2,3,4,6-tetra-*O*-methyl-D-mannose anilide m.p. and mixed m.p. 141° (after recrystallization from petroleum ether).[17]

(2) **2,3,4,6-Tetra-*O*-methyl-D-galactose.**—Treatment of a portion (50 mg.) of component 2, Table III, with aniline in alcohol, as under "1" above, afforded 2,3,4,6-tetra-*O*-methyl-D-galactose anilide which had m.p. and mixed m.p. 195°, $[\alpha]^{23}D$ −137° in pyridine (*c* 0.5) (after recrystallization from ethanol).[18]

(3) **2,3,6-Tri-*O*-methyl-D-mannose.**—Component 3, (0.5 g.) (see Table III), was oxidized with bromine at room temperature for 7 days. Isolation of the lactone in the usual way yielded 2,3,6-tri-*O*-methyl-D-mannono-γ-lactone, m.p. and mixed m.p. 81°, $[\alpha]^{24}D$ +61° initial value in water (*c* 1.0), after recrystallization from ether.[2]

(4) **2,3-Di-*O*-methyl-D-mannose.**—Component 4, (0.3 g.), was oxidized with nitric acid (sp. gr. 1.42) in the usual way. After esterification of the product with ethereal diazomethane, removal of solvent and distillation *in vacuo*, crystalline methyl dimethyl *meso*-tartrate was obtained and this yielded the crystalline bismethylamide m.p. and mixed m.p. 212°.[19]

(17) J. C. Irvine and D. McNicoll, *J. Chem. Soc.*, **97**, 1452 (1910).

(18) W. N. Haworth, J. V. Loach and C. W. Long, *ibid.*, 3146 (1927).

(19) W. N. Haworth and D. I. Jones, *ibid.*, 2349 (1927).

ST. PAUL, MINNESOTA

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE[1]]

Application of Tosylate Reductions and Molecular Rotations to the Stereochemistry of Lignans[2]

BY ANTHONY W. SCHRECKER AND JONATHAN L. HARTWELL

RECEIVED JULY 1, 1954

The *trans*-(2,3)-*trans*-(3,4) arrangement of α-conidendrin (III, R = H) has been confirmed by chemical evidence. Comparison of molecular rotations shows that the configuration at C_2 and C_3 of α-conidendrin, and hence of (+)-isolariciresinol (II, R = H, R′ = OH) and (−)-matairesinol (I, R = H), is identical with that of podophyllotoxin (IV, R = H, R′ = OH, R″ = CH_3) and related compounds. In turn, the configurations of these lignans have been correlated with those of (−)-guaiaretic acid (XIII, R = H) and of galbulin (II, R = CH_3, R′ = H) by the reduction of the tosylates XIV (R = CH_3, R′ = OTs) and II (R = CH_3, R′ = OTs) to the corresponding methyl compounds (R′ = H).

Significant progress has been made over the years in attempts to elucidate the relative configurations at the different asymmetric centers of lignans[3] and to interrelate stereochemically the various members of this class of compounds. Thus Haworth has demonstrated the *trans*-(2,3) arrangement of (−)-matairesinol (I, R = H)[4a,5] and shown that this relationship persists without any configurational change at C_2 and C_3 in (+)-isolariciresinol (II, R = H, R′ = OH)[4b] and hence in α-conidendrin (III, R = H).[5,6] Cyclization of diarylbutanes (I) to phenyltetralins (II, III) introduces a third asymmetric center (at C_4), and Haworth postulated a *trans*-(3,4) relation in the naturally-occurring lignans of this type, on the assumption that the most stable isomer should be formed during ring-closure.[7] Since the lariciresinol–isolariciresinol rearrangement[8] certainly proceeds by a carbonium ion mechanism, (+)-isolariciresinol, and therefore α-conidendrin, should be expected to possess the stable *trans*-(3,4) configuration in accordance with Haworth's postulate. A more direct proof, however, still appeared desirable. Moreover, Haworth's assumption does not necessarily apply to ring-closures proceeding under biologic conditions, and indeed it was shown that a group of naturally-occurring phenyltetralins, endowed with activity against experimental tumors (namely, podophyllotoxin (IV, R = H, R′ = OH, R″ = CH_3), desoxypodophyllotoxin (IV, R = R′ = H, R″ = CH_3),[9] demethylpodophyllotoxin (IV, R = R″ = H, R′ = OH),[10] α-peltatin (IV, R = OH, R′ = R″ = H),[11] and β-peltatin (IV, R = OH, R′ = H, R″ = CH_3)[11]), possess a *trans*-(2,3)-*cis*-(3,4) configuration.[12]

It has now become possible to interrelate the configurations of these biologically active lignans with those of α-conidendrin and (−)-matairesinol. A stereospecific series of reactions led from α-conidendrin dimethyl ether (III, R = CH_3) to α-retrodendrin dimethyl ether (V) with retention of configuration at all asymmetric centers.[13] α-Retrodendrin dimethyl ether fails to undergo base-catalyzed epimerization at C_3,[13] characteristic of the *trans*-(2,3)-*cis*-(3,4) lactones IV.[12] However, we have found that refluxing with sodium acetate in methanol converts it to methyl α-retrodendrate dimethyl ether (VI), a reaction which parallels the

(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

(2) Presented in part before the Medicinal Chemistry Division of the American Chemical Society in New York City, September 15, 1954.

(3) R. D. Haworth, *Nature*, **147**, 255 (1941).

(4) (a) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 154 (1939); (b) 1054 (1939).

