Structure of Phrymarolin-II

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From root extracts of *Phryma leptostachya* L. was isolated a new lignan. Its structure has been determined to be 1-acetoxy-2-(3,4-methylenedioxy)phenoxy-6-(2-methoxy-4,5-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octane on the basis of the chemical properties and spectra of its degradation products.

The lignans which possess a 3,7-dioxabicyclo[3.3.0]octane ring substituted by oxy-functions known to date are gmelinol,¹⁾ paulownin,²⁾ sesamol³⁾ and phrymarolin-I.⁴⁾

Gmelinol (I) and paulownin (II) are characterized by having a hydroxy group on the C-1 carbon atom of the dioxabicyclooctane ring, and sesamol (III) by incorporating a methylenedioxyphenoxy group on the C-2 carbon atom. Phrymarolin-I (IV) isolated from *Phryma leptostachya* L. is the first example of a lignan which incorporates an acetoxy group on the C-1 carbon atom and a methoxymethylenedioxyphenoxy group on the C-2 carbon atom.

Further investigation on root extracts of *Phryma leptostachya* L. had led to the isolation of another 1,2-dioxygenated-3,7-dioxabicyclo[3.3.0]octane lignan which we named phrymarolin-II. The structure (V) for phrymarolin-II has been briefly reported.⁵⁾ The detailed experimental data are described in this paper.

The ether-soluble neutral fraction of root extracts provided phrymarolin-II on silica-gel column chromatography, where it was preceedingly eluted near to phrymarolin-I.

Phrymarolin-II gave colorless rods, mp 160~161°C, $[\alpha]_D +118^\circ$, by crystallization

from ether and ethyl acetate. The crystals are soluble in acetone, ethyl alcohol and chloroform, but hardly soluble in petroleum ether.

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The molecular formula, $C_{23}H_{22}O_{10}$, was established by elementary analysis and mass spectrometry (M^+ 458).

In the IR spectrum of phrymarolin-II the presence of an acetoxy group was inferred from the absorptions at 1740 and 1230 cm^{-1} . Absorptions at 2770, 1115 and 930 cm^{-1} suggested the presence of a methylenedioxyphenoxy group.

In the NMR spectrum phrymarolin-II showed signals assignable to two methylenedioxy functions (τ 4.08, 4.09; each 2H), an aromatic methoxy group (τ 6.25; singlet, 3H), an acetoxy group (τ 7.88; singlet, 3H), and five aromatic hydrogens (τ 2.94; singlet, 1H, and τ 3.20~3.61; multiplet, 4H).

On alkaline hydrolysis phrymarolin-II gave a monohydric alcohol, desacetyl phrymarolin-II (Va), $C_{21}H_{20}O_9$, mp 98~110°C, which showed no carbonyl absorption in the IR spectrum and did not decolorize potassium permanganate even when heated at 60°C for several minutes, therefore the presence of carbonyl groups and aliphatic double bonds was ruled out.

The alcohol was acetylated with acetic anhydride on boiling water for an hour to yield phrymarolin-II. The easy acetylation of the hydroxy group had been also found on desacetyl phrymarolin-I.⁴⁾

Resemblance between the spectra (UV, IR and NMR) of phrymarolin-I and phrymarolin-

II, and also of their desacetyl derivatives suggested close relationship of their structures. Especially in addition to their molecular formulae, the NMR spectra implied that phrymarolin-II probably is a demethoxy-analog of phrymarolin-I. This assumption was conclusively proved by methanolysis.

On methanolysis desacetyl phrymarolin-I had yielded 2-methoxysesamol (VI) and two isomeric neutral compounds, 1-hydroxy-2-methoxy-6-(2-methoxy-4, 5-methylenedioxy)-phenyl-3, 7-dioxabicyclo [3.3.0] octanes (VII, VIII), together with the dimeric product (IX, tentatively proposed).⁴⁾ With respect to desacetyl phrymarolin-II, methanolysis resulted in the production of the same neutral compounds (VII~IX) together with sesamol (Fig. 1). These compounds were identified on TLC and IR spectra (Figs. 2 and 3).

