of **29** to give 277 mg of residue which was purified by preparative tlc (30% ethyl acetate in benzene) to yield 96 mg (83%) of an oil that was 95% one spot (R_f 0.35) on tlc. A second preparative tlc of this material did not increase its purity. This material is assigned structure **32** on the basis of its spectral properties: ir 3.67 (twice the strength of the same band in the spectra of **30a**, **30b**), 5.64, and 5.78 μ; nmr τ 0.03 (s, 1, CHO), 0.27 (t, 1, J = 1 Hz CHO), 2.45 (d, 1, J = 2.5 Hz, ArH), 2.73 (d, 1, J = 2.5 Hz, ArH), 4.75 (q, 1, J = 6 Hz, CO_2CH), 7.40 (t, 2, J = 6.5 Hz, CH_2CHO), 7.69 (s, 3, $COCH_3$), 7.71 (s, 3, $COCH_3$), 7.98 (t, 2, J = 6.5 Hz, CH_2), and 8.62 (d, 3, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 265 (7), 249 (6), 85 (100).

Registry No.—**1**, 17924-92-4; **2**, 34289-99-1; **4**, 34297-69-3; **5**, 34290-00-1; **6**, 34297-70-6; **7**, 34288-78-3; **8**, 34288-79-4; **10**, 34288-80-7; **11**, 34288-81-8; **12**, 34290-01-2; **13**, 34290-02-3; **15**, 34290-03-4; **16**, 34290-04-5; **17**, 34290-05-6; **18**, 34288-82-9; **19**, 34288-83-0; **20**, 34297-71-7; **20** triacetate, 34297-72-8; **21**, 34290-06-7; **22**, 34290-07-8; **23**, 34290-08-9; **24** α isomer, 29181-06-4; **24** β isomer, 29181-19-9; **24** cis isomer diacetate, 34290-11-4; **24** trans isomer diacetate, 34290-12-5; **25** dimethyl ether, 34290-13-6; **28**, 10513-52-7; **29**, 34290-14-7; **30a**, 34290-15-8; **30b**, 34290-16-9; **30c**, 34290-17-0; **31**, 34290-18-1; **32**, 34290-19-2.

Chemical Modifications of Zearalenone. II

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Substitution of carboxyl and formyl groups into the aromatic portion of zearalenone is described and the new structures are unambiguously determined. Elimination reactions occurring during Birch reduction are investigated and a mechanism is proposed that accounts for the obtained products and intermediates.

As part of a program directed toward chemical modifications of zearalenone[1] (**1**) we investigated some of its aromatic substitution and elimination products. Available literature data[2] seemed insufficient to predict, with assurance, the outcome of a Kolbe–Schmitt reaction on **1** since the carbonation of resorcinol is described as leading primarily to 2,4-dihydroxybenzoic acid, while a 90% yield of 2,6-dihydroxy-4-methylbenzoic acid had been obtained from 3,5-dihydroxy-1-methylbenzene. Because of the sensitivity of zearalenone, we decided on relatively short reaction times for carbonation, and found that using potassium carbonate at 175° and 800 psi carbon dioxide for 3 hr,[3] a single carboxylic acid **2a** was obtained in better than 50% yield.

Since physical data could not safely distinguish between the two possible positions for the carboxy group in the aromatic ring, chemical degradation had to be undertaken. The sequence of reactions is shown in Scheme I. Successive methylations of the purified Kolbe–Schmitt product with methyl sulfate and diazomethane afforded a dimethoxymethyl ester **2b**, which was submitted to ozonization. It was found best to oxidize immediately the presumed dialdehyde **3** to a crude diacid **4a**, which was esterified to **4b** and purified by chromatography. Hydrolysis of this triester gave a tricarboxylic acid **5a** which was best purified by reesterification to **5b**, chromatography, and renewed hydrolysis to the crystalline triacid. Although the nmr signal for the single aromatic proton at τ 2.6 was a clear indication that it is flanked by a methoxy and a carboxy group [*cf.* the signals at τ 2.8 and 3.25 of the two types of easily identifiable protons in 2,4-dimethoxybenzoic acid (**6**)[4]], we have been able to identify **5a** with an authentic sample[5] of 2,4-dimethoxybenzene-1,3,6-tricarboxylic acid, mp 240–241°.

It was of further interest to determine the structure of a monoformyl derivative **7** of zearalenone, which was obtained by a Friedel–Crafts type formylation.[6] To this end, both the purified formylation product **7** and the carboxylic acid **2a** were converted to the same carboxamide **9** as shown in Scheme I. Since the aldehyde **7** did give a monoxime **8a**, its further conversion to the nitrile **8b** and the corresponding carboxamide **9** did not present difficulties. This carboxamide was found to be identical with the one obtained directly from the methyl ester of acid **2a**, proving that both carboxylation and formylation of zearalenone have occurred at the same carbon atom.

Birch reduction of the aromatic nucleus was investigated using the ethylene ketal **10** of the saturated macrocycle. Reaction with 4 equiv of sodium (the minimum required for significant reduction) in liquid ammonia and *tert*-butyl alcohol afforded two homogeneous, oily products, each in *ca.* 30% yield. Both were rather unstable to conventional manipulations because of a marked tendency to aromatize.

