and allowing it to crystallize. In previous work 95% ethanol was the crystallizing solvent, but yields were lower.

The acid was further shown to be identical with the wilforine dibasic acid on the basis of X-ray diffraction data, ultraviolet spectra of the free and neutralized acid, and paper chromatography with three different solvents as previously described.[3] The results (R_f × 100) of the chromatography of the dibasic acids follow:

	A	B	C
Wilforine	92	90.5	87
Wilforzine	92	89.5	85.5

Polyhydroxy Nucleus of Wilforzine.—From the 28.00-mg. lot of wilforzine the polyhydroxy nucleus was isolated.[3] Its X-ray diffraction pattern was indistinguishable from the patterns of the polyhydroxy nuclei of wilforine, wilforgine, wilfordine and wilfortrine. Paper chromatography of the compound run simultaneously with the polyhydroxy nucleus from wilforine as described[3] showed no significant difference in results (R_f × 100) with the three different solvents:

	A	B	C
Wilforine	69	37	72
Wilforzine	68	36	72

Acetylation Studies.—To 4 mg. of wilforzine was added 0.5 ml. of acetic anhydride and 0.5 ml. of pyridine. After remaining at room temperature for 5 days the solution was evaporated to dryness on a 60° water-bath under reduced pressure. The resulting material was subjected to an 8-plate countercurrent distribution between a solution containing 40% hexane in benzene (v./v.) and 2% hydrochloric acid (Fig. 1). The distribution pattern when compared with that obtained from untreated wilforzine shows that no wilforzine remains after acetylation. The acetylated wilforzine, recovered from the countercurrent distribution, crystallized upon the addition of a few drops of methanol. An X-ray diffraction pattern of the crystals was identical with that obtained from crystals of wilforine. The *d/n* values (interplanar spacing in ångström units/order of diffraction) and intensity of lines (s = strong, m = medium, w = weak, v = very) obtained from both patterns are: 12.7 m, 10.3 vs, 8.0 s, 6.5 m, 5.9 vw, 4.85 s, 4.3 w, 3.7 w, 3.31 vw, 3.09 vw.

Attempted Methanolysis of Wilforine.—Wilforine was allowed to remain in contact with methanol for five days at room temperature, after which the product was tested for wilforzine by countercurrent distribution between a solution containing 40% hexane in benzene and 2% hydrochloric acid. None was found (see Fig. 1). The patterns of wilforine and acetylated wilforzine practically coincide and thereby constitute a further proof that the two compounds are identical.

BELTSVILLE, MD.

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

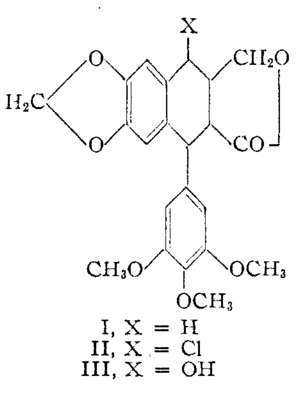
The Structure of Silicicolin[1a]

BY JONATHAN L. HARTWELL, ANTHONY W. SCHRECKER AND JAMES M. JOHNSON

RECEIVED DECEMBER 29, 1952

Silicicolin, obtained from the needles of *Juniperus silicicola*, has been prepared by hydrogenolysis of podophyllotoxin chloride, and is identical with desoxypodophyllotoxin.

In an earlier paper,[1b] silicicolin, a tumor-damaging substance obtained from the dried needles of *Juniperus silicicola* (Small) Bailey (Fam. *Pinaceae*) (Southern red cedar), had been characterized and tentatively assumed to be a lignan, perhaps the hitherto unknown desoxypodophyllotoxin (I). This assumption has now been shown to be correct. When podophyllotoxin chloride (II), prepared[2] from podophyllotoxin (III), was submitted to hydrogenolysis under the conditions of the Rosenmund reaction,[3] a 99% yield of desoxypodophyllotoxin, m.p. 168–169°, was obtained identical in all respects with the natural product[4] (Table I). Both the natural and synthetic compound could be epimerized to silicicolin-B (desoxypicropodophyllin), m.p. 169–173° and 170.5–172°, respectively, by heating with alcoholic solutions of sodium acetate or of piperidine, while both gave the same hydroxy acid (desoxypodophyllic acid) on saponification.