Then, on the ground of the structure of phrymarolin-I, it was deduced that phrymarolin-II is 1-acetoxy-2-(3,4-methylenedioxy)-phenoxy-6(2-methoxy-4,5-methylenedioxy)-phenyl-3, 7-dioxabicyclo[3. 3. 0]octane (aside from stereochemistry).

The NMR spectrum of phrymarolin-II (Fig. 4) was in accord with this, and the spectrum of desacetyl phrymarolin-II was consistent with that of the 1-hydroxyderivative. In addition to the proton groups already assigned, the spectra were analyzed as presented in the Table.

FIG. 1.

FIG. 2. TLC* of Methanolytic Products.

1. Products from desacetyl phrymarolin-I
2. 2-Methoxy-sesamol
3. Products from desacetyl phrymarolin-II
4. Sesamol

* SiO_2 /Benzene-Ethyl acetate (8:2), colored by chromotropic-sulfuric acid.

The isolated oxymethylene hydrogens, 8-H_a and 8-H_e, displayed a couple of doublet in an AB system. The other oxymethylene hydrogens, 4-H_a and 4-H_e, constituted the AB part of an ABX system due to coupling with the methine hydrogen, 5-H, which in turn coupled with the benzylic ether hydrogen, 6-H to show a triplet-like multiplet. The benzylic hydrogen showed a first-order doublet. The coupling constants, $|J_{4a,5}|$ and $|J_{4e,5}|$, were tentatively obtained by analysing the couple of quartet displayed from 4-H_a and 4-H_e, since the signal of 5-H was hardly resolved into each peak. But the value of $|J_{4a,5} + J_{4e,5} + J_{5,6}|$ seemed to agree with the range of the signal due to the methine hydrogen.

NMR chemical shift values were employed to assign stereochemistry to phrymarolin-II. That the signals of 2-H, 5-H and 8-H_e were shifted downfield by acetylating the neighbouring tertiary hydroxy group indicated

cis-relationship between the hydrogens and the hydroxy group⁶⁾ of desacetyl phrymarolin-II; otherwise an axial configuration for the methylenedioxyphenoxy group on the C-2 carbon atom. The absence of signals at the region of τ 6.5~6.7 permitted assignment of an equatorial configuration for the methoxy-methylenedioxyphenyl group on the C-6 carbon atom.⁷⁾

Thus, it was concluded that phrymarolin-II possesses the same stereochemistry as phrymarolin-I.

Further evidence for the structure was provided by degradation reactions and spectral data of the products (Fig. 5).

The benzylic ether linkage was readily splitted by hydrogenation on palladium catalyst to yield the dihydro-glycol (X), $\text{C}_{21}\text{H}_{24}\text{O}_9$, mp 133~134°C, which consisted of a primary and a tertiary hydroxy group.

The newly-born benzylic hydrogens and the neighbouring methine hydrogen resonated at the region of τ 7.0~7.8 to show a complex multiplet (3H) in the NMR spectrum, while there disappeared the doublet signal assignable to the benzylic ether hydrogen(6-H) of desacetyl phrymarolin-II. On the other hand, the methylene hydrogens of the newly-born hydroxymethyl group attached to an asymmetric carbon atom bearing no hydrogen showed a couple of doublet (τ 5.56, 5.81, $|J_{AB}|=12$) in the NMR spectrum of the acetate (XI).

On periodate oxidation the glycol gave formaldehyde and a 3-ketotetrahydrofuran derivative which showed a carbonyl absorption at 1770 cm^{-1} . The NMR spectrum of the ketone was in accord with 2-(3,4-methylenedioxy)phenoxy-4-(2-methoxy-4, 5-methylenedioxy)benzyltetrahydrofuran-3-one (XII): in addition to the proton groups on the aromatic nuclei, an isolated acetal hydrogen was apparent (τ 4.75, 1H, singlet), with oxymethylene hydrogens (τ 5.59, 5.96, 2H, octet). The

TABLE I. NMR SIGNALS OF PHRYMAROLIN-II AND DESACETYL PHRYMAROLIN-II.