(5) (a) R. D. Haworth and L. Wilson, *ibid.*, 71 (1950). (b) The "*trans*" and "*cis*" configurations of matairesinol and isomatairesinol,[5a] respectively, are designated with reference to the lactone ring and correspond to a (−) and a *meso* configuration in the open-chain diols[5a] derived from these compounds. Similarly, the substituents at C_2 and C_3 in (+)-lariciresinol dimethyl ether[4b] are *cis* with respect to the tetrahydrofuran ring, while they are *trans* (with respect to the tetralin ring) in the isolariciresinol dimethyl ether (II, R = CH_3, R′ = OH) derived from it. This change does not represent a true Walden inversion, but is produced by the difference in the reference ring systems and is more clearly visualized by examination of models. Hydrogenolysis of (+)-lariciresinol dimethyl ether[4b] and reduction of (−)-matairesinol dimethyl ether[5a] yield the same (−)-diol (XIV, R = CH_3, R′ = OH). In compounds like α-conidendrin (III, R = H), the *trans*-(2,3) arrangement refers to both the tetralin and the lactone rings.

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

(7) R. D. Haworth and F. H. Slinger, *J. Chem. Soc.*, 1321 (1940); R. D. Haworth, *ibid.*, 448 (1942).

(8) R. D. Haworth and W. Kelly, *ibid.*, 384 (1937).

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

(10) M. V. Nadkarni, J. L. Hartwell, P. B. Maury and J. Leiter, *ibid.*, **75**, 1308 (1953).

(11) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5924 (1953).

(12) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5916 (1953).

(13) M. E. Cisney, W. L. Shilling, W. M. Hearon and D. W. Goheen, *ibid.*, **76**, 5083 (1954).

conversion of isodesoxypodophyllotoxin (VIII) to methyl isodesoxypodophyllate[12] and thus establishes experimentally the *trans*-(2,3)-*trans*-(3,4) configuration[12] of V, and hence of α-conidendrin. It has been shown[14] that the molecular rotations[15] of lignans are not affected greatly by changes in the alkoxyl substituents on the aromatic rings. Since the molecular rotations of α-retrodendrin dimethyl ether (M_D −350)[13] and of isodesoxypodophyllotoxin (M_D +330)[12] are nearly equal in magnitude, but opposite in sign, while no such relation can be established with the known diastereoisomers[12] of isodesoxypodophyllotoxin, it follows that they must possess precisely opposite configurations at all three asymmetric centers.[14] This is confirmed by the opposite rotations of methyl α-retrodendrate dimethyl ether (VI) (M_D +100) and of methyl isodesoxypodophyllate (M_D −100).[12] Examination of other derivatives of α-conidendrin supports this conclusion. Thus the molecular rotations of (+)-isolariciresinol dimethyl ether (α-conidendryl alcohol dimethyl ether[13]) (II, R = CH_3, R′ = OH) (M_D +80)[8] and of anhydroisolariciresinol dimethyl ether (II, R = CH_3, R′R′ = O)[5a,8] (M_D −190) are similar in magnitude but opposite those of the diol (IX, R = OH) (M_D −90) and anhydro compound (IX, RR = O) (M_D +120), respectively, obtained from isodesoxypodophyllotoxin by reduction with lithium aluminum hydride, followed by dehydration. A similar relationship exists between the diol (VII, R = OH) (M_D +160)[13] and anhydro compound (VII, RR = O) (M_D −110)[13] obtained from β-conidendrin dimethyl ether, a compound which is known[16] to derive from α-conidendrin dimethyl ether (III, R = CH_3) by inversion at C_2, and the corresponding diol (X, R = OH) (M_D −130) and anhydro compound (X, RR = O) (M_D +80) prepared from desoxypicropodophyllin.[12]

Since desoxypodophyllotoxin (IV, R = R′ = H, R″ = CH_3) differs from isodesoxypodophyllotoxin (VIII) by its configuration at C_2 and C_3,[12] it follows that it must differ sterically from α-conidendrin (III, R = H) by its configuration at C_4 only. Thus the biologically active lignans IV are related to I, II and III by a common configuration at C_2 and C_3. Tumor-damaging potency has been found to be closely associated with stereochemical features.[17] It would, therefore, be interesting to obtain a correlation with other classes of natural products, such as sugars and amino acids, the absolute configurations of which are known. As a first step in this direction, it appeared desirable to relate the configurations of I, II, III and IV to that of the simplest known lignan, namely, (−)-guaiaretic acid (XIII, R = H),[18] which contains only one asymmetric carbon atom and may conceivably be degraded to even simpler compounds. This has been accomplished by the conversion of (−)-matairesinol dimethyl ether (I, R = CH_3) to (−)-dihydroguaiaretic acid dimethyl ether (XIV, R = CH_3, R′ = H). Lithium aluminum hydride reduction of I (R = CH_3)[5a] furnished the known[4b,5a] diol (XIV, R = CH_3, R′ = OH), which reacted in the cold with tosyl chloride in pyridine to give a 74% yield of the ditosylate (XIV, R = CH_3, R′ = OTs). The yield of ditosylate dropped when attempts were made to prepare it at room temperature, and it was assumed, in view of related findings,[19] that formation of the corresponding tetrahydrofuran (XIV, R = CH_3, R′R′ = O)[4b,5a] had occurred as a side-reaction. Indeed, this compound was obtained in 88% yield when the reaction was carried out at 100°, and this method of dehydration was found to be of general application, supplementing the alternative procedures employed in the past.[4b,5a,8,20] Reduction of the ditosylate with lithium aluminum hydride[21] in boiling tetrahydrofuran[21b] afforded, in 83% yield, (−)-dihydroguaiaretic acid dimethyl ether (XIV, R = CH_3, R′ = H). Reaction of the diol with mesyl chloride, followed by reduction[21c] of the dimesylate (XIV, R = CH_3, R′ = OMs) proved equally satisfactory. Since the configuration at C_3 remains unchanged in the reduction[18] of XIII (R = CH_3) to XIV (R = CH_3, R′ = H) and since the rotation of the product is identical in sign and magnitude with that of the material obtained from I (R = CH_3), the configuration at C_3 of (−)-matairesinol, (+)-isolariciresinol, α-conidendrin and of the lignans with the general formula IV (such as podophyllotoxin) is demonstrated to be identical with that of the single asymmetric carbon atom in (−)-guaiaretic acid. The same is true for the majority of the other naturally occurring lignans, insofar as they have been related to I, II or III[14]; this more general field will be discussed in a subsequent paper.

