room temperature for a day. The yellow crystalline product was recrystallized from 95% ethanol, 0.02 g. (63% yield), m.p. 178–180°. This product was identical with an authentic sample of 1,3-diphenyl-5-(*o*-nitrophenyl)-pyrazole.[6]

(b) β-(N-Methylcyclohexylamino)-2-nitrochalcone (V) was hydrolyzed in a similar manner, as in (a), to produce a 47% yield of *o*-nitrodibenzoylmethane. Almost half of the starting material was recovered after 12 hr. of reflux with 15% sulfuric acid.

(c) α-Diethylamino-4-nitrochalcone (X) (1.0 g.) was refluxed for 6 hr. with 20 ml. of 15% sulfuric acid and the reaction mixture cooled and extracted with ether. Evaporation of the ether extract produced an oily solid which was recrystallized from 95% ethanol after decolorizing with charcoal; m.p. 119–120°, wt. 0.70 g. (84.5% yield), *p-nitrobenzylphenyl diketone* (XII).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12. Found: C, 67.09; H, 4.34.

A 0.027-g. (0.001 mole) sample of XII was heated for a few minutes with 0.108 g. (0.001 mole) of *o*-phenylendiamine in 5 ml. of abs. ethanol. Cooling the mixture produced 2-(*p*-nitrobenzyl)-3-phenylquinoxaline (XIII); recrystallized from 95% ethanol, m.p. 124–125°, wt. 0.292 g. (86% yield).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 74.09; H, 4.29; N, 12.78.

(c) α-Diethylamino-3-nitrochalcone (XI) (1.0 g.) was refluxed with 20 ml. of 15% sulfuric acid for 3 hr., cooled and extracted with ether. Evaporation of the ether gave an oil which was dissolved in 5 ml. of abs. ethanol and warmed with 0.329 g. of *o*-phenylenediamine. Cooling produced 2-(*m*-nitrobenzyl)-3-phenylquinoxaline,[12] recrystallized from 95% ethanol, m.p. 120–121.5°, wt. 0.83 g. (78% yield).

2-(*p*-Nitrophenyl)-3-benzoylethylenimine (XIV).—A 4.13-g. (0.010 mole) sample of 2,3-dibromo-3-(*p*-nitrophenyl)-propiophenone was suspended in 50 ml. of abs. ethanol and the mixture saturated with anhydrous ammonia and allowed to stand in the dark at room temperature for one week. The dibromide dissolved in about three days. The solvent was removed under reduced pressure and the residue mixed with water and extracted with ether. Evaporation of the ether and recrystallization of the oily residue from 95% ethanol produced 2.23 g. (78% yield) of XIV, m.p. 142–143°. This product appears to be identical with that reported by Wieland[7] as either the ethylenimine ketone or a dimer having a piperazine structure, which he preferred. A mol. wt. determination by the cryoscopic method showed the structure of this product actually to be XIV.

No other identifiable products could be isolated from this reaction mixture.

LINCOLN, NEBRASKA

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

meso-Dihydroguaiaretic Acid and its Derivatives[2]

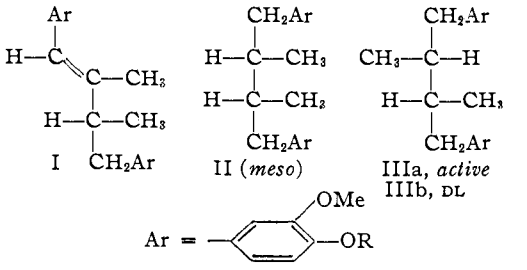
BY ANTHONY W. SCHRECKER

RECEIVED FEBRUARY 28, 1957

The contaminant of crude guaiaretic acid (I, R = H) has been identified as *meso*-dihydroguaiaretic acid (II, R = H). II (R = Me) and its DL-isomer have been synthesized by a stereospecific method. The infrared spectra of diastereoisomers in this series are discussed.

Guaiaretic acid (I, R = H), a key compound in the elucidation of the absolute configuration of lignans,[3] occurs in *Guaiacum officinale* L.[4] together with a number of related compounds.[5] Its isolation has, however, been complicated by the presence of a contaminant, which lowers the optical rotation of the crude product and from which it is not readily separated. Schroeter, who was the first to obtain pure I (R = H) (m.p. 99–100.5°, $[\alpha]_D$ −94° in ethanol),[6] informed Haworth[7] that his crude material was contaminated with an optically active (IIIa, R = H) and an inactive dihydro derivative of I (R = H), both of which occurred naturally in Guaiac resin; however, he never published these findings. He had previously prepared the dimethyl ethers of these dihydro compounds by reduction of I (R = Me) and assigned the *meso* configuration (II, R = Me) to the inactive ether, m.p. 100–101°, because of its mode of formation and because its diamino derivative could not be resolved.[6] Haworth,[7] however, prepared the same compound, m.p. 101–102°, by reduction of synthetic (DL)-I (R = Me) and named it "*dl*-dihydroguaiaretic acid dimethyl ether." He and Cartwright[8] later isolated I (R = Ac) and one of its dihydro derivatives from Guaiac resin after acetylation, but reported no optical rotations.[9]

