crystalline picrate (0.7 g.), m.p. 185–190° dec., was dissolved in 10 ml. of chloroform, and extracted once with 10% sodium hydroxide, then with 1% sodium bicarbonate until free of picric acid.

The chloroform solution was concentrated to dryness to yield colorless crystals which after sublimation weighed 0.2 g., m.p. 93.5–94°, $[\alpha]^{25}D$ +19°.

Anal. Calcd. for $C_{14}H_{25}NO_7$: C, 52.99; H, 7.30; N, 4.42; acetyl (3), 40.68; mol. wt., 317.3. Found: C, 52.94; H, 7.37; N, 4.34; acetyl, 39.15. Titration showed an equivalent weight of 319, $pK_b = 7.4$.

The mother liquors from the triacetylmycaminose picrate, which had precipitated a yellow gum on cooling, were concentrated to dryness, and freed of picric acid as described above. The product, 0.2 g., was sublimed once and recrystallized twice from hexane at −25° to yield 0.05 g. of a pure second isomer of mycaminose triacetate; m.p. 81.2–83°, $[\alpha]^{25}D$ +95°.

Anal. Calcd. for $C_{14}H_{25}NO_7$: C, 52.99; H, 7.30; N, 4.42; acetyl, 40.68. Found: C, 52.75; H, 7.31; N, 4.48; acetyl, 39.49.

The infrared absorption spectra of these isomeric triacetates are distinctive, and indicate that the two preparations are substantially free of one another.

Acknowledgments.—We are indebted to Dr. A. R. English for the antibacterial spectrum data and to Drs. J. F. Gardocki and S. Y. P'an for the toxicity measurements on this compound. We should like to thank Mr. G. B. Hess for spectral measurements, Mr. T. Toolan for the analyses, and Messrs. R. Kersey and F. Leghorn for the microbiological assays. We also thank Drs. R. L. Wagner and P. P. Regna for their interest and suggestions.

BROOKLYN 6, NEW YORK

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, CROWN ZELLERBACH CORPORATION]

Conidendrin. II.[1] The Stereochemistry and Reactions of the Lactone Ring[2]

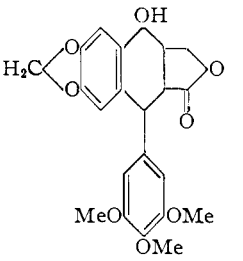
BY MERLE E. CISNEY, WILBUR L. SHILLING, W. M. HEARON AND DAVID W. GOHEEN

RECEIVED APRIL 5, 1954

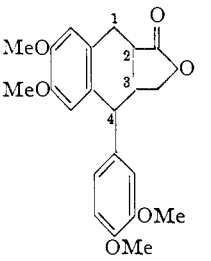
Dimethyl-α-retrodendrin (III), an isomer of dimethyl-α-conidendrin (II) with the lactone ring disposed as in podophyllotoxin (I), has been synthesized. However, it possessed no tumor-damaging activity. The (−)-α-conidendrin configuration has been demonstrated for III, dimethyl-α-conidendreic acid (VII, "Holmberg's acid") and dimethyl-(+)-isolariciresinol (XII) by the preparation of the C-2 epimer of XII, named dimethyl-β-conidendryl alcohol (XIV).

Podophyllotoxin (I) has been shown to possess tumor-necrotizing action on mouse Sarcoma 37,[3] while dimethyl-α-conidendrin (II) has no such effect. One major difference between these two compounds resides in the position of the lactone ring. In the hope that tumor-necrotizing activity but low toxicity could be obtained, we synthesized the isomer of dimethyl-α-conidendrin in which the lactone ring is reversed as in podophyllotoxin. This compound III which we have designated dimethyl-α-retrodendrin, was devoid of tumor-damaging activity, a result which may possibly be explained on the basis of the steric relationships to be discussed presently.

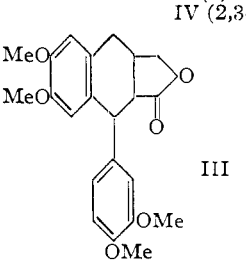
Omaki,[4] by suitable interconversions, has proved that (−)-α-conidendrin[5] has the same configuration about carbons 2 and 3 as (−)-matairesinol, while Haworth and Kelly[6] have shown that in (−)-matairesinol carbons 2 and 3 have the same absolute configuration. Hence, substituents at carbons 2 and 3 of II must be *trans*. Short heating of II with alcoholic sodium methoxide converts it to the *cis*-lactone, dimethyl-β-conidendrin (IV). This epimerization at C-2 seems to occur through enolization α to the carboxyl group. A completely analogous change of podophyllotoxin produces picropodophyllin, by epimerization about C-3. However, the change in the latter case is effected by much weaker bases, and occurs whenever the lactone ring is opened by alkali. Since the *cis*-lactone, picropodophyllin, does not cause necrosis of mouse sarcoma, it seemed essential that the *trans* relationship of the lactone ring be retained in the preparation of dimethyl-α-retrodendrin. By analogy with the facile epimerization of podophyllotoxin, it appeared likely that dimethyl-α-retrodendrin also would invert readily with base. Later work showed this not to be the case.



