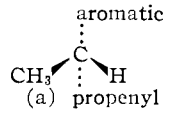
methyl and the hydrogen on C_β. Approach of the aromatic ring to C_γ is then from above the plane of the C_β–C_γ double bond. If the C_α–C_β bond were rotated so as to allow approach of the phenyl from below the plane of the double bond, there would be steric interaction between the C_α-methyl and the C_β-hydrogen. Reversal of the positions of the methyl and hydrogen on C_α would favor the transition state in which the aromatic ring approaches from below the plane of the double bond. In either case, if steric interaction between the C_α-methyl and the C_β-hydrogen is to be minimized, then one must predict that the configuration at C_γ in the alkylated phenol will be the same as that at C_α in the ether.[3]

We have recently demonstrated[4] that both Claisen O- and C-alkylation proceed with inversion. The products from the O- and C-alkylation of a phenol by an asymmetric alkyl halide will then have identical configurations. In the preparation of (−)-I by the Claisen procedure, Alexander and Kluiber also isolated some C-alkylate (II) which had a (+) rotation. Presumably, then, (−)-I and (+)-II have the same configurations. Claisen rearrangement of (−)-I gave (+)-II. These facts are clearly consistent with the proposal outlined above that the control of asymmetric induction in the transition state has steric origins.

para-Claisen rearrangement is more difficult to interpret. The *ortho* methyl groups become sterically involved, both in the first stage of the rearrangement (to the 2,2,6-trialkyldienone[5]) and in the second stage (to the 2,4,6-trialkyldienone). Examination of the models shows no clear-cut preferred orientation. Alexander and Kluiber's results indicate that (−)-α,γ-dimethylallyl 2,6-xylyl ether and (+)-4-(α,γ-dimethylallyl)-2,6-xylenol are configurationally related (based on O- and C-alkylation results). Rearrangement of the ether gave product of very low rotation (−0.08°) which indicates only slight stereospecificity in the *para* rearrangement.

(3) For the case shown, this would be (a). The C_β–C_γ bond is represented as *trans* because Alexander and Kluiber used *trans*-crotonaldehyde in their synthesis.



(a) propenyl

(4) H. Hart and H. S. Eleuterio, THIS JOURNAL, **76**, 516, 519 (1954).

(5) H. Conroy and R. A. Firestone, *ibid.*, **75**, 2530 (1953); K. Schmid, *et al.*, *Experientia*, **9**, 414 (1953); D. Y. Curtin and H. W. Johnson, Jr., THIS JOURNAL, **76**, 2276 (1954).

KEDZIE CHEMICAL LABORATORY
MICHIGAN STATE COLLEGE
EAST LANSING, MICHIGAN

Relationship of Anthricin, Hernandion and Cicutin to Desoxypodophyllotoxin

BY JONATHAN L. HARTWELL AND ANTHONY W. SCHRECKER

RECEIVED APRIL 1, 1954

Since our last paper on silicicolin,[1] new findings have been made which have enabled us to settle the structure and identity of the isomeric lactonic lignans anthricin, hernandion and cicutin. Anthricin and hernandion are shown to be identical with silicicolin (desoxypodophyllotoxin, DPT), while cicutin is essentially desoxypicropodophyllin (DPP), the C_3-epimer. The new data and their significance form the subject of this communication.

Anthricin.—This compound, isolated[2] from the roots of *Anthriscus sylvestris* Hoffm. (Fam. *Umbelliferae*) (wild chervil) had the physical constants given in Table I. It was believed[1] to consist essentially of DPT.

TABLE I

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

Substance	M.p., °C.	$[\alpha]_D$, degrees Chloroform	$[\alpha]_D$, degrees Pyridine
Desoxypodophyllotoxin (DPT) (Silicicolin)[1]	168–169	−115	−181
Desoxypicropodophyllin (DPP) (Silicicolin-B)[1]	170.5–172	+ 32	+ 43
Anthricin[2]	168	.....	−142.54
Anthricin[a]	167–169	−112	−171
Isoanthricin[2,b]	170	.....	−127.87
Isoanthricin[a]	170.5–171.5	.....	+ 45.5
Hernandion[3]	167–168	−112.4	.....
Isohernandion[3]	169–170	+ 36.6	.....
Cicutin[4]	171	.....	.....
Cicutin[1,a]	168.7–169.4	+ 15.2	− 14.4
Cicutin[c]	171–172	.....	+ 49
Desoxypodophyllic acid[1,d]	171–173(efferv.)	.....	−165

[a] Determined by us on a sample kindly provided by the original investigator. [b] Formulated as a monohydrate. [c] Purified compound, this paper. [d] Hydroxy acid, $C_{22}H_{24}O_8$.

