together with their amount are given in Table I. Since these all have been described previously, their identification has been made in the usual way by comparison of melting points, R_f values, rotations and ultraviolet spectra. Undoubtedly, with further effort and time the number of crystalline alkaloids isolated from Piaroa curare can be increased to several times the present list.

The Halochrome Reaction of C-Curarine-I.—When a sample of C-curarine-I chloride was dissolved in concentrated hydrochloric acid, it gave a deep violet solution whose ultraviolet absorption spectrum showed maxima and extinction values (calculated on the basis that C-curarine-I chloride is $C_{40}H_{44}ON_4Cl_2$) as follows: 262 mμ (ϵ, 2.18×10^4), 295 (ϵ, 1.26×10^4) and 550 (ϵ, 3.77×10^3). By comparison the ultraviolet spectrum C-curarine-I chloride in ethanol has maxima at 260 mμ (ϵ, 2.58×10^4) and 296 (ϵ, 1.18×10^4). After short periods of time, dilution of the concentrated acid solution gave back a solution having a pure C-curarine-I spectrum. On the other hand, solutions of C-curarine-I in strong acid which had been allowed to stand at room temperature for an hour showed a decrease of intensity at the longer wave lengths (550 mμ) to about one-half the original value. A solution of C-curarine-I in concentrated hydrochloric acid which had been allowed to stand under nitrogen until the original violet color had undergone a series of changes through various reddish-browns to an eventual yellow was investigated by paper chromatography using the methyl ethyl ketone mixture. C-Curarine-I could no longer be detected but, instead, there were spots corresponding to six new compounds. The fastest moving of these, having an R_c value of approximately 2.2, showed a bluish fluorescence reminiscent of C-curarine-III (fluocurarine). Comparative paper chromatography using *n*-butyl alcohol as solvent as well as the ultraviolet spectrum of the substance strongly supported the conclusion that it was C-curarine-III.

This experiment was then repeated on preparative scale using 104 mg. of C-curarine-I chloride in 10 ml. of concentrated hydrochloric acid. After standing under nitrogen at room temperature for 94 hours, the solution was evaporated and the residue was subjected to partition chromatography over powdered cellulose using the *n*-butyl alcohol solvent. The first fluorescent band was collected and on concentration gave 6.9 mg. of a gum. The identity of this product (fraction 1) with C-curarine-III chloride was established by the following comparison. Comparative paper chromatography using either the *n*-butyl alcohol or the methyl ethyl ketone solvent mixtures showed identical behavior for both fraction 1 and C-curarine-III. Paper electrophoresis of a mixture of the two using 5% acetic acid gave only one spot. The fluorescence and color reactions of both were identical. As shown in the table below, the ultraviolet absorption spectra of fraction 1 in water both with and without added base, were identical to the corresponding spectra of C-curarine-III.

ULTRAVIOLET SPECTRA

	Maxima, mμ
Neutral solution	
Fraction 1	242, 299, 361
C-Curarine-III	242, 299, 361
Basic solution	
Fraction 1	250, 315, 388
C-Curarine-III	250, 315, 388

Finally, the remainder of the gum was converted to the corresponding crystalline β-anthraquinonesulfonate, m.p. 308–310° dec.[24] The infrared spectrum of the crystalline β-anthraquinonesulfonate of fraction 1 using a potassium bromide wafer corresponded in all respects to that obtained from an authentic sample of the β-anthraquinonesulfonate of C-curarine-III.

That the C-curarine-III could not have risen from impurities present in the sample of C-curarine-I was demonstrated by very careful check of the purity of C-curarine-I. In tests using paper chromatography with various solvents and in paper electrophoresis experiments no evidence of impurity could be found.

As yet it has not been possible to identify the other products formed during the acid treatment of C-curarine-I, but these are still under investigation.