By a similar series of reactions, it has been possible to determine the relative configurations of two of the recently discovered lignans isolated from *Himantandra baccata* and *H. belgraveana*, the structures of which were proven by Hughes and Ritchie.[22] Reduction of ditosyl- or dimesyl-(+)-isolariciresinol dimethyl ether (II, R = CH_3, R′ = OTs or OMs) provided (−)-galbulin, which therefore has not only the structure[22] but also the configuration II (R = CH_3, R′ = H). Since the rotations of galbulin and of galcatin (XV) are of the same sign and essentially equal magnitude, the latter also very likely[14] possesses the same configuration.

A stereoisomer of galbulin, which we have named isogalbulin (VII, R = H), was prepared from β-conidendryl alcohol dimethyl ether (VII, R = OH)[13] *via* the ditosylate. The evidence available at present is insufficient for elucidating the rela-

(14) J. L. Hartwell, A. W. Schrecker, J. Leiter and W. L. Shilling, *Abstracts of Papers, Am. Chem. Soc.*, **125**, 11M (1954).

(15) M_D = $[\alpha]_D$ × mol. wt./100. The values reported refer to chloroform solutions. The unit figures are rounded off since they are not significant in most cases.

(16) (a) B. Holmberg, *Ber.*, **54**, 2389 (1921); B. Holmberg and M. Sjöberg, *ibid.*, p. 2406; (b) W. M. Hearon, H. B. Lackey and W. W. Moyer, THIS JOURNAL, **73**, 4005 (1951).

(17) J. Leiter and J. L. Hartwell, *Cancer Research*, **9**, 625 (1949); J. L. Hartwell, A. W. Schrecker and J. Leiter, *Proc. Am. Assoc. Cancer Research*, **1** (No. 2), 19 (1954).

(18) G. Schroeter, L. Lichtenstadt and D. Ireneu, *Ber.*, **51**, 1587 (1918).

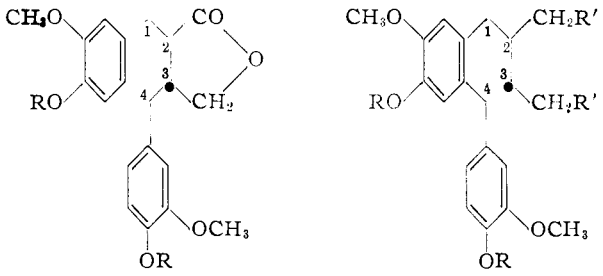
(19) D. D. Reynolds and W. O. Kenyon, THIS JOURNAL, **72**, 1593 (1950); G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).

(20) N. L. Drake and E. H. Price, THIS JOURNAL, **73**, 201 (1951).

(21) (a) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949); P. Karrer, H. Asmis, K. N. Sareen and R. Schwyzer, *ibid.*, **34**, 1022 (1951); (b) P. Karrer and G. Widmark, *ibid.*, **34**, 34 (1951); (c) J. Strating and H. J. Backer, *Rec. trav. chim.*, **69**, 638 (1950).

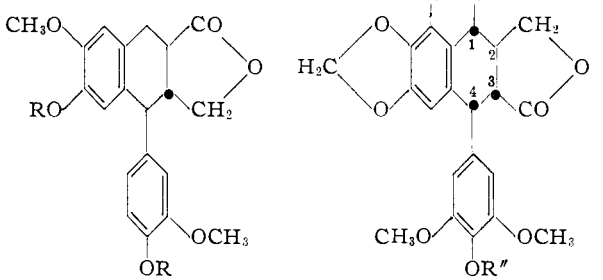
(22) G. K. Hughes and E. Ritchie, *Australian J. Chem.*, **7**, 104 (1954).

tionship of either galbulin or isogalbulin with another stereoisomer of galbulin, prepared[23] from galgravin (structure XVI, R = R′ = CH_3, R″ = H). The latter and galbacin (structure XVI, RR′ = CH_2, R″ = H) are closely related to olivil (structure



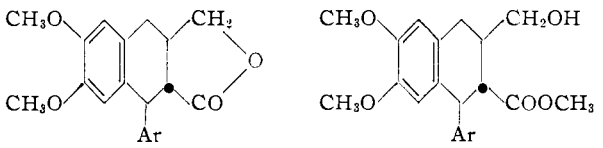
I

II



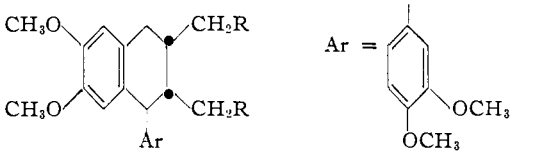
III

IV

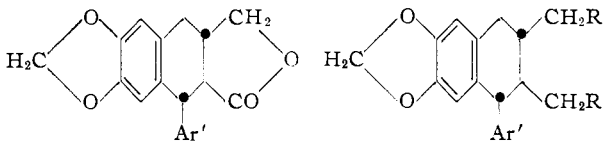


V

VI

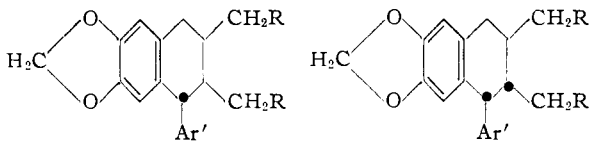


VII



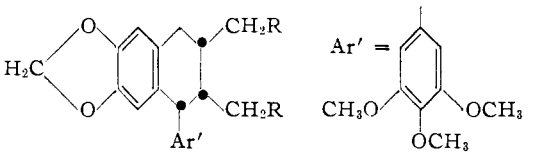
VIII

IX



X

XI



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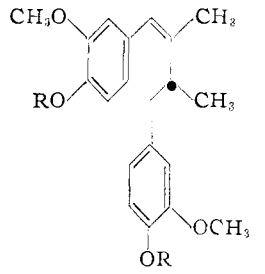

