Synthesis of Eriostoic Acid and Eriostemoic Acid[1)]

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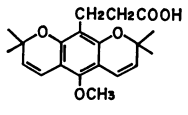
A 1,8-dioxaanthracenepropionic acid derivative (**5**), after being converted into methyl ester-methyl ether (**6**), was reduced with sodium borohydride to give methyl eriostate (**7**). Hydrolysis of the ester (**7**) with alkali afforded eriostoic acid (**1**). On the other hand, eriostemoic acid (**2**) was synthesized from methyl eriostemate (**10**), which was obtained from a 1,5-dioxaphenanthrenepropionic acid derivative (**8**) *via* four steps.

Eriostoic acid has been isolated from *Eriostemon differmis* and the structure has been elucidated to be a linear-type benzodipyran (10-methoxy-2,2,7,7-tetramethyl-2*H*,7*H*-1,8-dioxaanthracene-9-propionic acid) (**1**) on the basis of degradation and spectral evidence.[2)] On the other hand, eriostemoic acid isolated from *Eriostemon tomentellus* has been shown to be an angular-type benzodipyran derivative (9-methoxy-2,2,6,6-tetramethyl-2*H*,6*H*-1,5-dioxaphenanthrene-10-propionic acid) (**2**) which is closely related to **1**.[3)] The present paper reports on the synthesis of **1** and **2** for confirmation of the proposed structures of natural eriostoic and eriostemoic acids.



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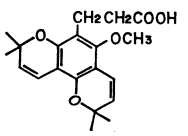
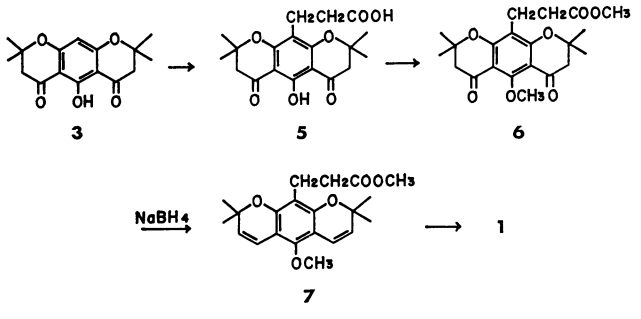


2

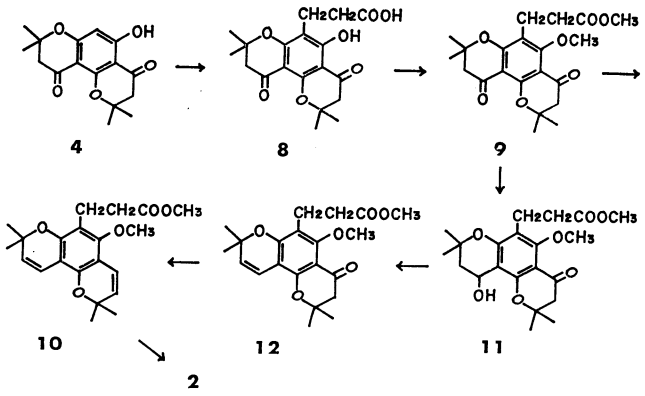
The condensation of a 1,8-dioxaanthracene derivative (**3**)[4)] with acrylic acid in the presence of polyphosphoric acid gave a 1,8-dioxaanthracenepropionic acid derivative (**5**). The exhaustive methylation of **5** with dimethyl sulfate afforded the corresponding methyl ester-methyl ether (**6**). The reduction of **6** with an excess of sodium borohydride[5)] in dry methanol containing a small amount of pyridine gave directly methyl eriostate (**7**). The NMR spectrum showed the presence of four vinylic protons as two overlapping doublets at δ 5.45 (2H) and 6.48 (2H) ppm, and the IR spectrum showed an olefinic group at 1630 cm^{-1} and the disappearance of the carbonyl group. Hydrolysis of **7** with 4% aqueous methanolic sodium hydroxide smoothly produced the desired acid (**1**) (mp 173—174 °C),[2)] which was shown to be identical with natural eriostoic acid on the basis of a mixed-melting-point determination and by NMR, IR, and UV spectral comparisons.