I



II (2,3-*trans*)
IV (2,3-*cis*)



III

Haworth and Sheldrick[7] reported the synthesis of structure III in several steps, starting with 3,3′,4,4′-

(1) Paper I, W. M. Hearon, H. B. Lackey and W. W. Moyer, THIS JOURNAL, **73**, 4005 (1951).

(2) Presented in part before the Medicinal Chemistry Division of the American Chemical Society at Los Angeles, Calif., March, 1953.

(3) J. Leiter, V. Downing, J. L. Hartwell and H. L. Shear, *J. Natl. Cancer Inst.*, 10, 1273 (1950).

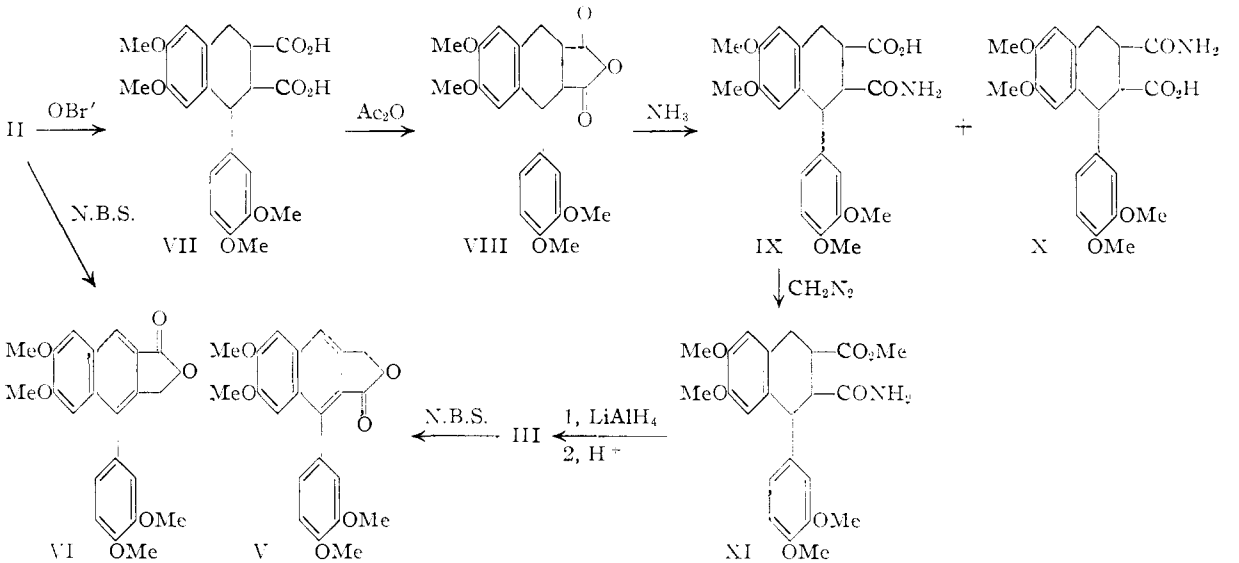
(4) T. Omaki, *J. Pharm. Soc. Japan*, **57**, 22 (1937).

(5) The designations α and β in the conidendrin series only indicate the *relative* spatial relationship of carbons 2, 3 and 4. However, it is to be understood that all of the derivatives reported in this paper have the same absolute configuration about carbons 3 and 4 as the naturally occurring (−)-α-conidendrin.

(6) R. D. Haworth and W. Kelly, *J. Chem. Soc.*, 384 (1937).