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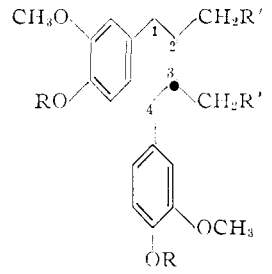
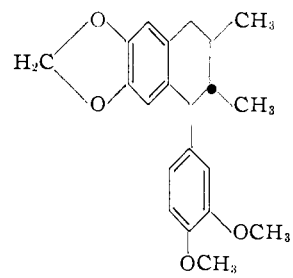
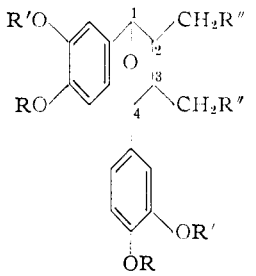


XIV



XV



XVI

(23) A. J. Birch, G. K. Hughes and E. Smith, *Australian J. Chem.*, **7**, 83 (1954).

XVI, R = H, R′ = CH_3, R″ = OH),[24] which is known[24,25] to be either *trans*-(1,2)-*trans*-(2,3)-*trans*-(3,4) or *cis*-(1,2)-*trans*-(2,3)-*cis*-(3,4). Some of the methods described in this paper may help to correlate the configurations of these compounds and of isoölivil[24,26] (which is most likely[24] *trans*-(2,3)-*trans*-(3,4)) with those of the other lignans.

Experimental[27]

Methyl α-Retrodendrate Dimethyl Ether (VI).—This compound was obtained in 87 and 66% yields, respectively, by methylation of α-retrodendric acid dimethyl ether[13] with diazomethane or by refluxing α-retrodendrin dimethyl ether (V)[13] with sodium acetate in methanol, using the procedures previously reported[12] for the preparation of methyl isodesoxypodophyllate. Recrystallizations from chloroform–hexane, then from methanol, provided colorless needles, m.p. 183.5–184°, $[\alpha]^{21}D$ +24.4 ± 1.2° (*c* 0.48, chloroform). The samples prepared by the different methods gave no mixed melting point depression and had identical infrared spectra, with an ester band at 5.79 μ (in chloroform).

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; OCH_3, 37.26. Found: C, 66.03; H, 6.75; OCH_3, 37.34.

Preparation of Diols.—The previously used procedures for the reduction of lactonic lignans[5a,13,20] were modified by the use of tetrahydrofuran[28] as a solvent in which most of the lactones and the metal–organic complexes of the diols were quite soluble. Decomposition with saturated ammonium chloride solution[29] rather than with hydrochloric acid decreases the likelihood of dehydration to cyclic ethers. In a typical run, a solution of 0.01 mole of the lactone in 40 to 80 ml. of tetrahydrofuran was added dropwise with magnetic stirring and cooling to a suspension of 3 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was stirred at room temperature for three hours, cooled in ice and, with continued stirring, decomposed by

(24) B. L. Vanzetti, *Monatsh.*, **52**, 163 (1929); *Gazz. chim. ital.*, **59**, 373 (1929); *Mem. reale accad. Italia, Classe sci. fis. mat. e nat.*, **8**, 411 (1937); B. L. Vanzetti and P. Dreyfuss, *Gazz. chim. ital.*, **68**, 87 (1938).

(25) H. Erdtman, *Svensk Kem. Tidskr.*, **48**, 236 (1936).

(26) L. H. Briggs and A. G. Frieberg, *J. Chem. Soc.*, 271 (1937).

(27) Melting points are corrected and were determined in Pyrex capillaries with the Hershberg apparatus. Infrared spectra were recorded with a Perkin–Elmer model 21 spectrometer.

(28) Purified by refluxing for several hours with, and distilling from, potassium hydroxide, then sodium, and finally lithium aluminum hydride.

(29) O. Schwarzkopf, H. J. Cahnmann, A. D. Lewis, J. Swidinsky and H. M. Wüest, *Helv. Chim. Acta*, **32**, 443 (1949).

the dropwise addition of 18 ml. of ethyl acetate, then of 17 ml. of saturated ammonium chloride solution, finally allowed to come again to room temperature. The precipitate was removed by filtration and extracted with boiling ethanol. The combined filtrates were evaporated, and the residue digested with water to dissolve inorganic salts. Some of the diols were directly obtained crystalline; they were collected, washed with water and dried (procedure A). Amorphous or oily products were dissolved in chloroform, the solutions washed with water, dried over magnesium sulfate, evaporated and the products crystallized or chromatographed (procedure B). In general, the diols were freely soluble in methanol, less so in chloroform and sparingly soluble in benzene.

(+)-Isolariciresinol dimethyl ether (II, R = CH_3, R′ = OH), obtained[5a] from α-conidendrin dimethyl ether (III, R = CH_3)[16] in 98% yield (procedure A), was crystallized from chloroform–benzene; m.p. 167–169° (lit. 166–167°,[3] 167–168,[5a] 168–172°[13]); $[\alpha]^{20}D$ +15.8 ± 0.3° (*c* 1.79, chloroform) (lit. +20°,[3] + 18°[5a]).