Assignment	τ -Values	Multiplicity	No. of protons	τ_A	τ_B	J_{AB}	J_{AX}	J_{BX}
Phrymarolin-II								
2-H	4.30	s	1					
4-Ha	5.88, 5.92, 6.05, 6.09	q	1		5.95	10		1.5
4-He	5.55, 5.66, 5.71, 5.83	q	1	5.71		10	7.6	
5-H	7.05~7.33	m	1					
6-H	5.10, 5.21	d	1	5.15			6.5	
8-Ha	6.15, 6.33	d	1		6.23	11		
8-He	5.31, 5.50	d	1	5.40		11		
-O $\searrow$ CH ₂	4.08	s	2					
-O $\nearrow$ CH ₂	4.09	s	2					
-OCH ₃	6.25	s	3					
ArH	2.94	s	1					
	3.20~3.61	m	4					
-OCOCH ₃	7.88	s	3					
Desacetyl phrymarolin-II								
2-H	4.75	s	1					
4-Ha	5.88, 5.93, 6.04, 6.08	q	1		5.95	9		2.8
4-He	5.53, 5.65, 5.68, 5.80	q	1	5.70		9	7.3	
5-H	7.36~7.63	m	1					
6-H	5.04, 5.15	d	1	5.10			6.5	
8-Ha	6.22, 6.38	d	1		6.28	10		
8-He	5.60, 5.77	d	1	5.72		10		
-O $\searrow$ CH ₂	4.09	s	2					
-O $\nearrow$ CH ₂	4.11	s	2					
-OCH ₃	6.28	s	3					
ArH	2.86	s	1					
	3.20~3.55	m	3					
	3.56	s	1					
-OH	6.95	br	1					

benzylic and methine hydrogens of the ketone showed complex signals at the region of τ 6.85~7.45.

On reduction with lithium aluminum hydride in dry ether the ketone quantitatively gave a monohydric secondary alcohol, C₂₀H₂₀O₈, mp 137~139°C, which was homogeneous on TLC. This suggested a stereoselective reduction of the chiral ketone to the *all-cis* alcohol (XIII), although further studies are needed to establish the stereochemistry.

Permanganate oxidation of the ketone afforded 2-methoxy-piperonylic acid (XIV) as an only recognizable product.

EXPERIMENTAL

Mps. were not corrected. NMR spectra were measured on a JNM-3H-60 spectrometer, using *ca.* 6% solution in deuterochloroform, with tetramethylsilane as an internal standard. Mass spectra were measured on a JMS-OISG spectrometer by direct insertion of samples. IR spectra were measured on a Shimadzu IR-27G spectrometer.

FIG. 3. IR Spectra of Compound-A and -B.

FIG. 4. NMR Spectrum of Phymarolin-II.

FIG. 5.

Isolation of phrymarolin-II (V). The ether extract of *P. leptostachya* L. (15 kg, fresh root wt.) was successively extracted with 5% sodium bicarbonate, 1% sodium hydroxide, 1% sulfuric acid, and then washed with water. The ether was dried over anhydrous sodium sulfate and evaporated up to 500 ml. The concentrated solution was kept in the cool to separate precipitates of phrymarolin-I. After being decanted, the ether was removed to give a glassy material (120 g).

Four grams of the material was dissolved in a small quantity of benzene and put on the top of a silica gel column (4.5 × 34 cm, Mallinckrodt silicic acid for chromatography, 100 mesh). Elution with 1 liter of a mixture of benzene and benzine (1:1, v/v) yielded an oily residue after removal of the solvent. Further elution with 500 ml of a mixture of benzene, benzine and ether (10:10:1, v/v) afforded a pale orange crystalline residue, which furnished colorless crystals by trituration with ether. Fractional crystallization from ether, ethyl acetate, and ethanol gave phrymarolin-II, colorless rods, mp 161~162°C (50 mg), with an appreciable amount of phrymarolin-I (8 mg), mp 155~157°C. In sum total, 1.6 g of phrymarolin-II were obtained. Phrymarolin-II gives a positive Labat test.

