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Fungichromin: Complete Structure and Absolute Configuration at C_{26} and C_{27}[1]

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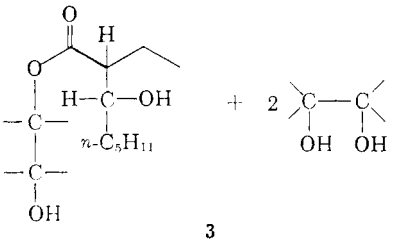
The structure of the antibiotic Fungichromin has been determined and proof is presented for the absolute configurations of two of twelve asymmetric carbon atoms. A new degradative procedure of general applicability for the determination of the carbon skeleton of complex polyhydroxy compounds is described.

Further work on the pentaene antifungal antibiotic Fungichromin[4] has led to determination of the complete structure and the absolute configurations of two of the twelve asymmetric carbon atoms. Dhar, Thaller and Whiting recently have reported partial and complete structures for the very similar antibiotic Lagosin.[5] Our structure determination, employing different experimental methods, leads to the same structure for Fungichromin as the one reported for Lagosin; however we found that Fungichromin consistently showed somewhat higher rotations [$[\alpha]_D$ -176 $\pm 4°$ (*c* 0.25, methanol)] than did Lagosin [$[\alpha]_D$ -160 $\pm 4°$ (*c* 0.25, methanol)]. The ultraviolet and infrared spectra of the two, and their behavior on paper chromatography in four different systems, are identical. X-Ray powder patterns[6] of the two antibiotics and their decahydro derivatives warrant an *a priori* judgment of identity but small differences exist between the two patterns which if not attributable to impurities or to differences in crystallinity might be ascribed to minor differences in chemical structure or hydration.

Fungichromin (**1**) was hydrogenated in methanol with platinum as catalyst to a crystalline decahydro derivative **2**, m.p. 166°. The uptake of hydrogen was 5.0 moles based on a molecular weight of 671, and microanalysis of decahydrofungichromin supported the molecular formula $C_{35}H_{68-70}O_{12}$. Its ultraviolet spectrum showed only weak end absorption (ϵ_{216} 172) indicating that decahydrofungichromin is a saturated compound.

The discrepancy between the number of oxygen atoms indicated by analysis of decahydrofungichromin and by the original analysis of Fungichromin[4] was settled when a sample of the antibiotic dried by azeotropic distillation of a benzene suspension after recrystallization from absolute methanol corresponded in analysis to $C_{35}H_{58-60}O_{12}$. After standing several weeks it was analyzed again and corresponded to $C_{35}H_{58-60}O_{13}$, unchanged after recrystallization from absolute methanol. Apparently Fungichromin forms a stable hydrate whereas the decahydro derivative does not.

Kuhn-Roth oxidation of Fungichromin and of decahydrofungichromin followed by separation of the volatile acids by paper chromatography[7] gave large spots for acetic and *n*-caproic acids and weak spots for propionic, *n*-butyric and *n*-valeric acids. When the same mixture was analyzed by gas chromatography (as methyl esters) it was found to consist of more than 90% *n*-caproic acid. (Methyl acetate was hidden by the ether peak.) Steam distillation of an alkaline aqueous suspension of Fungichromin yielded 1-hexanal, identified as its 2,4-dinitrophenylhydrazone. The infrared spectrum of Fungichromin (potassium bromide disk) showed a strong band at 1710 cm.$^{-1}$ which did not disappear on hydrogenation. Fungichromin and decahydrofungichromin each consumed two molar equivalents of periodate in neutral solution and three molar equivalents after treatment with sodium carbonate. These observations are in agreement with partial formula **3** in which one of the three 1,2-glycol systems is involved in formation of a lactone or ester grouping, and the 1-hexanal is formed by a retroaldol condensation.



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Determination of the exact number of carbon atoms in a compound with a molecular weight as large as Fungichromin presents a problem because elemental analyses and conventional methods for determination of molecular weight, *e.g.*, saponification equivalent, are not sufficiently accurate. We therefore proceeded to obtain a derivative retaining all of the carbon atoms of Fungichromin in their original arrangement and yet simple enough for direct proof of structure by unambiguous synthesis. The degradation sequence was the following: decahydrofungichromin was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to a polyol which was treated with red phosphorus in refluxing hydriodic acid. The hydroxyl-free but iodine-containing product was reduced with lithium aluminum hydride and then chromatographed on alumina. The hydrocarbon fractions were finally hydrogenated using platinum as catalyst. The product, obtained in an over-all yield of 13%, was homogeneous when analyzed by low and high temperature gas chromatography. Its

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(2) National Institutes of Health Postdoctoral Fellow, 1959–1960.

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

(4) A. C. Cope and H. E. Johnson, *J. Am. Chem. Soc.*, **80**, 1504 (1958), and references no. 2 and 3 in that paper.

(5) M. L. Dhar, V. Thaller and M. C. Whiting, *Proc. Chem. Soc.*, 118 (1958); 310 (1960). We are indebted to Dr. Whiting for supplying a sample of Lagosin.

(6) We are indebted to Prof. David P. Shoemaker for these determinations.

(7) C. F. Garbers, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **37**, 1336 (1954).

infrared spectrum was characteristic of a saturated hydrocarbon, C_nH_{n+2}, and its molecular weight was 492 as determined by mass spectrometry.[8] Its molecular formula was therefore $C_{35}H_{72}$. The possibility of rearrangement or loss of small fragments during the drastic reduction with hydriodic acid was eliminated when a polytosylate of the polyol reduced first with lithium aluminum hydride and then with hydrogen using platinum as catalyst gave the same hydrocarbon, as demonstrated by identity of the mass spectra and retention times on gas chromatography. The yield of hydrocarbon by the second method was, not unexpectedly, very low. Lithium aluminum hydride reductions of tosylates of secondary polyols (carbohydrates) often gave good yields of hydroxy compounds with little or no hydrocarbon.[9]

The molecular weight of the hydrocarbon proved that Fungichromin is a macrocyclic lactone rather than an ester. A non-cyclic structure would have given two fragments with a total number of 35 carbon atoms. The possibility that one such fragment would be sufficiently small to escape detection or to be lost during the isolation procedures appeared unlikely in view of the very close agreement of the elemental analyses and catalytic hydrogenation data with a C_{35}-formula and was ruled out by later experiments.

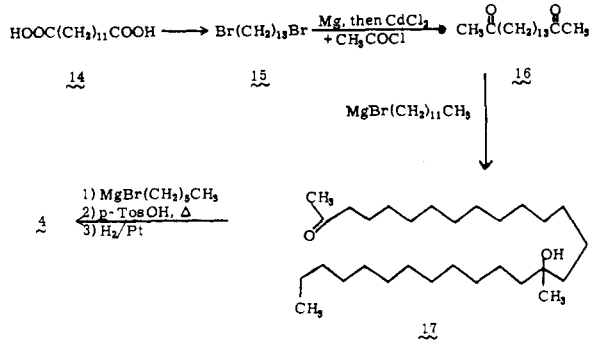
The C_{35}-hydrocarbon was oxidized with chromium trioxide in glacial acetic acid[10] and from the neutral fraction 2-octanone (**5**) and 2-tetradecanone (**6**) were isolated by gas chromatography. Preliminary identification by retention times was confirmed by comparison of their mass spectra with those of authentic samples. This result was in agreement with the position of the methyl groups in the C_{35}-hydrocarbon deduced from its mass spectrum, which exhibited prominent peaks at *m/e* 323 ($C_{23}H_{47}^+$) and *m/e* 407 ($C_{29}H_{59}^+$). The identity of the hydrocarbon from Fungichromin with 7,21-dimethyltritriacontane (**4**) was then confirmed by synthesis. 1,11-Undecanedicarboxylic acid (**14**) was converted to the dibromide **15** in 55% over-all yield, *via* lithium aluminum hydride reduction of the dimethyl ester and treatment of the resulting glycol with anhydrous hydrogen bromide. Addition of excess acetyl chloride to the organocadmium reagent prepared from the dibromide gave 2,16-heptadecanedione (**16**) (27% yield). Reaction of the diketone **16** with one molar equivalent of *n*-dodecylmagnesium bromide gave a complex mixture from which pure 16-methyl-16-hydroxy-2-octacosanone (**17**) was separated in 9% yield. Treatment of **17** successively with *n*-hexylmagnesium bromide, then with *p*-toluenesulfonic acid in refluxing benzene and finally with hydrogen using platinum as catalyst gave a 76% yield of pure 7,21-dimethyltritriacontane (**4**).