(24) Reference 3 gives 308–310° dec. as the m.p. of the β-anthraquinonesulfonate of C-curarine-III.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Fungichromin. Determination of the Structure of the Pentaene Chromophore

BY ARTHUR C. COPE AND HERBERT E. JOHNSON[1]

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Sodium periodate oxidation of fungichromin has been shown to yield, in addition to other products, 2-methyl-2,4,6,8,10-dodecapentaenedial. The structure of the dialdehyde was determined by reduction to 2-methyl-2,4,6,8,10-dodecapentaenediol, hydrogenation to 2-methyldodecane-1,10-diol and oxidation to 2-methyl-2,4,6,8,10-dodecapentaenedioic acid which was reduced to 2-methyldodecanedioic acid. Sodium periodate oxidation of hydrogenated fungichromin followed by oxidation of the aldehydes formed also yielded 2-methyldodecanedioic acid.

Fungichromin[2,3] is one of a number of crystalline antibiotic substances produced by members of the genus Streptomyces that have been isolated recently. Fungichromatin,[2] Fumagillin,[4-6] and Filipin[7,8] which are closely related to Fungichromin in molecular formula also have been produced, as have a large number of other similar antibiotic substances.[9] All of these substances are polyenic in character and are markedly similar in their antifungal activity.

Fungichromin was found to contain no methoxyl or acetoxyl groups, nitrogen, halogen or sulfur. A large active hydrogen value (lithium aluminum hydride in tetrahydrofuran) indicated the presence of 10–11 hydroxyl groups and C-methyl determinations gave a minimum value of 3–4 such groups. Absorption maxima in the ultraviolet spectrum occur at 311, 323.5, 339 and 357 mμ which upon correlation with other polyene compounds[9a] indicated a conjugated pentaene system. The molecular weight of

(1) National Institutes of Health Postdoctoral Fellow, 1955–1956.

(2) A. A. Tytell, F. J. McCarthy, W. P. Fisher, W. A. Bolhofer and J. Charney, "Antibiotics Annual, 1954-1955," Medical Encyclopedia, Inc., New York, N. Y., p. 716.

(3) F. J. McCarthy, W. P. Fisher, J. Charney and A. A. Tytell, *ibid.*, p. 719.

(4) T. E. Eble and F. R. Hanson, *Antibiotics & Chemotherapy*, **1**, 54 (1951).

(5) I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

(6) J. R. Schenck, M. P. Hargi, D. S. Tarbell and P. Hoffman, THIS JOURNAL, **75**, 2274 (1953).

(7) A. Ammann, D. Gottlieb and H. E. Carter, *Plant Disease Reporter*, **39**, 219 (1955).

(8) G. B. Whitfield, T. D. Brock, A. Ammann, D. Gottlieb and H. E. Carter, THIS JOURNAL, **77**, 4799 (1955).

(9) For compilations of the properties of these materials see (a) W. Oroshnik, L. C. Vining, A. D. Mebane and W. A. Taber, *Science*, **121**, 147 (1955); (b) L. C. Vining, W. A. Taber and H. A. Lecheralier, *Congr. intern. Botanique*, 106 (1954); (c) Y. Okami, R. Utahara, S. Kakamura and H. Umizawa, *J. Antibiotics (Japan)*, Ser. A, **1**, 98 (1954).

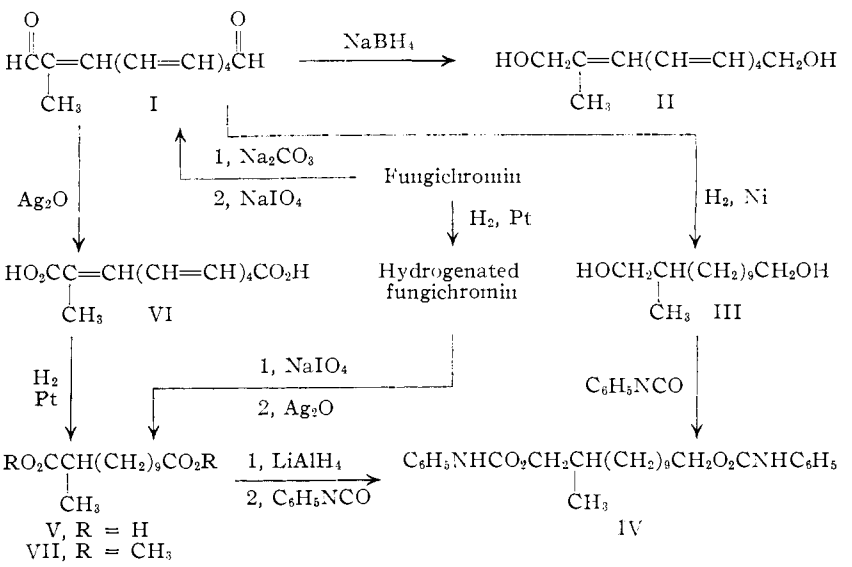
fungichromin and a molecular formula of $C_{35}H_{60}O_{13}$ previously have been reported as has the production, isolation and purification.[2,3]