Anal. Found: C, 60.12; H, 5.00%. mol. wt. (Rast), 450. Mass *m/e*: 458 (M^+). Calcd. for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84%. mol. wt. 458. $[\alpha]_D^{+117.6^\circ}$ ($c = 2.72$, dioxane). $UV\lambda_{max}^{EtOH}$ nm (ϵ): 296 (10000), 236 (8300) IR_{max}^{KBr} (cm^{-1}): 3080 (w), 3000, 2980, 2960, 2910, 2860, 2770 (w), 1740 (s), 1630, 1615, 1501 (s), 1482 (s), 1465, 1455 (sh), 1440 (w), 1426, 1383, 1367,

1339, 1308, 1276, 1267, 1258, 1245 (sh), 1230 (s), 1220 (sh), 1195 (sh), 1179 (s), 1155, 1140 (sh), 1128 (sh), 1115, 1095 (sh), 1088, 1071, 1055, 1030 (s), 1010 (s), 980, 940 (sh), 930, 919 (sh), 900, 890 (w), 860, 850, 815 (w).

Desacetyl phrymarolin-II (Va). A solution of phrymarolin-II (1.16 g) in 100 ml of 90% ethanol containing 4 g of potassium hydroxide was refluxed for 2 hr. The ethanol was removed *in vacuo*, and the residue was dissolved in ether and the solution was washed with water and dried (Na_2SO_4). The solvent was evaporated to give a crystalline residue. It was recrystallized from ether to give colorless prisms, mp 98~100°C (980 mg). *Anal.* Found: C, 60.77; H, 4.83. Mass *m/e*: 416.110 (M^+). Calcd. for $C_{21}H_{20}O_9$: C, 60.57; H, 4.84. mol. wt. 416.111. $UV\lambda_{max}^{EtOH}$ nm (ϵ): 296.5 (10030), 237 (8320). IR_{max}^{KBr} (cm^{-1}): 3540~3400, 3040 (w), 3010, 2920 (sh), 2900, 2850 (sh), 2770 (w), 1631, 1613, 1500 (s), 1485 (s), 1455, 1421, 1390 (w), 1370 (w), 1352 (w), 1331, 1310 (w), 1295 (w), 1280, 1255, 1195 (sh), 1183 (s), 1153, 1135, 1125, 1095, 1075, 1060, 1045 (sh), 1031 (s), 995 (s), 970, 950 (w), 930, 920 (sh), 910, 895 (w), 885, 855, 835, 810, 795.

A solution of desacetyl phrymarolin-II (0.45 g) in 3 ml of acetic anhydride was heated on a water bath for 1 hr. The reaction mixture was poured into ice-water to decompose the excess of acetic anhydride. After being dried over anhydrous sodium sulfate, the ether was removed to yield a crystalline product. It was recrystallized from ether to give colorless prisms (445 mg), mp 160~161°C, identical with phrymarolin-II on IR and mixed mp.

Methanolysis of desacetyl phrymarolin-II. A solution of desacetyl phrymarolin-II (200 mg) in 80 ml of distilled methanol containing 1 ml of 35% hydrochloric acid was refluxed gently for 3 hr, then 60 ml of the methanol was distilled out. To the remaining solution 30 ml of 5% sodium hydroxide was added, and the solution was extracted with ether. After the separation of the ether layer, the aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. The ether was washed with water, dried (Na_2SO_4) and removed.

A brown viscous residue was trituated with petroleum ether to yield a crystalline product. It was recrystallized from petroleum ether to afford colorless plates, mp 62~64°C. *Anal.* Found: C, 60.77; H, 4.42%. Calcd. for $C_7H_6O_3$: C, 60.87; H, 4.38. It was identified with *sesamol* on IR.

The ether layer was washed with water, dried

(Na_2SO_4) and removed to yield a glassy residue. It was fractionated by preparative TLC to give two isomeric crystalline compounds, mp 120°C (35 mg) and mp 150°C (40 mg), and an amorphous substance (55 mg). They were identical with *compound A*, *compound B* (tentatively 1-hydroxy-2-methoxy-6(2-methoxy-4, 5-methylenedioxy) phenyl-3, 7-dioxabicyclo [3. 3. 0] octanes), and *compound C*, respectively, which were obtained from desacetyl phymarolin-I by methanolysis,⁴ on the basis of IR, mixed mps. and cochromatography on a thin-layer plate.