β-Conidendryl alcohol dimethyl ether (VII, R = OH) was prepared from β-conidendrin dimethyl ether,[18] employing special precautions necessary to avoid the ready dehydration reported.[13] The precipitate of hydrated alumina was extracted at room temperature with acetone, then with methanol, and the combined filtrates evaporated in an air stream. Procedure B gave, after evaporation of the chloroform solution at room temperature, an oil, which was dissolved in cold benzene. Scratching induced separation of tiny needles, m.p. 104–115° (yield 88%). The compound was recrystallized in the same manner, using cold chloroform and benzene, without any improvement in the melting point; $[\alpha]^{20}D$ +40.4 ± 0.5° (*c* 2.00, chloroform) (lit.[13] + 41°). The product crystallizing with 0.25 mole of benzene, m.p. 131–132°,[13] could not be obtained. It is doubtful whether the anhydro compound (VII, RR = O) was present as a contaminant in any appreciable amount, since it is very soluble in benzene. The difference in melting points might be caused by polymorphism.[30]

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.97; H, 7.25.

The diol IX (R = OH) from **isodesoxypodophyllotoxin** (VIII)[12,31] (95% yield, procedure A) crystallized from chloroform–benzene in small colorless needles, m.p. 180–181°, $[\alpha]^{20}D$ −22.4 ± 0.5° (*c* 1.01, chloroform), $[\alpha]^{20}D$ −62 ± 1° (*c* 0.64, pyridine).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.89; H, 6.56.

The diol X (R = OH) from **desoxypicropodophyllin**[9,12] (91% yield, procedure A) formed colorless needles (from methanol–benzene), m.p. 237–238°, $[\alpha]^{20}D$ −32 ± 2° (*c* 0.225, chloroform), $[\alpha]^{20}D$ −84 ± 2° (*c* 0.54, pyridine).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.63; H, 6.49.

The diol XI (R = OH) from **desoxypodophyllotoxin** (IV, R = R′ = H, R″ = CH_3)[9,12] crystallized with difficulty from chloroform–ether–hexane in small prisms, m.p. 145–147° (82% yield, procedure B). It was further purified by dissolving in chloroform, adsorbing on alumina, eluting with chloroform–methanol (9:1) and recrystallizing from chloroform–ether–hexane; m.p. 149.6–150.7°, $[\alpha]^{20}D$ −158 ± 2° (*c* 0.74, chloroform), $[\alpha]^{20}D$ −230 ± 3° (*c* 0.53, pyridine).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.76; H, 6.41.

The diol XII (R = OH) from **isodesoxypicropodophyllin**[12,20] failed to crystallize[20] when isolated by procedure B. The material was dissolved in chloroform, adsorbed on alumina, developed with chloroform and eluted with chloroform–methanol (9:1). The eluate was evaporated, the residue dissolved in ether, the slightly turbid solution filtered and again evaporated. Drying *in vacuo* left an amorphous solid melting at *ca.* 60°, $[\alpha]^{20}D$ +120 ± 1.5° (*c* 0.60, chloroform) (lit.[20] +120°), $[\alpha]^{20}D$ +103 ± 1° (*c* 0.59, pyridine).

(30) In an article received by us after our manuscript had been submitted, B. Carnmalm, *Acta Chem. Scand.*, **8**, 806 (1954), describes the preparation of this diol from β-conidendrin dimethyl ether; double m. p. of 82–84° and 140–142°, $[\alpha]D$ + 46.2° (chloroform).

(31) The low solubility of VIII made it more convenient to add it directly to the suspension of lithium aluminum hydride.

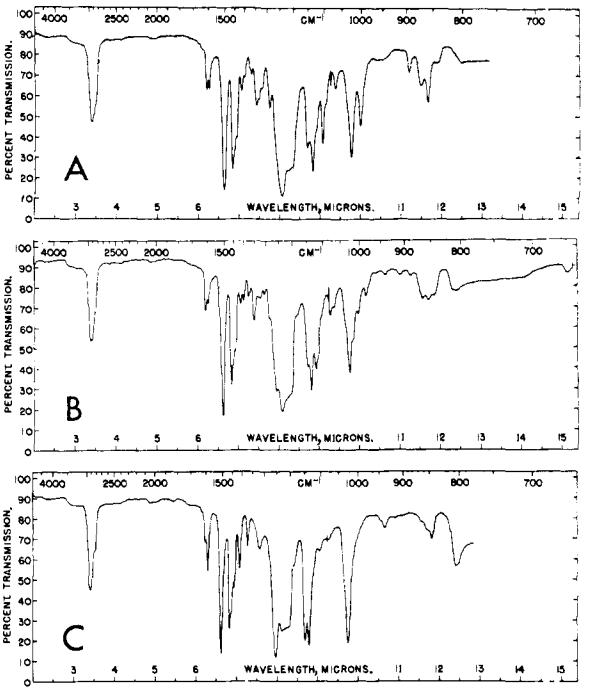


Fig. 1.—Infrared absorption spectra in chloroform (cell thickness 0.1 mm.) of: A, galbulin (II, R = CH_3, R′ = H); B, isogalbulin (VII, R = H); C, (−)-dihydroguaiaretic acid dimethyl ether (XIV, R = CH_3, R′ = H).

The diol XIV (R = CH_3, R′ = OH) was prepared in 91% yield (procedure B) from **(−)-matairesinol dimethyl ether** (I, R = CH_3),[32] which in turn was purified by chromatography on alumina, elution with chloroform and crystallization from methanol and thus obtained as colorless prisms, m.p. 128.3–128.8° (lit.127°,[4a] 126.5–127°,[32a] 127–128°[32b]; $[\alpha]^{20}D$ −32.6 ± 0.5° (*c* 1.74, chloroform) (lit. −32.3°,[4a] −35.6°.[32b] The diol crystallized from chloroform–hexane in colorless wedge-shaped prisms, m.p. 123.0–123.7° (lit. 121–122°,[4b] 119–120°[5a]; $[\alpha]^{21}D$ −34.0 ± 0.6° (*c* 1.10, chloroform) (lit. −26.2°,[4b] −29.6°[5a]).[33]

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.39; H, 7.84.

