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.

BETHESDA 14, MARYLAND

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

The Absolute Configuration of Lignans[2]

BY ANTHONY W. SCHRECKER AND JONATHAN L. HARTWELL

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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).

(8) A. W. Schrecker and J. L. Hartwell, *ibid.*, **21**, 381 (1956).

(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.

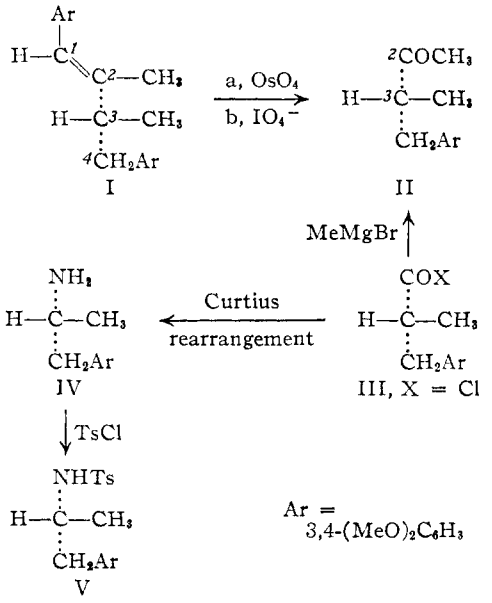
(18) R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1942).

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

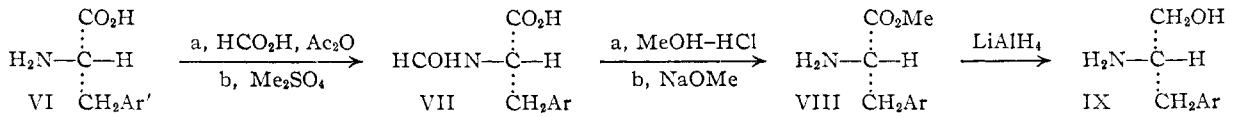
(20) Under different conditions, purification of optically-active ketones with Girard reagent may lead to extensive racemization; *cf.* K. Mislow and J. Brenner, THIS JOURNAL, **75**, 2319 (1953); R. B. Turner, *ibid.*, **72**, 878 (1950).

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

lated by a series of steps adapted from analogous reactions used in the phenylalanine and tyrosine series. Formylation[22] and methylation[23] of VI



provided *N*-formyl-L-3,4-dimethoxyphenylalanine (VII), m.p. 125–126°, $[\alpha]_D$ +72° (ethanol). Simultaneous[24] removal of the formyl group and



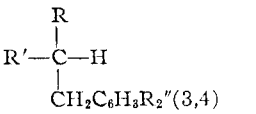
Ar = 3,4-$(MeO)_2C_6H_3$; Ar′ = 3,4-$(HO)_2C_6H_3$

esterification by means of methanolic hydrogen chloride yielded L-3,4-dimethoxyphenylalanine methyl ester (VIII) hydrochloride, m.p.158 –159° dec., $[\alpha]_D$ +7° (methanol). Reduction of VIII with lithium aluminum hydride[13,25] afforded L-3,4-dimethoxyphenylalaninol (IX), m.p. 79–80°, $[\alpha]_D$ −21.5° (ethanol), the *O*,*N*-ditosylate X, $[\alpha]_D$ −58° (ethanol), of which was further reduced[12] to *N*-tosyl-D-3,4-dimethoxy-α-methylphenethylamine[14] (V), m.p. 75.6–76.6°, $[\alpha]_D$ −29° (ethanol). Since IV yielded by direct tosylation the same levorotatory tosylate V, its absolute D-configuration,[14] and hence that of III, II and I is demonstrated unequivocally.

This result confirms the configurations previously[8] derived from rotational values. The assumption that introduction of phenolic ether groups into a benzene ring not directly attached to the asymmetric center would not greatly influence the sign and value of the optical rotation is in agreement with Tchúgaeff's rule.[26] Comparative rotational data on several phenyl and 3,4-dimethoxyphenyl derivatives, the configuration of which is pertinent to the present investigation, are shown in Table I.