An authentic specimen, recently received from Dr. Kawanami, gave no mixed melting point depression with DPT, the infrared spectra were identical, and the optical rotations in chloroform and pyridine showed a close correspondence with those of DPT, thus demonstrating the identity.

Isoanthricin.—This substance, prepared by base-catalyzed epimerization of anthricin, should be identical with DPP. A mixed melting point determination of a sample, provided by Dr. Kawanami, with DPP showed no depression, and the infrared spectrum and optical rotation in pyridine were confirmatory. However, our value for the specific rotation (+45.5°) differs remarkably from the value reported[2] by the authors (−127.87°). Our explanation for this discrepancy is that the Japanese investigators originally did not have the pure lactone but the hydroxy acid containing some lactone, and that the compound spontaneously lactonized during the twelve or more years since its isolation. We prepared this hydroxy acid[1] and called it desoxypodophyllic acid; its physical constants are given in Table I. This explanation is borne out by the original analysis of isoanthricin[2] which indicated one additional molecule of water, and the comparison of its original[2] optical rotation (−127.87°) with those of desoxy-

(1) J. L. Hartwell, A. W. Schrecker and J. M. Johnson, THIS JOURNAL, **75**, 2138 (1953).

(2) K. Noguchi and M. Kawanami, *J. Pharm. Soc. Japan*, **60**, 629 (1940). This paper had never been abstracted by the usual abstract journals. Prof. W. J. Gensler of Boston University kindly notified us of its existence, and one of us (J.L.H.) arranged for its abstracting [*C. A.*, **47**, 6386a (1953)].

podophyllic acid (−165°) and DPP (+43°). The observation[2] that isoanthricin was insoluble in cold caustic alkali is not inconsistent with the behavior expected from a mixture containing some alkali-insoluble lactone.

Hernandion and Isohernandion.—Hernandion was isolated by Hata[3] from the seed oil of *Hernandia ovigera* L. (Fam. *Hernandiaceae*). Direct comparison[3] of hernandion and isohernandion with anthricin and isoanthricin, respectively, showed no mixed melting point depression. The reported physical constants (Table I) also agree with ours for DPT and DPP, respectively. The identity of hernandion and isohernandion with the latter compounds is thus clear.

There remains only the question of the failure of isoanthricin to depress the melting point of isohernandion if the former was composed largely of desoxypodophyllic acid. We have found[1] that slow heating of the hydroxy acid in the melting point tube brings about complete lactonization to DPP. It is therefore quite possible that under certain conditions such a mixed melting point would show no depression.

Cicutin.—This lactone was isolated by Marion[4] from the roots of *Cicuta maculata* L. (Fam. *Umbelliferae*) (water hemlock). Although no chemical evidence, apart from the empirical formula and the identification of the substituent groups, was available, a sample of cicutin kindly provided by Dr. Marion, found by us[1] to have m.p. 168.7–169.4°, gave an infrared spectrum essentially identical with that of DPP, and the opinion was expressed that cicutin might be largely DPP. The optical rotation, however, showed that if it was DPP it was not pure. The sample was therefore refluxed with methanolic sodium acetate to epimerize any possible residual DPT, and chromatographed on alumina, which removed some ultraviolet-fluorescent material. The product thus obtained (colorless electrified needles,[1] from methanol) had m.p. 171–172°, which was not depressed on admixture with DPP, and $[\alpha]^{20}D$ + 49° (*c* 0.24, pyridine), corresponding to the optical rotation of DPP.