Although it is generally assumed[4] that Schroeter's inactive dimethyl ether does possess the *meso* rather than the DL-configuration, confirmatory proof was desired. This was accomplished by a stereospecific synthesis of both II and IIIb (R = Me). In addition, the contaminant that lowers the rotation of crude I (R = H) was identified as its



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

(2) Presented in part at the XIVth International Congress of Pure and Applied Chemistry in Zurich, Switzerland, July 22, 1955; *cf.* Congress Handbook, p. 45.

(3) A. W. Schrecker and J. L. Hartwell, *J. Org. Chem.*, **21**, 381 (1956); THIS JOURNAL, **79**, 3827 (1957).

(4) For leading references, see (a) H. Erdtman in Paech and Tracey, "Modern Methods of Plant Analysis," Vol. III, Springer-Verlag, Berlin, 1955, p. 428; (b) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955).

(5) F. E. King and J. G. Wilson, Congress Handbook, XVIth International Congress of Pure and Applied Chemistry, Paris, 1957; *J. Chem. Soc.*, to be published.

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

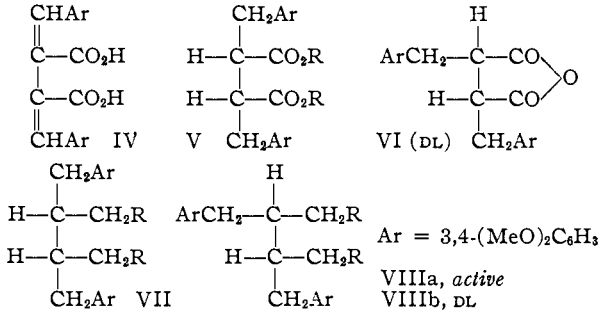
(7) R. D. Haworth, C. R. Mavin and G. Sheldrick, *J. Chem. Soc.*, 1423 (1934).

(8) N. J. Cartwright and R. D. Haworth, *ibid.*, 948 (1947).

(9) Inactive dihydroguaiaretic acid dimethyl ether, m.p. 102–103°, was also obtained by methylation of nordihydroguaiaretic acid, isolated from *Larrea divaricata*: *cf.* C. W. Waller and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **34**, 78 (1945).

meso-dihydro derivative II (R = H), while none of the diastereoisomeric IIIa (R = H) could be detected. The present paper deals with these findings.

Haworth and Woodcock[10] have shown that reduction of diveratrylidenesuccinic acid (IV) afforded *meso*-diveratrylsuccinic acid (V, R = H), which was converted to DL-diveratrylsuccinic anhydride (VI) by heating with acetic anhydride. The configurational assignments are correct because careful saponification of VI yielded an acid which was different from V (R = H) and which could be resolved.[10] *meso*-2,3-Diveratryl-1,4-butanediol (VII, R = OH), previously obtained[11] by lithium aluminum hydride reduction of isomatairesinol dimethyl ether, has now been prepared from V (R = H or Me) by the same method. Following the procedure employed in the synthesis of IIIa (R = Me),[12] the ditosylate VII (R = OTs) was converted to II (R = Me), which melted at 101.5–102° and was identical with the known inactive dihydroguaiaretic acid dimethyl ether. Therefore, the latter is definitely *meso*. VI was converted similarly, *via* VIIIb (R = OH and OTs), to DL-dihydroguaiaretic acid dimethyl ether (IIIb, R = Me), m.p. 70.4–71.2°.



The preparation of guaiaretic acid from Guaiac resin *via* the sodium salt by Schroeter's procedure[6] led to a product, m.p. 83–86°, $[\alpha]_D$ −48 to −51° (ethanol), from which pure I (R = H), m.p. 100.8–101.3°, $[\alpha]_D$ −91°, was obtained in low yield by repeated recrystallizations from ethanol. Attempts to separate the mixture by chromatography on silica or alumina failed. *meso*-Dihydroguaiaretic acid (II, R = H), m.p. 87–88°, was isolated by recrystallizing the crude sodium salt repeatedly from dilute ethanol; its dimethyl ether, m.p. 101.9–102.2°, was identical with the product prepared from VII (R = OTs). The crude phenol yielded a mixed dimethyl ether, $[\alpha]_D$ −51 to −54°, which would indicate the presence of 54–57% of I (R = Me) if the sole contaminant was II (R = Me). Since the percentage of unsaturated material, determined by hydrogen uptake, was about the same, the presence of the levorotatory IIIa (R = Me)[6,12] in any appreciable amount was unlikely.