The more polar product, which had retained one methoxy group, was assigned[7] structure **11a** on spectral grounds. On treatment with CrO_3 in pyridine it was converted into the aromatic, noncrystalline ketal **12a**, which was further characterized by acid hydrolysis to 2-(10-hydroxy-6-oxoundecyl)-6-methoxybenzoic acid μ-lactone (**12b**), mp 96–97°, identical in all respects with a sample prepared by methylation of authentic[8] 2-(hy-

(1) For leading references regarding isolation, structure, and total syntheses of this fungal metabolite see paper I: N. P. Jensen, R. D. Brown, S. M. Schmitt, T. B. Windholz, and A. A. Patchett, *J. Org. Chem.*, **37**, 1639 (1972). This paper also describes specifics of physical measurements and standard procedures.

(2) (a) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957); (b) F. Wessely, K. Benedikt, H. Benger, G. Friedrich, and F. Prillinger, *Monatsh. Chem.*, **81**, 1071 (1950).

(3) We thank Dr. W. H. Jones and associates for performing this reaction.

(4) Kindly supplied by Mr. H. L. Slates of these laboratories.

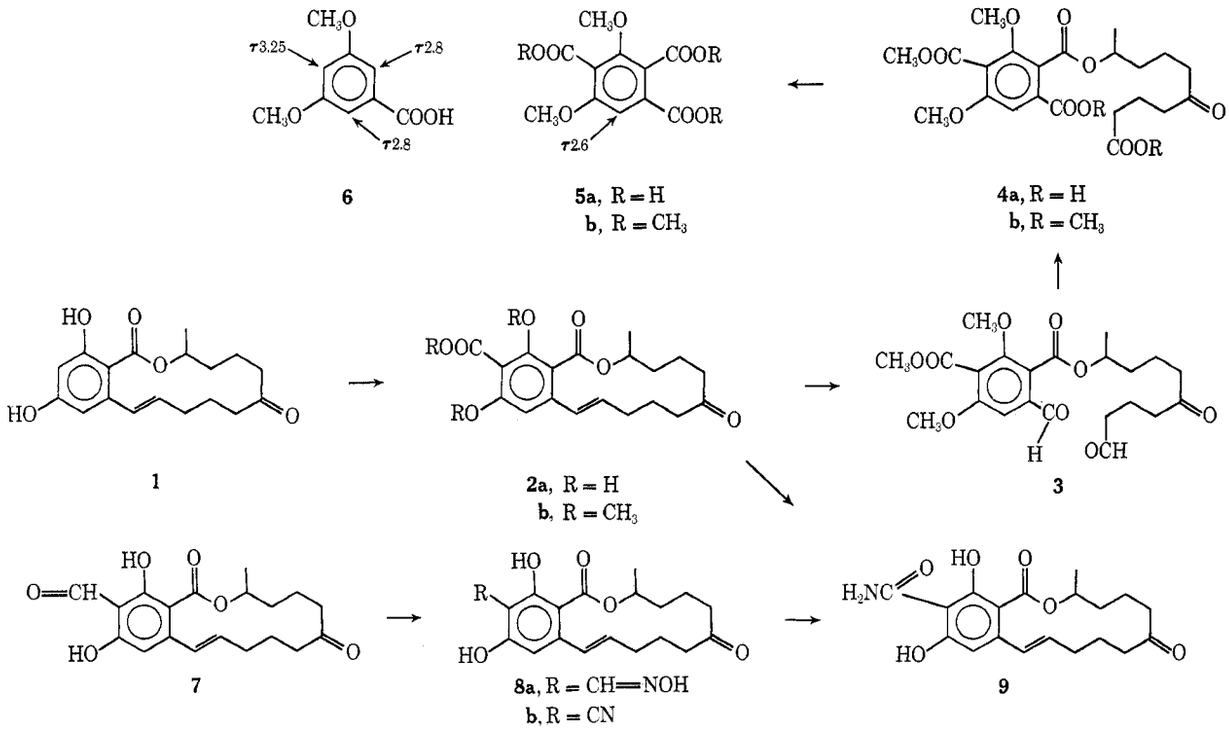
(5) I. Iwai and H. Mishima, *Chem. Ind. (London)*, 186 (1965). We are greatly indebted to Drs. Iwai and Mishima of Sankyo, Ltd. (Tokyo), for providing us with an authenticated sample for comparison.

(6) H. Gross, A. Rieche, and G. Matthey, *Chem. Ber.*, **96**, 308 (1963).