Dihydrodesacetylphymarolin-II (X). Desacetyl phymarolin-II (950 mg) was dissolved in 95 ml of ethyl acetate with suspending palladium catalyst, which was freshly prepared from 900 mg of palladium chloride in 100 ml of methanol. Hydrogenation was run at room temperature for 30 min, when hydrogen was consumed about 1.3 moles per mole of desacetyl phymarolin-II. Then the catalyst was removed from the reaction mixture and washed with 20 ml of ethyl acetate. The combined ethyl acetate was removed *in vacuo* to yield a crystalline product. It was recrystallized from ether and acetone to give colorless needles, mp $135\sim 136^\circ\text{C}$ (560 mg). *Anal.* Found: C, 60.20; H, 5.37%. Mass *m/e*: 418 (M^+). Calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_9$: C, 60.28; H, 5.30%. mol. wt. 418. $\text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}$ nm: 300, 237. $\text{IR}_{\nu_{\text{max}}}^{\text{CHCl}_3}$ (cm^{-1}): 3520, 3250, 3040 (sh), 3010, 2950, 2890, 2770 (w), 1630, 1620, 1500 (s), 1483 (s), 1470 (sh), 1465, 1455 (sh), 1421, 1380 $\sim$ 1320 (w, br), 1290 (sh), 1245, 1225, 1190 (s), 1180 (sh), 1158, 1126, 1060 (sh), 1040 (s), 1001, 935, 850, 820 (w).

$\text{NMR}_{\tau_{\text{Me}_4\text{Si}}}^{\text{CDCl}_3}$ (ppm): 3.18 $\sim$ 3.57 (5H, m, ArH); 4.09 (4H, s, methylenedioxy H); 4.50 (1H, s, acetal H); 4.9 $\sim$ 6.5 (4H, m, oxymethylene H); 6.24 (3H, s, methoxy H), 7.05 (2H, s, hydroxy H, D_2O exchangeable); 7.0 $\sim$ 7.8 (3H, m, benzylic H and methine H).

The dihydro-compound was acetylated with acetic anhydride under reflux for 1 hr. The crude product was purified by preparative TLC (silica gel G/benzene-ethyl acetate (7:3)) to give an amorphous *monoacetate* (XI).

$\text{NMR}_{\tau_{\text{Me}_4\text{Si}}}^{\text{CDCl}_3}$ (ppm): 3.19 $\sim$ 3.51 (5H, m, ArH); 4.10 and 4.11 (4H, methylenedioxy H); 4.64 (1H, s, acetal H); 5.56 (1H, d, J_{AB} 12, acetoxymethyl H); 5.81 (1H, d, J_{AB} 12, acetoxymethyl H); 5.8 $\sim$ 6.42 (2H, m, oxymethylene H); 6.25 (3H, s, methoxy H); 6.97 $\sim$ 7.56 (3H, m, benzylic H and methine H); 7.51 (1H, s, hydroxy H, D_2O exchangeable); 7.91 (3H, s, acetoxy H).

2-(3, 4-Methylenedioxy) phenoxy-4-(2-methoxy-4,5-

methylenedioxy)-benzyl-tetrahydrofuran-3-one (XII). To a solution of (X) (70 mg) in 5 ml of dioxane-methanol (3: 1) was added 40 mg of sodium metaperiodate in 2.5 ml of distilled water. The mixture was allowed to stand at room temperature for 24 hr, then extracted with ether after addition of 10 ml of distilled water. The ether layer was washed with water and dried (Na_2SO_4), then removed. A viscous oily residue was purified by preparative TLC (silica gel G/benzene-ethyl acetate (8: 2)) to yield a colorless viscous oil. $\text{IR}_{\nu_{\text{max}}}^{\text{CHCl}_3}$ (cm^{-1}): 3040 (sh), 3010, 2970 (sh), 2940 (sh), 2900, 2770 (w), 1770, 1630, 1501, 1481 (s), 1472 (sh), 1465, 1455 (sh), 1435 (sh), 1425, 1360, 1330 (w), 1300 (sh), 1275, 1245, 1190 (s), 1170 (sh), 1160 (sh), 1125, 1090, 1078, 1060 (sh), 1040(s), 1005, 935, 900 (w), 855, 820.