Different lots of commercial Guaiac resin varied considerably in quality[4a]; this made it difficult to obtain reproducible results. In subsequent experiments, therefore, *Guaiacum* heartwood was extracted by King and Wilson's[5] procedure. Pure I (R = H), identical in its properties with the compound isolated from the resin, was obtained by fractional recrystallization of the crude phenol. Pure II (R = Me or Ac, resp.), devoid of optical activity, was isolated by methylating or acetylating the material remaining in the mother liquors, then oxidizing the residual I. Saponification of II (R = Ac) afforded II (R = H), m.p. 87.8–88.6°. No trace of any derivative of IIIa could be detected.[13] This demonstrates the presence of II (R = H) in *Guaiacum officinale* L. and shows that it is the contaminant of crude guaiaretic acid.[14]

Infrared Spectra.—Solutions of diastereoisomers, as contrasted with those of enantiomers, generally do not possess identical infrared spectra.[17] The diastereoisomeric dihydrosmilagenin and dihydrosarsasapogenin, chloroform solutions of which exhibit essentially identical spectra,[18] are an exception to this rule. Similarly, the infrared spectra of II (R = Me), its dibromo and dinitro derivative,[19] and of the ditosylate VII (R = OTs) in chloroform solution differ from those of the corresponding diastereoisomers by only one or two minor bands (Fig. 1).[21] Interaction of the polar hydroxyl groups in the diols VII and VIII (R = OH) leads to somewhat larger differences. In all these compounds, free rotation between the asymmetric centers is possible. When free rotation is prevented by cyclization, the infrared spectra show pronounced differences in the 9–12.5 μ region, as in the case of the tetrahydrofurans VII and VIII (RR = O).

Experimental[22]

Veratrylidenesuccinic acid, prepared in 51–53% yield according to Horning and Walker,[23] melted at 172.5–173.5° dec. (lit. 169–171.5°,[23] 175°[24]). The dimethyl ester was obtained[25] by refluxing 30 g. of the acid with 450 ml. of

(10) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 154 (1939).

(11) R. D. Haworth and L. Wilson, *ibid.*, 71 (1950).

(12) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **77**, 432 (1955).

(13) This negative evidence renders the presence of (−)-dihydroguaiaretic acid (IIIa, R = H) (*cf.* ref. 7) unlikely, but does not exclude it definitively.

(14) The "guaiaretic acid" isolated by Doebner[15] and Herzig[16] was probably impure II (R = H); this follows from their methods of isolation and from the melting points of the substance and its derivatives.

(15) O. Doebner and E. Lücker, *Arch. Pharm.*, **234**, 590 (1896).

(16) J. Herzig and F. Schiff, *Monatsh.*, **18**, 714 (1897); *Ber.*, **30**, 378 (1897).

(17) F. A. Miller in Gilman, "Organic Chemistry," Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 136.

(18) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **77**, 641 (1955).

(19) The positions of the substituents in the dibromo and dinitro derivatives (Fig. 1) are postulated by analogy with the known bromination and nitration products of 3,4-dimethoxytoluene and 3,4-dimethoxypropylbenzene.[20]

(20) H. Thoms, *Ber.*, **36**, 854 (1903); T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, **111**, 903 (1917).

(21) Only the 9–12.5 μ region is illustrated because the spectra of the *meso* compounds and the corresponding diastereoisomers were entirely identical in the 2–9 μ region. As expected,[17] the solution spectra of the optically active and DL-isomers were completely identical, while the Nujol mull spectra of the *meso* compounds were quite different from those of their diastereoisomers.

(22) Melting points were determined in Pyrex capillaries and are corrected. Infrared spectra were obtained with a Perkin–Elmer model 21 spectrometer; 0.1-mm. sodium chloride cells were used for chloroform solutions. Optical rotations were measured with 1.5% solutions in ethanol, unless specified otherwise.

(23) E. C. Horning and G. N. Walker, THIS JOURNAL, **74**, 5147 (1952).

(24) H. Stobbe and K. Leuner, *Ann.*, **380**, 75 (1911).