In the present work, fungichromin was subjected to a short treatment with sodium carbonate solution and then oxidized with sodium periodate. A crystalline orange solid was isolated from the reaction mixture, and characterized as 2-methyl-2,4,6,8,10-dodecapentaenedial (I) as described below.

Reduction of the dialdehyde I with sodium borohydride gave a crystalline glycol, 2-methyl-2,4,6,8,-10-dodecapentaene-1,10-diol (II). The ultraviolet spectrum of II was nearly identical to the spectrum of fungichromin thus showing that no structural changes had taken place in the polyenic system and that the glycol II contained the chromophore that is present in fungichromin.

Sodium periodate oxidation of hydrogenated fungichromin followed by oxidation of the aldehydes that were formed with silver oxide in a solution containing sodium hydroxide gave a crystalline acid. Its neutral equivalent and a molecular weight determination of its methyl ester established that the compound was a dicarboxylic acid, and one C-methyl group was shown to be present by the Kuhn–Roth method. Comparison of its infrared spectrum with the spectrum of authentic 2-methyldodecanedioic acid[10] (V) and a mixed melting point of the two compounds showed them to be identical.

Oxidation of the dialdehyde I with silver oxide and base gave 2-methyl-2,4,6,8,10-dodecapentaenedioic acid (VI) which could be hydrogenated to the saturated acid V.[11] Hydrogenation of the dialdehyde I over nickel gave 2-methyldodecane-1,10-diol which was characterized as its bis-phenylurethan. The same derivative was prepared by reduction of synthetic V with lithium aluminum hydride followed by conversion to its bis-phenylurethan.



Experimental[12]

Sodium Periodate Oxidation of Fungichromin. Isolation of 2-Methyl-2,4,6,8,10-dodecapentaenedial (I).—A mixture of 521 mg. of fungichromin, 110 mg. of potassium carbonate, 15 ml. of methanol and 5 ml. of water was boiled gently on a steam-bath for 30 minutes. The dark orange solution was cooled and a solution of 3.0 g. of sodium periodate in 60 ml. of water was added. After shaking the mixture at room temperature for 16 hours it was acidified with dilute sulfuric acid to dissolve precipitated potassium iodate. The flocculent orange solid was separated by centrifugation, washed well with water and dried giving 135 mg. of material, m.p. 140–145°. Two crystallizations from cyclohexane gave the dialdehyde I as yellow-orange needles, m.p. 140–144°; λ_{max}^{EtOH} mμ (ε): 222 (7,640), 284 (6,200), 384 (77,000), 402 (75,000).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.37; H, 6.99.

2-Methyl-2,4,6,8,10-dodecapentaene-1,10-diol (II).—A solution of 59 mg. of the dialdehyde I in 15 ml. of absolute methanol was prepared and 12 mg. of sodium borohydride added. The solution became orange and then changed to a pale yellow. After standing for 45 minutes at room temperature a solution of 0.5 ml. of concentrated ammonium hydroxide in 30 ml. of water was added. Nearly colorless crystals formed and were collected by filtration; 44 mg., m.p. 160–164°. Two crystallizations from ethanol–water gave II as nearly colorless blades, m.p. 160–165°; λ_{max}^{EtOH} mμ (ε): 240 (approximately 3500), 319 (65,300), 334 (107,000), 351.5 (108,500).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.02; H, 9.09.