I, X = H
II, X = Cl
III, X = OH

The literature contains references to (a) two different "desoxypicropodophyllins," prepared by hydrogenation of α-[5] and of β-apopicropodophyllin,[6] respectively; (b) a natural product, anthricin,[7] isolated from the roots of *Anthriscus sylvestris* Hoffm. (Fam. *Umbelliferae*) (wild chervil), which has also been assigned structure I and can be epimerized to isoanthricin; and (c) another natural product, cicutin,[8] separated from the roots of *Cicuta maculata* L. (Fam. *Umbelliferae*), (water hemlock), about whose structure all that is known is that it has the empirical formula $C_{22}H_{22}O_7$ and contains three methoxyl groups and a lactone ring. Table I gives comparative physical constants on all the lactones mentioned here. Since all but one of the compounds listed has a melting

---

(1) (a) Presented before the Division of Medicinal Chemistry at the 123rd National Meeting of the American Chemical Society, Los Angeles, Calif., March 15–19, 1953; (b) J. L. Hartwell, J. M. Johnson, D. B. Fitzgerald and M. Belkin, THIS JOURNAL, **74**, 4470 (1952).

(2) J. L. Hartwell and A. W. Schrecker, *ibid.*, **73**, 2909 (1951).

(3) E. B. Hershberg and J. Cason, *Org. Syntheses*, **21**, 84 (1941); R. P. Barnes, *ibid.*, **21**, 110 (1941).

(4) We have been unable to find any prior reference to this useful extension of the Rosenmund reaction to benzhydryl-type halides. The advantage of this technique lies in the fact that the course of the reaction can be followed readily by measuring the hydrogen chloride evolved.

(5) W. Borsche and J. Niemann, *Ann.*, **494**, 126 (1932); *cf.* A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **74**, 5676 (1952).

(6) N. L. Drake and E. H. Price, *ibid.*, **73**, 201 (1951).

(7) K. Noguchi and M. Kawanami, *J. Pharm. Soc. Japan*, **60**, 629 (1940).

(8) L. Marion, *Can. J. Research*, **20B**, 157 (1942).

point of around 170°, a consideration of these compounds for possible identity is in order. Optical rotations and infrared absorption spectra serve to make distinctions.

TABLE I

PHYSICAL CONSTANTS OF LACTONES, $C_{22}H_{22}O_7$

Substance	M.p., °C.	$[\alpha]_D$, degrees Chloroform	Pyridine
Silicicolin	171–172[b]	−119	−196
Desoxypodophyllotoxin	168–169[b]	−115	−181
Silicicolin-B	169–173[b]	+ 31.5	+ 40
Desoxypicropodophyllin (DPPP)	170.5–172[b]	+ 32	+ 43
DPPP of Borsche[5]	169–170	.....	.....
DPPP of Drake[6]	200–201	−114	− 69.5[c]
Anthricin[7]	168	.....	−142.54
Isoanthricin[7,a]	170	.....	−127.87
Cicutin[8]	171 168.7–169.4[b,c]	+ 15.2[c]	− 14.4[c]

[a] Formulated as a monohydrate; insoluble in cold caustic alkali. [b] Corrected melting points. [c] Determined by us on a sample kindly provided by the original investigator.

A supposition, based on the similarity of optical rotation, that anthricin may be identical with silicicolin (desoxypodophyllotoxin), is open to the objection that their respective alkali-isomerization products, isoanthricin and silicicolin-B (DPPP), differ in their reported properties. However, in the absence of authentic samples for examination, no valid conclusions can be drawn about the identities of anthricin and isoanthricin. As to the three "desoxypicropodophyllins," information is lacking on the optical rotation of Borsche's DPPP[9]; on the other hand, our DPPP is certainly different from Drake's, not only in melting point and optical rotation but also in infrared spectrum. In the original report on cicutin,[8] the nature of two of the seven oxygen atoms was unexplained. We have found that cicutin gives the Gaebel test[10] for the methylenedioxy group, thus accounting for all the oxygen atoms in the molecule. There is no chemical evidence[8] that cicutin has the structure I. However, its optical rotation is consistent for a mixture of desoxypicropodophyllin with a lesser amount of desoxypodophyllotoxin, although calculated values obtained with the two solvents do not agree. While mixed melting point determinations with desoxypicropodophyllin were not definitive, the infrared spectra of the two compounds were essentially identical. In its isolation, cicutin had undergone treatment with methanolic sodium hydroxide. It is possible, therefore, that *Cicuta maculata* originally contained desoxypodophyllotoxin, which, in the course of separation, was largely epimerized.