(25) Gordon N. Walker, unpublished procedure.

methanol and 18 ml. of concd. sulfuric acid for 6 hr. and removing 360 ml. of the solvent by distillation. The chilled residue was treated with ether and ice-water, and the ether phase was washed with water and sodium carbonate solution, dried and evaporated. Distillation yielded 26.4 g. (80%) of pale yellow oil, b.p. 188–192° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17; OCH_3, 42.18. Found: C, 61.39; H, 6.47; OCH_3, 42.22.

Diveratrylidenesuccinic Acid (IV).—The published procedure[24] resulted in a very low yield, while other attempts[10] to isolate the compound failed. The following method gave reproducible results. A suspension of 21.4 g. of 93.6% sodium methoxide in 100 ml. of dry ether was treated with stirring in an ice-bath with a mixture of 46.1 g. of veratraldehyde, 24.2 g. of ethyl succinate and 150 ml. of ether dropwise during 1 hr., stirred in the ice-bath for another hour and kept at room temperature overnight. Ether was then distilled off while 300 ml. of absolute ethanol was added gradually to maintain the volume of liquid. Distillation was continued, with removal of 400 ml. of solvent, while 150 ml. of water was added in portions. The solution was cooled, diluted with water to about 300 ml. and neutralized to *p*H 7 with hydrochloric acid. Dark impurities were extracted with chloroform, and the solution was made strongly acid. The yellow gum was extracted repeatedly with boiling water until it became crystalline, in order to remove monoveratrylidenesuccinic acid. Digesting the dried solid with 150 ml. of boiling ethyl acetate and cooling provided 15.2 g. (26%) of yellow solid, m.p. 213–215° dec. A similar run yielded 22% of material, m.p. 217–219° dec. (lit.[24] 220°).

IV also was obtained from 12.95 g. of veratraldehyde, 22.9 g. of dimethyl veratrylidenesuccinate and 4.77 g. of sodium in 110 ml. of ethanol by the general method of Horning and Walker.[23] The reaction mixture was neutralized with 26 ml. of 2 *N* hydrochloric acid, extracted with chloroform and made strongly acid. The yellow solid, digested with 150 ml. of boiling ethyl acetate, yielded 26.1 g. (81%) of IV, m.p. 217° dec. Refluxing the acid with acetyl chloride[24] gave **diveratrylidenesuccinic anhydride**, yield 92%, orange-red plates from benzene, m.p. 172–173° (lit.[24] 172–173°).

***meso*-Diveratrylsuccinic acid (V, R = H)**, previously obtained[10] by sodium-amalgam reduction of a reaction mixture containing IV, was prepared more conveniently by reducing 10.76 g. of IV in 320 ml. of 10% sodium hydroxide with 32 g. of Raney nickel–aluminum alloy at 90°.[26] The crude acid was redissolved in dilute sodium hydroxide and reprecipitated by stirring the solution into dilute hydrochloric acid; yield 10.78 g. (99%), m.p. 198–215°. Recrystallization from glacial acetic acid afforded 6.14 g. (57%) of colorless needles, m.p. 222–223° dec. (lit.[10] 223–224°).

V was also prepared by hydrogenating 15.1 g. of IV in 78 ml. of *N* sodium hydroxide with 3 g. of W-7 Raney nickel catalyst[27] at 80° and 1000 p.s.i. for 18 hr. The filtrate was acidified and the precipitate recrystallized from glacial acetic acid; yield 9.37 g. (62%), m.p. 221–222° dec.

Dimethyl *meso*-Diveratrylsuccinate (V, R = Me).—A suspension of 3.12 g. of V (R = H) in 30 ml. of acetone and 30 ml. of methanol was treated with ethereal diazomethane (distilled from 8.2 g. of nitrosomethylurea), kept for 24 hr., evaporated and the residue dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate and sodium chloride, dried and concentrated with addition of ethanol to yield 3.06 g. (92%) of colorless needles, m.p. 142.2–143.5°. A sample, chromatographed on neutral alumina, eluted with chloroform and recrystallized from ethanol, melted at 143.2–143.7°.

Anal. Calcd. for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77; OCH_3, 41.70. Found: C, 64.61; H, 6.85; OCH_3, 41.60.

DL-Diveratrylsuccinic anhydride (VI)[10] crystallized from benzene–hexane in rosettes of colorless prisms, m.p. 111–113° (lit.[10] 110–112°).