2-Methyldodecane-1,10-diol (III). A. By Hydrogenation of I.—A 47-mg. sample of the dialdehyde I was added to a suspension of Raney nickel previously saturated with hydrogen in 20 ml. of ethanol. The mixture was stirred at 26° in an atmosphere of hydrogen for 80 minutes at which time the hydrogenation had stopped and 34 ml. of hydrogen (82% of 7 molar equivalents) had been absorbed. Removal of the catalyst by filtration and evaporation of the ethanol left 43 mg. of a colorless viscous oil. Fifty milligrams of phenyl isocyanate was added, the mixture was heated for 10 minutes at 95°, and then allowed to stand overnight. One crystallization of the crude derivative from hexane gave 63 mg., m.p. 92–98°. Further crystallization from hexane gave minute blunt needles, m.p. 101–103°. A mixed melting point with an authentic sample (see part **B** below) was undepressed and the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{27}H_{38}N_2O_4$: C, 71.33; H, 8.43; N, 6.16. Found: C, 71.27; H, 8.50; N, 6.00.

B. By Reduction of 2-Methyldocanedioic Acid (V).—A solution of 122 mg. of V[10] in 20 ml. of absolute ether was prepared and 100 mg. of lithium aluminum hydride added. After refluxing the mixture for 1.5 hours it was poured over cracked ice and enough 40% sulfuric acid was added to dissolve the precipitated salts. The ether layer was separated and the aqueous phase extracted twice with ether. The extracts were dried over magnesium sulfate and then evaporated, leaving 103 mg. of a colorless viscous oil. The bis-phenylurethan was prepared by reaction with 103 mg. of phenyl isocyanate as described above to give colorless crystals, m.p. 101–103°.

Sodium Periodate Oxidation of Hydrogenated Fungichromin. Isolation of 2-Methyldodecanedioic Acid (V).—Fungichromin was hydrogenated in ethanol (about 80 ml. per g.) in the presence of Adams platinum catalyst at atmospheric pressure and room temperature. About 4.5 molar

(10) P. Chuit, F. Boelsing, J. Hausser and G. Malet, *Helv. Chim. Acta*, **10**, 167 (1927).

(11) We are indebted to Dr. Bernard T. Gillis for the results of this experiment.

(12) Melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. C-Methyl determinations were obtained from Microchemical Specialties Co., Berkeley 3, Calif.

equivalents of hydrogen was absorbed under these conditions, and the reduction product, which was obtained as a colorless, amorphous glass by removal of the solvent, was oxidized without further purification. To a solution of 644 mg. of hydrogenated fungichromin in 25 ml. of methanol was added a solution of 3.0 g. of sodium periodate in 50 ml. of water and the mixture was allowed to stand at room temperature for 19 hr. After dilution with 200 ml. of water the mixture was extracted four times with chloroform. The extracts were dried over magnesium sulfate and then evaporated, leaving 719 mg. of a nearly-colorless viscous oil. Two grams of silver oxide and 30 ml. of 3 *N* sodium hydroxide solution were added to the oil and the mixture was heated at 90° on a steam-bath for 45 minutes. The solids were then removed by filtration and the filtrate, after acidification with dilute hydrochloric acid, was extracted four times with chloroform. Upon evaporation of the dried (magnesium sulfate) extracts 262 mg. of a light-yellow oil was obtained that slowly solidified. Digestion of the oil with boiling hexane left 101 mg. of insoluble material and cooling of the hexane gave 68 mg. of crystals. Several additional crystallizations from hexane gave colorless blunt needles, m.p. 73–74.4°. A Kuhn–Roth C-methyl determination on the dicarboxylic acid V showed 0.87 C-methyl (calcd. 1.0). A mixed melting point with a synthetic sample of 2-methyldodecanedioic acid[10] showed no depression and the infrared spectra of the two samples were identical in every respect. Subsequent studies of the reaction of hydrogenated fungichromin with sodium periodate for shorter periods of time[11] have indicated that the results described here can be explained only by hydrolysis of an ester or lactone group masking one of the hydroxyl groups in hydrogenated fungichromin prior to the cleavage with periodate.

