thiourea[6] which melted at 100–101° and gave no depression when mixed with authentic phenylisopropylthiourea.

Repetition of this reduction using 0.2 mole of 2-nitropropane and differing only by the addition of 0.2 ml. of 36% hydrochloric acid resulted in an 87% conversion to amine in nine hours. Modification of the original procedure with the addition of 1.0 ml. of glacial acetic acid increased the time required to 13 hr. and the conversion was 89%. When 10.0 ml. of glacial acetic acid was added only 35% of the required hydrogen was absorbed in 40 hr. and the experiment was discontinued.

The reduction of nitromethane proceeded more slowly than the other nitro compounds and when 0.2 g. of catalyst was used in the above procedure 38 hr. were necessary for absorption of 91% of the required amount of hydrogen.

(6) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 193.

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## Components of Podophyllin. X.[1] Relation of α-Peltatin to β-Peltatin

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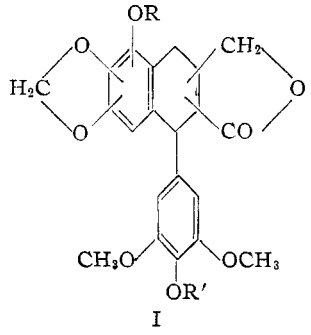
In a previous communication,[2] the empirical formula $C_{22}H_{22}O_8$ was proposed for α-peltatin, which would make it an isomer of β-peltatin and podophyllotoxin. However, it was pointed out that the analyses of the compound and of some of its derivatives were equally consistent with an alternate formula, $C_{21}H_{20}O_8$. A renewed investigation of the methyl ethers derived from the peltatins has now demonstrated unequivocally that the latter formula is actually correct and that α-peltatin itself is 4′-demethyl-β-peltatin, as indicated in formula I.




I

α-Peltatin: R = R′ = H
β-Peltatin: R = H, R′ = $CH_3$

In the original experiments,[2] treatment of α- and of β-peltatin with diazomethane gave levorotatory methyl ethers, m.p. 124–126°, $[\alpha]_D$ −116° or −118°, which were believed not to be identical since mixtures of the two gave a melting point depression of a few tenths of a degree. Similarly, a slight melting point depression was noticed with mixtures of α-peltatin-B dimethyl ether (m.p. 180–183°, $[\alpha]_D$ +10.0°) and β-peltatin-B methyl ether (m.p. 183–184°, $[\alpha]_D$ +9.4°), prepared with dimethyl sulfate and alkali.

(1) Paper IX: A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, 74, 5676 (1952).

(2) J. L. Hartwell and W. E. Detty, *ibid.*, 72, 246 (1950).

When the methylation with diazomethane was now repeated, products were obtained which after several recrystallizations melted at 162.6–163.6° and had $[\alpha]_D$ −120°. Samples from α-peltatin and from β-peltatin showed no mixed melting point depression and, furthermore, had indistinguishable infrared absorption spectra (Fig. 1). This established their identity. It has not been possible to prepare again the material, m.p. 124–126°. At the beginning of the present reinvestigation, previously obtained samples, 3 to 4 years old, still showed the original melting points; recrystallization from ethanol, however, yielded material melting at 162.6–163.6°. It seems that the two substances are polymorphic modifications. Similar polymorphism had already been encountered in the case of podophyllotoxin.[3]

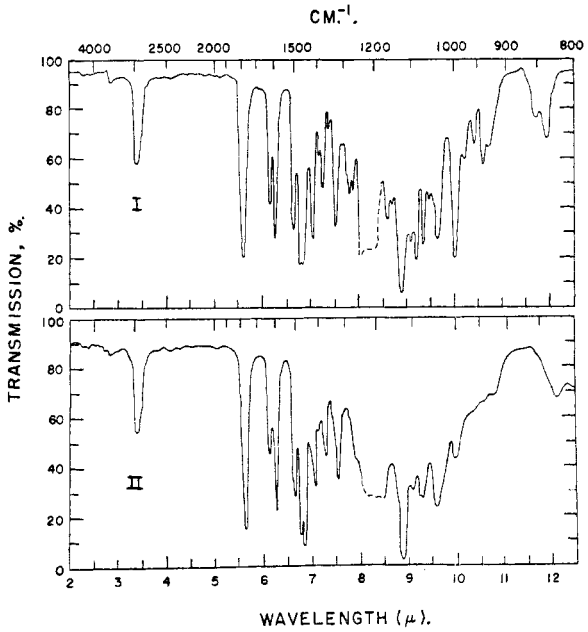



Fig. 1.—Infrared spectra in chloroform: I, β-peltatin-A methyl ether (α-peltatin-A dimethyl ether); II, β-peltatin-B methyl ether (α-peltatin-B dimethyl ether).