Preparation of Anhydro Compounds.—The preparation of the **anhydro compound XIV (R = CH_3, R/R′ = O)**[4b,5a] derived from (−)-matairesinol dimethyl ether is listed as an example of the generally used procedure. A solution of 390 mg. (1 mmole) of the diol XIV (R = CH_3, R′ = OH) in 4 ml. of anhydrous pyridine was heated on the steam-bath with 248 mg. (1.3 mmoles) of tosyl chloride for two hours. It was then cooled, acidified with 2 *N* hydrochloric acid and extracted with chloroform. The chloroform solution was washed with water and aqueous sodium carbonate, then dried over magnesium sulfate and evaporated. The residue was dissolved in ethyl acetate, chromatographed on alumina and eluted with the same solvent. Evaporation and crystallization from 50% methanol yielded 328 mg. (88%) of colorless prisms, m.p. 116.6–118.6°. Recrystallization from methanol provided material, m.p. 117.7–118.8°, $[\alpha]^{21}D$ −44.0 ± 0.7° (*c* 0.90, chloroform).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.98; H, 7.64.

The material did not depress the melting point of a sample prepared by dehydration with potassium hydrogen sulfate[4b,5a] and also purified by chromatography; m.p. 118.4–

(32) (a) L. H. Briggs, D. A. Peak and J. L. D. Woolloxall, *J. Proc. Roy. Soc. N. S. Wales*, **69**, 61 (1935); (b) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 633 (1935).

(33) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 4 (1953), obtained the same diol from pinoresinol dimethyl ether (a) by catalytic hydrogenolysis, m. p. 121–122°, $[\alpha]^{20}D$ −26.1° (chloroform); and (b) by sodium–alcohol reduction, m. p. 120–121°, $]\alpha]^{20}D$ −37° (chloroform).

119.7° (lit. 118–119°,[4b] 117–118°[5a]); $[\alpha]^{20}D$ −46.2 ± 0.8° (*c* 0.83, chloroform) (lit. −58.9°,[4b] −54.5°[5a]). In view of the discrepancy between the reported rotations and ours, the sample was once more recrystallized; it then had m.p. 118.8–119.8° and $[\alpha]^{21}D$ −46.0 ± 0.9° (*c* 0.80, chloroform).

Anhydroisolariciresinol dimethyl ether (II, R = CH_3, R′R′ = O)[5a,8] was similarly obtained in 47% yield as small colorless prisms (from methanol), m.p. 149.2–150.0° (lit. 147–148°,[5a] 146–147°,[8] 149.5–150.5°[13]); $[\alpha]^{20}D$ −50.0 ± 0.5° (*c* 1.51, chloroform) (lit.[13] −52°); $[\alpha]^{20}D$ −35.2 ± 0.5° (*c* 0.99, acetone) (lit. −33.9°,[5a] −33.4°[8]); no depression with an authentic sample prepared with potassium hydrogen sulfate.[5a,8,13]

The anhydro compound IX (RR = O) derived from isodesoxypodophyllotoxin (VIII) (38% yield from IX, R = OH) formed colorless prismatic needles (from methanol), m.p. 171.5–172.6°, $[\alpha]^{21}D$ +30.7 ± 0.8° (*c* 0.527, chloroform).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 68.73; H, 6.29. Found: C, 68.75; H, 6.35.

The anhydro compound X (RR = O) from desoxypicropodophyllin (85% yield) crystallized from methanol in colorless needles, m.p. 175.7–176.3°, $[\alpha]^{20}D$ +20.5 ± 0.2° (*c* 1.95, chloroform).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 68.73; H, 6.29. Found: C, 68.99; H, 6.19.

The anhydro compound XI (RR = O) from desoxypodophyllotoxin (IV, R = R′ = H, R″ = CH_3) was obtained in 79% yield as an amorphous solid, m.p. 65–85°, which could not be crystallized. Vacuum sublimation gave an amorphous sample, m.p. 65–85°, $[\alpha]^{20}D$ −71 ± 1° (*c* 0.91, chloroform).

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 68.73; H, 6.29. Found: C, 68.80; H, 6.24.

The anhydro compound XII (RR = O)[20] **from isodesoxypicropodophyllin** crystallized from methanol in long colorless needles (38% yield), m.p. 165.4–166.5° (lit.[20] 162.7–163.7°), $[\alpha]^{20}D$ +70 ± 1° (*c* 0.94, chloroform) (lit.[20] + 64°).

Preparation of Sulfonic Esters.—The preparation of **ditosyl-(+)-isolariciresinol dimethyl ether** (II, R = CH_3, R′ = OTs) is a typical example of the method. To an ice-cooled solution of 8.84 g. (6 moles/mole) of tosyl chloride in 30 ml. of anhydrous pyridine was added 3.0 g. of II (R = CH_3, R′ = OH), and the mixture stirred magnetically until the diol had dissolved. It was kept at 0° for two hours, decomposed with ice, left in the cold for another hour, and extracted with chloroform. The extract was washed with cold dilute hydrochloric acid, sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated. The residual oil crystallized readily from methanol in colorless needles (4.04 g., 75%), m.p. 161–162°. Recrystallization from chloroform–ethanol provided a product, m.p. 161.4–162.6°, $[\alpha]^{20}D$ +2.2 ± 0.3° (*c* 1.53, chloroform). The compound, like most of the other sulfonic esters, was rather sparingly soluble in methanol or ethanol.