It is to be concluded, therefore, that silicicolin is one of the stereoisomers represented by I, with the same configurations around C_2, C_3 and C_4 as podophyllotoxin (III). While it is possible that anthricin and cicutin consist essentially of desoxypodophyllotoxin and desoxypicropodophyllin, respectively, no positive conclusions can be drawn about their identity at this time.

Experimental[11,12]

Silicicolin (I).—In the following procedure, extractions were performed by manual shaking with a solvent at room temperature, until further treatment failed to remove appreciable additional material; three or four extractions usually were sufficient. When the fraction to be extracted was gummy, the process was facilitated by breaking up the gum with a stirring rod or triturating it in a mortar. Solvent was removed from the fractions by evaporation on the steam-bath under a current of air.

Extraction of 5276 g. of the dried ground needles of *Juniperus silicicola*[13] with 58 l. of acetone yielded 332 g. of dark viscous oil. Treatment of this with 8 l. of ligroin (b.p. 60–90°) left 64.2 g. of a dark, gummy, insoluble fraction. Solution of the insoluble fraction in 825 cc. of absolute ethanol and passage through a tower containing 720 g. of activated alumina,[14] eluting with absolute ethanol, afforded a first cut (judged by low solids content of test samples) which yielded 31.2 g. of a dark reddish-brown solid. Treatment of this solid with 1200 cc. of ethyl acetate removed an insoluble fraction and gave 27.5 g. of a dark, solid, soluble product. Extraction of the latter with 700 cc. of xylene, removal of 2.1 g. of insoluble material and concentration of the solution yielded, on standing in the ice-box, a crop of pale greenish crystals of crude silicicolin. Recrystallization from absolute ethanol (decolorizing carbon) gave 5.78 g. (0.11%) of colorless needles, m.p. 168–169°, $[\alpha]_D$ −113° (*c* 0.47, chloroform). Further purification yielded large, colorless, transparent prisms, m.p. 171–172°[15]; $[\alpha]^{19}_D$ −119° (*c* 0.40, chloroform), $[\alpha]^{19}_D$ −196° (*c* 1.09, pyridine).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57; 3-OCH_3, 23.37; mol. wt., 398.4. Found: C, 66.34; H, 5.52; OCH_3, 23.25; mol. wt. (Rast, camphor), 395.

Silicicolin-B (I).—A solution of 200 mg. of silicicolin in 3 cc. of absolute ethanol containing 40 mg. of anhydrous sodium acetate was refluxed for 17 hours, then diluted with an equal volume of hot water. On cooling, then warming, the product formed small, colorless, electrified, silky needles. The yield was 150 mg. (75%), m.p. 167–171°. Recrystallization from ethanol gave fine silky needles, m.p. 169–173°, $[\alpha]^{19}_D$ +30° (*c* 0.43, chloroform), $[\alpha]^{19}_D$ +40° (*c* 0.41, pyridine).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.52; H, 5.77.

Silicicolin-B was also prepared in 95% yield, m.p. 169–170°, by refluxing 80 mg. of silicicolin with 100 mg. of anhydrous sodium acetate and 2 cc. of methanol for 22 hours, diluting with excess hot water and cooling, and in 45% yield, m.p. 168–170°, by boiling 150 mg. of silicicolin with 1.5 cc. of ethanol, 0.6 cc. of water and 0.03 cc. of piperidine for one hour, then diluting as above. Recrystallization from 30% ethanol gave tiny colorless needles, m.p. 169–170.5°, $[\alpha]^{20}_D$ +33° (*c* 0.57, chloroform).