The question of whether cicutin, which was extracted from the plant by means of methanolic sodium hydroxide, is an artifact or not cannot be resolved at this time. Either DPT or DPP originally present in the plant would be expected to yield DPP by the method of isolation used. Since *Cicuta maculata* L. and *Anthriscus sylvestris* Hoffm. are both *Umbelliferae*, and since lignans belonging to the "picro" series are extremely rare in nature, it is a reasonable assumption that cicutin exists originally in the plant in the form of its epimeric precursor, DPT.

In summary, the naturally-occurring lignans anthricin, hernandion and silicicolin have all been shown to be identical; it is proposed to discard all these names in favor of desoxypodophyllotoxin, a name which indicates the chemical and steric relationship to podophyllotoxin, the first lignan of this type discovered. Cicutin has been shown to be identical with desoxypicropodophyllin.

Acknowledgment.—The authors wish to express their sincere thanks to Dr. Léo Marion, National Research Council, Canada, for a sample of cicutin; to Dr. M. Kawanami, Osaka, Japan, for samples of anthricin and isoanthricin; to Mrs. Priscilla B. Maury for determining the optical rotations; and to Mrs. Iris J. Siewers for measuring the infrared spectra.

LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD.

(3) C. Hata, *J. Chem. Soc. Japan*, **63**, 1540 (1942). This paper was called to our attention by Mr. M. E. Cisney of Crown Zellerbach Corp. Through an error in abstracting [*C. A.*, **41**, 2917b (1947)], this compound (under an erroneous systematic name) was given the empirical formula $C_{21}H_{32}O_5$, and so was missed in our earlier literature survey. A correction abstract was carried by *C. A.*, **47**, 10872c (1953). This paper does not appear to have been abstracted by any of the other chemical abstract journals.

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

The Separation and Characterization of Serum Albumin from Extracts of a Lymphatic Organ[1]

BY E. L. HESS, MILDRED CAMPBELL AND AILENE HERRANEN

RECEIVED DECEMBER 30, 1953

In the course of the chemical fractionation of bovine palatine tonsils we have isolated in a relatively pure form one of the components present in the initial extract. Characterization of the substance reveals that many of its properties are identical with those of bovine serum albumin. The purpose of this communication is to report that serum albumin seems present in considerable quantity in the cytoplasmic extracts of a lymphatic organ.

Experimental

Details concerning procedures used in electrophoretic, sedimentation velocity, spectrophotometric and nitrogen analyses have been published previously.[2] Unless otherwise specified all electrophoretic patterns are photographs of descending limbs after 120 minutes under a potential gradient of 6.4 volts cm.$^{-1}$ in veronal buffer *p*H 8.6, μ 0.10. A modified Ouchterlony technique[3,4] was used in the serological comparison.[5] Details of the earlier steps in the fractionation procedure have been published.[2] The component labeled M2 in Fig. 2A, B, C, of the earlier publication has been considered in the present investigation. The starting material in this report has been the *p*H 4.2 supernatant (Spnt. C) in Fig. 1 of the above mentioned report.[2] This supernatant when lyophilized, yielded about 0.6–0.8 g. of solids for each 100 g. of fresh tonsil; this amounts to about 5% of the dry weight of the whole organ and to about 14% of the cytoplasmic extract. The electrophoretic pattern of the starting fraction (4.2S) is shown in Fig. 1A. The albumin peak amounts to approximately 30% of the pattern.

Five grams of lyophilized 4.2S solids was dissolved in one liter of distilled water (2°) and the *p*H adjusted to 6.9 with 0.05 *N* NaOH. To this solution was added 82 g. of solid ammonium sulfate and 1000 ml. of cold saturated ammonium sulfate (70 g. of solid ammonium sulfate in 1000 ml. of water at 5°). The *p*H of this solution was 6.0. The solution was stirred 20 minutes and the precipitate removed by centrifugation. This precipitate called 6P amounted

(1) This report represents work done under contract with the U. S. Atomic Energy Commission, Project No. 6 to Contract AT(11-1)-89 with Northwestern University.

(2) E. L. Hess, W. Ayala and A. Herranen, THIS JOURNAL, **74**, 5410 (1952).

(3) O. Ouchterlony, *Lancet*, **2**, 346 (1949).

(4) R. K. Jennings, *J. Immunol.*, in press.

(5) We are grateful to Dr. Jennings of this Institute who kindly performed the serological studies.