Anal. Calcd. for $C_{36}H_{40}O_{10}S_2$: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.35; H, 5.69; S, 9.29.

Dimesyl-(+)-isolariciresinol dimethyl ether (II, R = CH_3, R′ = OMs) was prepared similarly by adding 1.2 ml. (6 moles/mole) of mesyl chloride in one lot to a chilled solution of 1.0 g. of II (R = CH_3, R′ = OH) in 10 ml. of anhydrous pyridine. The solid, obtained after decomposing the mixture with ice, was washed thoroughly with water and air-dried (1.37 g.; m.p. 121–152°), then crystallized from chloroform–ethanol to yield 1.30 g. (93%) of colorless felt-like needles, m.p. 148.0–149.5°, unchanged after further recrystallization, $[\alpha]^{20}D$ +7.0 ± 0.4° (*c* 0.98, chloroform).

Anal. Calcd. for $C_{24}H_{32}O_{10}S_2$: C, 52.92; H, 5.92; S, 11.78. Found: C, 53.00; H, 5.98; S, 11.76.

Ditosyl-β-conidendryl Alcohol Dimethyl Ether (VII, R = OTs).—This compound and the corresponding dimesylate (both prepared from VII, R = OH) are readily decomposed in the presence of pyridine or at high temperatures; therefore additional precautions are necessary. The reaction mixture was decomposed with ice, kept at 0° for an hour, acidified slightly with ice-cold dilute hydrochloric acid and extracted with chloroform. The extract was washed and dried as usual, then evaporated at room temperature. The residual oil was dissolved in cold methanol. Crystallization proceeded slowly, affording colorless needle-shaped prisms (yield 76%), m.p. 118.5–122.5°. The compound, which was more soluble in methanol than the α-isomer, was purified by dissolving again in chloroform, and evaporating and crystallizing from methanol as above; m.p. 120–122°, $[\alpha]^{21}D$ +53.6 ± 0.7° (*c* 1.17, chloroform).

Anal. Calcd. for $C_{36}H_{40}O_{10}S_2$: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.15; H, 6.10; S, 8.93.

Dimesyl-β-conidendryl Alcohol Dimethyl Ether (VII, R = OMs).—Decomposition of the reaction mixture with ice produced a gummy solid, which hardened after acidifying and stirring. It was collected, washed with water, dissolved in cold ethanol and the solution diluted with water to incipient turbidity, then kept in the refrigerator overnight. The gel-like solid (m.p. 90–110°) was dissolved in methanol below 40°. Cooling provided pale yellowish prismatic needles, m.p. 133.5–135° (yield 70%). Low-temperature recrystallization from chloroform–methanol, as in the case of the ditosylate, afforded colorless prismatic needles, m.p. 134–135°, $[\alpha]^{20}D$ +54.4 ± 0.7° (*c* 1.29, chloroform). Attempts to recrystallize the compound from hot ethanol resulted in decomposition.

Anal. Calcd. for $C_{24}H_{32}O_{10}S_2$: C, 52.92; H, 5.92; S, 11.78. Found: C, 52.63; H, 5.93; S, 11.63.

The ditosylate XIV (R = CH_3, R′ = OTs), obtained from (−)-matairesinol dimethyl ether (I, R = CH_3) *via* the diol XIV (R = CH_3, R′ = OH), crystallized immediately when the reaction mixture was decomposed with ice. The solid was washed with water, digested with hot ethanol, and the colorless needles collected after cooling; yield 74%, m.p. 166–169°. Recrystallization from chloroform–ethanol provided a product, m.p. 172–173°, $[\alpha]^{21}D$ +3.8 ± 0.3° (*c* 1.49, chloroform).

Anal. Calcd. for $C_{36}H_{42}O_{10}S_2$: C, 61.87; H, 6.06; S, 9.18. Found: C, 61.99; H, 5.98; S, 9.23.

The dimesylate XIV (R = CH_3, R′ = OMs) separated in quantitative yield upon decomposition of the reaction mixture; m.p. 172–174°. Crystallization from chloroform–ethanol yielded 94% of colorless needles, m.p. 175–176°. Two additional recrystallizations gave a product which melted with darkening at 178–179° when immersed at 150°, and at 181–182° when immersed at 175°; $[\alpha]^{20}D$ −4.5 ± 0.5° (*c* 0.97, chloroform).

Anal. Calcd. for $C_{24}H_{34}O_{10}S_2$: C, 52.73; H, 6.27; S, 11.73. Found: C, 52.87; H, 6.24; S, 11.71.

(−)-Dihydroguaiaretic Acid Dimethyl Ether (XIV, R = CH_3, R′ = H).—To a suspension of 0.5 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran[28] was added with magnetic stirring over 15 minutes a solution of 1.0 g. of the ditosylate XIV (R = CH_3, R′ = OTs) in 50 ml. of tetrahydrofuran. Stirring was continued at room temperature for another 30 minutes, then at the boiling point[21b] (electric heating mantle) for three hours. After cooling in ice, the mixture was decomposed with water, acidified with dilute hydrochloric acid and extracted twice with ether. The extracts were washed with dilute hydrochloric acid, water, dilute sodium hydroxide solution and again water, dried over magnesium sulfate and evaporated. Chromatography on alumina, using ethyl acetate, followed by crystallization from aqueous methanol yielded 425 mg. (83%) of colorless shiny scales (lit.[18] flat prisms), m.p. 86–87°. Another recrystallization from dilute methanol afforded a sample, m.p. 86.7–87.4° (lit.[18] 86–87°), $[\alpha]^{21}D$ −28.2 ± 0.3° (*c* 1.18, ethanol) (lit.[18] −27°), $[\alpha]^{21}D$ −31.4 ± 0.3° (*c* 1.52, chloroform).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3, 34.63. Found: C, 73.73; H, 8.35; OCH_3, 34.67.