Methylation with dimethyl sulfate gave material, m.p. 183.8–184.6°, $[\alpha]_D$ +11°. Here again, the identity of the products obtained from α- and β-peltatin was proven by the mixed melting point and by the infrared spectra (Fig. 1). Since the presence of two phenolic hydroxyl groups in α-peltatin renders the compound sensitive to autoxidation in alkaline solution, the previously used alkylation procedure[2] had to be modified in order to obtain a pure product.

The identity of the methyl ethers of α- and β-peltatin in both the "A" and "B" series[2] demonstrates that β-peltatin is a monomethyl-α-peltatin. This, together with the results of the oxidation of the ethyl ethers[2] proves that α-peltatin is 4′-demethyl-β-peltatin (I, R = R′ = H).

The infrared spectra of the methyl ethers (Fig. 1) substantiate the previous assumption[2] that a lactone ring is present in the peltatins and indicate further that it is a γ-lactone ring. The carbonyl band lies in the range commonly associated with

(3) J. L. Hartwell and A. W. Schrecker, *ibid.*, 73, 2909 (1951).

TABLE I

ANALYSES OF α-PELTATIN AND DERIVATIVES

| Compound | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Methoxyl, % Calcd. | Methoxyl, % Found | Acetyl, % Calcd. | Acetyl, % Found |
|---|---|---|---|---|---|---|---|---|---|
| α-Peltatin[a] | $C_{21}H_{20}O_8$ | 63.0 | 63.4 | 5.0 | 5.3 | 15.5 | 15.7 | .. | .. |
| α-Peltatin-B[a] | $C_{21}H_{20}O_8$ | 63.0 | 63.3 | 5.0 | 4.9 | 15.5 | 15.8 | .. | .. |
| | | | 63.1 | | 5.1 | | | | |
| α-Peltatin-A dimethyl ether[b] | $C_{23}H_{24}O_8$ | 64.5 | 64.4 | 5.6 | 5.8 | 29.0 | 28.9 | .. | .. |
| α-Peltatin-B dimethyl ether[b] | $C_{23}H_{24}O_8$ | 64.5 | 64.5 | 5.6 | 5.8 | 29.0 | 28.9 | .. | .. |
| α-Peltatin-B diethyl ether[a] | $C_{25}H_{28}O_8$ | 65.8 | 65.4 | 6.2 | 6.4 | 27.2 | 26.5 | .. | .. |
| | | | 65.3 | | 6.4 | | | | |
| Diacetyl α-peltatin-A[a] | $C_{25}H_{24}O_{10}$ | 62.0 | 62.4 | 5.0 | 5.4 | 12.8 | 13.2 | 17.8 | 16.4 |
| Diacetyl α-peltatin-B[a] | $C_{25}H_{24}O_{10}$ | 62.0 | 62.5 | 5.0 | 5.2 | 12.8 | 12.9 | 17.8 | 17.1 |
| | | | | | | | | | 17.7 |
| α-Peltatic acid[b] | $C_{21}H_{22}O_9 \cdot H_2O$ | 57.8 | 57.5 | 5.5 | 5.8 | 14.2 | 14.6 | .. | .. |
| | | | 57.2 | | 5.7 | | | | |

[a] Previously reported figures for found values (see ref. 2). [b] Analyses obtained on newly prepared material.

an unconjugated γ-lactone[4]; furthermore, the frequencies of the maxima in the "A" (1780 cm.$^{-1}$) and "B" series (1770 cm.$^{-1}$) are identical with those of epipodophyllotoxin ethyl ether and epipicropodophyllin ethyl ether,[5] respectively. The shift toward lower frequencies corresponding to the passage from the "A" to the "B" series, although possibly lying within the limits of experimental error, appears to indicate lessening of strain; this is consistent with the irreversible isomerization of the "A" to the "B" compounds and analogous to similar phenomena in the case of podophyllotoxin and its derivatives.[3,5] Thus it seems that the γ-lactone ring is *trans* in the "A" and *cis* in the "B" series.[3,5] Chemical evidence for the presence of the lactone ring in α- and β-peltatin has also now been obtained by the preparation of the corresponding hydroxy acids, named α- and β-peltatic acid. Relactonization of these acids yields the "B"-lactones.