***meso*-2,3-Diveratryl-1,4-butanediol (VII, R = OH)** was prepared by the procedure employed for analogous diols,[12] except that the diacid (V, R = H) (2.0 g.) or the diester (V, R = Me) (2.8 g.) was added directly to an ice-cold suspension of lithium aluminum hydride (2.0 g.) in tetrahydrofuran, which was then stirred at room temperature for 3 hr., refluxed in the case of the acid for 0.5 hr. and decomposed as usual.[12] The residue obtained from the combined filtrate and ethanol extract was dissolved in ethyl acetate and the solution washed with water, dried, concentrated and diluted with hexane. Scratching caused slow separation of colorless rhombic plates; yields 62 and 75%, m.p.'s 90–92° and 91–93°, respectively, from V (R = H) and V (R = Me). Recrystallization from ethyl acetate–hexane afforded a product, m.p. 93.1–94.0°, unchanged after further recrystallization. Haworth and Wilson[11] report prisms, m.p. 94–95° for the same compound, prepared by reduction of isomatairesinol dimethyl ether.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.68; H, 7.53.

Heating the diol with potassium hydrogen sulfate[11] gave ***meso*-3,4-diveratryltetrahydrofuran (VII, RR = O)**, which

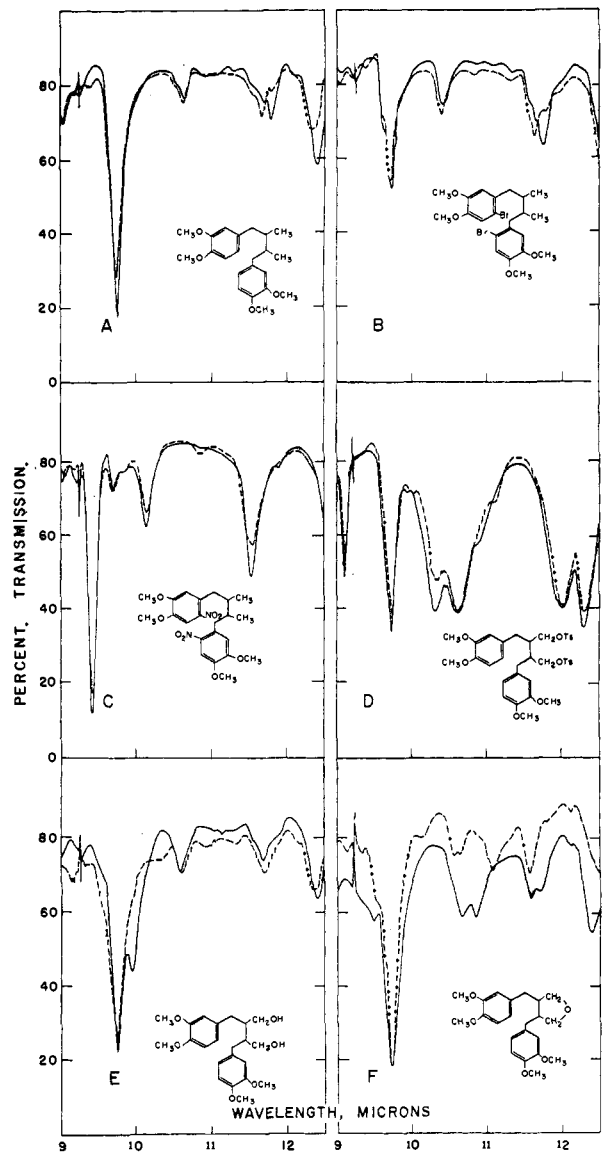


Fig. 1.—Infrared absorption spectra in chloroform of the optically active (———) and *meso* (— — —) isomers of: A, dihydroguaiaretic acid dimethyl ether; B, dibromo-A; C, dinitro-A; D, ditosyl-2,3-diveratryl-1,4-butanediol; E, 2,3-diveratryl-1,4-butanediol; F, 3,4-diveratryltetrahydrofuran.

(26) E. Schwenk, D. Papa, B. Whitman and H. F. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(27) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

was purified like its (−)-isomer.[12] It crystallized from methanol in colorless leaflets, m.p. 120.0–120.4° (lit.[11] prisms, m.p. 114–115°).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.14; H, 7.68.

DL-**2,3-Diveratryl-1,4-butanediol** (VIIIb, **R** = OH) was obtained in 88% yield from 4.10 g. of VI and 3.1 g. of lithium aluminum hydride, following the procedure used for the (−)-isomer.[12] It crystallized from benzene in small colorless prisms, m.p. 128.7–129.6°.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.79; H, 7.96.

DL-**3,4-Diveratryltetrahydrofuran** (VIIIb, **RR** = O) crystallized from methanol in colorless flat elongated prisms, m.p. 90.0–90.5°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.04; H, 7.90.

meso-**Ditosyl-2,3-diveratryl-1,4-butanediol** (VII, **R** = **OTs**) was prepared from VII (R = OH) in 96% yield like the corresponding VIIIa (R = OTs).[12] It crystallized from chloroform–ethanol in colorless needles, m.p. 140.5–141.0°.