(7) R. D. Haworth and G. Sheldrick, *ibid.*, 636 (1935).

tetramethoxybenzophenone and ethyl succinate or, in better yield, using veratrole and ethyl hydroxymethylenesuccinate. Depending on the subsequent steps of the synthesis, there were obtained two products, termed the "α-" and "β-forms" of III, melting at 187° and 209–210°, respectively. These were apparently diastereoisomeric products, representing two of the four possible racemic forms of III. Walker,[8] using recently developed techniques, carried out the same synthesis and also obtained the "α"-isomer. However, "β-form" was later[8b] found to be not isomeric with III but a Δ^2-derivative of it. Haworth and Sheldrick showed that both forms gave the corresponding aromatic lactone V on dehydrogenation with lead tetraacetate, whereas dimethyl-α-conidendrin gave the isomeric lactone VI.



The starting material for our synthesis of dimethyl-α-retrodendrin was the acid VII, first prepared by Holmberg[9] by the alkaline hypobromite oxidation of II. We propose the name dimethyl-α-conidendreic acid for this dibasic acid.[10] The structure of VII was demonstrated by Erdtman,[11] who also prepared the anhydride VIII.

Treatment of VIII with ammonia gave a mixture of amic acids (IX and X) which could be separated readily. The less soluble component, making up 85% of the mixture, proved to be the desired isomer IX. Reduction of the methyl ester XI of IX with one mole equivalent of lithium aluminum hydride at room temperature and hydrolysis and lactonization of the product gave dimethyl-α-retrodendrin (III). Similar reactions were carried out using dimethylamine instead of ammonia.

Other efforts to prepare dimethyl-α-retrodendrin were much less successful. The reduction of the anhydride VIII with limited amounts of lithium aluminum hydride gave mostly II, while the use of aluminum amalgam in moist ether gave II exclusively. Desulfurization of thiol half-esters of VII with Raney nickel catalyst gave some of both II and III, but a satisfactory preparation of the required esters could not be found.

The structure of dimethyl-α-retrodendrin was proved by its dehydrogenation to the aromatic lactone V, previously prepared by Haworth and Sheldrick.[7] We have found that N-bromosuccinimide is a more convenient reagent for this purpose than lead tetraacetate.

Having demonstrated the structure of dimethyl-α-retrodendrin, we next considered its configuration. Reduction of III with excess lithium aluminum hydride gave dimethyl-(+)-isolariciresinol (XII), which with potassium acid sulfate gave the anhydro derivative XIII. This diol, which may also be called dimethyl-α-conidendryl alcohol, has been prepared by the lithium aluminum hydride reduction of dimethyl-α-conidendrin.[12] Because of this, Haworth assigned to it the (−)-α-conidendrin configuration, on the implicit assumption that the strongly basic reagent had not caused epimerization. While it has now become generally accepted that lithium aluminum hydride does not affect asymmetric centers adjacent to reducible groups,[13] we verified this by carrying out the same reaction on the already epimerized dimethyl-β-conidendrin (IV). The product was a new diol, dimethyl-β-conidendryl alcohol (XIV), which is best characterized as its anhydro derivative XV. The dimethyl ester of dimethyl-α-conidendreic acid[11] was also reduced with lithium aluminum hydride to dimethyl-α-conidendryl alcohol.

Since the *trans*- or α-conidendrin configuration persisted through the preparation of the dibasic acid VII (employing warm alkali) and of the anhydride VIII (employing boiling acetic anhydride), it was of interest to try to induce epimerization in some of the compounds which we have prepared. However, VIII was unchanged by refluxing in acetic anhydride for 16 hours. Nor did any inversion take place when the dimethyl ester of VII was refluxed 20 hours in dry pyridine or 12 hours in eth-

(8) (a) G. N. Walker, THIS JOURNAL, **75**, 3387, 3393 (1953); (b) R. D. Haworth and G. N. Walker, *ibid.*, **76**, 3596 (1954).

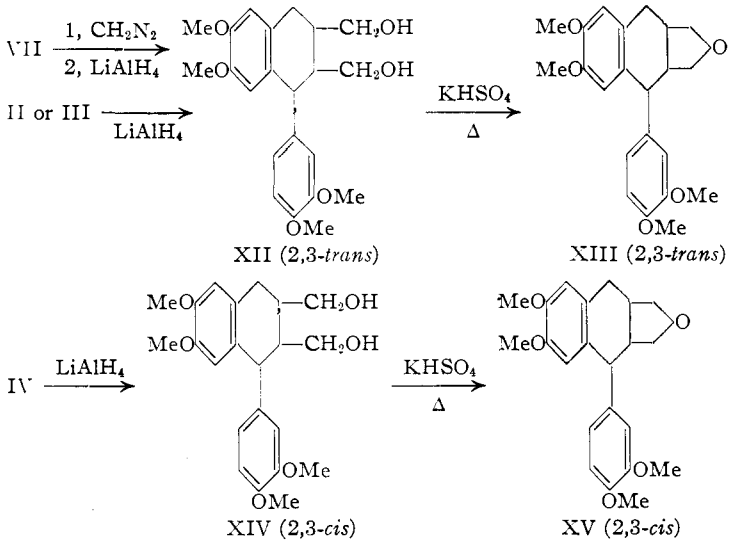
(9) B. Holmberg, *Ann. Acad. Sci. Fennicae*, **29A**, No. 6 (1927).