Since the calculated analytical values for α-peltatin and its derivatives, as published previously,[2] were based on the earlier formula $C_{22}H_{22}O_8$, it may be desirable to compare the analytical results with the revised theoretical figures, as shown in Table I.

Revision of some of the earlier statements[2] is necessitated by the new empirical formula for α-peltatin and employment of 15.50% instead of 14.98% for the calculated methoxyl value. In the chromatography, α-peltatin fractions containing up to 14% (not 20%) β-peltatin were obtained. Corrected yields of α-peltatin and β-peltatin should be increased and decreased, respectively, by 0.3%; the average yield of α-peltatin was thus 5.5%, and of β-peltatin, 5.7%. The best samples of α-peltatin obtained contained no β-peltatin (not 6%), while the derivatives of α-peltatin were made from material containing up to 5% (not 12%) β-peltatin. Finally, since molecular absorption coefficients were calculated on the basis of a molecular weight of 414.4 instead of 400.4, they should be reduced by 3.4%; the effect on the ultraviolet absorption curve, however, is negligible.

It is of interest to point out that the new structural relationship found for the peltatins isolated from *P. peltatum* finds an exact parallel in the podophyllotoxin and 4′-demethylpodophyllotoxin isolated from *P. emodi*.[6]

(4) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950).

(5) Paper XII: A. W. Schrecker and J. L. Hartwell, *ibid.*, to be published.

### Experimental[7]

**α-Peltatin-A Dimethyl Ether** (I, R = R′ = $CH_3$).—An increased yield was obtained by the following modification of the previously used[2] procedure. A solution of 1.5 g. of α-peltatin in 37.5 cc. of hot methanol was cooled in ice, an ethereal diazomethane solution (54 cc., from 4.2 g. of nitrosomethylurea) added, and the mixture evaporated in a stream of air after 36 hours at room temperature. Addition of 10 cc. of ether to a solution of the solid in 5 cc. of hot ethanol yielded 0.90 g. (58%) of colorless needles, m.p. 156–160°. Several recrystallizations from absolute ethanol gave material melting at 162.6–163.6° (sintering at 162.3°), with no change after further recrystallization; $[\alpha]^{21}D$ −120.6° (*c* 1.02, chloroform).

*Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; 4 $OCH_3$, 28.98. Found: C, 64.41; H, 5.78; $OCH_3$, 28.88.

**β-Peltatin-A Methyl Ether** (I, R = R′ = $CH_3$).—When β-peltatin was methylated similarly, using acetone as a solvent, there was obtained a 75% yield of crude material, m.p. 158–161°, which after recrystallization from ethanol formed colorless needles, m.p. 162.6–163.6° (sintering at 162.4°), $[\alpha]^{20}D$ −120.0° (*c* 0.98, chloroform).

*Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; 4 $OCH_3$, 28.98. Found: C, 64.67; H, 5.55; $OCH_3$, 28.79.

A mixture of 0.10 g. each of pure α-peltatin-A dimethyl ether and β-peltatin-A methyl ether was recrystallized from absolute ethanol to yield 0.19 g. of material melting at 162.6–163.6° (sintering at 162.4°).

**α-Peltatin-B Dimethyl Ether** (I, R = R′ = $CH_3$).—To a suspension of 4.07 g. of α-peltatin-B[2] in 50 cc. of 80% methanol, kept under nitrogen, 17 cc. of 2 *N* methanolic potassium hydroxide was added. The mixture was refluxed, then 11.9 cc. of dimethyl sulfate was added to the solution in four portions, refluxing 30 minutes between each addition and keeping the *p*H between 7 and 8 by the gradual addition of a total of 49 cc. of 2 *N* methanolic potassium hydroxide. Another 12.5 cc. of methanolic potassium hydroxide was then added, the solution refluxed for another 15 minutes, diluted with water, concentrated to remove methanol, and filtered. The filtrate was acidified with hydrochloric acid and heated at 100° for an hour. The colorless solid (4.14 g., 95%) had m.p. 176–181°. A solution in chloroform was chromatographed on alumina,[8] and the zone that showed a pale blue fluorescence under ultraviolet light eluted with

(6) M. V. Nadkarni, P. B. Maury and J. L. Hartwell, *ibid.*, **74**, 280 (1952); M. V. Nadkarni, J. L. Hartwell, P. B. Maury and J. Leiter, *ibid.*, in press.