(8) We are indebted to Prof. Klaus Biemann and his associates for mass spectra and for helpful discussions.

(9) R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 164 (1953), and N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 855–873, and references there given.

(10) J. Cason, J. S. Fessenden and C. L. Agre, *Tetrahedron*, **7**, 289 (1959).

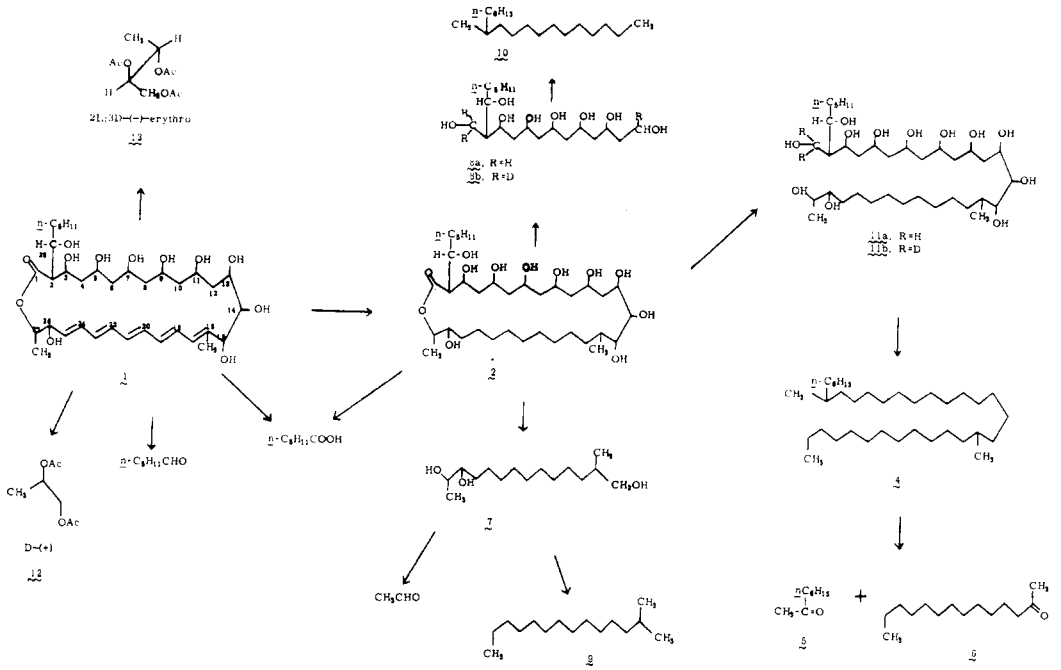
After establishment of the carbon skeleton the next problem was to place the twelve oxygen atoms. Partial structure **3** summarizes the data at hand: a macrocyclic lactone grouping and three 1,2-glycol systems, one of which is involved in formation of the lactone, and a hydroxyl group in the C_6-side chain β to the lactone carbonyl group. Cleavage of decahydrofungichromin with neutral periodate followed by lithium aluminum hydride reduction of the carbonyl compounds gave a mixture of two crystalline polyols, $C_{15}H_{32}O_3$ and $C_{19}H_{40}O_8$, readily separable because of their very different solubility properties. The crude polyols



were each converted to the corresponding hydrocarbons by the phosphorus–hydriodic acid method devised for the C_{35}-polyol from Fungichromin itself. The hydrocarbons were, respectively, 2-methyltetradecane (**9**) and 7-methyloctadecane (**10**), shown by identity of their mass spectra[11] with those of synthetic samples. 2-Methyltetradecane was synthesized by addition of *n*-dodecylmagnesium bromide to acetone followed by dehydration of the resulting tertiary alcohol and catalytic hydrogenation; 7-methyloctadecane analogously from 2-tridecanone and *n*-hexylmagnesium bromide. The possibility of skeletal rearrangement during the drastic hydriodic acid treatment was again eliminated by the fact that the hydrocarbon prepared from the C_{19}-polyol *via* reduction of its polytosylate also had a mass spectrum identical with that of synthetic 7-methyloctadecane. We noted, however, that gas chromatographic analysis of each of the crude hydrocarbons **9** and **10** obtained by the phosphorus–hydriodic acid method showed some contamination (*ca.* 5%) by the respective straight chain isomers, *n*-pentadecane and *n*-nonadecane. This indicated that carbonium ion rearrangement did occur to a small extent during the phosphorus–hydriodic acid reduction since no *n*-nonadecane was detected in the crude hydrocarbon from the polytosylate. It was of future importance to note also that among the contaminants of crude **9** no 2-methyldodecane could be found.

Since the polyol $C_{19}H_{40}O_8$ was inert to periodate (quantitative titration) and contained the C_5H_{11}-CHOH– side chain (shown by the conversion to 7-

(11) Identity of retention times did not usually suffice to distinguish between position isomers on our columns although one could reliably distinguish a branched isomer from the straight chain one. See, for example, D. T. Downing, Z. H. Kranz and K. E. Murray, *Austral. J. Chem.*, **13**, 80 (1960).



methyloctadecane) it could be assigned the unique structure **8a** which placed eight of the twelve oxygen atoms of Fungichromin. The ninth and tenth oxygen atoms then had to be placed on C-14 and C-15 of **1** to accommodate the periodate data and the formation of the C_{15}-triol. Structure **7** was required for the triol because on oxidation with one equivalent of periodate it gave a 76% yield of acetaldehyde, isolated as the 2,4-dinitrophenylhydrazone. This placed the eleventh and twelfth oxygen atoms of **1**.

It was next necessary to determine the nature of all the oxygen functions not already established as lactone or hydroxyl groups. Acetyl analysis of an amorphous polyacetate of Fungichromin indicated the presence of nine acetoxy groups, suggesting that all but one of the non-lactonic oxygens were hydroxyl groups. Diagnostic tests for the presence of ketonic carbonyl or epoxide groupings were negative; the absence of both these groupings (as well as of a larger ether ring) was proved conclusively in the following way: reduction of ketones or oxides with lithium aluminum deuteride introduces one deuterium atom for each of these groups present; reduction of a lactone introduces two deuterium atoms per group. Lithium aluminum deuteride reduction of decahydrofungichromin gave a crystalline polyol (**11b**), $C_{35}H_{70}D_2O_{12}$, having no carbonyl absorption in the infrared. Analysis showed the presence of 2.71 atom per cent. excess of deuterium. The calculated value for two atoms of deuterium per molecule is 2.78% and for three 4.16%. Sodium periodate oxidation of decahydrofungichromin followed by lithium aluminum deuteride reduction and separation of the polyols as before gave **8b** containing 7.42 atom per cent. excess of deuterium. This value corresponded to the introduction of three deuterium atoms, two by reduction of the lactone and one by reduction of the aldehyde group formed by the periodate oxidation. The calculated values are 7.50% and 10.00% for three and four deuterium atoms, respectively.

The last remaining structural question, the position of closure of the macrocyclic lactone, now limited to C-26 or C-27, was settled in the following way: Fungichromin was ozonized in methanol solution and the ozonide reduced catalytically. Direct oxidation with sodium periodate followed by lithium aluminum hydride reduction and acetylation gave 1,2-propanediol diacetate in 39% yield from Fungichromin. It was identified by comparison with an authentic sample (retention time and infrared spectrum). This was proof that the lactone ring was closed at C-27 since had closure been at C-26 instead the product isolated from the degradation sequence would have been 1,2,3-butanetriol triacetate. No trace of this compound was detected by gas chromatographic analysis.