TABLE I

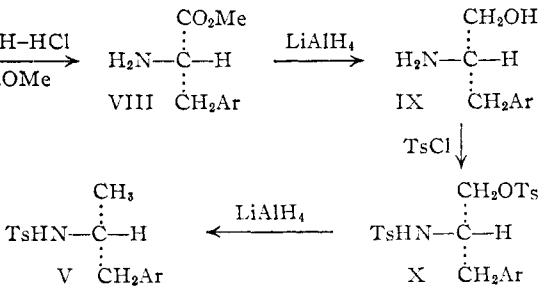
SPECIFIC AND MOLECULAR ROTATIONS OF COMPOUNDS OF THE TYPE



R	R′	$[\alpha]_D$, degrees R″ = H	R″ = OMe	$[M]_D$, degrees R″ = H	R″ = OMe	Solvent
CO_2H	NHCHO	+75[a]	+72	+145	+181	Ethanol
CO_2Me	NH_2·HCl	+17	+ 7	+ 37	+ 19	Methanol
CH_2OH	NH_2	− 4[b]	−21	− 6	− 45	Ethanol
CH_2OTs	NHTs	−51[c,d]	−58	−232	−301	Ethanol
CH_3	NH_2	−34[c,e]	−32[g]	− 47	− 62	Ethanol
CH_3	CO_2H	−28[c,f]	−28	− 46	− 63	Chloroform

[a] Ref. 22. [b] Ref. 25. [c] Calculated from the reported rotation of the enantiomer. [d] Ref. 12. [e] W. Leithe, *Ber.*, **65**, 660 (1932). [f] Ref. 9b. [g] Ref. 7.

Discussion of the stereochemistry of I is not complete without mentioning the arrangement of the substituents about the ethylenic linkage. The *trans* configuration of sphingosine has been proved[27] by application of Bruni's rule.[28] By a similar reasoning it appears very likely that the hydrogen at C_1 and the methyl group at C_2 are *trans* in I. Indeed, *meso*-dihydroguaiaretic acid dimethyl ether[8] and I are isomorphous, as shown in Fig. 1, and hence the shape of their molecules should be very similar.



The relative configuration of a number of naturally-occurring lignans,[29] especially diarylbutanes (matairesinol, hinokinin, savinin) and 4-aryltetralins (conidendrin, podophyllotoxin, desoxypodophyllotoxin, α- and β-peltatin, galbulin), is now established; in addition it has been demonstrated that they possess the same configuration at C_3 as I.[30] The present findings, therefore, establish their absolute configuration.[31] The configuration

(22) E. Fischer and W. Schoeller, *Ann.*, **357**, 1 (1907); *cf.* V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **98**, 295 (1932).

(23) N. Izumiya and A. Nagamatsu, *Bull. Chem. Soc. Japan*, **25**, 265 (1952); *C. A.*, **48**, 3929*i* (1954).

(24) S. G. Waley, *Chemistry & Industry*, 107 (1953).

(25) P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

(26) L. Tchúgaeff, *Ber.*, **31**, 360 (1898); *cf.* ref. 5, pp. 204 and 78, resp.

(27) G. Fodor and J. Kiss, *Nature*, **171**, 651 (1953).

(28) G. Bruni and F. Gorni, *Atti reale accad. Lincei*, [5] **8**, **I**, 454 (1899); [5] **13**, **I**, 626 (1904); *Chem. Zentr.*, **70**, **II**, 4 (1899); **75**, **II**, 412 (1904).

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

(30) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **77**, 432 (1955); *cf.* J. L. Hartwell, A. W. Schrecker, J. Leiter and W. L. Shilling, *Abstracts of Papers, Am. Chem. Soc.*, **125**, 11M (1954).

(31) The formulas previously published by us[30] to show the relative configurations of a number of lignans also happen to represent their absolute configurations. These formulas were drawn according to Linstead's "black dot" convention,[32] in which a black dot indicates that the hydrogen atom is above (or in front of) the molecule. In the Klyne and McCasland convention,[15] rings are drawn edgewise, so that the right side (numbered 1, 2, 3, 4) represents the front edge; the configuration at an asymmetric atom is then D, if the reference group[15b] is to the right. Thus a "black dot" indicates a D-configuration at the corresponding asymmetric center.[33]

of tetrahydrofuran derivatives, such as lariciresinol and pinoresinol, is not yet known in all the details, but that at two of their asymmetric carbon atoms also has been correlated with I[30,34] and now can also be expressed in absolute terms. Thus the stereochemistry of another important class of natural products has largely been elucidated.