(7) All melting points are corrected; they were determined with the Hershberg apparatus. Infrared absorption spectra were measured with a Perkin-Elmer model 21 spectrometer. Analyses were carried out by the Microanalytical Laboratory under the direction of Dr. W. C. Alford.

(8) Alcoa activated alumina, grade F-20.

chloroform. Concentration of the eluate with addition of ethanol yielded 3.43 g. of long fine needles, m.p. 183–184°. Two recrystallizations from ethanol provided material with a constant melting point of 183.8–184.6° (sintering at 183.2°), $[\alpha]^{21}D$ +11.0° (*c* 1.02, chloroform).

*Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; 4 $OCH_3$, 28.98. Found: C, 64.50; H, 5.79; $OCH_3$, 28.92.

**β-Peltatin-B Methyl Ether** (I, R = R′ = $CH_3$).—Crude material, m.p. 180–182°, was obtained in 98% yield from β-peltatin by the method just described, except that it was not necessary to employ a nitrogen atmosphere. Two recrystallizations from ethanol furnished a product melting at 183.8–184.6° (sintering at 183.6°), $[\alpha]^{21}D$ +10.9° (*c* 1.07, chloroform), $\lambda_{max}^{EtOH}$ 280 mμ (log ε 3.39), $\lambda_{min}^{EtOH}$ 260.5 mμ (log ε 3.09). A mixture of 0.20 g. each of pure α-peltatin-B dimethyl ether and β-peltatin-B methyl ether gave, when recrystallized from ethanol, 0.35 g. of homogeneous material, m.p. 183.8–184.6° (sintering at 183.2°).

**α-Peltatic Acid.**—A solution of 1.0 g. of α-peltatin in 80 cc. of *N* sodium hydroxide was boiled for 15 minutes, then cooled in ice and, after addition of 60 cc. of chloroform, acidified by adding slowly 50 cc. of 2 *N* acetic acid with vigorous shaking. The suspension was kept in the ice-box for a short time, and the solid collected and washed with ice-cold water and chloroform; yield 0.82 g. (54%). It was recrystallized twice by dissolving it in ethanol, and diluting with chloroform, then with water. The acid formed tiny colorless needles, which melted, like α-peltatin-B,[2] at 275–276° (darkening) when immersed below 220°, but melted with foaming, resolidified, and melted again at 275–276° when immersed above 220°. When dried at room temperature, it was found to contain one mole of water of crystallization, which was not completely removed by drying in a vacuum at 80°; if the temperature was raised to 100°, partial lactonization took place. The solvated product had $[\alpha]^{20}D$ −95° (*c* 1, 10% sodium bicarbonate).

*Anal.* Calcd. for $C_{21}H_{22}O_9 \cdot H_2O$: C, 57.79; H, 5.54; $OCH_3$, 14.22. Found: C, 57.47, 57.21; H, 5.76, 5.75; $OCH_3$, 14.64.

**β-Peltatic Acid.**—This compound was prepared in 94% yield from β-peltatin by the method used for the preparation of α-peltatic acid and purified analogously. The acid crystallized in small colorless needles, which did not contain any solvent after drying in a vacuum at room temperature; m.p. 202° (foaming), $[\alpha]^{19}D$ −123.5° (*c* 1, 10% sodium bicarbonate).

*Anal.* Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.07; H, 5.66.

When this acid was heated at 210°, and the melt recrystallized from dilute ethanol, β-peltatin-B was obtained as colorless long needles; m.p. 210–212°, $[\alpha]^{21}D$ +37° (*c* 0.45, acetone) [lit.[2] m.p. 212.3–213.3°, $[\alpha]^{21}D$ +40° (*c* 1, acetone)].

**Acknowledgment.**—The authors are indebted to Mrs. Iris J. Siewers of the National Heart Institute for determining the infrared spectra.