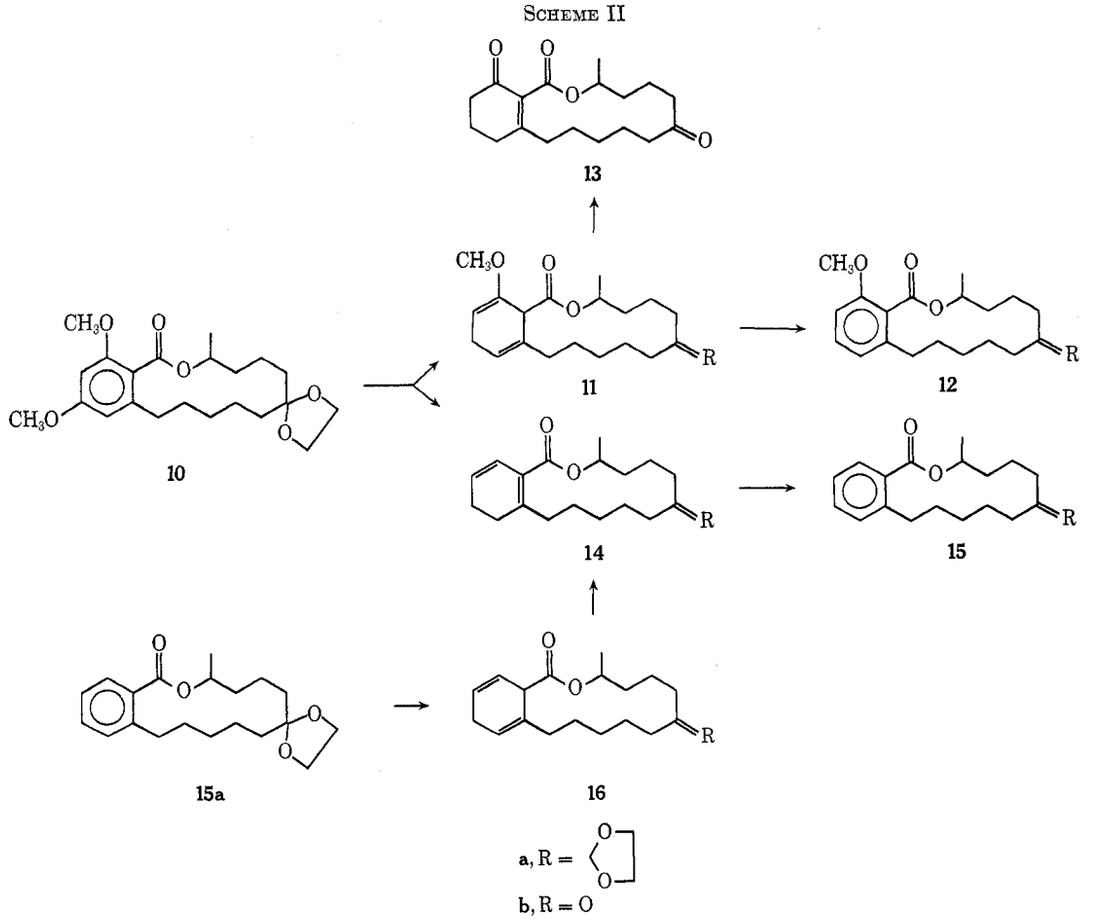
(7) Uv data of dihydroaromatic compounds are omitted, since they reflect the presence of small amounts of aromatic contaminants also detected in the nmr spectra.

(8) D. B. R. Johnston, C. A. Sawicki, T. B. Windholz, and A. A. Patchett, *J. Med. Chem.*, **13**, 941 (1970).

SCHEME I



SCHEME II



droxy-6-oxoundecyl)-6-hydroxybenzoic acid μ-lactone. Acid treatment of **11a** yields 2-(10-hydroxy-6-oxoundecyl)-6-oxo-1-cyclohexene-1-carboxylic acid μ-lactone (**13**).

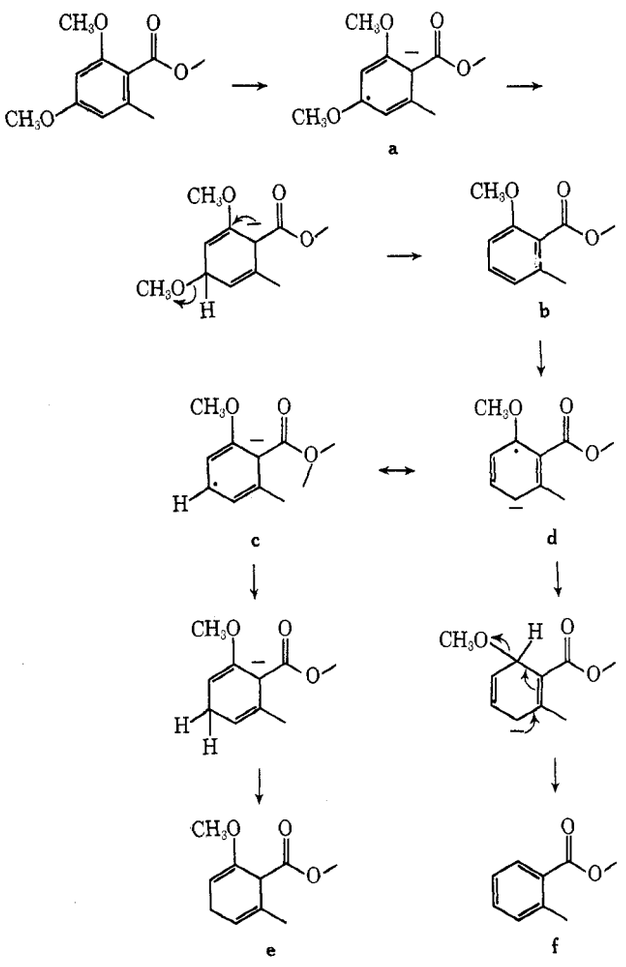
The less polar product from the Birch reduction (see Scheme II) had no methoxy group and was assigned the dihydroaromatic structure **14a**. Aromatization (CrO_3–pyridine) followed by mild acidic hydrolysis converts **14a** into the known[8] 2-(10-hydroxy-6-oxoundecyl)-benzoic acid μ-lactone (**15b**), mp 89–91°. The sup-

position that **14a** was obtained by subsequent reduction of the initially formed dideoxy zearalenone ketal **15a** was confirmed when, upon Birch reduction of an independently prepared[8] sample of **15a**, a new dehydroaromatic product was isolated in 90% yield. It was assigned structure **16a**, based on its spectral data. Base treatment of **16a** (KOH–methanol, room temperature) resulted in rearrangement to **14a**, confirming the possibility that, during work-up of the mixture[9] resulting from the Birch reduction of **10**, the initially formed **16a** was isomerized to **14a**. On the other hand, acid treatment of **16a** had no effect on the double bonds, and only caused ketal reversal to **16b**.