(10) H. Erdtman, *Ann.*, **516**, 164 (1935).

(11) H. Erdtman, *ibid.*, **513**, 229 (1934).

(12) R. D. Haworth and L. Wilson, *J. Chem. Soc.*, 71 (1950).

(13) D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).



anolic sodium ethoxide. Finally, dimethyl-α-retrodendrin was not epimerized by refluxing with methanolic sodium methoxide for 20 hours. These reactions have been used previously to interconvert the stereoisomers of similarly constituted derivatives.[14]

The contrast between the action of bases on podophyllotoxin (I) and dimethyl-α-retrodendrin (III) is further experimental evidence for the suggestion of Haworth[15] that α-conidendrin has the all-*trans* configuration. There is little obvious steric opposition to epimerization at C-2 in such a configuration, but epimerization at C-3, as would take place in III, would lead to an all-*cis* product whose formation might well be strongly opposed, especially by the repulsion of the aromatic ring. Indeed, Schrecker and Hartwell[16] have shown recently that isodesoxypodophyllotoxin is all-*trans* and quite resistant to epimerization. These authors also showed that I is 2,3-*trans*-3,4-*cis*. Since III has been shown to be 2,3-*trans*, it is clear from the reactions of these closely analogous podophyllotoxin derivatives that III must be 3,4-*trans* as well.

Isodesoxypodophyllotoxin's reported lack of significant activity against mouse Sarcoma 37 parallels the lack of activity of III and all of the other derivatives elaborated in the present study.[17] However, the configuration of these derivatives may be related to that of their analogs in the podophyllotoxin series as objects to mirror images, so the lack of activity is not structurally significant. The synthesis of stereoisomeric derivatives of some of the compounds prepared in this work is in progress.

Experimental

All melting points are uncorrected.

Dimethyl-α-conidendreic Acid (VII).—Dimethyl-α-conidendrin (II) (100 g., 0.26 mole) was oxidized with alkaline hypobromite as described by Erdtman.[11] The ketone (3.1 g.) was separated by filtration and the excess hypobromite destroyed with sodium bisulfite. The crude acid, after precipitation with 1400 g. of dilute sulfuric acid (1:2.5) and standing overnight, was collected by filtration and dissolved as completely as possible in a hot solution of 100 g. of sodium carbonate in one liter of water. The filtered solution was acidified with 160 ml. of glacial acetic acid, cooled and the precipitated acid VII was collected by filtration and washed with water. It was dissolved in 135 ml. of hot glacial acetic acid, 80 ml. of water was added and the solution set aside to cool. The acid (46.4 g., 43.0%) separated as small colorless needles, melting at 188–189° (lit.[11] 192–193°). Further acidification of the carbonate solution precipitated crude *o*-veratroylveratric acid (19.8 g., 22.1%), which, after recrystallization from dilute acetic acid, melted at 220–222° (lit.[11] 221–222°).

Dimethyl-α-conidendreic Anhydride (VIII).—This compound was prepared from VII essentially as described by Erdtman,[11] using acetyl chloride, and also by using acetic anhydride or thionyl chloride. It is recrystallized readily from benzene (1 part in 30) in 65% yield or from acetic anhydride (1 part in 3.5) in 80% yield. The melting point depends on the rate of heating, but when immersed in a block heated to 185° and the temperature raised 3° per minute it melted at 220–222°, softening at 215°, $[\alpha]^{25}D$ −73° (*c* 1.5, acetone).

Dimethyl-α-conidendreamic Acid (IX).—Dimethyl-α-conidendreic acid anhydride (VIII) (25 g., 0.063 mole) was dissolved in acetone (1500 ml.) at 45° and treated with a mixture of 50 ml. of concentrated ammonium hydroxide in 125 ml. of acetone. The precipitate, which formed immediately, became granular after stirring 10–15 minutes and was collected and air-dried. The solid was dissolved in a mixture of 2 liters of water and 200 ml. of acetone and the filtered solution was acidified with 300 ml. of 2 *N* hydrochloric acid. The precipitate was collected, washed with water and recrystallized from 750 ml. of a 1:2 mixture of acetic acid–water, yielding 20.5 g (79%) of the amic acid (IX) as bundles of colorless needles, m.p. 225–227°, $[\alpha]^{26}D$ +50° (*c* 0.6, dioxane). Dilution of the mother liquor gave a second crop (1.64 g.), m.p. 222–225°; total yield 86.4%.