The 1,2-propanediol diacetate from Fungichromin was optically active, $[\alpha]_D$ +2.0°. D-(+)-1,2-Propanediol diacetate, $[\alpha]_D$ +1.55°, was synthesized from D-(+)-calcium lactate by methylation, lithium aluminum hydride reduction and acetylation. Thus the absolute configuration at C-27 in Fungichromin is D. If C-26 also had the D-configuration the C-27, C-26 relationship would be *threo;* if C-26 were L the relationship would be *erythro.* The configuration at C-26 was determined as follows: ozonolysis of Fungichromin followed by catalytic hydrogenation, lithium aluminum hydride reduction and acetylation gave 2L:3D-(−)-*erythro*-1,2,3-butanetriol triacetate, isolated in 45% yield based on Fungichromin. It contained no *threo* isomer, which demonstrated that no base-catalyzed epimerization of C-26 at the α-hydroxy aldehyde stage (in the lithium aluminum hydride mixture before reduction was complete) occurred since in that case both isomers would be expected. The identity of the *erythro*-1,2,3-butanetriol tri-

acetate from Fungichromin was shown in three different ways. Its infrared spectrum was superimposable with that of synthetic *dl-erythro*-1,2,3-butanetriol triacetate and different from that of the *threo* isomer, especially in the 1140–1165 cm.$^{-1}$ region. Its retention time was identical with that of the synthetic *erythro* isomer; admixture with the latter gave one peak, while admixture with the synthetic *threo* isomer gave two peaks. The refractive indices of the synthetic *threo* (1.4287) and *erythro* (1.4273) isomers differed significantly and that of the triacetate from Fungichromin was very close to the latter value (1.4270).

We have found only two previous references to a 1,2,3-butanetriol triacetate.[12,13] We obtained *dl-erythro*-1,2,3-butanetriol triacetate from *trans*-crotyl alcohol (containing 8% of the *cis* isomer) by treatment with peracetic acid followed by opening of the epoxide with acetic anhydride. This method is known to give *trans* addition to a double bond. The small amount of *threo* isomer arising from the *cis*-crotyl alcohol impurity was almost completely removed by fractional distillation. *dl-Threo*-1,2,3-butanetriol triacetate was prepared by treating *trans*-crotyl acetate (also containing 8% of the *cis* isomer) under the conditions of the "wet Prevost reaction,"[14] which in this case was not completely stereospecific (*cis* hydroxylation) since the product consisted of an 82:18 *threo:erythro* mixture. The pure *threo* isomer was obtained by fractional distillation followed by preparative gas chromatography.

It was stated previously that no 2-methyldodecane was detected in the 2-methyltetradecane obtained from the crude C_{15}-triol **7** by the phosphorus–hydriodic acid reduction sequence. This fact proves that Fungichromin is entirely in the form of a macrocyclic lactone closed at C-27. The presence of any open form or of a smaller lactone ring would permit periodate cleavage between C-27 and C-26 and give rise to some 2-methyldodecane.

With the structure of Fungichromin established we wish to describe briefly a singular transformation unrelated to the structure proof. Solutions of decahydrofungichromin in dilute (0.2 *N*) sodium methoxide were found to develop intense ultraviolet absorption after standing at room temperature for a few hours. The spectrum was in every detail characteristic of a conjugated triene (λ_{max} 265, 275, 287 mμ), although the extinctions were low and differed among experiments (ϵ_{275} 11,000–25,000). No other maxima were present although there was appreciable end absorption (ϵ_{215} 5000). Acidification destroyed the fine structure and a broad peak at 271 mμ of somewhat lowered intensity appeared instead. Addition of base restored the earlier spectrum. Under the same conditions Fungichromin behaved identically. The presence of the pentaene absorption, however, complicated the spectrum, which showed the two separate chromophores overlapping. Attempts to isolate and characterize a compound containing the new chromophore were not successful; nor did the degradative sequences undertaken to determine the location of the triene system give a conclusive result.

Some precedent for our observations could be found in the chemistry of oleandomycin[15] and neomethymycin[16] where under similar conditions a *ketonic* carbonyl group triggered β-elimination of hydroxyl groups to give in the first case an α,β-unsaturated ketone, and in the second an α,β,γ,δ-unsaturated ketone. In the case of Fungichromin no ketonic carbonyl group is present, but our evidence indicates that the *lactone* carbonyl and the hydroxyl group at C-29 and/or the one at C-3 are involved in a β-elimination reaction. The details of this and of the transformations that follow are as yet obscure.

Experimental[17]

Purification of Fungichromin (1) (Preparation of Anhydrous Material).—Twenty grams of 66% Fungichromin[18] and 250 ml. of benzene[19] were placed in a 500-ml. round-bottomed flask equipped with a reflux condenser and a Dean–Stark trap. After heating under reflux until no more water collected, the suspension was cooled and the Fungichromin was collected by filtration and recrystallized from methanol. The three crops of crystals obtained, a total of 5.7 g., all showed the characteristic pentaene ultraviolet spectrum[4] with $E^{1\%}_{1cm}$ 1420–1450 at 338 mμ. One gram of the third crop was further purified by a second recrystallization from methanol to give 530 mg. of an analytical sample (sample A). One third of sample A was placed in a distilling flask with 20 ml. of benzene, about 10 ml. of which was slowly distilled. The suspension was then cooled and filtered (sample B). Another third of sample A was placed in a distilling flask with 70 ml. of ethanol and 30 ml. of benzene and the solvents were slowly distilled under reduced pressure (140–150 mm.). At the start of the distillation about 90% of the material was in solution. Distillation was continued until only a few ml. of the solvents remained. The precipitated Fungichromin was then filtered (sample C). The three samples were dried at 33° (0.05 mm.) and immediately submitted for analysis.

Anal. Calcd. for $C_{35}H_{60}O_{13}$: C, 61.21; H, 8.78. For $C_{35}H_{58}O_{12}$: C, 62.67; H, 8.71. Found: A: C, 61.01; H, 8.65. B: C, 62.46; H, 8.69. C: C, 62.17; H, 8.75.

A second set of microanalyses several weeks later gave virtually identical results (C, 61.2 ± 0.2) for all three samples. Apparently, therefore, the initially anhydrous samples B and C hydrated on standing.

Paper Chromatography of Fungichromin and of Lagosin.—The two antibiotics were chromatographed simultaneously in the systems shown in the table, using Whatman No. 1 paper. The spots were detected by their intense greenish fluorescence in ultraviolet light.

Preparation of Decahydrofungichromin (2).—To 50 mg. of platinum oxide prereduced in methanol (5 ml.) was added a suspension of 500 mg. (0.745 mmole) of Fungichromin in methanol (45 ml.). As hydrogenation proceeded the Fungichromin gradually dissolved. Hydrogen uptake was 90.4

(12) A. Lieben and S. Zeisel, *Monatsh.*, **1**, 818 (1880), obtained the compound from crotyl alcohol (presumably mostly *trans*) by addition of bromine, hydrolysis of the dibromide and acetylation. This product was probably largely *erythro* isomer.

(13) R. Delaby, *Ann. chim.*, [9] **19**, 275 (1923), prepared the compound by addition of bromine to methylvinylcarbinol followed by treatment with potassium acetate. This was presumably a mixture of isomers.

(14) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 6256 (1957); R. B. Woodward and F. V. Brucher, Jr., *ibid.*, **80**, 209 (1958).

(15) F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro and R. B. Woodward, *J. Am. Chem. Soc.*, **82**, 3225 (1960).

(16) C. Djerassi and O. Halpern, *Tetrahedron*, **3**, 255 (1958).

(17) Melting points are corrected and boiling points are uncorrected. Deuterium analyses were performed by Mr. Josef Nemeth, Urbana, Ill., using the falling drop method.

(18) From Merck Sharp and Dohme Research Laboratories, West Point, Pa.

(19) Benzene was distilled from sodium; methanol and ethanol from calcium hydride. The solvents were stored under nitrogen and the operations were carried out under nitrogen.

System	R_F Fungichromin	R_F Lagosin
Methyl isobutyl ketone: 1-butanol:water, 50:15.3	0.73	0.72
Methyl isopropyl ketone: water (saturated, *ca.* 1.6%)	.35	.35
Methyl isopropyl ketone: 1-butanol:water, 50:10:3.5	.76	.76
Methyl isopropyl ketone: methanol:water, 50:1:0.4	.47	.47

ml. at 22° (5.0 molar equivalents) and was complete in 2 hr. The catalyst was separated, the filtrate evaporated to dryness, and the colorless solid residue recrystallized three times from dioxane and dried for 24 hr. at 77° (0.05 mm.); m.p. 166°. The yields of purified material obtained by this procedure were 65–70%. Samples showed no tendency to hydrate on standing.

Anal. Calcd. for $C_{35}H_{68}O_{12}$: C, 61.73; H, 10.07. For $C_{35}H_{70}O_{13}$: C, 60.09; H, 10.00. Found: C, 61.64; H, 10.24.