$\text{NMR}_{\tau_{\text{Me}_4\text{Si}}}^{\text{CDCl}_3}$ (ppm): 3.12 $\sim$ 3.5 (5H, m, ArH); 4.05 and 4.07 (4H, methylenedioxy H); 4.75 (1H, s, acetal H); 5.45, 5.55, 5.60, 5.70 (1H, q, $J_{\text{AB}}=9$, $J_{\text{AX}}=6$: oxymethylene H, ABX-system*), 5.85, 5.90, 6.00, 6.05 (1H, q, $J_{\text{AB}}=9$, $J_{\text{BX}}=3$: oxymethylene H)*; 6.24 (3H, s, methoxy H); 6.85 $\sim$ 7.45 (3H, m, benzylic and methine H).

The aqueous layer was subjected to steam distillation. To the distillate a 2,4-dinitrophenylhydrazine reagent was added. Yellow precipitates were collected and purified on TLC (silica gel/benzene-ethyl acetate, 8: 2). The crystals of mp $162\sim 164^\circ\text{C}$ were identified with an authentic sample of 2,4-dinitrophenylhydrazone of formaldehyde on mixed mp and TLC.

2-(3, 4-Methylenedioxy) phenoxy-4-(2-methoxy-4, 5-methylenedioxy)benzyl-tetrahydrofuran-3-ol (XIII). To a solution of XII (55 mg) in dry ether was added in portions 20 mg of lithium aluminum hydride, then the mixture was allowed to stand at room temperature for 2 hr. The reaction mixture was extracted with ether after being added 10 ml of 10% hydrochloric acid. The ether was washed with water and dried (Na_2SO_4) and removed. A crystalline residue was recrystallized from ethanol and ether to give fine colorless needles, mp $137\sim 139^\circ\text{C}$. *Anal.* Found: C, 62.03; H, 5.16%. Mass *m/e*: 388 (M^+). Calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_8$: C, 61.85; H, 5.19%; mol. wt. 388. $\text{IR}_{\nu_{\text{max}}}^{\text{CHCl}_3}$ (cm^{-1}): 3600 $\sim$ 3300, 3010, 2970, 2930, 2870, 2850 (sh), 2770 (w), 1620, 1500, 1485 (s), 1470 (sh), 1465 (sh), 1455 (sh), 1420, 1385 (w, br), 1240 (sh), 1225 (sh), 1190 (s), 1156, 1110 $\sim$ 1070 (w, br), 1040 (s), 1020 (sh),

* The coupling constants, $|J_{\text{AX}}|$ and $|J_{\text{BX}}|$, was tentatively obtained from the AB part of ABX-system.

1005 (sh), 930, 850.

2-Methoxy-piperonylic acid (XIV). (a) To a warm acetone solution of XII (100 mg) was added in portions 500 mg of a pulverized mixture of potassium permanganate and magnesium sulfate (6: 5) for 1 hr, and then the mixture was heated on boiling water for 4 hr. The reaction mixture was basified with sodium hydroxide, and the hot mixture filtered. Acetone was removed, and the remained aqueous solution was extracted with ether. The manganese dioxide was washed with boiling water. The combined alkaline solution was acidified with hydrochloric acid and extracted with ether. The ether was washed with water, dried (Na_2SO_4) and removed. A residue was purified on TLC and sublimation *in vacuo* to afford a crystalline product. It was recrystallized from ether. The colorless crystals, mp $147\sim 149^\circ\text{C}$, were identified with an authentic sample of 2-methoxy-piperonylic acid on UV and cochromatography on thin-layer plates. $\text{UV}_{\text{max}}^{\text{EtOH}}$ nm: 317, 257, 222.

(b) A solution of desacetyl phymarolin-II (200 mg) in acetone (30 ml) was treated with potassium permanganate (500 mg) for 6 hr under reflux. Then the reaction mixture was basified with sodium hydroxide, and the hot mixture was filtered. Acetone was removed, and a remained aqueous solution was extracted with ether. The manganese dioxide was washed with hot water. The combined alkaline solution was acidified with hydrochloric acid, and extracted with ether, the ether was washed with water, dried (Na_2SO_4) and removed. A residue was purified on TLC and sublimation *in vacuo*. The sublimate was recrystallized

from ether to give colorless needles, mp $148\sim 150^\circ\text{C}$. It was identified with 2-methoxy-piperonylic acid on TLC and UV absorptions.

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