Experimental[36,37]

D-(−)-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone (II). (a) From Guaiaretic Acid Dimethyl Ether[3] (I).—A solution of 2.80 g. of I, m.p. 92.3–92.8°, $[\alpha]^{22}D$ −94° (*c* 1.00, ethanol), in 75 ml. of dry ether and 1.4 ml. of dry pyridine[18] was kept with 2.08 g. of osmium tetroxide in 75 ml. of dry ether for 24 hr. at room temperature and the supernatant decanted from the black resin. Vacuum-evaporation provided a small amount of additional complex. The combined residues in 40 ml. of methylene chloride were shaken with 16 g. of mannitol and 5.33 g. of potassium hydroxide in 160 ml. of water for 1.5 hr., and the organic layer was washed with 0.5 *N* sulfuric acid, 0.5 *N* sodium hydroxide, then worked up.[37] The yellow gum, presumably a mixture of diastereoisomeric glycols, could not be crystallized. Its solution in 40 ml. of methanol was kept with 2.52 g. of sodium metaperiodate and 0.71 ml. of glacial acetic acid in 60 ml. of water at room temperature during 2 hr., diluted with more water and extracted with chloroform four times. The extracts were washed with aqueous sodium bicarbonate and evaporated.[37] The residual yellow oil (3.06 g.) was refluxed with 8.0 g. of Girard reagent P,[38] 8.0 ml. of glacial acetic acid and 106 ml. of methanol for 1 hr., the solution cooled, poured into an ice–water slurry (about 570 ml.) containing 6.66 g. of sodium carbonate and extracted twice with ether. The aqueous phase was then treated with 100 ml. of 8 *N* sulfuric acid, covered with 200 ml. of ether and kept with frequent shaking during 0.5 hr. It was then extracted twice with additional ether (150 + 100 ml.), and the extracts were washed with 0.5 *N* sulfuric acid and sodium bicarbonate.[37] The pale oil thus obtained (1.87 g., 107%) was further purified by repeating the treatment with Girard reagent P.[39] Distillation in a bulb tube assembly[40] provided 1.51 g. (86.5%) of colorless oil, b.p. 95° (air-bath temperature) (0.005 mm.), $n^{20}D$ 1.5252, $[\alpha]^{20}D$ −35.3° (*c* 4.30, chloroform).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.43, 70.10; H, 8.14, 8.10.

The semicarbazone was prepared by heating 1.0 g. of the ketone in 15 ml. of 30% methanol with 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate for a short time. Chilling yielded 1.19 g. (95%) of colorless solid, m.p. 158–159°, which after recrystallization from 30% methanol formed shiny scales, m.p. 159.5–160.0°, $[\alpha]^{20}D$ −48.0° (*c* 2.00, chloroform).

Anal. Calcd. for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.58; N, 15.04. Found: C, 60.05; H, 7.57; N, 15.08.

II also was obtained in low yield by stirring 3.4 g. of I in 5 ml. of methylene chloride with 25 ml. of hydrogen peroxide–*t*-butyl alcohol reagent,[41] 20 mg. of vanadium pentoxide[42] and 5 g. of anhydrous sodium sulfate magnetically during 1 hr., keeping for 64 hr., and evaporating the filtrate *in vacuo*. Treatment with Girard reagent, then with semicarbazide provided 0.15 g. of impure semicarbazone, m.p. 155–156.5°, $[\alpha]^{20}D$ −45° (chloroform).