Kuhn–Roth Oxidations of Fungichromin and of Decahydrofungichromin.—Two milligrams of Fungichromin was oxidized following the modified procedure of Garbers, Schmid and Karrer.[7] The paper chromatogram showed large spots corresponding to acetic and *n*-caproic acids, and smaller spots corresponding to *n*-valeric, *n*-butyric and propionic acids.

When 2 mg. of decahydrofungichromin was oxidized in an identical manner only large spots for acetic and *n*-caproic acids could be detected.

Fungichromin (40 mg.) was oxidized with 2 ml. of a chromium trioxide–sulfuric acid mixture and 10 ml. of water following the method of Entschel, Eugster and Karrer[20] for higher and branched side chains. The distillate (15 ml.) was collected and extracted with ether. The ether extract was dried over sodium sulfate and treated with diazomethane. The ether was slowly distilled and the remaining methyl esters were dissolved in *n*-hexane and passed over neutral alumina, activity 2. Gas chromatographic analysis at 120° using a column of 30% silicone grease on 60–80 mesh Chromosorb showed the presence of the methyl esters of *n*-caproic, *n*-valeric, *n*-butyric and propionic acids. The amount of methyl caproate was about 10 times the combined amounts of the other esters. Authentic samples of the methyl esters were used as standards for retention times.

Isolation of Hexanal from Fungichromin.—Fungichromin (1.00 g.) was added to a solution of 0.38 g. of sodium hydroxide in 150 ml. of water, and the suspension was steam distilled into a solution of 2,4-dinitrophenylhydrazine in aqueous hydrochloric acid until precipitation of 2,4-dinitrophenylhydrazones ceased. The mixture was allowed to stand overnight and the precipitate was collected, dried (140 mg.) and chromatographed on a silicic acid–Celite (2:1) column. The early fractions, eluted with ether–hexane mixtures, gave about 45 mg. of hexanal 2,4-dinitrophenylhydrazone which was recrystallized from hexane, m.p. 103–107°. A mixed melting point with authentic material, m.p. 105–107°, was undepressed. Acetaldehyde 2,4-dinitrophenylhydrazone was also identified in the later fractions.

Quantitative Periodate Oxidations of Fungichromin and of Decahydrofungichromin.[21] **A. Sodium Periodate.**—A sample of Fungichromin, 1.0004 g., was dissolved in 600 ml. of a 1:1 ethanol–water mixture and to it was added exactly 300 ml. of 0.0173 *M* sodium metaperiodate solution. The resulting solution was diluted with water to exactly 1 l. Aliquots (25 ml.) were removed for titration by the thiosulfate method at intervals beginning at 2 hr. and continuing until 22 hr. The values ranged between 1.84 and 2.05 molar equivalents of periodate consumed, and the 2 and 22 hr. values did not differ significantly (1.98 and 2.00). The same procedure was followed for decahydrofungichromin except one-half the above quantities were used to prepare the reaction solution. The values ranged between 1.98 and 2.13 molar equivalents, with no significant difference between 1 hr. and 48 hr. values.

B. Sodium Periodate with Prior Base Treatment.—To a solution of 1.0004 g. of Fungichromin in 100 ml. of ethanol and 50 ml. of water was added 30 ml. of 0.055 *N* sodium hydroxide solution. The solution was refluxed for 30 min., then cooled and titrated to *p*H 9 with hydrochloric acid. To it was then added exactly 300 ml. of 0.0233 *M* sodium metaperiodate solution and the whole was diluted with water to exactly 1 l. Aliquots (25 ml.) were removed at intervals for titration by the thiosulfate method. The values ranged between 2.89 and 3.05 molar equivalents of periodate consumed, and the 2 and 14 hr. values did not differ significantly.

General Methods for the Conversion of Polyols to Hydrocarbons. A. Reduction with Phosphorus and Hydriodic Acid.—A mixture of approximately equal weights of the polyol and red phosphorus was heated under reflux for 24 hr. in excess constant-boiling hydriodic acid (*ca.* 10 ml. hydriodic acid/300 mg. polyol). Water was added to precipitate the organic material, which was then extracted with ether or chloroform. The organic extracts were washed with 2% sodium thiosulfate solution, then with water, and dried over magnesium sulfate. Removal of solvent gave an iodine-containing oil which was dissolved in tetrahydrofuran and refluxed overnight with 1–2 times its weight of lithium aluminum hydride. The unchanged hydride was destroyed with ethyl acetate. After evaporation of the solvents the residue was chilled in an ice-bath, the inorganic material dissolved in 10% sulfuric acid, and the organic material was extracted with hexane. The hexane solution, after being washed with 5% sodium carbonate solution and dried over sodium carbonate, was concentrated and chromatographed on a column of neutral alumina (Woelm, activity 1). The fractions containing the hydrocarbon (eluted with hexane and determined by gas chromatography) were combined, concentrated and hydrogenated in hexane or hexane–ethyl acetate mixtures using platinum oxide as catalyst. The catalyst was separated and the solvent evaporated to give the hydrocarbon.

B. Lithium Aluminum Hydride Reduction of a Polytosylate.—The polyol was dissolved in *ca.* 20 times its weight of dry pyridine, and a solution of *p*-toluenesulfonyl chloride (30% excess) in *ca.* 5 times its weight of pyridine was added with cooling and swirling. The solution was allowed to stand in an ice-box for 6 days, after which most of the pyridine was removed under reduced pressure at room temperature. The residue was dissolved in chloroform, and then water and ice-cold 20% sulfuric acid were added dropwise with cooling until the aqueous layer had *p*H 2. The layers were separated and the aqueous phase was extracted twice with chloroform. The combined organic phases were washed with 5% sodium bicarbonate solution and saturated sodium chloride solution. Removal of the solvent under reduced pressure at room temperature yielded an oil, which was dried at 0.1 mm. at room temperature for 24 hr. A solution in anhydrous tetrahydrofuran of the crude tosylate so obtained was added slowly to a solution of a tenfold excess of lithium aluminum hydride in tetrahydrofuran. The total amount of solvent was adjusted to result in a 5–10% solution of the hydride after addition was complete. The mixture was stirred and heated under reflux for 2 days. The excess hydride was decomposed with ethyl acetate, pentane was added, and the cooled and stirred mixture was acidified to *p*H 1 with 20% sulfuric acid. The layers were separated, and the aqueous phase was extracted twice with pentane. The combined extracts were washed with 20% sulfuric acid, then with 10% sodium carbonate solution, and dried over magnesium sulfate. Removal of the solvents gave brown oils which contained large amounts of sulfur-containing compounds. These were removed by chromatography on neutral alumina (activity 1), eluting with pentane. The fractions containing the hydrocarbon (as determined by gas chromatography) were concentrated to a small volume and hydrogenated, using platinum oxide as catalyst and glacial acetic acid as solvent. The catalyst was removed by filtration, and pentane and water were added to the filtrate. The layers were separated, the aqueous layer was extracted twice with pentane, and the combined extracts were washed with sodium carbonate solution and dried over potassium carbonate. Removal of the solvent gave the hydrocarbon.

Isolation of 7,21-Dimethyltritriacontane (4) from Decahydrofungichromin.—Five grams of decahydrofungichromin was dissolved in 300 ml. of tetrahydrofuran and excess

(20) R. Entschel, C. H. Eugster and P. Karrer, *Helv. Chim. Acta*, **39**, 1263 (1956).

(21) Corrections for blank runs are included in all results.

lithium aluminum hydride was added gradually. The mixture was refluxed for 2 days. The unchanged hydride was then destroyed with ethyl acetate and the mixture was evaporated nearly to dryness under reduced pressure. The residue was chilled, dilute sulfuric acid was added to dissolve the inorganic material, and the polyol was extracted with 1-butanol. The combined extracts were washed with 10% sodium carbonate solution, then with water, and the butanol was removed under reduced pressure. After drying for 24 hr. at 0.1 mm., 4.70 g. of non-crystalline polyol was obtained.

A. *Via* **Reduction with Phosphorus and Hydriodic Acid.**—The polyol (2.5 g.) was heated under reflux with red phosphorus and hydriodic acid and treated subsequently as described in the general procedure. The yield of 7,21-dimethyltritriacontane, a colorless oil, was 0.209 g. (13% from decahydrofungichromin). Its infrared spectrum (liquid film) was typical of a saturated hydrocarbon. Gas chromatography at 340° using an 85 × 0.8-cm. column packed with 20% SE-30 silicone rubber (General Electric Co.) on 80–100 mesh Chromosorb W gave one major peak (>95%) with a retention time identical with that of an authentic sample of **4** and one minor peak (<5%) with a retention time corresponding approximately to a C_{30}-hydrocarbon. Gas chromatography at lower temperatures showed that no lower hydrocarbons were present. The mass spectrum of the major component indicated the presence of some olefinic impurities but otherwise showed the same fragmentation pattern as that of authentic 7,21-dimethyltritriacontane and the same molecular weight (492).