2-Methyl-2,4,6,8,10-dodecapentaenedioic Acid from 2-Methyl-2,4,6,8,10-dodecapentaenedial (I).[11]—A solution of 1.05 g. of sodium hydroxide in 25 ml. of water was added slowly with swirling to 705 mg. of the dialdehyde I and 2.96 g. of silver nitrate in 50 ml. of ethanol and 25 ml. of water. After the addition was complete 25 ml. of water was added and the reaction mixture was allowed to stand overnight. The mixture then was filtered and the precipitate was washed with water several times. Ethanol was removed from the filtrate under reduced pressure, 25 ml. of water was added, and the filtrate was extracted with three 75-ml. portions of ether. The yellow aqueous phase was brought to *p*H 3.5 by the addition of hydrochloric acid. The precipitated yellow dicarboxylic acid was removed by filtration and dried under vacuum, giving 606 mg., m.p. 247–249° dec. An additional 16 mg. was obtained from the mother liquors. Recrystallization of the dicarboxylic acid from ethanol–water and from methanol–water yielded pure 2-methyl-2,4,6,8,10-dodecapentaenedioic acid, m.p. 252.5–253° dec.; λ_{max}^{EtOH} mμ (ε), 211 (8,000), 270 (4,400), 350 (56,000), 364.5 (86,000), 382.5 (81,000).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.71; H, 6.03.

2-Methyldodecanedioic Acid from 2-Methyl-2,4,6,8,10-dodecapentaenedioic Acid.[11]—Hydrogenation of a 72-mg. sample of 2-methyl-2,4,6,8,10-dodecapentaenedioic acid in 15 ml. of glacial acetic acid over 103 mg. of prereduced platinum oxide resulted in the absorption of 5 molar equivalents of hydrogen. The catalyst was removed by filtration and washed with acetic acid. Evaporation of the acetic acid left a colorless oil that crystallized on cooling, yielding 73 mg. of colorless 2-methyldodecanedioic acid, m.p. 72–74°. Crystallization from hexane gave the pure dicarboxylic acid, m.p. 74–75°. A mixed melting point determination with authentic 2-methyldodecanedioic acid (m.p. 73–74.5°) was undepressed; m.p. 73.8–75°.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of *Ormosia panamensis* Benth. and Related Species

BY H. A. LLOYD AND E. C. HORNING

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Seeds of the Venezuelan tree *Ormosia dasycarpa* Jacks. were reported in 1919 to contain two alkaloids of unknown structure, one of which was described as possessing analgesic action. In an investigation of this problem, it was found that seeds of *Ormosia panamensis* Benth. and related species contained a number of alkaloids; three of these, panamine, ormosinine and ormosanine were oxygen-free bases, and at least two additional oxygen-containing (amide) bases also were present. The major alkaloid, panamine, was found to undergo air oxidation to yield a substance with potent hypotensive properties in dogs. This material may be a *t*-amine oxide. A substance corresponding to the analgesic alkaloid ormosine was not found, although there were some similarities between the properties of panamine and those described for ormosine.

In 1919, Hess and Merck[1] reported that seeds of a Venezuelan tree of the Leguminosae, *Ormosia dasycarpa* Jacks., contained two alkaloids of unknown structure. The major alkaloid, ormosine, was obtained as a hydrate $C_{20}H_{33}N_3 \cdot 3\text{–}4\ H_2O$, m.p. 85–87°; the other base, ormosinine, m.p. 203–205°, had the same molecular formula $C_{20}H_{33}N_3$, but it did not correspond to water-free ormosine. It was also reported that ormosine had a strong narcotic action resembling that of morphine.

In an investigation of this problem, ormosinine and several new alkaloids were isolated from seeds of *O. panamensis* Benth. (from Cuba and Panama) and *O. jamaicensis* Urb. (from Jamaica). These were also present, as indicated by paper chromatography, in several other *Ormosia* species from Central and South America.

The alkaloids were isolated by conventional extraction and fractionation procedures. It was found desirable to remove the wax–lipid components from the seeds by hexane extraction before proceeding with the alkaloid extraction with methanol. The total alkaloid content of the seeds, amounting usually to 2.5–2.8%, was extracted selectively from aqueous (basic) solution with ether to yield a fraction containing ormosinine, two new compounds which have been named ormosanine and panamine, and small quantities of several additional alkaloids. The remaining organic base fraction was extracted with chloroform and this provided a mixture whose major component was panamine. The composition of these fractions and the composition of column effluent fractions resulting from column chromatography separations were followed by paper chromatography.

Ormosinine was described previously as a colorless base, m.p. 203–205°, with only a slight solubility in alcohol and ether. The corresponding material obtained in this work had a higher melt-

(1) K. Hess and E. Merck, *Ber.*, **52**, 1976 (1919).