3 5 6 7

Scheme 1.

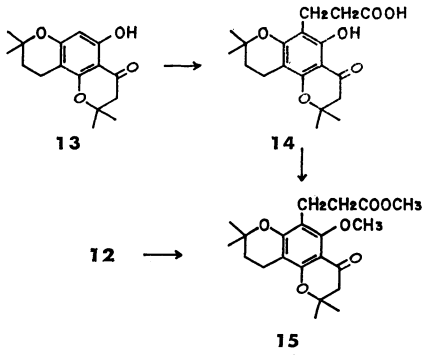
In a similar manner, the 1,5-dioxaphenanthrenepropionic acid derivative (**8**), which was obtained by the condensation of a 1,5-dioxaphenanthrene derivative (**4**)[4)] with acrylic acid and whose structure was confirmed by NMR and IR spectra, was converted into the corresponding methyl ester-methyl ether (**9**). The reduction of **9** with sodium borohydride gave methyl eriostemate (**10**) in a poor yield. Hydrolysis of **10** with dilute alkali afforded the desired acid (**2**) (mp 101—102 °C),[3)] which was shown to be identical with natural eriostemoic acid on the basis of a mixed-melting-point determination and by NMR, IR, and UV spectral comparisons.



Scheme 2.

In view of the low yield of methyl eriostemate, an alternate method of preparing this compound was further investigated. The methyl ester-methyl ether (**9**) was converted into an alcohol derivative (mp 114—115 °C) (**11**) by catalytic reduction with Raney nickel in methanol under atmospheric conditions. The dehydration of the alcohol (**11**) with freshly-fused potassium hydrogensulfate in dry toluene was smoothly effected to give the corresponding dihydro-1,5-dioxaphenanthrenepropionic acid derivative (**12**). The NMR spectrum showed the presence of one vinyl group as a pair of doublets at δ 5.37 and 6.48 ppm and one methylene group as a singlet at δ 2.51 ppm, and the IR spectrum showed the presence of an olefinic group at 1637 cm^{-1} and the disappearance of the hydroxyl group. The reduction of **12** with sodium borohydride in dry tetrahydrofuran gave methyl eriostemate (**10**) in a 37% yield, which was identical with the sample synthesized in the manner described above.

The reduction of **12** with palladium charcoal in methanol gave the corresponding tetrahydro-1,5-dioxaphenanthrenepropionic acid derivative (**15**), which was identical with that derivative (**15**) obtained from



Scheme 3.

a tetrahydro-1,5-dioxaphenanthrene derivative (**13**)[4] *via* two steps, as shown in Scheme 3. Therefore, structure of the alcohol derivative (**11**) was elucidated on the basis of the facts described above.

Experimental

The melting points are uncorrected. The IR spectra were taken with a Hitachi 215 Spectrophotometer, and the UV spectra with a Hitachi 124 Spectrophotometer. The NMR spectra were determined with a JOEL PS-100 Spectrometer (100 MHz) using tetramethylsilane as an internal standard (δ, ppm). Column chromatography was carried out on Kieselgel 60 (70—230 mesh) (Merck).