B. *Via* **Reduction of the Polytosylate.**—The polyol (460 mg.) was converted to the polytosylate which was then reduced with lithium aluminum hydride as described in the general procedure. The yield of 7,21-dimethyltritriacontane was 6 mg. (2% from decahydrofungichromin). Gas chromatography on the above silicone rubber column showed a single component with the same retention time as authentic **4**. Its mass spectrum was identical with that of authentic **4**.

Chromium Trioxide Oxidation of 7,21-Dimethyltritriacontane.—Fifty-eight mg. of the hydrocarbon from decahydrofungichromin was oxidized with 74 mg. of chromium trioxide in 3.5 ml. of glacial acetic acid for 2 hr. at 65° according to the procedure of Cason.[10] The cooled solution was very carefully neutralized with 5% aqueous potassium hydroxide and immediately extracted with ether. After washing the extract with water and drying it over sodium sulfate the ether was distilled through a short column. Gas chromatographic analysis of the residue at 220° on a 20% silicone grease column showed two peaks of equal area with the same retention times as 2-octanone and 2-tetradecanone. The two compounds were collected on the same column and their mass spectra were identical with those of the respective authentic ketones.

Synthesis of 7,21-Dimethytritriacontane (4).—Twenty-five grams of 1,11-undecanedicarboxylic acid (**14**) (Aldrich Chemical Co.) was esterified with excess diazomethane in ether. The ether solution was concentrated to *ca.* 400 ml. and added slowly to a stirred slurry of 8 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was heated under reflux for 24 hr., cooled, and the excess hydride was decomposed by careful addition, in that order, of 8 ml. of water, 8 ml. of 15% aqueous sodium hydroxide solution and 24 ml. of water. The precipitated salts were removed by filtration and washed several times with ether. Evaporation of the combined filtrates and crystallization of the residue from ether gave 17.0 g. (77% yield) of crude 1,13-tridecanediol, m.p. 63–78° (lit.[22] m.p. 76.4–76.6°), which was converted with anhydrous hydrogen bromide to 1,13-dibromotridecane (**15**). The dibromide obtained in 71% yield after fractionation had b.p. 139–148° (0.2–0.3 mm.), $n^{25}D$ 1.4882 (lit.[22] b.p. 185–187° at 9 mm.).

A Grignard reagent was prepared from 15.80 g. of **15** and 2.42 g. of magnesium powder in 70 ml. of ether. After the initial reaction had subsided the mixture was heated under reflux for 18 hr. It was cooled with ice, and 9.7 g. of anhydrous cadmium chloride was added with vigorous stirring. After warming to room temperature, an additional 2.0 g. of cadmium chloride was added and the mixture was stirred and heated under reflux for 1 hr. The ether was removed by distillation, and 150 ml. of anhydrous benzene was added to the residue. After another 30 ml. of solvent was removed by distillation, the mixture was stirred and heated under reflux for 30 min. Acetyl chloride (15.0 g.) in 50 ml. of benzene was added, and heating was resumed for 4 hr., after which the mixture was allowed to stand at room temperature for 16 hr. A mixture of 60 g. of ice and 1.3 ml. of concentrated sulfuric acid was added, the layers were separated, and the aqueous phase was extracted with 30 ml. of benzene. The combined benzene solutions were washed with water, 5% sodium carbonate solution, and again with water, dried over magnesium sulfate and finally treated with activated charcoal. Evaporation of the solvent gave 11.0 g. of a yellow semi-crystalline residue which was crystallized from a mixture of benzene and hexane (1:4), yielding 4.42 g. of 2,16-heptadecanedione (**16**), m.p. 83–85°. This product was purified further by sublimation at 100–110° (bath temperature) and 0.1 mm., giving 3.3 g. (27% yield) of the pure diketone, m.p. 85–87° (lit.[23] m.p. 87°).

A Grignard reagent was prepared from 2.40 g. of *n*-dodecyl bromide (Eastman Kodak Co. white label) and 0.5 g. of magnesium turnings in 10 ml. of ether. After heating under reflux overnight the mixture was transferred to a dropping funnel from which it was added slowly to a stirred boiling suspension of 2.59 g. of **16** in 20 ml. of ether. Heating was continued for 18 hr. Water (30 ml.) and sufficient acetic acid to dissolve all solids were added, and the layers were separated. The aqueous layer was extracted with three 50-ml. portions of ether, and the combined ether solutions were washed with dilute sodium carbonate solution, then with water, and dried over magnesium sulfate. The oily residue (3.96 g.) obtained after removal of the solvent consisted of unchanged **16**, 16-methyl-16-hydroxy-2-octacosanone (**17**) and 13,27-dimethyl-13,27-nonatriacontanediol, the latter being formed by addition of two moles of *n*-dodecylmagnesium bromide to one mole of the diketone; small amounts of dodecane and tetracosane were also present as determined by gas chromatography. A small sample of the product mixture (*ca.* 5 mg.) was dehydrated by heating with *p*-toluenesulfonic acid in benzene. Gas chromatographic analysis on an 85 × 0.8-cm. column packed with 20% by weight of SE-30 silicone rubber (General Electric Co.) on 80–100 mesh Chromosorb W at 340° showed the presence of two compounds, which had retention times expected for a C_{29}-ketone and a doubly branched C_{41}-hydrocarbon. The desired **17** was separated from the other products by chromatography on alumina; a colorless semi-solid was obtained in 9% yield (390 mg.). Gas chromatographic analysis both before and after dehydration (see above) indicated that it was 98–99% pure.

Anal. Calcd. for $C_{29}H_{58}O_2$: C, 79.38; H, 13.33. Found: C, 79.10; H, 12.96.

A solution of 377 mg. of **17** in 30 ml. of benzene was added to a Grignard reagent prepared from 0.90 g. of *n*-hexyl bromide (Eastman Kodak Co. white label) and 0.39 g. of magnesium turnings in 20 ml. of ether. After heating under reflux for 20 hr. the complex was decomposed with an aqueous solution of ammonium chloride. The layers were separated, and the aqueous phase extracted with two 10-ml. portions of pentane. The combined extracts were distilled until the boiling point reached 80°. *p*-Toluenesulfonic acid (560 mg.) was added, and slow distillation was resumed for *ca.* 1 hr. until the volume of the residue was 10 ml. Pentane (20 ml.) was added after cooling, the solution was washed free of acid with 10% sodium carbonate solution, and dried over anhydrous potassium carbonate. The solvent was removed, the residue dissolved in a mixture of 20 ml. of ethyl acetate and 10 ml. of cyclohexane and added to 520 mg. of prereduced platinum oxide in 15 ml. of glacial acetic acid. The mixture was hydrogenated until uptake ceased. The catalyst was removed by filtration, and water (20 ml.) and pentane (20 ml.) were added to the filtrate. The layers were separated, and the aqueous phase was extracted with 10 ml. of pentane. The combined organic phases were washed with sodium carbonate solution and dried over potassium carbonate. The solvent was removed and the residue was chromatographed on neutral alumina (activity 1), eluting with pentane. Removal of the solvent from the hydrocarbon fraction gave a colorless liquid, which was heated to 80° under reduced pressure (0.1 mm.) until the weight remained constant. The yield of 7,21-dimethyltritriacontane (**4**) was 320 mg. (76%). Gas chromato-

(22) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926).

(23) L. Canonica and T. Bacchetti, *Atti acad. nazl. Lincei, Rend. Classe sci. fis., mat. e nat.*, **15**, 278 (1953); *C. A.*, **49**, 8121 (1955).

graphic analysis using the silicone rubber column described above showed the hydrocarbon to be 98% pure.

Anal. Calcd. for $C_{35}H_{72}$: C, 85.28; H, 14.72. Found: C, 85.16; H, 14.55.

