heated at 100° for 1 hour, and treated with sodium bicarbonate solution. The *lactone* (III) was collected; it crystallised from chloroform–methyl alcohol in colourless slender needles (1·9 g.), m. p. 223—224° (Found: C, 69·9; H, 5·7. $C_{23}H_{22}O_6$ requires C, 70·1; H, 5·6%), which gave no depression in m. p. when mixed with the lactone, m. p. 223—224°, obtained by the action of lead tetra-acetate on *l*-arctigenin ethyl ether.

The *lactone* of 6 : 7-*dimethoxy*-1-3′-*methoxy*-4′-*ethoxyphenyl*-2-*hydroxymethylnaphthalene*-3-*carboxylic acid* (V), prepared similarly from the methylene acid (d ii), crystallised from chloroform–methyl alcohol in colourless needles, m. p. 214—215° (Found: C, 69·9; H, 5·7. $C_{23}H_{22}O_6$

requires C, 70·1; H, 5·6%). A mixture of the lactone (V) and the lactone, m. p. 223—224°, from *l*-arctigenin ethyl ether melted at 200—205°.

Spectroscopic Data.—The measurements were made in approx. *M*/12,000-alcoholic solutions.

	$\lambda_{max.}$ (A.).	$\epsilon_{max.} \times 10^{-4}$.
l-Arctigenin ethyl ether.....	2,800	1·45
Synthetic lactone (I; R = Et)	2,800	1·45
Synthetic lactone (II; R = Et)	2,800	1·95

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