(b) From D-(−)-3,4-Dimethoxy-α-methylhydrocinnamic Acid[7] (III, X = OH).—The acid chloride (III, X = Cl), prepared by refluxing 1.95 g. of the acid with 2.25 ml. of oxalyl chloride for 1 hr., evaporating *in vacuo* and re-evaporating twice after addition of dry benzene, was dissolved in 14 ml. of dry ether. The solution was stirred magnetically with exclusion of moisture and treated dropwise at −74° during 10 minutes with 12.1 ml. of 0.7 *M* ethereal methylmagnesium bromide, stirred at −74° for another hour and allowed to come to −10° over a period of 45 minutes. It was then treated dropwise at −10° with water and 2 *N* sulfuric acid. The aqueous phase was extracted with additional ether, and the ether solutions were washed with 0.5 *N* sulfuric acid and bicarbonate, then worked up as usual.[37] The residual oil, treated with semicarbazide, provided 0.41 g. (17%) of the **semicarbazone**, which recrystallized thrice from 30% methanol melted at 159.3–160.0° (no depression with material prepared under (a)) and had $[\alpha]^{20}D$ −47.5° (*c* 1.99, chloroform).

A few other runs, carried out without any change in procedure, led to a considerably racemized product.

L-(+)-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone semicarbazone, obtained in 17% yield from L-(+)-3,4-dimethoxy-α-methylhydrocinnamic acid,[7] had m.p. 156.5–157.5°, $[\alpha]^{21}D$ +47° (*c* 2.00, chloroform), and an infrared spectrum identical with that of the (−)-semicarbazone prepared above under (a). It was also prepared, although partially racemized, by treating the acid chloride with dimethylcadmium. In a representative run, 18.2 ml. of 0.65 *M* methylmagnesium bromide was stirred and refluxed with 1.19 g. of cadmium chloride (precipitated from its aqueous

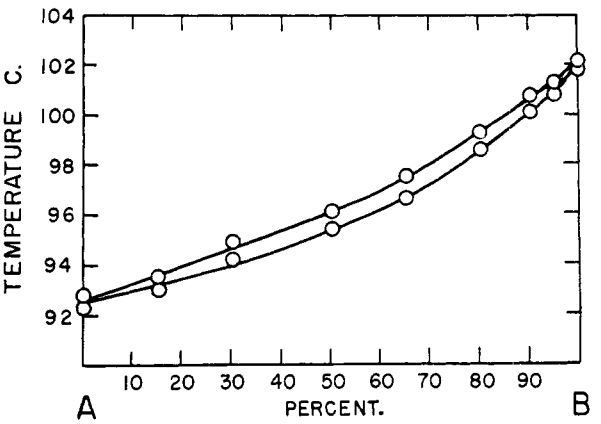


Fig. 1.—Initial and final melting temperatures of mixtures of: A, guaiaretic acid dimethyl ether (I), and B, *meso*-dihydroguaiaretic acid dimethyl ether (ref. 3), as determined by the method of H. Rheinboldt, *J. prakt. Chem.*, **111**, 242 (1925).

(32) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(33) While the "black dot" convention has primarily been employed for cyclic compounds, it was also used in our previous paper[18] to illustrate the configuration of open-chain lignans, in order to show their relation to the aryltetralin derivatives. Examination of a three-dimensional model demonstrates the equivalence of our previous formula XIII[30] and the present formula I. The aryltetralins were all numbered as 4-aryl derivatives so as to illustrate more clearly their relationship to guaiaretic acid. This numbering system is correct for derivatives of 4-aryl-2-naphthoic acid (*e.g.*, conidendrin), but it does not conform to standard nomenclature[16] for compounds like podophyllotoxin (our previous formula IV[39]), which are named more correctly as derivatives of 1-aryl-2-naphthoic acid. The configuration of podophyllotoxin, expressed previously[8] as $1D,2L,3D,4D^{15a}$ (aryl at 4), then becomes $1L,2L,3D,4L$ or $L(1,2,4)A^{15b}$ (aryl at 1). This change is, of course, merely a matter of nomenclature and does not affect the true spatial relationships.

(34) The (−)-diol which was reduced to the (−)-dihydro derivative of I[30] could be obtained by hydrogenolysis[35] of lariciresinol and pinoresinol dimethyl ethers.

(35) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1054 (1939).

(36) Melting points are corrected and were determined in Pyrex capillaries with the Hershberg apparatus. Optical rotations were measured in 4-dm. tubes.