Anal. Calcd. for $C_{36}H_{42}O_{11}S_2$: C, 61.87; H, 6.06; S, 9.18. Found: C, 61.76; H, 6.15; S, 9.46.

DL-**Ditosyl-2,3-diveratryl-1,4-butanediol** (VIIIb, **R** = **OTs**) (77% yield from VIIIb, R = OH) formed colorless needles (from chloroform–ethanol), m.p. 174.5–175.5°.

Anal. Found: C, 62.12; H, 6.17; S, 8.83.

meso-**Dihydroguaiaretic acid dimethyl ether** (II, **R** = **Me**) was prepared in 83% yield by the procedure used for the (−)-isomer,[12] except that VII (R = OTs) was added directly to a suspension of lithium aluminum hydride in tetrahydrofuran. It crystallized from methanol in colorless prismatic needles, m.p. 101.5–102.0°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.74; H, 8.62.

II (R = Me) gave the following known derivatives[19]: dibromo, colorless silky needles (from methanol), m.p. 133.3–133.9° (lit. 130.5–131.5°,[6] 131–132°[7]); dinitro, pale yellow flat transparent prisms (from ethanol), m.p. 138.2–138.9° (metastable), or cubic and hexagonal prisms (from ethanol), m.p. 152.9–153.6° (lit. 150–151°,[6] 151–152°[7]).

DL-**Dihydroguaiaretic acid dimethyl ether** (IIIb, **R** = **Me**), obtained from VIIIb (R = OTs) in 81% yield, crystallized from methanol in colorless prisms, m.p. 70.4–71.2°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.83; H, 8.30.

The dibromo derivative[19] formed colorless flat prisms (from methanol), m.p. 104.0–104.8°.

Anal. Calcd. for $C_{22}H_{28}Br_2O_4$: C, 51.18; H, 5.47; Br, 30.96. Found: C, 51.16; H, 5.35; Br, 30.91.

The dinitro derivative,[19] pale yellow flat prisms from chloroform–ethanol, melted at 181.1–181.9°.

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: C, 58.92; H, 6.29; N, 6.25. Found: C, 58.75; H, 6.07; N, 6.05.

The following known derivatives were prepared from (−)-dihydroguaiaretic acid dimethyl ether[12] (IIIa, R = Me) and recrystallized from methanol: dibromo, colorless shiny flat prisms, m.p. 122.5–123.0° (lit.[6] 121–122°); dinitro, lemon-yellow flat prisms, m.p. 124.0–124.8° (lit.[6] 122–123°).

Guaiaretic Acid (I, **R** = H). (a) **From Guaiac Resin.**—The sodium salts (60–61 g.), obtained from 450 g. of resin[28] by Schroeter's procedure,[6] were suspended in 300 ml. of hot methanol and treated with 30 ml. of glacial acetic acid. The mixture was filtered (Celite) and the residue washed with 100 ml. of methanol. The filtrate and washings, diluted with 250 ml. of water, abandoned 34–35 g. of colorless flakes, m.p. 83–86°, $[\alpha]^{20}D$ −48 to −51°.[29] This crude phenol (11 g.), recrystallized thrice from ethanol, afforded 1.3 g. of I (R = H), m.p. 100.8–101.3° (lit. 100–101°,[5] 99–100.5°[6]), $[\alpha]^{20}D$ −91° (lit. −91°,[5] −94°[6]).

(b) **From the Heartwood.**[5]—The material soluble in both hot hexane and methanol (278 g.)[30] from 45.4 kg. of *Guaiacum officinale* L. wood chips was treated with 800 g. of 5% sodium hydroxide. The precipitate was collected after 64 hr. and additional sodium salt obtained by increasing the alkali concentration to 7%. The salts were washed with 7% sodium hydroxide and acetone, suspended in water and decomposed with carbon dioxide. The mixed phenols (120 g.) were recrystallized first from 3.5 l. of hexane (yield 87 g., $[\alpha]D$ −61°), then from 65% methanol (by vol.) (yield 75 g., $[\alpha]D$ −67°) and finally several times from 1.3 vol. of ethanol (thorough chilling, systematic recrystallization of second and third crops). The yield of pure I (R = H), m.p. 100.8–101.4°, $[\alpha]^{22}D$ −91°, was 29 g.

Methylation[6] of I (R = H), followed by chromatography on alumina, elution with chloroform and crystallization from ethanol, provided **guaiaretic acid dimethyl ether** (I, **R** = **Me**), colorless prismatic needles, m.p. 92.3–92.8° (lit.[6] 94–95°), $[\alpha]^{22}D$ −94° (*c* 1.00) (lit.[5,6] −92°).