Hydroxy Acid from Silicicolin.—Silicicolin (300 mg.) was dissolved in 40 cc. of 3% sodium hydroxide solution by boiling for a few minutes. After cooling, a small amount of solid material was removed by filtration, and the clear solution of the sodium salt acidified with dilute hydrochloric acid. The gelatinous product was extracted with ethyl acetate, the solution dried over sodium sulfate and evaporated to dryness. The white crystalline product weighed 226 mg. (72%) and had m.p. 166–168°. Recrystallization

---

(9) In work on the hydrogenation of the apopicropodophyllins to be published, Borsche's DPPP has been obtained and it appears to be identical with our DPPP by optical rotation and infrared spectrum.

(10) G. O. Gaebel, *Arch. Pharm.*, **248**, 225 (1910).

(11) Melting points, taken on the Hershberg apparatus, are corrected.

(12) Analyses were carried out by the Microanalytical Laboratory under the direction of Dr. W. C. Alford. Infrared spectra were measured by Mrs. Iris J. Siewers and Miss Alice Bernardi of the National Heart Institute on a Perkin–Elmer model 21 spectrometer. The optical rotations were determined by Mrs. Gertrude Y. Greenberg and Mrs. Priscilla B. Maury.

(13) Provided through the courtesy of Mr. R. A. Bonninghausen, Florida Board of Forestry, Tallahassee, Fla.

(14) Alcoa activated alumina, grade F-20.

(15) A higher melting point first reported[1] represented the product from one run only and has never been reproduced; it may actually denote a less pure product since it had $[\alpha]^{19}_D$ −115° (*c* 0.55, chloroform).

from absolute alcohol gave colorless, transparent needles, m.p. 177.5–177.8° (efferv.) (immersed at room temperature), 171–173° (efferv.) (immersed at 150°), $[\alpha]^{20}\text{D}$ −165° (*c* 0.43, pyridine). The resolidified material melted at 167–170° and showed no depression on admixture with desoxypicropodophyllin.

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; 3-OCH_3, 22.36. Found: C, 63.39; H, 5.88; OCH_3, 22.61.

Recrystallization of the crude hydroxy acid from hot dilute ethanol, followed by drying at room temperature, gave colorless, fine needles, m.p. 171–172° (efferv.).

Anal. Calcd. for $C_{22}H_{24}O_8\cdot{}^1/_2H_2O$: C, 62.11; H, 5.92. Found: C, 61.97; H, 5.63.

Desoxypodophyllotoxin (I).—Hydrogen was bubbled through a mixture of 2.79 g. of podophyllotoxin chloride,[2] 0.28 g. of 5% palladium–barium sulfate catalyst[16] and 28 cc. of anhydrous toluene, which was stirred and boiled under reflux. The rate of hydrogen chloride evolution, which was measured by titration with *N* sodium hydroxide,[3] became slow at the end of three hours; therefore another 0.28 g. of catalyst was added and the reaction continued for three hours. The catalyst was removed (Celite), washed with hot chloroform, and the combined filtrate and washings evaporated. Addition of hexane to the oil, and chilling, provided 2.55 g. (99%) of pale tan solid, m.p. 163–165°. The crude material was recrystallized from ethanol, further purified by chromatography on alumina and elution with chloroform, then recrystallized from 50% ethanol, from methanol, and finally from ethanol to yield large, colorless, glistening prisms, m.p. 167.8–168.8°, $[\alpha]^{20}\text{D}$ −115° (*c* 0.50, chloroform), $[\alpha]^{20}\text{D}$ −181° (*c* 0.61, pyridine). The melting point was unchanged after further recrystallization. There was no mixed melting point depression with silicicolin, and the infrared spectra of the two substances were identical.

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.62; H, 5.66.

Desoxypicropodophyllin (I).—A mixture of 200 mg. of desoxypodophyllotoxin, 400 mg. of anhydrous sodium acetate and 3 cc. of absolute ethanol was refluxed for 17 hours, then diluted with 15 cc. of hot water to yield 187 mg. (93%) of tiny, colorless, electrified needles, m.p. 170.4–172.0°. Recrystallization from 30% ethanol gave material melting at 170.7–172.0°, $[\alpha]^{21}\text{D}$ +32° (*c* 0.50, chloroform), $[\alpha]^{21}\text{D}$ +43° (*c* 0.52, pyridine). Mixed m.p. determination and the infrared spectra proved the identity of the compound with silicicolin-B.