(37) Extracts were washed with dilute acid and base (if so specified), then with dilute sodium chloride solution, dried with sodium sulfate and evaporated *in vacuo* at room temperature, using a rotating evaporator (Rinco Instrument Co., Greenville, Ill.).

(38) Arapahoe Chemicals, Inc., Boulder, Colo.

(39) The ketone, after the first purification with Girard reagent, had $[\alpha]D$ −31° (chloroform) and still appeared to contain veratraldehyde, as indicated by the yield, the low rotation and by a low C analysis. In the second purification, 4.0 g. of Girard reagent was used, and the solution diluted with 285 ml. of water (sodium carbonate and extraction of non-ketonic materials omitted) and made 0.5 *N*, instead of *N*, with sulfuric acid.

(40) A. W. Schrecker, *Anal. Chem.*, **29**, In press (1957).

(41) N. A. Milas and S. Sussman, THIS JOURNAL, **58**, 1302 (1936)

(42) N. A. Milas, *ibid.*, **59**, 2342 (1937).

solution with acetone and dried at 110°) for 40 minutes; the mixture was then treated at 0° with the acid chloride from 2.03 g. of the (+)-acid and stirred at room temperature for 3 hr. The whole procedure was performed under dry argon. The mixture was decomposed and worked up as in the reaction with the Grignard reagent, yielding 46% of partially racemic semicarbazone, m.p. 155–156°, $[\alpha]^{21}D$ + 36° (chloroform). A portion of the crude ketone was purified with Girard reagent; the yield and rotation of the semicarbazone were unchanged. When the ether was replaced with benzene before the addition of the acid chloride, the yield of semicarbazone, $[\alpha]D$ +26°, was 8%. Refluxing the benzene suspension of dimethylcadmium with the acid chloride yielded 33% of semicarbazone, $[\alpha]D$ +5.5°; the crude reaction mixture also deposited a small amount of **5,6-dimethoxy-2-methyl-1-indanone** as needles from benzene–hexane, m.p. 132–133° (lit.[43] m.p. 129–130°).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; OCH_3, 30.10. Found: C, 70.05; H, 6.66; OCH_3, 29.93.

DL-4-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone semicarbazone, prepared by cocrystallizing the enantiomers from 30% methanol, formed small rectangular plates, m.p. 164.4–164.7°.

***N*-Formyl-L-3,4-dimethoxyphenylalanine (VII).**—A solution of 10.0 g. of L-3,4-dihydroxyphenylalanine (VI), $[\alpha]^{22}D$ −12.2° (*c* 1, *N* hydrochloric acid),[44] in 90 ml. of 90% formic acid was stirred and treated with 30 ml. of acetic anhydride (temperature rise to 63°), allowed to stand for 0.5 hr., evaporated *in vacuo* below 70° with magnetic stirring (Teflon-coated stirring bar) and re-evaporated several times after addition of water. The residual gummy *N*-formyldihydroxyphenylalanine, which could not be crystallized, was dissolved in about 15 ml. of water and treated, under argon and with magnetic stirring, with 15 ml. of 10 *N* sodium hydroxide, then with four 9.5-ml. portions of methyl sulfate at 20-minute intervals. The temperature was maintained at 35° and the *p*H kept at 7–8 by the dropwise addition of 29 ml. of 10 *N* sodium hydroxide. Finally, 0.5 hr. after all the methyl sulfate had been added, the solution was treated with another 2 ml. of 10 *N* sodium hydroxide, stirred for an additional 0.5 hr., chilled and acidified with 16 ml. of 8 *N* sulfuric acid. The mixture was extracted with ether continuously for 20 hr., and the partly gummy solid which separated from the extract was crystallized from ethyl acetate to give 7.69 g. of colorless solid, m.p. 123–126°. An additional 0.41 g., m.p. 124–126°, was isolated from the mother liquor, bringing the yield to 63%. A sample, recrystallized from ethyl acetate, formed colorless elongated prisms, m.p. 125–126°, $[\alpha]^{24}D$ +71.6° (*c* 2.00, ethanol).

***N*-Formyl-DL-3,4-dimethoxyphenylalanine**, prepared similarly from DL-3,4-dihydroxyphenylalanine in 77% yield, formed small colorless prisms, m.p. 134–135.5°.