When **10** was subjected to Birch reduction using 8–18 equiv of sodium, only small amounts of **11a** were found, **14a** being the major identifiable product, isolated in *ca.* 36% yield.

Scheme III shows our interpretation of the course and mechanism[10] of the reactions reported above. Single-electron addition to the dimethoxy derivative **10** forms the anion radical a, which upon protonation and further reduction causes immediate elimination of the para-situated 4-methoxy group, with facile rearomatization to b. Under the conditions of the reaction, electron addition to b leads to an anion radical to which c and d are major contributing structures. Further reduction and protonation (see Scheme III) leads to both e and f, the latter product apparently favored by an excess of sodium metal. The dehydroaromatic product **2**, actually isolated from the reaction, must result from further reduction of the initially formed derivative f.

SCHEME III



Experimental Section

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone (2a).—A mixture of 3.18 g of zearalenone[1] and 10 g of anhydrous potassium carbonate was heated at 175° under 800-psi carbon dioxide pressure for 3 hr. The resulting solid was pulverized and stirred with 200 ml of saturated monosodium phosphate solution for 2 hr. The remaining solid was filtered, dried, and washed with acetone. The crude salt (2.7 g) was suspended in 50 ml of methanol, and 4.5 ml of 2.5 *N* hydrochloric acid was gradually added. Partial solution followed by reprecipitation was observed, and the suspension was stirred for 2 hr at room temperature, then poured into 300 ml of water. The obtained precipitate was filtered and dried, yielding 1.8 g (50% yield) of **2a**. A sample was crystallized from methanol: mp 158–160°; uv max 330 mμ (ε 3800), 280 (17,500), and 227.5 (17,900); ir 5.90 (C=O), 6.09 (C=O), and 6.19 μ (C=O); nmr τ −2.70 (s, 1, exchangeable), −1.0 (s, 1, exchangeable), 3.00 (d, 1, *J* = 16 Hz, C=CH), 3.41 (s, 1, ArH), 8.55 (d, 3, *J* = 6.5 Hz, CH_3); mass spectrum (70 eV) *m/e* 362.

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.93; H, 6.09.

2,4-Dimethoxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone 3-Methyl Ester (2b).—A 1.0-g sample of **2a** was suspended in 4 ml of dimethyl sulfate and 15 ml of a 20% solution of sodium hydroxide was added. An exothermic reaction followed. The temperature was maintained at 90° for 60 min, during which time 2 ml of dimethyl sulfate and 5 ml of the sodium hydroxide solution were added. The reaction mixture was cooled to 0° and neutralized with concentrated hydrochloric acid. The crude product was collected on a filter and washed with water. The dried solid was dissolved in 10 ml of tetrahydrofuran and 20 ml of ether and directly treated with 20 ml of a 1 *M*, ethereal diazomethane solution. After standing for 45 min, the excess diazomethane was destroyed with acetic acid and the solution was concentrated. The crude product (800 mg, 70%) was characterized as **2b**: ir 5.75 (C=O), 5.85 μ (C=O); nmr τ 3.23 (s, 1, ArH), 3.56 (d, 1, *J* = 16 Hz, C=CH), 6.13 (s, 3, OCH_3), 6.16 (s, 3, OCH_3), 6.19 (s, 3, OCH_3), 8.68 (d, 3, *J* = 6.5 Hz, CH_3).

A crystalline sample was obtained by preparative tlc (1000-μ plates, 4:1 mixture of methylene chloride–ether) and recrystallized from ether, mp 111–113°.

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.57; H, 7.01.

Degradation of 2,4-Dimethoxy-6-(10-hydroxy-6-oxoundec-1-enyl)-1-isophthalic Acid μ-Lactone 3-Methyl Ester (2b).—A 500-mg sample of **2b** dissolved in 60 ml of methanol at −80° was treated with O_3 until the effluent gas gave a positive starch iodide test and then continued for another 10 min. The solution was flushed with nitrogen, 1 ml of dimethyl sulfide was added, and the cold solution was allowed to stand overnight at room temperature. The solution was concentrated and the obtained product was purified by preparative tlc (1000-μ plates, with a 4:1 mixture of methylene chloride–ether). The isolated 460 mg of presumed dialdehyde **3** was immediately oxidized in 25 ml of acetone at 0° with the dropwise addition of 1.62 ml of Jones reagent. After 20 min the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried and concentrated *in vacuo*. The product (460 mg, 85%) was characterized as the diacid **4a**: ir 2.85, 3.10 (COOH), 5.72, 5.80, 5.85 μ (C=O); nmr τ 2.61 (s, 1, ArH), 6.07 (s, 3, OCH_3), 6.12 (s, 3, OCH_3), 6.17 (s, 3, OCH_3), 8.68 (d, 3, *J* = 6.5 Hz, CH_3).

The diacid was best purified as its methyl ester. To this effect, 285 mg of **4a** was dissolved in 5 ml of ether, treated with 20 ml of 1 *M* solution of diazomethane, and worked up as above. The isolated 280 mg of crude **4b** was purified by preparative tlc (1000-μ plates, 4:1 mixture of CH_2Cl_2–ether).