Refluxing 1.0 g. of I (R = H) with 5 ml. of acetic anhydride and 1 g. of sodium acetate for 1 hr. and treating the mixture with water yielded 1.23 g. (98%) of **diacetylguaiaretic acid** (I, **R** = Ac), m.p. 83–85°, which after chromatography as above and recrystallization from aqueous methanol formed colorless prisms, m.p. 84.0–85.0° (lit.[8] 86–87°), $[\alpha]^{20}D$ −66°.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.89; H, 7.04.

meso-**Dihydroguaiaretic Acid** (II, R = H). (a) **From the Resin.**—The mixed sodium salts[6] (24.6 g.) were recrystallized thrice from aqueous ethanol, decomposed with acetic acid in methanol, and the product (5.4 g.) was recrystallized from 60% methanol (by vol.) to yield 4.2 g. of colorless rectangular plates, m.p. 87–88°, $[\alpha]^{20}D$ −0.1 ± 0.1°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.44; H, 7.86.

Methylation[6] and chromatography afforded II (**R** = **Me**), colorless prismatic needles (from methanol), m.p. 101.9–102.2°, no depression with a sample prepared from VII (R = OTs).

(b) **From the Wood.**—The hexane, aqueous methanol and ethanol mother liquors from the purification of I (R = H) were evaporated, and a portion of the residual mixed phenols was methylated. The mixed dimethyl ethers were treated with peracetic acid in acetic acid at room temperature to oxidize I (R = Me). The solution was diluted with water, extracted with benzene, and the extract was washed with alkali, dried and chromatographed on alumina. Elution with benzene and crystallization from aqueous methanol afforded II (R = Me), m.p. 101.4–102.1° (no depression with a sample prepared from VII, R = OTs), $[\alpha]^{22}D$ +0.1 ±0.1° (*c* 8.0, chloroform). No IIIa (R = Me) ($[\alpha]D$ −31° in chloroform[12]) could be detected.

Another portion of the residual phenols was acetylated and the product dissolved in benzene and treated with osmium tetroxide and pyridine.[8] The mixture was chromatographed on alumina, which retained preferentially the black osmate complex formed from I (R = Ac). Elution with benzene and crystallization from ethanol provided *meso*-**diacetyldihydroguaiaretic acid** (II, **R** = **Ac**), m.p. 115.2–116.0° (lit.[8] 112°), $[\alpha]^{19}D$ −0.04 ± 0.05° (*c* 4.0, chloroform). No other compound could be detected in the mother liquor.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.46; H, 7.05.

Saponification of II (R = Ac) with potassium hydroxide in 50% ethanol afforded II (**R** = H) as small elongated plates (from 60% methanol), m.p. 87.8–88.6°.

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(28) Glassy Select Guaiac Gum N.F., S. B. Penick & Co., New York, N. Y.

(29) Other lots gave much lower yields. Methylation[6] of the crude phenol provided a mixed dimethyl ether m.p. 93.5–94.5°, $[\alpha]^{20}D$ −51 to −54° (*c* 1).

(30) Supplied by S. B. Penick & Co.

the extraction of Guaiac wood. Miss Mary M. Trail carried out a portion of the experimental procedures and the determination of rotations and spectra. Microanalyses were performed by Dr. W. C. Alford and his staff.

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

The Absolute Configuration of Lignans[2]

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Guaiaretic acid dimethyl ether (I) has been correlated stereochemically with L-3,4-dihydroxyphenylalanine (VI) *via* (−)-4-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (II), (−)-3,4-dimethoxy-α-methylhydrocinnamic acid (III, X = OH) and (−)-3,4-dimethoxy-α-methylphenethylamine (IV). I, II, III and IV belong to the D-series. This establishes the absolute configuration of a number of naturally-occurring lignans.

The stereochemical correlation of guaiaretic acid dimethyl ether[3] (I)[4] with (−)-3,4-dimethoxy-α-methylhydrocinnamic acid[7] (III, X = OH) has been reported in a preceding communication.[8] The enantiomer of III (X = OH) has the same sign and about the same magnitude of rotation as (+)-α-methylhydrocinnamic acid,[7,9] which by the Curtius degradation[7,10,11] yields the same (+)-α-methylphenethylamine that has been obtained[12,13] from D-phenylalanine. This led us to postulate that III, and hence I, possess the absolute D-configuration.[14]

A more rigorous demonstration than this proof by analogy has now been accomplished by correlating III with L-3,4-dihydroxyphenylalanine (VI), a natural amino acid, the absolute configuration of which is established.[17] The object of the present report is to present these new findings and the experimental details missing from our preliminary communication.