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.99; H, 5.95; N, 5.52.

L-3,4-Dimethoxyphenylalanine Methyl Ester (VIII).—A solution of 8.06 g. of VII in 80 ml. of methanol was saturated with dry hydrogen chloride, refluxed for 1 hr. and evaporated *in vacuo*. The residual oil, digested with ether, gave a gum. Recrystallization from ethanol–ether (1:3) provided the **hydrochloride** as colorless needles, which were dried in a vacuum-desiccator over solid potassium hydroxide; yield 4.58 g., m.p. 151–155° dec. An additional 1.95 g., m.p. 142–152°, was isolated from the mother liquor, bringing the yield to 75%. A sample, recrystallized from ethanol–ether, had m.p. 158–159° dec. and $[\alpha]^{20}D$ +6.8° (*c* 2.00, methanol).

Anal. Calcd. for $C_{12}H_{18}ClNO_4$: Cl, 12.86. Found: Cl, 12.74.

The free base was obtained by treating a magnetically stirred solution of 2.17 g. of the hydrochloride in 10 ml. of methanol at −30° with 0.181 g. of sodium in 4.5 ml. of methanol, then with 10 ml. of ether. The mixture was stirred at −30° for 15 minutes, filtered and the filtrate evaporated *in vacuo;* the residue was dissolved in methylene chloride, the solution refiltered, re-evaporated and evaporated again after addition of dry benzene. The residue, dried in a high vacuum, formed a yellowish oil; yield 1.74 g. (92%).

DL-3,4-Dimethoxyphenylalanine Methyl Ester.—The hydrochloride, obtained in 76% yield, formed colorless needles, m.p. 185–186° dec.

Anal. Calcd. for $C_{12}H_{18}ClNO_4$: Cl, 12.86. Found: Cl, 12.86.

The free base was obtained in 85% yield with sodium methoxide as above but in 42% yield only by treating an aqueous solution of the hydrochloride with potassium carbonate and extracting with ether.

L-Phenylalanine methyl ester hydrochloride, prepared analogously from L-phenylalanine[45] *via* the *N*-formyl derivative,[22] crystallized from methanol–ether in colorless needles, m.p. 159–160° dec., $[\alpha]^{20}D$ +17.2° (*c* 2.00, methanol), $[\alpha]^{20}D$ −4.5° (*c* 4.00, water).[46]

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: Cl, 16.44. Found: Cl, 16.19.

L-3,4-Dimethoxyphenylalaninol (IX).—A magnetically stirred suspension of 0.828 g. of lithium aluminum hydride in 22 ml. of dry ether was treated during 15 minutes with 1.74 g. of VIII in 23 ml. of ether, refluxed for 1.5 hr., cooled in ice, treated dropwise with 6.1 ml. of ethanol in 12 ml. of ether, then with 4.7 ml. of saturated sodium chloride solution and filtered through Celite. The residue was extracted with about 80 ml. of hot ethanol, and the combined filtrate and extract were evaporated *in vacuo*. The residue was dissolved in benzene, filtered from inorganic salts and re-evaporated to yield 1.47 g. of dark yellow oil, which was dissolved in hot ethanol and treated with 0.438 g. of oxalic acid dihydrate in a little water. The **neutral oxalate**, yield 1.32 g. (69.5%), was recrystallized from water–ethanol; colorless scales, m.p. 210–211.5° dec., $[\alpha]^{20}D$ −16.8° (*c* 3.96, water).

Anal. Calcd. for $2C_{11}H_{17}NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 55.27; H, 7.15; N, 5.37; H_2O, 1.73. Found: C, 55.25; H, 6.93; N, 5.35; wt. loss at 139°, 1.59.

The oxalate (1.12 g.) was treated with 10 *N* sodium hydroxide, the mixture extracted with benzene continuously for 19 hr. and the extract evaporated *in vacuo* to yield 0.90 g. (99%) of the **free base** as a colorless oil, which crystallized on standing, m.p. 78–79°. Recrystallization from methylene chloride–pentane afforded long needles, m.p. 79–80°, $[\alpha]^{20}D$ −21.5° (*c* 7.99, ethanol).