Isolation of 13-Methyl-2,3,14-tetradecanetriol (7) and 12-Hydroxymethyl-1,3,5,7,9,11,13-octadecaneheptaöl (8a). To a stirred and cooled suspension of 761 mg. of decahydrofungichromin (**2**) in 15 ml. of chloroform and 5 ml. of water was added dropwise a solution of 1.02 g. of sodium metaperiodate in 10 ml. of water. After stirring at 0° for 1 hr. and at room temperature for 4 hr., the chloroform was removed under reduced pressure and the residual aqueous suspension was extracted with two 15-ml. and three 5-ml. portions of 1-butanol. The combined extracts were washed with water until the washings gave a negative test for periodate ion, and the 1-butanol solution was concentrated to dryness under reduced pressure at room temperature. The residue was kept at 0.1 mm. and room temperature for 2 hr. and then dissolved in 15 ml. of tetrahydrofuran. The solution was filtered and added dropwise to a cold stirred solution of 1.02 g. of lithium aluminum hydride in 30 ml. of tetrahydrofuran. The mixture was stirred and heated under reflux for 36 hr. after which the excess hydride was decomposed with a water–tetrahydrofuran mixture and the solvent was removed under reduced pressure. To the residual white solid was added 15 ml. of chloroform, 5 ml. of water, and, with cooling and stirring, sufficient 20% sulfuric acid to dissolve the inorganic salts. The layers were separated, and the aqueous phase was extracted with two 10-ml. portions of chloroform. The combined extracts were washed with 20% sulfuric acid, 10% sodium carbonate solution and saturated sodium chloride solution. The product obtained by removal of the solvent was dried at 0.1 mm. for 18 hr., then dissolved in tetrahydrofuran, and the solution was filtered to remove inorganic salts. Concentration to dryness gave 272 mg. (93% yield) of crude 13-methyl-2,3,14-tetradecanetriol (**7**), m.p. 38–45°. A purer sample of this triol, m.p. 57–59°, was obtained in a similar way, but using sodium borohydride in *t*-butyl alcohol as reducing agent. An analytical sample, prepared by crystallization from ether–petroleum ether, had m.p. 63.0–64.5°, $[\alpha]^{26}D$ −7.2° (*c* 2, chloroform).

Anal. Calcd. for $C_{15}H_{32}O_3$: C, 69.18; H, 12.39. Found: C, 68.94; H, 12.67.

The aqueous layer from the chloroform extraction was combined with the washings and extracted with two 15-ml. portions and three 5-ml. portions of 1-butanol. The combined extracts were washed with 5 ml. of 20% sulfuric acid, 5% sodium bicarbonate solution until the washings were basic, and saturated sodium chloride solution. The solvent was removed at room temperature under reduced pressure, and the residue was dried at 0.1 mm. for 18 hr. The yield of crude 12-hydroxymethyl-1,3,5,7,9,11,13-octadecaneheptaöl (**8a**), m.p. 65–82°, was 350 mg. (79%). Repeated crystallization from ethyl acetate gave needles of the pure polyol, m.p. 100–101°, $[\alpha]_{3660\ Å}^{25}$ −6.1° (*c* 0.65, methanol), after drying at 64° (0.1 mm.) for 24 hr. The fact that this sample was crystalline was substantiated by an X-ray photograph.

Anal. Calcd. for $C_{19}H_{40}O_8$: C, 57.55; H, 10.17. Found: C, 57.61; H, 10.02.

Quantitative titration showed that the polyol did not react with sodium metaperiodate. Its infrared spectrum indicated the absence of a carbonyl group and of unsaturation, and it showed no absorption in the ultraviolet region (215–400 mμ).

Isolation of 12-Hydroxymethyl-d_2-1,3,5,7,9,11,13-octadecane-1-d_1-heptaöl (8b).—The procedure described above for the isolation of the undeuterated heptaöl **8a** was followed with the exception that lithium aluminum deuteride[24] was used as the reducing agent. The yield of crude **8b**, m.p. 75–85°, was 89%. The analytical sample had m.p. 100–102°.

Anal. Calcd. for $C_{19}H_{37}D_3O_8$: C, 57.12; H + D, 10.18; 3 atoms of deuterium per molecule, 7.50 atom % excess D. Found: C, 57.34; H + D, 10.18; atom % excess D, 7.42.

Isolation of 7-Hydroxymethyl-d_2-21-methyltritriacontane-6,8,10,12,14,16,18,19,20,31,32-undecaöl (11b).—To a stirred solution of 627 mg. of lithium aluminum deuteride[24] in 35 ml. of anhydrous tetrahydrofuran was added, over a period of 90 min., a solution of 322 mg. of decahydrofungichromin (**2**) in 35 ml. of tetrahydrofuran. The mixture was stirred and heated under reflux for 64 hr. The excess deuteride was decomposed with a mixture of tetrahydrofuran and water, and the solvent was removed under reduced pressure. 1-Butanol (15 ml.) and water (5 ml.) were added to the residue, and the stirred and cooled mixture was acidified with 20% sulfuric acid. The layers were separated, and the aqueous phase was extracted with one 10-ml. and two 5-ml. portions of 1-butanol. The combined extracts were washed with 20% sulfuric acid, 10% sodium carbonate solution, and water. Removal of the solvent under reduced pressure at room temperature and drying of the residue at 0.1 mm. for 24 hr. gave 313 mg. (96%) of crude **11b**, m.p. 126–131°. Three recrystallizations from isopropyl alcohol gave an analytical sample, m.p. 138–140°. An X-ray powder photograph showed only a few sharp lines, indicating that the polyol was only partially crystalline. Its infrared spectrum (Nujol mull) showed no carbonyl band.

Anal. Calcd. for $C_{35}H_{70}D_2O_{12}$: C, 61.19; H + D, 10.60; 2 atoms of deuterium per molecule, 2.78 atom % excess D. Found: C, 60.90; H + D, 10.58; atom % excess D, 2.71.

Reduction of 13-Methyl-2,3,14-tetradecanetriol (7) to 2-Methyltetradecane (9).—A sample of crude **7** prepared as described above from 1.14 g. of Fungichromin was reduced to the parent hydrocarbon by the red phosphorus–hydriodic acid method (see above). The 2-methyltetradecane obtained (183 mg., 51% yield based on decahydrofungichromin) was contaminated by *ca.* 10% of other hydrocarbons (7-methyloctadecane and *n*-pentadecane but no 2-methyldodecane). Preparative gas chromatography on a 30% silicone grease column at 210° afforded a sample of the pure hydrocarbon, the mass spectrum of which was identical with that of an authentic sample of 2-methyltetradecane.[25]

Reduction of 12-Hydroxymethyl-1,3,5,7,9,11,13-octadecaneheptaöl (8a) to 7-Methyloctadecane (10). A. By Reduction with Phosphorus and Hydriodic Acid.—A sample of crude **8a**, prepared from 389 mg. of decahydrofungichromin, was reduced using the general procedure described above. The hydrocarbon fraction obtained weighed 39 mg. (25% yield based on decahydrofungichromin); it consisted of *ca.* 70% of 7-methyloctadecane (**10**) and 30% of three hydrocarbons having retention times on gas chromatography identical with those of heptadecane, octadecane and nonadecane, respectively. The mass spectrum of a sample of **10**, isolated by preparative gas chromatography, indicated that it still contained some olefinic impurities; otherwise it showed the same fragmentation pattern as the spectrum of authentic **10**.

B. By Reduction of the Polytosylate.—Crude **8a** (654 mg.) was converted to the tosylate which was then reduced by the general procedure, yielding 13 mg. of 7-methyloctadecane (**10**; 3% yield based on **8a**). Its purity was 97% as determined by gas chromatography on a 20% silicone grease column at 230°. A small sample was purified by preparative gas chromatography. Its mass spectrum was identical with that of a synthetic sample of 7-methyloctadecane.

Synthesis of 2-Methyltetradecane (9).—To the Grignard reagent prepared from *n*-dodecyl bromide (12.5 g.) and magnesium turnings (1.20 g.) in ether (40 ml.) was added a solution of 2.9 g. of dry acetone in 10 ml. of ether. The mixture was refluxed for 2 hr., then cooled and acidified to *p*H 3 with 20% sulfuric acid. The layers were separated and the aqueous phase was extracted with two 10-ml. portions of ether. The combined extracts were washed with water, 10% sodium carbonate solution and saturated sodium chloride solution. Benzene (25 ml.) was added, and the mixture was distilled slowly until the boiling point reached 80°. *p*-Toluenesulfonic acid monohydrate (2.0 g.) was added to the residual benzene solution which was then heated under reflux for 0.5 hr. After cooling, water (10 ml.) was added, the layers were separated, and the organic phase was washed with 10% sodium carbonate solution and dried over potassium carbonate. The solvent was removed and the residue on distillation through a semi-micro column gave 5.7 g. (54%) of C_{15}-olefin of >99% purity as determined by gas chromatography at 220° on a 30% silicone grease column. The olefin (2.13 g.) was hydrogenated in a mix-

(24) Metal Hydrides, Inc., Beverly, Mass.: minimum isotopic purity 99.99%.