The isolated product (210 mg) was homogeneous on repeat

(9) While it is not possible to state that compound **16** was initially present in the mixture obtained from the Birch reduction of **10**, only compounds **11** and **14** were isolated in significant amounts and satisfactory purity.

(10) *Cf.* H. E. Zimmerman, *Tetrahedron*, **16**, 169 (1961), and F. J. Kakis in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1968, p 267.

tlc: ir 5.79 μ (C=O); nmr τ 2.70 (s, 1, ArH), 6.11 (m, 12, four OCH_3), 6.33 (s, 3, OCH_3), 8.65 (d, 3, J = 6.5 Hz, CH_3). This sample was hydrolyzed by dissolving it in 2 ml of DMSO, adding 1.2 ml of 20% NaOH solution, and refluxing for 2 hr under nitrogen. The reaction product was poured into water and extracted with chloroform. The aqueous phase was acidified with 2.5 N hydrochloric acid and extracted with chloroform. This chloroform solution was washed with water and saturated salt solution, dried, and concentrated *in vacuo*. The crude product (150 mg) was reasterified in 5 ml of tetrahydrofuran with 4 ml of 1 M diazomethane, worked up as usual, and applied on three preparative tlc plates of 250 μ. It was developed with 4:1 CH_2Cl_2–ether and the material (**5b**) of R_f 0.6 (40 mg, 32%) was isolated: ir 5.72, 5.77 μ (C=O); nmr τ 2.72 (s, 1, ArH), 6.09 (m, 15, five OCH_3); nmr (acetone-d_6) τ 2.63 (s, 1, ArH), 6.06 (s, 3, OCH_3), 6.12 (two s, 6, OCH_3), 6.16 (two s, 6, OCH_3).

For identification, 35 mg of **5b** was hydrolyzed in 2 ml of methanol with 0.5 ml of 2.5 N sodium hydroxide by heating on the steam bath for 3 hr. The reaction mixture was poured into water and extracted with ether. The aqueous phase was acidified with 2.5 N hydrochloric acid and extracted three times with ethyl acetate. The organic solutions were combined, dried, and concentrated. The crude crystalline product was recrystallized from ethyl acetate–hexane to give 15 mg (50%) of the triacid **5a**, mp 239–240°, identical in all respects (mixture melting point, ir, and nmr) with an authentic sample of 2,4-dimethoxybenzene-1,3,6-tricarboxylic acid, mp 240–241°.[5]

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)-isophthalaldehydic Acid μ-Lactone (7).—A 21-g sample of zearalenone (**1**) was dissolved in 400 ml of ethyl orthoformate and heated to 60°, and 13.2 g of aluminum chloride was added in small portions over 0.5 hr. The temperature was kept at 60° for an additional 1.5 hr, then lowered to 25°, and a 525-ml solution of 2.5 N HCl was added dropwise at such a rate that the temperature never exceeded 25°. The acidified reaction mixture was extracted four times with ethyl acetate, and the combined extracts were washed three times with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (24.8 g) was dissolved in 150 ml of methylene chloride and absorbed on a dry column (90 mm d) of 1.5 kg of silica gel (E. Merck, grade H). The column was eluted with a 7:1 mixture of methylene chloride–ether, and 200 fractions of 20 ml each were collected.

Fractions 42–87 contained 7.2 g (31%) of aldehyde **7**, which crystallized spontaneously: uv max (dioxane) 3375 mμ (ε 5800), 3030 (15,700), 251 (26,800); ir 5.92 (C=O) and 6.05 μ (C=O); nmr τ −3.22 (s, 1, ArOH), −2.43 (s, 1, ArOH), −0.40 [s, 1, C(=O)H], 2.98 (d, 1, J = 16 Hz, C=CH), 3.58 (s, 1, ArH), 8.60 (d, 3, J = 6 Hz, CH_3). The analytical sample, recrystallized from isopropyl alcohol, had mp 160–164°.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.48; H, 6.48.

2-(10-Hydroxy-6-oxoundec-1-enyl)-4,6-dihydroxy-5-hydroxyiminomethylbenzoic Acid μ-Lactone (8a).—A 2-g sample of aldehyde **7** was dissolved in a cold solution containing 60 ml of pyridine, 80 ml of absolute ethanol, and 440 mg of hydroxylamine hydrochloride. The reaction mixture was stirred at 0° for 45 min under nitrogen, poured into ice water, neutralized with 2.5 N HCl, extracted with ether, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (2.7 g) was dissolved in 20 ml of methylene chloride and absorbed on a 1.75-in.-diameter column which had been packed under vacuum with 200 g of dry silica gel H. The column was eluted with 1500 ml of a solution containing a 6:1 ratio of methylene chloride to ether and 150 fractions were collected using an automatic fraction collector. Fractions 13–22 contained 1.1 g of crystalline oxime **8a**: uv max 337.5 mμ (ε 7250), 297.5 (14,500), 257 (37,500); ir 3.12 (OH), 3.80 (C=O), 6.05 (C=O), 6.15 μ (C=N); nmr τ 1.21 [s, 1, C(=NOH)H], 2.98 (d, 1, J = 16 Hz, C=CH), 3.48 (s, 1, ArH), 8.61 (d, 3, J = 6 Hz, CH_3).