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## Observations on the Degradation of 12-Ketosapogenins to Pregnane Derivatives

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It has been demonstrated by Fukushima and Gallagher[1] that treatment of a $\Delta^{16}$-20-ketosteroid with alcoholic potassium hydroxide results in the conversion of the α,β-unsaturated ketone system to an equilibrium mixture of the unsaturated and 16-alkoxy ketones. These authors have pointed out that the products reported by Marker[2] from the alcoholic hydroxide treatment of oxidized 12-ketopseudosapogenins are quite probably the 16-alkoxy compounds rather than 17-hydroxy derivatives. These findings seem to eliminate any uncertainties concerning the conversion of 12-ketosapogenins to pregnane derivatives.[2,3]

We have had occasion to reinvestigate the degradation of kammogenin to compounds of the pregnane series and wish to record the properties of the products obtained. Aqueous alcoholic potassium bicarbonate hydrolysis of the oxidation product of pseudokammogenin triacetate furnished the expected **5,16-pregnadien-2,3β-diol-12,20-dione diacetate.** Methanolic and ethanolic potassium hydroxide hydrolyses, followed by acetylation, yielded products with properties and analyses which indicate them to be **16α-methoxy-5-pregnen-2,3β-diol-12,20-dione diacetate** and **16α-ethoxy-5-pregnen-2,3β-diol-12,20-dione diacetate,** respectively.[4] We were unable to obtain a product corresponding to the compound reported by Marker.[2]

The ultraviolet absorption maximum of the 12-keto-$\Delta^{16}$-20-ketone obtained in this work occurs at 225 mm.; a similar hypsochromic shift was observed in the spectrum of 16-allopregnen-3β-ol-12,20-dione acetate ($\lambda_{max.}$ 228 mm.).[5] This displacement thus appears to be characteristic of $\Delta^{16}$-12,20-diones.

### Experimental

All melting points are corrected.

**Oxidation of Pseudokammogenin Triacetate.**—Pseudokammogenin triacetate[6] prepared from 6.0 g. of kammogenin (m.p. 238–242°) was dissolved in 125 cc. of glacial acetic acid and treated at 20–23° for 95 minutes with 4.5 g. of chromium trioxide. The solution was diluted with water and extracted with ether. The ether solution was washed with potassium carbonate solution and water and evaporated to a pale yellow glass.

**Potassium Bicarbonate Hydrolysis.**—One-half of the material from the oxidation was dissolved in 25 cc. of methanol. To the hot solution was added a solution of 2.5 g. of potassium bicarbonate in 10 cc. of water. The resulting cloudy amber solution was warmed for 4 min. and then diluted with water (100 cc.) until the steroid began to precipitate. After cooling, the solution was extracted with ether and the ethereal solution was washed with water, dried with magnesium sulfate and evaporated. The poorly crystalline residue was reacetylated with acetic anhydride and pyridine and the product was then crystallized from ether as small white crystals. The material had the following properties: m.p. 242–244°, $\alpha^{25}D$ −1.2° (chloroform), $\lambda_{max.}^{alc.}$ 225 mμ (log ε 3.9).

*Anal.* Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.93; H, 7.51.

**Methanolic Potassium Hydroxide Hydrolysis.**—One-fourth of the oxidation product was dissolved in 30 cc. of methanol and the solution was refluxed gently with 1.0 g. of potassium hydroxide in 5 cc. of water for 15 min. The dark brown solution was treated with 0.7 cc. of acetic acid to neutralize the base and was then concentrated to a volume of 15 cc. After diluting with water, the solution was extracted with ether. The ether solution was washed with potassium bicarbonate solution, then with water. After drying with magnesium sulfate the solution was evaporated to an oily residue which could not be in-

(1) D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, 73, 196 (1951).

(2) R. E. Marker, *ibid.*, 71, 4149 (1949).

(3) R. B. Wagner, J. A. Moore and R. F. Forker, *ibid.*, 71, 3865, 4159 (1949).

(4) The configurations of the 16-alkoxy groups have been assigned by D. K. Fukushima and T. F. Gallagher.

(5) R. B. Wagner, J. A. Moore and R. F. Forker, THIS JOURNAL, 72, 1856 (1950).

(6) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, 69, 2167 (1947).