In a similar run, 782 mg. of dimesylate (XIV, R = CH_3, R′ = OMs) (which was much less soluble than the ditosylate) was added directly to 0.5 g. of lithium aluminum hydride in 30 ml. of tetrahydrofuran. The product (400 mg., 78%), m.p. 86.2–87.2°, did not depress the melting point of the sample obtained from the ditosylate.

Galbulin (II, R = CH_3, R′ = H).—This compound was obtained from ditosyl- and from dimesyl-(+)-isolariciresinol dimethyl ether (II, R = CH_3, R′ = OTs or OMs) in yields of 88 and 83%, respectively, following exactly the procedure used in the preparation of XIV (R = CH_3, R′ = H). It crystallized from methanol in colorless needles, m.p. 132.8–133.6° (unchanged after further recrystallization), $[\alpha]^{21}D$

$-8.5 \pm 0.3°$ (c 1.90, chloroform). The compound did not depress the melting point of an authentic sample, isolated[22] from *Himantandra baccata* and purified to a constant m.p. of 132.6–133.4° cor. (lit.[22] 135° uncor.), $[\alpha]^{21}D$ $-8.5 \pm 0.2°$ (c 1.92, chloroform) (lit.[22] $-8.0°$). Both had identical infrared spectra.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.22; H, 7.62.

Isogalbulin (VII, R = H).—In view of the easy decomposition of the ditosylate VII (R = OTs), it was considered desirable to start the reaction at a low temperature. Therefore the suspension of lithium aluminum hydride was cooled in Dry Ice–acetone while the solution of the ditosylate was added. It was then allowed to come to room temperature gradually, stirred for one hour, finally refluxed during three hours. The mixture was worked up as usual, except that chloroform and neutral alumina[34] were used in the chromatography. Crystallization from methanol yielded 59% of material, m.p. 85–98°. Two further recrystallizations gave colorless needles, m.p. 87–89° and 87.8–89.6°, respectively. A third recrystallization provided what appeared to be a polymorphic modification, also needles, m.p. 100.5–101.5°. The lower-melting form could not be obtained again. Material recovered from the mother liquors melted at 100–101.5°. The final product had $[\alpha]^{21}D$ $+48 \pm 2°$ (c 0.296, chloroform). The compound was quite soluble even in cold methanol. In an attempt to prepare it from the dimesylate (VII, R = OMs), several zones were detected on the chromatogram by examination under ultraviolet light. No isogalbulin could be isolated. It appears that reduction of the dimesylate may have led mainly to the diol (VII, R = OH), which in turn may have undergone partial dehydration[13] to VII (RR = O). Formation of the alcohol rather than the hydrocarbon in sulfonic ester reductions has been observed with other classes of compounds.[21a]

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.14; H, 8.07.

Acknowledgments.—The authors are greatly indebted to Prof. L. H. Briggs for a supply of (−)-matairesinol dimethyl ether, to Prof. G. K. Hughes for a sample of galbulin and to Dr. W. M. Hearon and Dr. W. L. Shilling for large amounts of α-conidendrin dimethyl ether and β-conidendrin, as well as samples of α-retrodendrin dimethyl ether and α-retrodendric acid dimethyl ether. We also wish to express our thanks to Mrs. Iris J. Siewers and Miss Fleur C. Bateman for the infrared spectra and to Dr. W. C. Alford and collaborators for the microanalyses.

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(34) An excellent grade, produced by M. Woelm in Eschwege (Germany), is now available from Alupharm Chemicals, 54 C Street, Elmont, Long Island, N. Y.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Unsaturated Amines. II. Determination of the Proximity of Nitrogen to a Double Bond by Ultraviolet Absorption Spectra[1]

BY NELSON J. LEONARD AND DAVID M. LOCKE[2]

RECEIVED JUNE 23, 1954

The ultraviolet absorption spectra have been determined for several groups of α,β-unsaturated, β,γ-unsaturated and related saturated tertiary amines. A definite shift toward longer wave length and higher intensity of absorption is observed consistently with the introduction of α,β-unsaturation. Thus, comparison of the ultraviolet absorption spectrum of an unsaturated tertiary amine with that of the corresponding saturated amine provides a convenient empirical method for differentiating between an α,β-unsaturated amine and one in which the double bond is further removed from the nitrogen.

The previous paper in this series[1] has demonstrated the use of infrared absorption spectra in differentiating between an α,β-unsaturated tertiary amine and one in which the double bond is further removed from the nitrogen. The present paper is devoted to the application of ultraviolet absorption spectra for the solution of the same structural problem. The method is most safely employed when the spectra of both the unsaturated and the corresponding saturated amines are obtained for comparison.

Studies on the vacuum ultraviolet spectra of certain primary amines,[3] cyclic secondary amines,[4] and related primary, secondary and tertiary aliphatic amines[5] indicate that the tertiary amines absorb at longer wave lengths than do the less substituted amines. Unsaturation adjacent (α,β) to the tertiary amine nitrogen induces ultraviolet absorption in a range more readily measurable in solution. Thus, the wave length of the absorption maximum for 1-butenylpiperidine (in hexane) is 228 mμ,[6,7] indicating that the amino group possesses a conjugating power similar to that of C=C, by interaction of the unshared pair of electrons on the nitrogen with the π-electrons of the multiple bond.[8] Maxima in the region 229–236 mμ (in ether) have been used by Herr and Heyl[9,10] to characterize the α,β-unsaturated amines obtained on condensation of certain steroidal aldehydes and ketones with piperidine and pyrrolidine. In the cases cited,[6–10] neither related saturated amines nor unsaturated amines other than the $\Delta^{\alpha,\beta}$-type have been used for spectral comparison. In the present investigation, ultraviolet maxima (or apparent maxima)[11–14] are

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