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.80; H, 8.39; N, 6.54.

DL-3,4-Dimethoxyphenylalaninol.—The neutral oxalate formed colorless micro-crystals, m.p. 228–229° dec.

Anal. Calcd. for $2C_{11}H_{17}NO_3 \cdot C_2H_2O_4$: C, 56.24; H, 7.88; N, 5.47. Found: C, 56.19; H, 7.03; N, 5.70.

The free base, recovered from the oxalate, melted at 63–64.5° and was not recrystallized. It was very soluble in water.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.69; H, 8.30; N, 6.03.

***O,N*-Ditosyl-L-3,4-dimethoxyphenylalaninol (X).**—A solution of 0.70 g. of IX and 2.1 g. of tosyl chloride in 5.7 ml. of dry pyridine was prepared at 0°, kept at room temperature for 24 hr., treated with ice and water, kept 15 minutes and extracted with chloroform. The extract was washed with 21 ml. of 4 *N* hydrochloric acid and with sodium bicarbonate solution, then worked up.[37] The residual yellow gum, which could not be crystallized, was dried at 80° (0.05 mm.), yield 1.65 g. (96%), $[\alpha]^{24}D$ −58° (*c* 1.99, ethanol).

Anal. Calcd. for $C_{25}H_{29}NO_7S_2$: C, 57.78; H, 5.63; S, 12.34. Found: C, 58.29; H, 5.79; S, 11.14.

***O,N*-Ditosyl-DL-3,4-dimethoxyphenylalaninol.**—The washed and dried chloroform extract was diluted with four volumes of hexane to yield 71% of pale yellow crystals, m.p. 133–135°. Recrystallization from chloroform–pentane provided small colorless prisms, m.p. 135.5–136.0°.

Anal. Calcd. for $C_{25}H_{29}NO_7S_2$: C, 57.78; H, 5.63; S, 12.34. Found: C, 57.72; H, 5.41; S, 12.15.

(43) F. Šorm, J. Gut and J. Krupička, *Chem. Listy*, **45**, 240 (1951); *C. A.*, **47**, 8702*i* (1953).

(44) Supplied by California Foundation for Biochemical Research, Los Angeles, Cal.

(45) Kindly supplied by Dr. Jesse P. Greenstein.

(46) B. F. Erlanger, H. Sachs and E. Brand, THIS JOURNAL, **76**, 1806 (1954), reported $[\alpha]^{25}D$ +3.9° (*c* 2.67, water) (calcd. as free ester) for the enantiomer prepared by direct esterification of D-phenylalanine.

N-Tosyl-D-3,4-dimethoxy-α-methylphenethylamine[14] (V). (a) **From X.**—The gummy ditosylate (1.64 g.) in 58 ml. of dry purified[30] tetrahydrofuran was added dropwise during 15 minutes with magnetic stirring to a suspension of 0.82 g. of lithium aluminum hydride in 33 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 0.5 hr., refluxed for 3 hr., chilled, treated with water and 4 *N* hydrochloric acid and extracted with chloroform. The extract was washed with sodium chloride and potassium carbonate solutions, dried with potassium carbonate, concentrated, chromatographed on neutral alumina and the product eluted with chloroform. Evaporation and crystallization from ether–pentane yielded 0.93 g. (84%) of colorless elongated prisms arranged in rosettes, m.p. 74.5–76.0°. Recrystallization from ether–pentane provided material, m.p. 75.6–76.6°, $[\alpha]^{20}D$ −29.3° (*c* 2.00, ethanol), $[\alpha]^{20}D$ −10.0° (*c* 2.00, chloroform).

(b) **From D-(−)-3,4-Dimethoxy-α-methylphenethylamine**[7] **(IV).**—A solution of 1.00 g. of IV and 3 g. of tosyl chloride in 15 ml. of dry pyridine was kept at room temperature for 1 hr. and poured into a slurry of ice, water and 20 ml. of concd. hydrochloric acid. The oil, which crystallized on standing in the refrigerator, was washed with water, then chromatographed and recrystallized as above; yield 1.20 g. (67%), m.p. 75.6–76.6° (no depression with a sample prepared under (a)), $[\alpha]^{20}D$ −28.9° (*c* 2.26, ethanol), $[\alpha]^{21}D$ −9.8° (*c* 2.00, chloroform). Samples prepared under (a) and (b) had identical infrared spectra.