An analytical sample recrystallized from ether–hexane had mp 180–182°.

Anal. Calcd for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.37; H, 6.14; N, 3.96.

2-(10-Hydroxy-6-oxoundec-1-enyl)-4,6-dihydroxy-5-cyanobenzoic Acid μ-Lactone (8b).—A 500-mg sample of oxime **8a** was refluxed in 20 ml of acetic anhydride for 3.5 hr under nitrogen. The reaction mixture was poured into ice–bicarbonate solution, extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was dissolved in 200 ml of ether and an impurity crystallized from the solution. The ether solution was concentrated, leaving 600 mg of an amorphous material which was identified as **8b** diacetate: ir 4.50 (C=N), 5.60 (C=O), 5.80 μ (C=O); nmr τ 2.68 (s, 1, ArH), 3.47 (d, 1, J = 16 Hz, C=CH), 7.60 [s, 3, $CH_3C(=O)O$], 7.65 (s, 3, CH_3C=O).

A sample crystallized from ether–hexane had mp 73–75°.

Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90; N, 3.28. Found: C, 65.02; H, 5.83; N, 3.37.

A 500-mg sample of **8b** diacetate was dissolved in 15 ml of methanol containing 3.5 ml of 2.5 N sodium hydroxide and stirred for 2 hr at room temperature under nitrogen. The reaction mixture was poured into ice water, neutralized with 2.5 N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and concentrated *in vacuo* and yielded 420 mg of crude dihydroxy nitrile **8b**. A sample of 270 mg of clean product was isolated after preparative tlc (9:1 solution of methylene chloride–methanol) using 1000-μ silica gel G commercial plates.

A sample was recrystallized from ether–methylene chloride: mp 120–122°; uv max 3250 mμ (ε 7100), 2780 (15,100), 2425 (34,000); ir 3.15 (OH), 4.51 (C≡N), 5.88 (C=O), 6.07 μ (C=O); nmr τ 2.98 (d, 1, J = 16 Hz, C=CH), 3.40 (s, 1, ArH), 8.59 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.15; H, 6.36; N, 3.82.

2,4-Dihydroxy-6-(10-hydroxy-6-oxoundec-1-enyl)isophthalamic Acid μ-Lactone (9). A.—A 900-mg sample of the acid **2a** was dissolved in 15 ml of pyridine and 2 ml of acetic anhydride. The reaction mixture was heated on the steam bath for 2 hr under nitrogen, cooled to room temperature, poured into ice water, and acidified to pH 3 using 2.5 N hydrochloric acid. The resulting amorphous solid was filtered and dissolved in ethyl acetate, and the solution was washed with water, dried, and concentrated to a foam. This crude diacetate (1.0 g, 90%) was identified: ir 3.20, 5.65, 5.83, and 5.90 μ; nmr τ −0.75 (s, 1, COOH, exchangeable), 2.77 (s, 1, ArH), 3.46 (d, 1, J = 16 Hz, C=CH), 7.68 [s, 3, $CH_3C(=O)O$], 7.72 [s, 3, $CH_3C(=O)O$], and 8.65 (d, 3, J = 6.5 Hz, CH_3).

A 500-mg sample of the crude diacetate was dissolved in 50 ml of tetrahydrofuran and then cooled to 0°, and 4 ml of an approximately 1 M diazomethane solution was added.

After 10 min the excess reagent was decomposed with acetic acid in the usual way. The reaction mixture was concentrated *in vacuo*, yielding 540 mg of a crude methyl ester which was characterized by its ir and nmr spectrum: ir 5.68 (2, C=O) and 5.86 μ (2, C=O); nmr τ 2.83 (s, 1, ArH), 3.02 (d, 1, J = 16 Hz, C=CH), 6.18 (s, 3, OCH_3), 7.70 [s, 3, $CH_3C(=O)O$], 7.76 [s, 3, $CH_3C(=O)O$], and 8.67 (d, 3, J = 6 Hz, CH_3).

This methyl ester (540 mg) was dissolved in 5 ml of methanol and transferred into a stainless steel pressure tube which contained 5 ml of liquid ammonia. After heating for 6 hr at 70°, the reaction mixture was cooled to room temperature, poured into cold water, and acidified with 2.5 N hydrochloric acid. The obtained precipitate was filtered, washed with water, and dried to yield 540 mg of crude material. The latter was recrystallized from methanol, yielding a total of 220 mg of crystalline product, mp 175–178°, which was homogeneous by tlc and was recognized as the isophthalamic acid lactone **9**: uv max 328 mμ (ε 5100), 2800 (14,400), and 2500 (26,400); ir 2.97 (NH_2), 5.88 (C=O), 6.08 (C=O), 6.21 μ (O=CNH_2); nmr τ −4.54 (s, 1, ArOH), −4.46 (s, 1, ArOH), 3.02 (d, 1, J = 16 Hz, C=CH), 3.49 (s, 1, ArH), 8.59 (d, 3, J = 6.5 Hz, CH_3).

A sample recrystallized for analysis had mp 180–182°.

Anal. Calcd for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.24; H, 6.52; N, 3.70.

B.—A 150-mg sample of cyano diacetate (**8b** diacetate) was dissolved in 10 ml of 75% sulfuric acid and stirred for 40 hr at room temperature. The reaction mixture was poured over ice and the precipitate was filtered. The crude product (100 mg) was purified by preparative tlc on a 1000-μ silica gel G commercial plate developed in a 4:1 mixture of methylene chloride–ether. A recovered sample was recrystallized from methanol and afforded material of mp 180–181° that was identical with the above prepared amide **9** by mixture melting point and ir and nmr spectra.