Methyl Dimethyl-α-conidendreamate (XI).—The amic acid (IX) (20.5 g., 0.045 mole) was suspended in a mixture of 350 ml. of dioxane and 70 ml. of methanol and treated with an excess of an ethereal solution of diazomethane. The next day the reaction mixture was concentrated at the water-pump to a thick mass of crystals. Filtration and washing with cold methanol yielded 8.8 g., m.p. 227–229°. Evaporation of the mother liquor followed by dilution with 80% aqueous methanol and filtration produced 5.6 g. more of the ester (total yield 68%). The material was soluble in dioxane and acetic acid, slightly soluble in hot methanol and ethanol and insoluble in ether, chloroform, ethyl acetate, water and alkali. Recrystallization from hot methanol gave fine white needles, m.p. 230–231°, $[\alpha]^{26}D$ +51° (*c* 0.7, dioxane).

Anal. Calcd. for $C_{23}H_{27}O_7N$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.32; H, 6.21; N, 3.39.

N,N-Dimethyldimethyl-α-conidendreamic Acid.—Dimethyl-α-conidendreic anhydride (VIII), prepared from 12.5 g. (0.03 mole) of the acid VII, without purification was suspended in 150 ml. of acetone and 40 ml. (0.2 mole) of a 23.5% aqueous solution of dimethylamine in 100 ml. of acetone was added. Solution of the anhydride was rapid and after 10 minutes the solution was evaporated at the water-pump to a light brown sirup. This was dissolved in 150 ml. of water and the mixture acidified with 6 *N* sulfuric acid. The solution was extracted three times with chloroform, the chloroform was washed with water, dried with magnesium sulfate and evaporated under reduced pressure to give a brown foam. The foam was crystallized by the addition of 50 ml. of hot benzene. After one-half hour, the crystals were collected and washed with benzene; yield 9.3 g. (70%). The material was dissolved in 50 ml. of boiling chloroform and 100 ml. of isopropyl alcohol was added, affording 8.8 g. of short colorless needles, m.p. 167–168.5°, $[\alpha]^{26}D$ +27° (*c* 5, acetone).

(14) R. D. Haworth and F. H. Slinger, *J. Chem. Soc.*, 1321 (1940).

(15) R. D. Haworth, *ibid.*, 448 (1942).

(16) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **75**, 5916 (1953).

(17) These results will be described elsewhere by Dr. J. Leiter and his associates at the National Cancer Institute. An abstract of some of the work has appeared: J. Leiter and J. L. Hartwell, *Cancer Research*, **9**, 625 (1949).

Anal. Calcd. for $C_{24}H_{29}O_7N$: C, 65.00; H, 6.59. Found: C, 65.16; H, 6.82.

The amic acid was very soluble in acetone, acetic acid, chloroform, ethanol and dioxane, soluble in bicarbonate solution, slightly soluble in hot water, insoluble in benzene and ether. Treatment with diazomethane gave a methyl ester which failed to crystallize.

The mother liquor from the crystallization above deposited flat, colorless needles on standing (1.84 g., 14%), m.p. 120–125°, raised to 126–129° by recrystallization from acetone, $[\alpha]^{26}D$ +61° (*c* 3, acetone). This compound is probably the other possible N,N-dimethylamic acid (isomeric with the above acid m.p. 167–168.5°) carrying the substituted carbamyl group at C-2.

Dimethyl-α-retrodendrin (III).—A dioxane solution of methyl dimethyl-α-conidendreamate (XI) (9.6 g., 0.022 mole) was treated with 50 ml. of approximately 0.4 *M* lithium aluminum hydride solution in ether. After a half-hour, the suspension was treated carefully with water and acid, and boiled to remove the organic solvents. The mixture was made alkaline, extracted with chloroform, acidified strongly and refluxed two hours, an excess of sodium bicarbonate was added and the lactonic fraction extracted with chloroform. The residue after removal of the solvent was crystallized from a 4:1 mixture of methanol–chloroform; yield 4.7 g. (55%), m.p. 189.5–191.5°, $[\alpha]^{26}D$ −58° (*c* 2.1, acetone), −90° (*c* 3.1, chloroform).