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.54; H, 5.46.

This compound was also prepared in 48% yield by refluxing 135 mg. of desoxypodophyllotoxin with 1.25 cc. of ethanol, 0.5 cc. of water and 0.025 cc. of piperidine for one hour, and diluting with 4 cc. of water; m.p. 170.5–172.0°, $[\alpha]^{20}\text{D}$ +33.5° (*c* 0.49, chloroform).

Desoxypodophyllic Acid.—A solution prepared by boiling 500 mg. of desoxypodophyllotoxin with 500 mg. of sodium hydroxide, 4 cc. of water and 2 cc. of ethanol for five minutes was diluted with 10 cc. of water, cooled in ice and, after addition of 10 cc. of chloroform, acidified with shaking by the addition of 7 cc. of 2 *N* hydrochloric acid. The colorless, crystalline hydroxy acid (518 mg., 95%) was collected and washed with cold water and chloroform; m.p. 161–163° (dec., rapid heating). Recrystallization by dissolving in a small amount of ethanol, and diluting with chloroform, then with water, yielded material which, after drying in air, contained one molecule of water of crystallization and melted with effervescence at 161–162° when immersed at 150° (heating rate 2°/min.), $[\alpha]^{20}\text{D}$ −160° (*c* 0.52, pyridine). The resolidified material remelted at 170–172° and did not depress the melting point of desoxypicropodophyllin.

Anal. Calcd. for $C_{22}H_{24}O_8\cdot H_2O$: C, 60.82; H, 6.03. Found: C, 60.80; H, 6.13.

Acknowledgment.—The authors wish to express their sincere appreciation to Professor Nathan L. Drake, University of Maryland, for a sample of his desoxypicropodophyllin,[6] and to Dr. Léo Marion, National Research Council, Canada, for a sample of cicutin.

BETHESDA, MARYLAND

---

(16) Baker and Co., Inc., Newark, N. J.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE, MONTREAL GENERAL HOSPITAL]

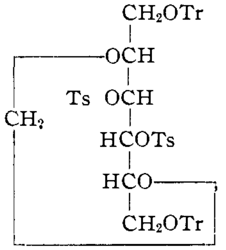
Epoxy Glycitols. I. Synthesis and Properties of 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (= D-Altritol)

BY SAMUEL B. BAKER[1] AND GABRIEL KOHANYI

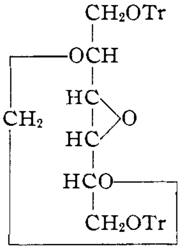
RECEIVED NOVEMBER 18, 1952

An anhydro hexitol derivative has been synthesized in which the anhydro group was of the ethylene oxide type and which was on two secondary carbon atoms rather than on a primary and a secondary atom. This anhydro glycitol was found to be unusually stable to alkali and a methylene acetal group on the same molecule was found to be very labile to acid.

Recent interest in anhydro glycitols has led us to describe our investigations on the possibility of synthesizing monoepoxy sugar alcohols in which the epoxy rings are substituted on the secondary alcohol positions of hexitols and their derivatives. This publication describes the results of the work on the synthesis and properties of 3,4-anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I). The latter compound (I) was prepared by two methods, namely, by the action of sodium methoxide in methanolic chloroform and by saponification with alcoholic potassium hydroxide of 2,5-methylene-3,4-ditosyl-1,6-ditrityl-D-mannitol (II). Inasmuch as mannitol has end-to-end symmetry the tosyl groups on C-3 and C-4 are equivalent and it is therefore immaterial which tosyloxy group is removed in the formation of the epoxy ring.



II



I

A relatively concentrated solution of alcoholic potassium hydroxide was found necessary to convert II to I and, as expected, the anhydride proved to be unusually stable to the action of alkali. In this it resembles 1,2–5,6-diisopropylidene-D-talitol which Bladon and Owen[2] found to be unaffected by

---

(1) To whom inquiries should be addressed.

(2) P. Bladon and L. N. Owen, *J. Chem. Soc.*, 605 (1950).