The osmate complex formed from I with osmium tetroxide was decomposed with alkaline mannitol solution,[18] a procedure which proved to be more satisfactory than reductive decomposition with alkaline formaldehyde.[19] The crude diol thus obtained, presumably a mixture of diastereoisomers, was cleaved with periodate. Separation of the oily (−)-4-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (II), $[\alpha]_D$ −35° (chloroform), from veratraldehyde was accomplished with Girard reagent. A number of pilot experiments showed that this treatment did not cause any detectable racemization.[20] II was characterized by its semicarbazone, m.p. 159.5–160°, $[\alpha]_D$ −48° (chloroform).

Reaction of (−)-3,4-dimethoxy-α-methylhydrocinnamoyl chloride[7] (III, X = Cl) with a nearly equivalent amount of methylmagnesium bromide at low temperature afforded a mixture from which the semicarbazone of II was isolated in 17% yield. The product rotated −47.5° (chloroform) and proved to be identical with the semicarbazone obtained from I. The optical antipode of II, again isolated as the semicarbazone, $[\alpha]_D$ + 47°, was similarly derived from the enantiomer of III (X = Cl). Reaction of the acid chloride with dimethylcadmium,[21] while affording better yields (up to 46%), was always accompanied by partial racemization.

The Curtius degradation of III (X = Cl) to (−)-3,4-dimethoxy-α-methylphenethylamine[7] (IV) proves[11] that IV and III (and hence I and II) have identical configurations. IV and VI were corre-

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

(2) Presented in part before the Biological Chemistry Division of the American Chemical Society at Miami, Florida, April 8, 1957; *cf.* Abstracts of Papers, **131**, 19-C (1957).

(3) G. Schroeter, L. Lichtenstadt and D. Ireneu, *Ber.*, **51**, 1587 (1918); A. W. Schrecker, THIS JOURNAL, **79**, 3823 (1957).

(4) The projection formulas, which are drawn according to Klyne,[5] conform to the Fischer convention and represent absolute configurations.[5,6]

(5) J. A. Mills and W. Klyne in Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, p. 178; W. Klyne in Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 74.

(6) J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951).

(7) A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).

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(9) (a) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **83**, 1005 (1903); (b) R. H. Pickard and J. Yates, *ibid.*, **95**, 1011 (1909).

(10) L. W. Jones and E. S. Wallis, THIS JOURNAL, **48**, 169 (1926).

(11) Retention of configuration in the Curtius rearrangement is well established; *cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 500.

(12) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(13) Retention of configuration in lithium aluminum hydride reductions has been demonstrated by D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

(14) The assignment of the D-configuration to I, II, III, IV and V conforms to the convention proposed by Klyne and by McCasland,[15] according to which formulas are drawn so that the lower-numbered end of the chain[16] is at the top. The prefix "D" then refers to the fact that the reference group[15b] is to the right. VI, VII, VIII, IX and X are L in agreement with the nomenclature conventionally[5] used for amino acids and their derivatives. The shift from L to D in the conversion of X to V does not represent an actual change of configuration but is simply a matter of nomenclature. In X, the NHTs group is the reference group,[15b] while it becomes the chief function[16] and CH_3 becomes the reference group in V. Formula V (first series of formulas) is derived from V (second series) by a double interchange of substituents; therefore, both formulas represent an identical configuration.

(15) (a) W. Klyne, *Chemistry & Industry*, 1022 (1951); (b) G. E. McCasland, "A New General System for the Naming of Stereoisomers," Chemical Abstracts, Columbus, Ohio, 1953.

(16) The *Chem. Abstracts* numbering system gives the smallest number for the chief function (determined from the "order of precedence"), then for double bonds; *cf. C. A.*, **46**, 12411 (1952).

(17) E. Waser and M. Lewandowski, *Helv. Chim. Acta*, **4**, 657 (1921); E. Waser and E. Brauchli, *ibid.*, **7**, 740 (1924). *Cf.* A. Neuberger, *Advances in Protein Chem.*, **4**, 319 (1948); J. P. Greenstein, *ibid.*, **9**, 124 (1954); W. Klyne, ref. 5, pp. 184 and 88, resp.

(18) R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1942).

(19) H. Reich, M. Sutter and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

(20) Under different conditions, purification of optically-active ketones with Girard reagent may lead to extensive racemization; *cf.* K. Mislow and J. Brenner, THIS JOURNAL, **75**, 2319 (1953); R. B. Turner, *ibid.*, **72**, 878 (1950).

(21) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).