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29; OCH_3, 32.29. Found: C, 68.41; H, 6.55; OCH_3, 31.77.

The compound had a strong tendency to separate from solution in an almost gelatinous form, but by very slow cooling could be obtained as long hair-like colorless crystals, soluble in acetone, dioxane, acetic acid and hot benzene, slightly soluble in hot diisopropyl ether, insoluble in hot water. The compound dissolved in warm dilute alkali and on careful acidification the hydroxy acid, dimethyl-α-retrodendric acid, separated as long fine colorless needles. After recrystallization from methanol, it melted 185–187° (foaming), $[\alpha]^{25}D$ +31° (*c* 2.6, acetone), +35° (*c* 2.1, chloroform). On boiling with dilute acid it formed dimethyl-α-retrodendrin, as is evident from the method of isolation of the latter.

In a similar fashion, the N,N-dimethyl homolog of IX (m.p. 167–168.5°) was converted to the (sirupy) methyl ester and reduced with lithium aluminum hydride, producing III in 18% yield, but the optimal conditions were not employed.

An attempt was made to epimerize III by refluxing it for 20 hours with methanolic sodium methoxide. However, after acidifying and relactonizing, the product was unchanged starting material.

Dehydrogenation of Dimethyl-α-conidendrin.—Dimethyl-α-conidendrin (II) (1.0 g., 2.59 millimoles), N-bromosuccinimide (1.03 g., 5.83 millimoles), benzoyl peroxide (0.0357 g., 0.26 millimole), and 100 ml. of dry carbon tetrachloride were placed in a 250-ml. erlenmeyer flask carrying a condenser and a calcium chloride tube. The flask was heated and after refluxing for one minute, the solution turned red-brown; two minutes later succinimide began to precipitate on the walls of the flask and at the end of four minutes, hydrogen bromide began to pass through the condenser. Further heating for about one-half hour caused the solution, as well as the deep red-brown effluent from the condenser, to become almost colorless. The mixture was filtered hot, the succinimide washed with hot carbon tetrachloride and the combined filtrates evaporated to dryness. The residue was recrystallized three times from methanol–chloroform and yielded 0.4 g. (40%) of VI as colorless, microscopic, slender, rectangular plates, m.p. 209–211° (lit.[7] 215–216°).

Dehydrogenation of Dimethyl-α-retrodendrin.—Dimethyl-α-retrodendrin (III) (132 mg., 0.342 millimole) was treated with N-bromosuccinimide (136 mg., 0.764 millimole) and benzoyl peroxide (4.7 mg., 0.034 millimole) in 25 ml. of dry carbon tetrachloride in the same manner as used to dehydrogenate dimethyl-α-conidendrin. The yield of product, after three recrystallizations from methanol–chloroform, was 30 mg. (23%) of slightly yellow, small prisms (V) melting at 245–249° (lit.[7] 254–255°).

Lithium Aluminum Hydride Reduction of Dimethyl-α-retrodendrin.—Dimethyl-α-retrodendrin (1.084 g., 0.0028 mole) in anhydrous dioxane (60 ml.) was treated with 10 ml. of approximately 0.5 *M* lithium aluminum hydride solution in ether. After 90 minutes the excess reagent was decomposed with water (1 ml.) and most of the solvent distilled at 60° at the water-pump. The thick suspension was treated with 100 ml. of water, acidified with sulfuric acid and extracted with chloroform. Distillation of the solvent as before gave white crusts in nearly quantitative yield, m.p. 169–172°. Recrystallized from 30 ml. of ethylene glycol dimethyl ether, the product XII formed dendrites, m.p. 168–172°, melting point on admixture with dimethyl-(+)-isolariciresinol (synonym dimethyl-α-conidendryl alcohol) monohydrate prepared as described by Haworth and Wilson[12] (m.p. 166–173°) was 167–173°, $[\alpha]^{25}D$ +21° (*c* 0.5, 95% ethanol). The compound was characterized as the anhydro derivative (XIII)[12] (70% yield), m.p. 149–150°, m.p. on admixture with authentic anhydro diol (m.p. 149–150.5°) was 149–150°, $[\alpha]^{25}D$ −52° (*c* 2.1, chloroform).