*10-Hydroxy-2,2,7,7-tetramethyl-4,5-dioxo-3,4,5,6-tetrahydro-2*H,*7*H-*1,8-dioxaanthracene-9-propionic Acid* (**5**). 10-Hydroxy-2,2,7,7-tetramethy-4,5-dioxo-3,4,5,6-tetrahydro-2*H*,7*H*-1,8-dioxaanthracene (**3**) (5.6 g), which was prepared according to a procedure described by Jefferson *et al.*,[4] and acrylic acid (3 g) were heated in the presence of freshly-prepared polyphosphoric acid (90 g) with stirring at 80—85 °C for 2 h and then poured into ice-cold water (300 ml). The diluted reaction mixture was allowed to stand overnight at room temperature to afford a white precipitate. The precipitate, after being dissolved in chloroform (200 ml), was extracted with 5% aqueous sodium carbonate (50 ml×3), and the alkalin solution was acidified with dilute hydrochloric acid to give acid **5** (3 g, 43%), which produced a light brown ferric chloride reaction in ethanol and which was obtained as colorless needles upon recrystallization from methanol: mp 190—191 °C; IR ν_{max}^{KBr}: 1610, 1675, 1735 cm^{-1}; NMR ($CDCl_3$) δ: 1.46 (s, 12H, CH_3 × 4), 2.66 (s, 4H, CH_2CO × 2), 2.37—2.92 (m, 4H, CH_2CH_2), 13.76 (s, 1H, OH). Found: C, 62.73; H, 6.19%. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12%.

*Methyl 10-Methoxy-2,2,7,7-tetramethyl-4,5-dioxo-3,4,5,6-tetrahydro-2*H,*7*H-*1,8-dioxaanthracene-9-propionate* (**6**). A mixture of acid **5** (3 g), dimethyl sulfate (7 g), and anhydrous potassium carbonate (8 g) was heated under reflux in dry acetone (100 ml) for 25 h. The resulting product was recrystallized from methanol to give methyl ester-methyl ether (**6**) (2.5 g, 77%) as colorless needles: mp 121.5—122.5 °C; IR ν_{max}^{KBr} 1693, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (s, 12H, CH_3 ×4), 2.63 (s, 4H, CH_2CO×2), 2.34—2.96 (m, 4H, CH_2CH_2), 3.67 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3). Found: C, 64.61; H, 6.73%. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71%.

Methyl Eriostate (**7**). Sodium borohydride (0.16 g) was added portionwise to a solution of methyl ester-methyl ether **6** (0.39 g) in a mixture of dry methanol (15 ml) and pyridine (3.5 ml) with stirring for 1 h at room temperature, and the mixture was further warmed at 45 °C for 9 h. The reaction mixture was then cooled, acidified with dilute hydrochloric acid and extracted with ether, and the ethereal solution was washed with a saturated aqueous solution of sodium chloride and dried, and the solvent was evaporated. The residue was purified by column chromatography with silica gel and benzene to give an oil (**7**) (61 mg, 17%), which was crystallized from hexane as colorless prisms (mp 96—97 °C, lit, mp 94 °C[2]): IR ν_{max}: 1630, 1735 cm^{-1}; NMR ($CDCl_3$) δ: 1.39 (s, 12H, CH_3×4), 2.36—2.94 (m, 4H, CH_2-CH_2), 3.66 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 5.45 and 6.48 (each d, 2H, J=10 Hz, CH=CH). Found: C, 70.13; H, 7.40%. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31%.

Eriostoic Acid (**1**). Methyl eriostate (**7**) (22 mg) was hydrolyzed with 4% aqueous methanolic sodium hydroxide (20 ml) at 80 °C for 30 min. The reaction mixture was then acidified with dilute hydrochloric acid to afford eriostoic acid (**1**) as white precipitates, which was recrystallized from ethyl acetate as colorless prisms (20 mg, 95%) (mp 173—174 °C, lit, mp 173—174 °C,[2] no depression in a mixed-melting-point determination with natural eriostoic acid): IR ν_{max}^{KBr}: 1630, 1718 cm^{-1}; NMR ($CDCl_3$) δ: 1.40 (s, 12H, CH_3×4), 2.43—2.97 (m, 4H, CH_2CH_2), 3.70 (s, 3H, OCH_3), 5.45 and 6.48 (each d, 2H, J=10 Hz, CH=CH); UV λ_{max}^{EtOH} nm (log ε): 259 (4.60), 268 (4.59), 340 (3.52). Found: C, 69.87; H, 7.18%. Calcd for $C_{20}H_{24}O_5$: C, 69.74; H, 7.02%.