2-(10-Hydroxy-6,6-ethylenedioxyundecyl)-4,6-dimethoxybenzoic acid μ-lactone (10) was prepared from the corresponding ketone, as previously described.[1] It was recrystallized from ether–petroleum ether (bp 30–60°) and isolated in 78% yield: mp 91–93°; uv max 282.5 mμ (ε 2560) and 24 (4500); ir 5.87

μ (C=O); nmr τ 3.68 (m, 2, ArH), 6.11 (s, 4, OCH_2CH_2O), 6.22 (s, 6, CH_3O), 8.64 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.21; H, 8.21.

2-(10-Hydroxy-6,6-ethylenedioxyundecyl)benzoic acid μ-lactone (15a) which was prepared as above, from compound **15** previously described,[8] was crystallized from petroleum ether in 61% yield: mp 61–63°; uv max 2770 mμ (ϵ 840), 227 (5950); ir 5.83 μ (C=O); nmr τ 2.35 (m, 1, ArH), 2.80 (m, 3, ArH), 6.7 (s, 4, OCH_2CH_2O), and 8.68 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.49; H, 8.25.

Birch Reduction of 10.—A 1.5-g sample of **10** was dissolved in 20 ml of dry tetrahydrofuran and added to a solution of 120 ml of distilled dry liquid ammonia and 20 ml of *tert*-butyl alcohol. Sodium metal (465 mg) was added in small portions. All the sodium had reacted after 8 min and the color of the reaction mixture turned yellow. Ammonium chloride (1 g) was added, the ammonia was evaporated, and a liter of water was added to this mixture. After extracting it three times with ether, the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to a crude oily mixture of 1.45 g.

A 485-mg sample of this mixture was applied onto five 1000-μ tlc plates (eluent acetone–hexane 3:7). A homogeneous, more polar, oily product of 125 mg was identified as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-6-methoxy-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (11a)**: ir 5.80 (C=O), 5.90, and 6.00 μ (C=COMe); nmr τ 4.37 and 5.20 (m, C=CH), 6.12 (s, 4, $-OCH_2CH_2O-$), 6.48 (s, 3, OCH_3), 7.18 (m, 2, $C=CCH_2$), 8.75 (d, J = 6.5 Hz, CH_3), and 8.83 (d, J = 6.5 Hz, CH_3).

A second, less polar, homogeneous oil (150 mg) was characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14a)**: ir 5.83 μ (C=O); nmr τ 3.76 (d, 1, J = 9 Hz, C=CH), 4.24 (d, 1, J = 9 Hz, C=CH), 6.12 (s, 4, $-OCH_2CH_2O-$), 7.83 (s, 4, $C=CCH_2$), and 8.71 (d, 3, J = 6.5 Hz, CH_3).

Aromatization Experiments.—A 45-mg sample of **11a** was dissolved in 0.5 ml of pyridine and added to an ice cold suspension of 45 mg of CrO_3 in 0.5 ml of pyridine. The mixture was stirred at room temperature overnight and worked up by adding 5 ml of ethyl acetate and filtering the insoluble salts. The filtrate was repeatedly washed with water, dried, and concentrated *in vacuo*. The obtained product (37 mg) was characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-6-methoxybenzoic acid μ-lactone (12a)**: ir 5.82 μ (C=O); nmr τ 2.70, 3.20, 3.22 (m, 3, ArH), 6.10 (s, 4, $-OCH_2CH_2O-$), 6.21 (s, 3, OCH_3), and 8.63 (d, 3, J = 6.5 Hz, CH_3).

A sample of ketal **14a** (80 mg) was similarly treated with 80 mg of CrO_3 in pyridine. The resulting product (64 mg) had all the spectral characteristics of **15a** prepared independently by ketalization of the ketone **15b**.

Acidic Hydrolyses.—A 55-mg sample of **11a** was dissolved in 5 ml of dioxane containing 4 drops of 2.5 N hydrochloric acid. The solution was kept for 16 hr under nitrogen and then poured into ice water. The mixture was extracted with ether, and the solvent solution was dried and concentrated. The obtained product (36 mg) was crystallized from methanol. It had mp 48–50° and was identified as **2-(10-hydroxy-6-oxoundecyl)-6-oxo-1-cyclohexene-1-carboxylic acid μ-lactone (13)**: uv max 238 mμ (ϵ 12,000); ir 5.73, 5.80, 5.92, and 6.10 μ (C=O); nmr τ 8.66 (d, 1, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.44. Found: C, 70.41; H, 8.55.

Ketal **12a** (37 mg) was treated with HCl as shown above and the obtained 25 mg of product was found to be identical with an authentic sample of **2-(10-hydroxy-6-oxoundecyl)-6-methoxybenzoic acid μ-lactone (12b)** prepared as shown further below. Similarly, a 43-mg sample of the crude ketal **15a** was hydrolyzed to the known[8] **2-(10-hydroxy-6-oxoundecyl)benzoic acid μ-lactone (15b)**, mp 89–91°.