Lithium Aluminum Hydride Reductions in the Conidendrin Series. A. Preparation of Methyl Dimethyl-α-conidendrate.—Dimethyl-α-conidendric acid (hydroxy acid of II,[18] 3.0 g., 0.0075 mole) in a mixture of 160 ml. of ethyl acetate and 125 ml. of chloroform was treated with excess diazomethane in ether. The next day the solvents were evaporated, ether was added to induce crystallization and then removed. Recrystallized from 30 parts of a 1:3 benzene–cyclohexane mixture, the product (2.7 g.) melted at 121–122°. The colorless bulky needles could be recrystallized from about 10 parts of a 2:1 diisopropyl ether–methanol mixture, although prolonged heating appeared to cause some reversion to II. After 3 recrystallizations it melted at 125–126.5°, $[\alpha]^{23}D$ +44° (*c* 2.5, acetone).

B. Reduction.—Methyl dimethyl-α-conidendrate (1.0 g., 0.0024 mole) in 50 ml. of dry benzene was added to 60 ml. of an approximately 0.2 *M* lithium aluminum hydride solution in ether, causing the immediate separation of a white precipitate. Water and excess dilute hydrochloric acid were added after 5.5 hours and the organic solvents were evaporated. Extraction with chloroform removed the precipitated diol XII (quant. yield) which was recrystallized from 100 parts of 50% aqueous methanol and then from benzene–cyclohexane, m.p. 164–167° (lit.[12] 167–168°).

C. Preparation of Methyl Dimethyl-β-conidendrate.—Dimethyl-β-conidendric acid[18] (4.7 g., 0.012 mole) in methanol was treated with an excess of ethereal diazomethane and after 30 minutes was worked up in the same manner as for the α-isomer. After recrystallization from dilute methanol, it softened at 88° and melted at 94–97°, $[\alpha]^{26}D$ +60° (*c* 3.5, acetone). The colorless stout needles were very soluble in methanol and very difficult to purify because of the ready reversion to IV.

D. Reduction to Dimethyl-β-conidendryl Alcohol.—Using the same procedure as for the α-isomer above, the product melted at 90–95°. Recrystallization from 18 parts of 2:1 benzene–cyclohexane raised this to 106–111°, but it appeared that hot recrystallization was causing dehydration to the anhydro-β-diol (XV, m.p. 97–98.5°). A larger amount of the β-diol was obtained by the reduction of 20 g. (0.052 mole) of dimethyl-β-conidendrin (IV) in a 1:2.5 ether–benzene mixture (350 ml.) by the addition of excess lithium aluminum hydride in 225 ml. of ether. The next day, 60 ml. of ethyl acetate and 50 ml. of water containing 15 g. of ammonium chloride were added. The following day the solvent was decanted and the residue extracted with ethyl acetate at 40–50°. Evaporation of the solvents at room temperature left a crystalline residue which was dissolved in 2 l. of benzene at 40–50° and allowed to crystallize slowly by cooling and evaporation. The first crop (8 g.), rosettes of colorless fine needles containing one-fourth of a molecule of benzene per mole, melted at 131–132°, $[\alpha]^{25}D$ +41° (*c* 4.0, chloroform).

Anal. Calcd. for $C_{22}H_{28}O_6 \cdot {}^1/_4C_6H_6$: C, 69.18; H, 7.29; OCH_3, 30.43. Found: C, 69.14; H, 7.09; OCH_3, 30.50.

A second crop (2.2 g.) melted at 129–131°, but further crops melted variously between 90 and 120°; they could be purified by a similar low temperature crystallization, but boiling benzene reduced the m.p. to below 110°.

E. Reduction of Dimethyl Dimethyl-α-conidendreate.—This compound[11] (m.p. 148–149°) was reduced exactly as in B above; yield, 0.74 g. of once recrystallized material, m.p. 166–172°, mixed with XII from B above, it melted 166–172°.

F. 2,3-Bis-(hydroxymethyl)-6,7-dimethoxy-4-(3′,4′-dimethoxyphenyl)-naphthalene.—Dehydrogenated dimethyl-

(18) B. Holmberg, *Ber.*, **54**, 2406 (1921).

α-conidendrin (VI) (1.0 g., 0.00264 mole) in 400 ml. of dry benzene was treated with an excess of an ether solution of lithium aluminum hydride. After one hour, the excess reagent was decomposed by the cautious addition of water and the solvent was evaporated at reduced pressure. The residue was treated with dilute sulfuric acid and the mixture extracted with chloroform. The chloroform solution was washed with water, dried, evaporated almost to dryness and methanol added. Colorless, fine needles separated and after three recrystallizations from methanol–chloroform melted at 188–189°.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.75; H, 6.29. Found: C, 69.02; H, 6.35.