*9-Hydroxy-2,2,6,6-tetramethyl-4,8-dioxo-3,4,7,8-tetrahydro-2*H,*6*H-*1,5-dioxaphenanthrene-10-propionic Acid* (**8**). 9-Hydroxy-2,2,6,6-tetramethyl-4,8-dioxo-3,4,7,8-tetrahydro-2*H*,6*H*-1,5-dioxaphenanthrene (**4**)[4] (6 g) and acrylic acid (3 g) were heated in the presence of freshly-prepared polyphosphoric acid (90 g) with stirring at 80—85 °C for 2 h. The reaction mixture was similary treated as described for the preparation of **5** to give acid **8** (3.4 g, 45%), which showed a light brown ferric chloride reaction in ethanol, as colorless needles: mp 192—193 °C; IR ν_{max}^{KBr}: 1632, 1687, 1706 cm^{-1}; NMR ($CDCl_3$) δ: 1.45 (s, 6H, CH_3×2), 1.53 (s, 6H, CH_3×2), 2.63 (s, 2H, CH_2CO), 2.72 (s, 2H, CH_2CO), 2.44—2.96 (m, 4H, CH_2-CH_2), 12.94 (s, 1H, OH). Found: C, 62.83; H, 6.12%. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12%.

*Methyl 9-Methoxy-2,2,6,6-tetramethyl-4,8-dioxo-3,4,7,8-tetrahydro-2*H,*6*H-*1,5-dioxaphenanthrene-10-propionate* (**9**). A mixture of acid **8** (4 g), dimethyl sulfate (7 g), and anhydrous potassium carbonate (8 g) was heated under reflux in dry acetone (100 ml) for 25 h. The product was recrystallized from methanol to give methyl ester-methyl ether **9** (3.5 g, 81%) as colorless needles: mp 105—106 °C; IR ν_{max}^{KBr}: 1683, 1725 cm^{-1}; NMR ($CDCl_3$) δ: 1.45 (s, 6H, CH_3×2), 1.49 (s, 6H, CH_3×2), 2.64 (s, 4H, CH_2CO×2), 2.36—2.94 (m, 4H, CH_2CH_2), 3.65 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3). Found: C, 64.45; H, 6.77%. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71%.

Methyl Eriostemate (**10**). Sodium borohydride (0.24 g) was added portionwise to a solution of methyl ester-methyl ether **9** (0.5 g) in a mixture of dry methanol (20 ml) and pyridine (4 ml) with stirring for 1 h at room temperature, and the mixture was maintained at 45 °C for 9 h. The reaction product thus obtained was purified by column chromatography with silica gel and benzene to give methyl eriostemate (liquid) (**10**) (28 mg, 6%): IR ν_{max}: 1635, 1735 cm^{-1}; NMR (CCl_4) δ: 1.38 (s, 6H, CH_3×2), 1.40 (s, 6H, CH_3×2), 2.28—2.79 (m, 4H, CH_2CH_2), 3.60 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 5.33 (d, 2H, J=10 Hz, CH=CH), 6.38 and 6.48 (each d, 1H, J=10 Hz, CH=CH). Found: C, 70.24; H, 7.40%. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31%.