(25) H. J. Lunshof, J. Van Steenis and H. I. Waterman, *Rec. trav. chim.*, **66**, 348 (1947).

ture of ethyl acetate (15 ml.) and acetic acid (10 ml.) using prereduced platinum oxide as catalyst. After 1.5 hr., uptake stopped at 98% of the theoretical amount. The catalyst was removed by filtration, and water (15 ml.) and pentane (15 ml.) were added to the filtrate. The layers were separated and the aqueous phase extracted once with pentane (5 ml.). The combined organic phases were washed with 10% sodium carbonate solution and dried over magnesium sulfate. Removal of the solvent and distillation of the residue through a semi-micro column gave 1.78 g. (83%) of 2-methyltetradecane, b.p. 131–132° (12 mm.), $n^{25}D$ 1.4284 (lit.[25] $n^{25}D$ 1.42844).

Synthesis of 7-Methyloctadecane (10).—This hydrocarbon was prepared in 49% over-all yield by addition of 2-tridecanone (Armour and Co., Chicago, Ill.) to *n*-hexylmagnesium bromide followed by dehydration and hydrogenation as described for the synthesis of 2-methyltetradecane. The hydrocarbon had b.p. 103° (0.07 mm.), $n^{25}D$ 1.4387 (lit.[26] $n^{20}D$ 1.44125).

Isolation of Acetaldehyde from 13-Methyl-2,3,14-tetradecanetriol (7).—A solution of the triol (130 mg.) and sodium metaperiodate (120 mg.) in 10 ml. of water and 5 ml. of *t*-butyl alcohol was allowed to stand overnight and then was steam distilled into 50 ml. of a 0.32% solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid until precipitation ceased. The precipitate was collected and washed with water; after drying it weighed 84 mg. (76% yield) and melted at 146°. One recrystallization from hexane raised the m.p. to 163°. A mixed m.p. with authentic acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 163–165°, was undepressed.

Isolation of D-(+)-1,2-Propanediol Diacetate (12) from Fungichromin.—A solution of 1.11 g. of Fungichromin in 100 ml. of methanol was cooled with ice and ozone was introduced until ozonolysis was complete. The colorless solution was concentrated to *ca.* 60 ml. under reduced pressure at a temperature below 10°. Platinum oxide (450 mg.) was added and the mixture was hydrogenated at 0° for 3 hr. The platinum was removed by filtration, and to the cooled (ice-bath) and stirred filtrate was added, during 15 min., a solution of 3.51 g. of sodium metaperiodate in a mixture of water (30 ml.) and methanol (15 ml.). After stirring at 0° for 3 hr. the thick precipitate of sodium iodate was removed by filtration, and the filtrate was concentrated to *ca.* 40 ml. under reduced pressure. Water (30 ml.) was added, the solution was saturated with sodium chloride and then extracted with one 15-ml. and three 5-ml. portions of chloroform. The extracts were washed twice with saturated sodium chloride solution and concentrated to dryness under reduced pressure. The residual white solid weighed 713 mg. Extraction of the aqueous phase with 1-butanol (one 20-ml. and three 5-ml. portions), followed by removal of the solvent, yielded another 410 mg. of a solid which had an infrared spectrum identical with that of the product from the chloroform extraction. The solids were combined, dissolved in 30 ml. of anhydrous tetrahydrofuran, and the solution was filtered and added dropwise to a stirred cold solution of 2.50 g. of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran. The mixture was stirred and heated under reflux for 10 hr., the excess hydride was decomposed with acetic acid, and the solvent was removed at room temperature under reduced pressure. To the residual white solid were added 50 ml. of ether, 18 g. of acetic anhydride and 20 ml. of pyridine, and the mixture was stirred and heated under reflux for 6 hr. After cooling the mixture was filtered, the filter cake was stirred and heated under reflux with 30 ml. of ether and again filtered. This operation was repeated twice more. The combined ether solutions were washed with ice-cold 20% sulfuric acid, 5% sodium bicarbonate solution and saturated sodium chloride solution, and dried over magnesium sulfate. Most of the solvent was removed by slow distillation through a semi-micro column. The amount of 1,2-propanediol diacetate (12) present in the residual liquid was determined by gas chromatography on a 30% silicone grease column at 175°, using ether solutions of authentic 12 as standards. The yield of 12 was 103 mg. (39% based on Fungichromin). A peak corresponding to 1,2,3-butanetriol triacetate, a sample of which was synthesized (see below), was completely absent in the gas chromatogram. The volatile products were distilled without fractionation at 0.2 mm. and 130° (bath temperature) into a trap cooled with Dry Ice–acetone, and 78 mg. of 1,2-propanediol diacetate, $[\alpha]^{28}D$ +2.0° (*c* 6.7, chloroform), was isolated from the distillate by preparative gas chromatography. Its infrared spectrum was identical with that of an authentic sample of *dl*-1,2-propanediol diacetate.

Synthesis of D-(+)-1,2-Propanediol Diacetate (12).—A mixture of 1.25 g. of anhydrous D-(+)-calcium lactate, $[\alpha]^{27}D$ +5.3° (*c* 5, water) [lit. $[\alpha]^{25}D$ +7.8° (*c* 2.7, water);[27] $[\alpha]^{25}D$ +5.32° (*c* 4.95, water[28])], 1.59 g. of dimethyl sulfate, 0.87 g. of anhydrous potassium carbonate, 20 ml. of acetone and 5 ml. of methanol was stirred and heated under reflux for 6 hr. The cooled mixture was filtered and the filter cake washed repeatedly with anhydrous tetrahydrofuran. The combined filtrates were concentrated by distillation through a semi-micro column until the bath reached a temperature of 100°. Tetrahydrofuran (25 ml.) was added to the residual liquid, which was then filtered and added slowly to a cooled and stirred solution of 2.1 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was stirred and heated under reflux for 64 hr. The excess hydride was decomposed with ethyl acetate, and the solvent was removed completely at room temperature under reduced pressure. To the residual white solid were added 100 ml. of ether, 40 ml. of pyridine and 30 g. of acetic anhydride, and the mixture was stirred and heated under reflux for 45 hr. The cooled mixture was filtered and the filter cake extracted in a Soxhlet extractor with 100 ml. of ether. The combined filtrate and extract were cooled and acidified with 20% sulfuric acid. The layers were separated, and the aqueous phase was extracted with two 30-ml. portions of ether. The combined ether solutions were washed free of acid with 10% sodium carbonate solution and saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was removed and the residue distilled through a semi-micro column giving 0.77 g. (42% yield based on calcium lactate) of D-(+)-1,2-propanediol diacetate (12), b.p. 93–96° (22 mm.), $n^{25}D$ 1.4104–1.4132 [lit.[29] for *dl*-1,2-propanediol diacetate b.p. 88° (20 mm.), $n^{20}D$ 1.4148], $[\alpha]^{27}D$ +1.55° (*c* 17.7, chloroform). Its infrared spectrum was identical with that of an authentic sample of *dl*-1,2-propanediol diacetate.