Dimethylanhydro-β-conidendryl Alcohol (XV).—Dimethyl-β-conidendryl alcohol (XIV) (1.5 g., 3.9 millimoles) was heated (oil-bath) with potassium acid sulfate (3.0 g., 0.022 mole) for 30 minutes at 160°. The mixture was digested with 20 ml. of hot water and the solution decanted to remove the inorganic salt. The residue was extracted with three 10-ml. portions of methanol, the combined extracts concentrated to about 15 ml. and an equal volume of water added. On cooling and scratching, the anhydro compound XV separated, yield 0.92 g., m.p. 94–97°. On further dilution of the mother liquor, 0.24 g. of the material was obtained (total yield 81%). The compound is very soluble in benzene, soluble in hot cyclohexane and insoluble in low-boiling petroleum ether. Recrystallization from cyclohexane containing a small amount of benzene gave large colorless needles and long hollow rectangular pyramids, m.p. 97–98°, $[\alpha]^{26}D$ −33° (*c* 3.2, acetone), −29° (*c* 2.2, chloroform).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; OCH_3, 33.50. Found: C, 71.58; H, 7.32; OCH_3, 33.91.

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Purines. III. The Preparation of Certain Purine and Triazolopyrimidine Derivatives[1]

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The utilization of 2,6-dichloro-4-amino-5-nitropyrimidine in the preparation of a series of new purine derivatives and their azapurine analogs is described.

Since the discovery that 6-mercaptopurine possesses marked inhibitory properties[2] there has been an increasing interest in purine antagonists which has carried over into the triazolopyrimidine homologs.[3] In this Laboratory a new series of these derivatives has been prepared from 2,6-dichloro-4-amino-5-nitropyrimidine.[4]

This intermediate is readily converted to the corresponding methoxy and methylmercapto derivatives by treating it with alcoholic solutions of sodium methoxide or sodium methylmercaptide.

Both 2,6-dimethoxy-4-amino-5-nitropyrimidine and 2,6-dimethylmercapto-4-amino-5-nitropyrimidine were reduced catalytically without any difficulty to the diamine and the reduction product isolated as the rather insoluble sulfate. The sulfates were in turn cyclized to the corresponding purines.[5] 2,6-Dimethoxypurine was found to have an indefinite melting point; apparently it rearranges during fusion. This behavior has been noted in the case of 2,4-dimethoxypyrimidine.[6] The treatment of 2,6-dichloro-4-amino-5-nitropyrimidine with sodium hydrosulfide simultaneously thionated and reduced the nitropyrimidine to yield 2,6-dimercapto-4,5-diaminopyrimidine directly. This diamine was formylated and cyclized to yield 2,6-dimercaptopurine.

The preparations of the triazolopyrimidines were quite straightforward. The diamine free bases (or their sulfates) were treated with excess nitrous acid to yield the insoluble triazolo derivative.

5,7-Dimercapto-1-γ-triazolo[d]pyrimidine made by the above procedure was almost completely insoluble in all the usual solvents. With hot sodium hydroxide it is possible to solubilize the compound; however, reprecipitation with acid yields a product with different solubility characteristics; *i.e.*, solubility in ammonium hydroxide. This compound has recently been prepared by another method by Bahner and co-workers[7] who reported absorption maxima at 343 and 283 mμ at both *p*H 6.5 and 10. In this Laboratory the maximum at 343 mμ was confirmed but the other maximum was found at 273 mμ. This maximum was relatively strong at *p*H 10 and very weak at *p*H 6.5. However, the data were reproducible upon changing the *p*H back and forth so that the fading of this maximum (at 273) may be accounted for on the basis of enolization.

Experimental[8]

2,6-Dimethoxy-4-amino-5-nitropyrimidine.—2,6-Dichloro-4-amino-5-nitropyrimidine (5.0 g.) was dissolved in 110 ml. of cold absolute methanol and the mixture was slowly added over a period of 30 minutes to a solution prepared by dissolving 1.1 g. of sodium in 50 ml. of absolute methanol. The temperature was maintained between 15–20° during the reaction by means of an ice-bath. After the addition the bath was removed and the solution was stirred for three additional hours. The solution was then brought to boiling for three minutes and cooled; yield (80%) 3.85 g. of white needles, m.p. 179–179.5°; recrystallization from methanol–water gave m.p. 180–181°.

Anal. Calcd. for $C_6H_8N_4O_4$: N, 28.0. Found: N, 27.9.

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