Eriostemoic Acid (**2**). Methyl eriostemate (**10**) (25 mg) was hydrolyzed with 4% aqueous methanolic sodium hydro-

xide (20 ml) at 80 °C for 30 min. The reaction mixture, after being acidified with dilute hydrochloric acid, was extracted with ether and the ethereal solution was washed with water and dried, and the solvent was evaporated. The residue was eluted over a silica gel column with chloroform–ethyl acetate (4 : 1) to give the desired acid (**2**) (20 mg, 83%), which was recrystallized from hexane as colorless prisms (mp 101—102 °C, lit, mp 101 °C,[3]) no depression in a mixed-melting-point determination with natural eriostemoic acid): IR ν_{max}^{KBr}: 1640, 1708 cm^{-1}; NMR ($CDCl_3$) δ: 1.39 (s, 12H, $CH_3\times4$), 2.43—2.93 (m, 4H, CH_2CH_2), 3.69 (s, 3H, OCH_3), 5.45 (d, 2H, $J=10$ Hz, CH=CH), 6.46 and 6.59 (each d, 1H $J=10$ Hz, CH=CH). UV λ_{max}^{EtOH} nm (log ε): 206 (4.29), 254 (4.33), 258 (4.33), 280 (4.13), 331 (3.39), 347 (3.29). Found: C, 70.03; H, 7.09%. Calcd for $C_{20}H_{24}O_5$: C, 69.74; H, 7.02%.

*Methyl 4-Hydroxy-9-methoxy-2,2,6,6-tetramethyl-8-oxo-3,4,7,8-tetrahydro-2H,6H-1,5-dioxaphenanthrene-10-propionate (**11**).* Methyl ester-methyl ether **9** (0.95 g) was hydrogenated over Raney nickel (6 g) in methanol (30 ml) under atmospheric pressure at room temperature. After the uptake of hydrogen ceased, the solution was filtered and the solvent was evaporated under reduced pressure. The residue thus obtained was purified in column chromatography with silica gel and chloroform–ethyl acetate (20 : 1) to afford a colorless solid, showing lower R_f value (0.32) than that (0.39) of the starting material. The solid was recrystallized from light petroleum ether (40—50 °C) to give alcohol derivative **11** (0.44 g, 46%) (mp 114—115 °C) as colorless prisms: IR ν_{max}^{KBr}: 1665, 1738, 3460 cm^{-1}; NMR ($CDCl_3$) δ: 1.39 (s, 3H, CH_3), 1.47 (s, 6H, $CH_3\times2$), 1.53 (s, 3H, CH_3), 2.04 (d, 2H, CH_2), 2.68 (s, 2H, CH_2CO), 2.37—2.95 (m, 4H, CH_2CH_2), 3.68 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.92 (t, 1H, CHOH). Found: C, 64.12; H, 7.28%. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19%.

*Methyl 9-Methoxy-2,2,6,6-tetramethyl-8-oxo-7,8-dihydro-2H,6H-1,5-dioxaphenanthrene-10-propionate (**12**).* Alcohol **11** (0.45 g) was refluxed with freshly-fused potassium hydrogensulfate (2 g) in toluene (5 ml) for 7 h. The mixture was then filtered and the filtrate was evaporated under reduced pressure to give a colorless oil, which was purified over a silica gel column with chloroform–methyl ethyl ketone (50 : 1) to give colorless needles **12** (0.4 g, 93%) (mp 85—86 °C, crystallization from light petroleum ether): IR ν_{max}: 1637, 1678, 1735 cm^{-1}; NMR (CCl_4) δ: 1.45 (bs, 12H, $CH_3\times4$), 2.51 (s, 2H, CH_2CO), 2.27—2.83 (m, 4H, CH_2CH_2), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 5.37 and 6.48 (each d, 1H, $J=10$ Hz, CH=CH). Found: C, 67.09; H, 7.11%. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00%.

*Another Synthesis of Methyl Eriostemate (**10**).* Sodium borohydride (90 mg) was added portionwise to a solution of methyl ester **12** (0.145 g) in dry tetrahydrofuran (15 ml) with stirring for 1 h at room temperature, and the mixture was refluxed for 6 h. The reaction mixture was cooled and treated as described above to give an oil. The oil was eluted over a silica gel column with benzene to give methyl eriostemate (liquid) (**10**) (52 mg, 37%), the identity of which was confirmed by spectroscopic comparison with the methyl eriostemate synthesized above. The starting material **12** (90 mg) was also recovered.