Anal. Calcd. for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.18. Found: C, 61.86; H, 6.42; N, 4.12; S, 8.96.

***N*-Tosyl-L-3,4-dimethoxy-α-methylphenethylamine,** prepared from L-(+)-3,4-dimethoxy-α-methylphenethylamine[7] in 59% yield, formed rosettes of colorless elongated prisms, m.p. 76.2–77.2°, $[\alpha]^{20}D$ +29.4° (*c* 2.00, ethanol), $[\alpha]^{20}D$ +10.6° (*c* 2.01, chloroform).

***N*-Tosyl-DL-3,4-dimethoxy-α-methylphenethylamine** was obtained by mixing the enantiomers or (in 68% yield) by reduction of ditosyl-DL-3,4-dimethoxyphenylalaninol. It was crystallized with difficulty by slow evaporation of its ether solution at 3° and melted at 63–67°. Its infrared spectrum in chloroform was identical with that of the D-isomer.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Reaction of Steroids with Diazomethane[1]

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The action of diazomethane in ether–methanol upon certain steroids has been investigated. This reagent not only saponifies acetate groups at C-21 but also causes homologation of the side chain. Evidence is presented that the new compounds are homologous 20,22-epoxides. A model compound possessing this structure was prepared and correlated with a known compound.

The recent report on the use of diazomethane as a catalyst in transesterification[2] led us to investigate that method in the hydrolysis of the 21-acetates of a number of physiologically active steroids, since the usual methods of saponification cause concomitant side reactions.[3]

When 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,-20-trione 21-acetate[4] (Ia) was exposed to the action of an excess of diazomethane in ether–methanol solution, the ester group was lost, but the resulting product was not identical with the predicted hydrolysate Ib. Although its melting point was similar to that of 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,20-trione[4] (Ib) and no depression of this melting point was observed upon admixture with the new material, the two compounds were definitely not identical, as shown by their infrared spectra, optical rotations and migration rates in paper chromatography. The same material could also be obtained directly from non-acetylated 17α,21-dihydroxy-Δ[1,4]-pregnadiene-3,11,20-trione (Ib). Elemental analysis indicated that the new substance was a homolog of its alcohol precursor. It could be monoacetylated and resaponified.

The new material possessed a high intensity maximum at 239 mμ in the ultraviolet. This could arise from either the original dienone or a newly formed enone chromophore. However, survival of the dienone system was indicated by the characteristic absorption doublet in the infrared at 6.16 and 6.22 μ[4] and by polarographic data.[5] Failure of diazomethane to attack the ring system was not entirely unexpected, since the work of Wettstein[6] and that of Djerassi and Scholz[7] has shown that the double bond of a steroidal Δ[4]-3-ketone is resistant to that reagent.[8]

(1) Part of the results reported in this paper were published in a communication to the editor of *Chemistry & Industry*, 1313 (1956); other parts were presented before the Miami Meeting of the American Chemical Society, April 7–12, 1957.

(2) H. Bredereck, R. Sieber and L. Kamphenkel, *Chem. Ber.*, **89**, 1169 (1956).

(3) See, for instance, N. L. Wendler and R. P. Graber, *Chemistry & Industry*, 549 (1956).

(4) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(5) Peter Kabasakalian and James McGlotten, THIS JOURNAL, **78**, 5032 (1956). We are indebted to Mr. T. Coniglio of these laboratories for his kind assistance in the measurement of the polarographic reductions.

(6) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(7) Carl Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 661 (1949).

(8) Addition of diazomethane to α,β-unsaturated ketones was first described by E. Azzarello, *Gazz. chim. ital.*, II, **36**, 50 (1906). The validity of the statement[7] that the addition of diazomethane to steroidal α,β-unsaturated ketosteroids is characteristic of the Δ[16]-20-one-moiety has received further support from the failure of 3,17-diketo-Δ[1]-androstene to add diazomethane: Carl Djerassi and Alexander L. Nussbaum, unpublished experiment performed at Wayne State University.