The remaining 970 mg of crude product isolated from the Birch reaction described above was hydrolyzed under identical conditions using 2 ml of 2.5 N hydrochloric acid in 33 ml of dioxane. The total crude mixture obtained was absorbed on a 30-g dry column of silica gel and eluted with a 3:7 mixture of acetone–hexane. Fractions containing material of uv max 238 mμ were combined and crystallized, yielding 265 mg (32%) of lactone **13** identical in all respects with the product described above.

2-(10-Hydroxy-6-oxoundecyl)-6-methoxybenzoic Acid μ-Lactone (12b).—A 400-mg sample of 2-(10-hydroxy-6-oxoundecyl)-6-hydroxybenzoic acid μ-lactone[8] was suspended in 1 ml of dimethyl sulfate, and 4 ml of a 20% NaOH solution was added in one portion. An exothermic reaction set in after a few minutes and the mixture was stirred without further heating for 2 hr. The product crystallized during this period and was filtered, washed with water, dried, and recrystallized from methanol to yield 300 mg (72%) of **12b**: mp 96–97°; ir 5.79 and 5.82 μ (C=O); nmr τ 2.76, 3.20, and 3.31 (m, 3, ArH), 6.22 (s, 3, OCH_3), and 8.65 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.39; H, 8.42.

Birch Reduction of 10 with a Large Excess of Reagent.—A 300-mg sample of dimethoxy ketal **10** dissolved in 5 ml of tetrahydrofuran was added to a solution of 40 ml of distilled dry ammonia and 5 ml of *tert*-butyl alcohol. Then 320 mg of sodium metal was added and the blue reaction mixture was stirred for 15 min at −40°. The reaction was then quenched with 0.5 ml of methanol, the ammonia was evaporated, and 30 ml of water was added. The aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried, and concentrated *in vacuo*. The crude product was purified by preparative tlc (on 250-μ plates, solvent system 0.5% methanol in chloroform). The major product, which was the least polar one, was isolated in 36% yield; it was the only fully characterized compound, **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14a)**, having ir and nmr spectra identical with those of the previously isolated sample.

The balance of the isolated material contained a mixture of **14b** and **15b** in *ca.* 30% yield, as well as approximately 15% of unchanged hydrolyzed starting material **10**.

A 43-mg sample of **14a** was dissolved in 3 ml of dioxane containing 3 drops of 2.5 N hydrochloric acid. The solution was kept for 16 hr under nitrogen and then poured into ice water. The mixture was extracted with ether and the ethereal solution was dried and concentrated *in vacuo*. The obtained product, 32 mg (86%), was characterized as **2-(10-hydroxy-6-oxoundecyl)-1,5-cyclohexadiene-1-carboxylic acid μ-lactone (14b)**: ir 5.88 μ (C=O); nmr τ 3.68 (d, 1, J = 9 Hz, C=CH), 4.25 (m, 1, C=CH), 7.80 (s, 4, $C=CCH_2$), and 8.67 (d, 3, J = 6.5 Hz, CH_3).

Birch Reduction of 15a.—A 900-mg sample of **15a** dissolved in 15 ml of tetrahydrofuran was added to a mixture of 120 ml of dry ammonia and 15 ml of *tert*-butyl alcohol. Then 1 g of sodium metal was added in small portions, the blue reaction mixture was stirred for 30 min, and finally 2 g of ammonium chloride was added. The ammonia was evaporated and the reaction was worked up as usual. An oil (800 mg, 89%) was isolated and characterized as **2-(10-hydroxy-6,6-ethylenedioxyundecyl)-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (16a)**: ir 5.82 μ (C=O); nmr τ 2.72, 4.21, and 4.40 (3, C=CH), 6.14 (s, 4, $-OCH_2CH_2O-$), 7.25 (m, 2, $C=CHCH_2$), 8.77 (d, J = 6.5 Hz, CH_3), and 8.83 (d, J = 6.5 Hz, CH_3).

An 30-mg sample of compound **16a** was hydrolyzed with HCl–dioxane as usual.

The isolated product (60 mg, 85%) was characterized as **2-(10-hydroxy-6-oxoundecyl)-2,5-cyclohexadiene-1-carboxylic acid μ-lactone (16b)**: ir 5.78 and 5.82 μ (C=O); nmr τ 2.70, 4.28 (m, C=CH), 4.30 (m, C=CH), 7.22 (m, 2, $C=CCH_2$), 8.72 (d, J = 6.5 Hz, CH_3), and 8.80 (d, J = 6.5 Hz, CH_3). When the ketal **16a** (30 mg) was treated for 16 hr at room temperature under nitrogen, with a solution of 40 mg of KOH in 2 ml of MeOH and 0.5 ml of water, and the obtained product (20 mg) was isolated by dilution with water and ether extraction. It was found to be identical in all respects with ketal **14a**.

Registry No.—**1**, 17924-92-4; **2a**, 34246-32-7; **2b**, 34246-33-8; **4a**, 34246-34-9; **4b**, 34246-35-0; **5a**, 2411-45-2; **5b**, 34246-37-2; **7**, 34246-38-3; **8a**, 34246-39-4; **8b**, 34246-40-7; **8b** diacetate, 34246-41-8; **9**, 34246-42-9; **10**, 34246-43-0; **11a**, 34246-44-1; **12a**, 34246-45-2; **12b**, 34246-46-3; **13**, 34246-47-4; **14a**, 34280-39-2; **14b**, 34246-48-5; **15a**, 34246-49-6; **15b**, 28684-53-9; **16a**, 34246-51-0; **16b**, 34246-52-1.