Isolation of (2L:3D)-(−)-*erythro*-1,2,3-Butanetriol Triacetate (13) from Fungichromin.—Fungichromin (1.16 g.) was ozonized and the ozonide was reduced catalytically as described above for the isolation of 12. After removal of the catalyst the methanol solution was concentrated to dryness under reduced pressure, keeping the temperature below 15°. The residual white solid was dried at room temperature (0.2 mm.), then dissolved in 40 ml. of anhydrous tetrahydrofuran, and added slowly to a stirred solution of 1.54 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was stirred under reflux for 17 hr., then cooled, and the excess hydride was decomposed with glacial acetic acid. The solvent was removed under reduced pressure, and to the residual white powder were added 80 ml. of ether, 30 g. of acetic anhydride and 50 ml. of pyridine. After heating to reflux and stirring for 15 hr., the mixture was filtered and the filter cake was extracted continuously with ether. The combined extracts and filtrate were acidified with 20% sulfuric acid, keeping the temperature below 15°. The layers were separated, and the aqueous phase was extracted with 30 ml. of ether. The combined ether solutions were washed with 5 ml. of 20% sulfuric acid, two 5-ml. portions of water, 10% sodium carbonate solution, saturated sodium chloride solution, and dried over magnesium sulfate. Most of the ether was removed by slow distillation through a semi-micro column. The yield of (2L:3D)-(−)-*erythro*-1,2,3-butanetriol triacetate (13), determined by gas chromatography on a 30% silicone grease column at 195° using ether solutions of authentic *dl-erythro*-1,2,3-butanetriol triacetate as standards, was 180 mg. (45%). The volatile products were distilled without fractionation at 0.1 mm. and 150° (bath temperature), into a trap cooled with Dry Ice–acetone, and a sample of the triacetate was isolated from the distillate by preparative gas chromatography. It had $n^{25}D$ 1.4270, $[\alpha]^{28}D$ −1.9° (*c* 6.1 chloroform). Its infrared spectrum (carbon disulfide solution) was identical

(26) J. S. Sörensen and N. A. Sorensen, *Acta Chem. Scand.*, **2**, 166 (1948).

(27) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **67**, 329 (1926).

(28) M. N. Camien and M. S. Dunn, *ibid.*, **211**, 593 (1954).

(29) H. C. Chitwood and B. T. Freure, *J. Am. Chem. Soc.*, **68**, 680 (1946).

with that of authentic *dl-erythro*-1,2,3-butanetriol triacetate. Its retention time on gas chromatography at 195° using a column packed with 30% of Viton A-HV[30] on 80–100 mesh Chromosorb W, was 16.1 min., identical with that of an authentic sample of *dl-erythro*-1,2,3-butanetriol triacetate. The *threo* isomer, which under these conditions had a retention time of 18.4 min., was absent in the chromatogram of **13** obtained from Fungichromin.

Synthesis of *dl-erythro*-1,2,3-Butanetriol Triacetate.—The *trans*-crotyl alcohol used in this preparation had b.p. 120°, $n^{25}D$ 1.4262 (lit.[31] b.p. 121.2°, $n^{25}D$ 1.4262). Its infrared spectrum was the same as that published.[32] However, gas chromatography of its acetate at 85° on a column packed with 30% of a saturated solution of silver nitrate in tetraethylene glycol on 60–80 mesh Chromosorb showed it to be a mixture of 92% of the *trans* and 8% of the *cis* isomer. To a solution of 6.53 g. of this (largely) *trans*-crotyl alcohol in 10 ml. of glacial acetic acid was added slowly, with stirring, 21.6 g. of 40% peracetic acid.[33] After stirring for 1 hr., acetic anhydride (20 g.) and concentrated sulfuric acid (1 ml.) were added, and the mixture was stirred at 70° for 2 hr. After cooling to room temperature it was poured on ice, and extracted with four 20-ml. portions of chloroform. The combined extracts were washed free of acid with 10% sodium carbonate solution, and dried over magnesium sulfate. Analysis by gas chromatography showed that only partial acetylation had occurred. The chloroform was removed, and the residue (17.1 g.) was mixed with 30 ml. of pyridine and 15 g. of acetic anhydride. The mixture was allowed to stand at room temperature for 3 days and then was poured on ice and extracted with three 20-ml. portions of chloroform. The combined extracts were washed with 20% sulfuric acid, 10% sodium carbonate solution and saturated sodium chloride solution, and dried (magnesium sulfate). Removal of the solvent and distillation of the residue gave 7.83 g. (37% yield) of impure *dl-erythro*-1,2,3-butanetriol triacetate. Redistillation afforded a sample, b.p. 70° (0.2 mm.), $n^{25}D$ 1.4273, which was contaminated only by 1% of the *threo* isomer as shown by gas chromatography.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.96; H, 6.63.

Synthesis of *dl-threo*-1,2,3-Butanetriol Triacetate.—To a vigorously stirred mixture of 1.45 g. of *trans*-crotyl acetate (b.p. 130–131°, $n^{25}D$ 1.4149, containing 8% of the *cis* isomer; see above), 38 ml. of glacial acetic acid, 0.36 ml. of water and 5.36 g. of silver acetate was added finely ground iodine (3.24 g.) over a period of 50 min. Stirring was continued at room temperature for 1 hr., then at 95° for 5 hr. The cooled mixture was filtered and the filter cake was washed with glacial acetic acid. The combined filtrate and washings were concentrated to *ca.* 6 ml. by distillation through a semi-micro column (at 35 mm. and a bath temperature of 55–60°). To the filtered residue were added 15 g. of acetic anhydride and 30 ml. of pyridine. The mixture was allowed to stand at room temperature overnight and then was poured on ice and extracted with three 30-ml. portions of ether. The combined extracts were washed with ice-cold 20% sulfuric acid, 5% sodium bicarbonate solution, sodium thiosulfate solution and concentrated sodium chloride solution, and dried over magnesium sulfate. Distillation through a semi-micro column afforded 2.27 g. (77%) of a mixture, b.p. 82° (0.2 mm.), $n^{25}D$ 1.4286, containing 82% of *dl-threo*-1,2,3-butanetriol triacetate and 18% of the *erythro* isomer. A sample further enriched (92%) in the higher boiling *threo* isomer was obtained by fractionation using a short spinning band column.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.96; H, 6.83.

Pure *dl-threo*-1,2,3-butanetriol triacetate was isolated from this sample by preparative gas chromatography at 195°, using a column packed with 30% of Viton A-HV on 80–100 mesh Chromosorb W. It had $n^{25}D$ 1.4287; its infrared spectrum (carbon disulfide solution) was very similar to that of the *erythro* isomer, the most prominent difference being a band of medium intensity at 1140 cm.$^{-1}$ which was absent in the spectrum of the *erythro* isomer. The latter had a similar band at 1165 cm.$^{-1}$, not found in the spectrum of the *threo* isomer.

(30) Kindly supplied by the Elastomer Chemicals Department, E. I. du Pont de Nemours and Co., Wilmington, Del.

(31) L. F. Hatch and S. S. Nesbitt, *J. Am. Chem. Soc.*, **72**, 727 (1950).

(32) C. F. Hiskey, H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

(33) The temperature rose to 80° during the addition. The yield of the triacetate could probably be improved considerably by keeping the temperature between 30 and 40°.

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2,2′-Bipyrrole

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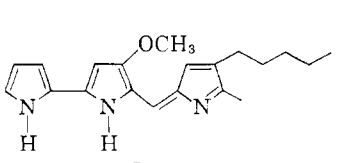
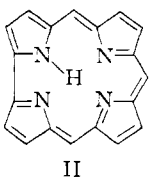
Interest in the 2,2′-bipyrrole system has led to an examination of several methods of synthesizing this compound. One method, the condensation of 2-pyrrolidinone with pyrrole followed by dehydrogenation of the resulting pyrroline, is of particular interest, since it gives a good yield and is potentially applicable to a wide variety of compounds in this little investigated area of polypyrrole chemistry.

In view of the importance of 2,2′-bipyrrole in naturally occurring compounds as well as the general lack of information available on the chemistry of this system, we have undertaken an examination of several syntheses of the unsubstituted 2,2′-bipyrrole which potentially are applicable to problems involving specifically substituted bipyrroles. Naturally occurring compounds which contain the bipyrrole nucleus are prodigiosin (I) and related pigments[2a,b] and vitamin B_{12},[3] the



I



II

parent aromatic ring system of which is corrole (II). Although several bipyrroles have been reported in the literature, most of the synthetic methods used are of a limited nature, employing drastic coupling-type reactions and resulting in highly substituted, symmetrical bipyrroles.[4] As

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(2) (a) H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, **84**, 635 (1962); (b) H. H. Wasserman, J. E. McKeon, L. Smith and P. Forgione, *ibid.*, **82**, 506 (1960).

(3) R. Bonnett, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith and A. Todd, *J. Chem. Soc.*, 1158 (1957).

(4) *E.g.*, H. Fischer and A. Stackel, *Z. physiol. Chem.*, **258**, 121 (1939); J. L. A. Webb and R. R. Threlkeld, *J. Org. Chem.*, **18**, 1406 (1953).