*9-Hydroxy-2,2,6,6-tetramethyl-8-oxo-3,4,7,8-tetrahydro-2H,6H-1,5-dioxaphenanthrene-10-propionic Acid (**14**).* 9-Hydroxy-2,2,6,6-tetramethyl-8-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-1,5-dioxaphenanthrene (**13**)[4] (1.9 g) and acrylic acid (1.5 g) were heated in the presence of polyphosphoric acid (45 g) with stirring at 60—65 °C for 1.5 h, and the reaction mixture was poured into ice-cold water (200 ml). The mixture was allowed to stand overnight at room temperature, and a white precipitate was collected and purified by column chromatography with silica gel and a mixed solvent of chloroform–methanol (190 : 9) to give an acid **14** (0.5 g, 21%) (mp 202—203 °C; recrystallization from methanol as colorless prisms). It gave a dark blue ferric chloride reaction in ethanol: IR ν_{max}^{KBr} 1635, 1708 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 6H, $CH_3\times2$), 1.44 (s, 6H, $CH_3\times2$), 1.74 and 2.53 (each t, 2H, $J=6$ Hz, CH_2), 2.43—2.95 (m, 4H, CH_2CH_2), 2.65 (s, 2H, CH_2CO), 12.17 (s, 1H, OH). Found: C, 65.50; H, 7.04%. (s, 2H, CH_2CO), 12.17 (s, 1H, OH). Found: C, 65.50; H, 7.04%. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94%.

*Methyl 9-Methoxy-2,2,6,6-tetramethyl-8-oxo-3,4,7,8-tetrahydro-2H,6H-1,5-dioxaphenanthrene-10-propionate (**15**).* A mixture of acid **14** (0.13 g), dimethyl sulfate (0.3 g), and anhydrous potassium carbonate (2 g) was heated under reflux in dry acetone (50 ml) for 24 h. The product was purified by column chromatography on silica gel with chloroform–ethyl acetate (20 : 1) to give a colorless oil (**15**). The oil was crystallized from light petroleum ether (40—50 °C) as colorless prisms (70 mg, 50%) (mp 79—80 °C): IR ν_{max}: 1673, 1735 cm^{-1}; NMR ($CDCl_3$) δ: 1.33 (s, 6H, $CH_3\times2$), 1.43 (s, 6H, $CH_3\times2$), 1.75 and 2.52 (each t, 2H, $J=6$ Hz, CH_2), 2.36—2.94 (m, 4H, CH_2CH_2), 2.60 (s, 2H, CH_2CO), 3.68 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). Found: C, 66.97; H, 7.59%. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50%.

*Additional Synthesis of **15**.* Methyl ester **12** (0.11 g) was hydrogenated over palladium charcoal (95 mg) in methanol (20 ml) at room temperature. After the uptake of hydrogen ceased within 40 min, the solution was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with chloroform–ethyl acetate (20 : 1) to give a colorless oil (0.10 g, 90%). The oil was crystallized from light petroleum ether to give colorless prisms **15** (mp 79—80 °C; not depressed upon mixture with the sample synthesized above).

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References

1) This has previously been reported in preliminary form: M. Nakayama, S. Hayashi, M. Tsukayama, T. Horie, and M. Masumura, *Chem. Lett.*, **1975**, 55.

2) A. M. Duffield, P. R. Jefferies, and P. H. Lucich, *Aust. J. Chem.*, **15**, 812 (1962).

3) A. M. Duffield and P. R. Jefferies, *Aust. J. Chem.*, **16**, 123 (1963).

4) A. Jefferson, I. Moor, and F. Scheimann, *J. Chem. Soc., C*, **1967**, 151.

5) J. Nickl, *Chem. Ber.*, **92**, 1989 (1959).