[Contribution from the Institute of Organic Chemistry
University of Budapest]

DIMERIC PROPENYL PHENOL ETHERS. XIV. THE RACEMIC CONFIGURATION OF DIISOHOMOGENOL

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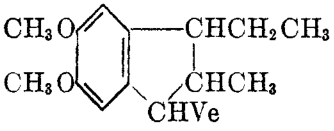
Diisohomogenol represents one of the four theoretically possible racemates of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindan (I) (1, *cf.* 2). The unknown configuration of this racemate is of special interest to the acid-catalyzed dimerization of the propenylphenol ethers, since its formation is highly stereospecific. Therefore, an investigation was made into the steric interrelation of the three presently known diastereoisomeric racemates of indan I.



I

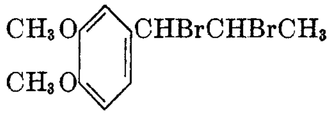
$$\text{Ve} = C_6H_3(OCH_3)_2\text{-}3,4$$

Of these racemates, (*a*) diisohomogenol represents the α-racemate, which is readily accessible by known methods (3, 4, 5). It forms densely packed clusters of long very slender needles of m.p. 106° and gives no color reaction with a dilute solution of bromine dissolved in anhydrous acetic acid. Bromination affords a 6′-monobromo derivative, thin needles of m.p. 125°. (*b*) Catalytic hydrogenation of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (X) leads to the β-racemate, (6, 7, 8), which forms sturdy lancets, melting likewise at 106° (depression with the α-racemate). This affords an intense purple-violet coloration in the bromine test (8). The monobromo derivative, stout prisms, melts at 125–126° (depression with the bromo derivative of the α-racemate). (*c*) A bromo derivative of diisohomogenol, obtained by Haraszti and Széki (9) from α-veratryl-α,β-dibromopropane (II) with finely divided copper, affords on dehydrobromination and subsequent catalytic hydrogenation the γ-racemate (3), that was found to be present in small amounts also in the crude dimerizate of isohomogenol. This exists as polyhedra or cubes of m.p. 100–101° which give a purple-violet coloration in the bromine test; however, this is only about half as intense than that given by the β-racemate. The bromo derivative (3), flat prisms, melts at 110°.

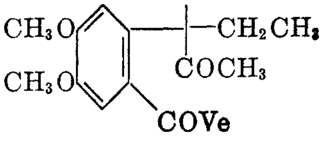
These diastereoisomeric racemates are shown by their stability against interconversion (*cf.* 8) to exist as individuals.[1] The structural identities follow from

[1] A diisohomogenol of m.p. 94–96° also has been repeatedly mentioned in the literature. The dimerizate (3) of *cis*-isohomogenol (10) obtained with methanolic hydrogen chloride, or of commercial—mainly *trans* (11) isohomogemol, formed in toluene in the presence of iodine (*Cf.* 12), although often melting at about 95°, can be converted by an adequate

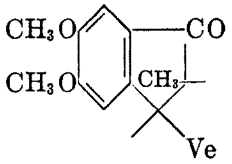
the fact that on careful oxidation with chromic acid all three racemates produce the same racemic 3,3′,4,4′-tetramethoxy-6-α-acetopropylbenzophenone (III) (*cf.* 8), in agreement with the prediction that oxidative scission of the alicyclic ring of an indan I structure (*cf.* 2) will reduce the number of the asymmetric centers in all diastereoisomeric forms to one.



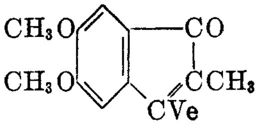
II



III



IV



V

The configuration of the β-racemate. The β-racemate, having been obtained by catalytic hydrogenation of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (X), would be expected to have the C^2/C^3-*cis* configuration (*cf.* 13). Since both the Δ^1- and the Δ^2-isomers of 1-*p*-anisyl-2-methyl-3-ethyl-6-methoxyindene were available, it was possible to show that these indenes on hydrogenation produce—regardless the position of the C,C double bond in the actual precursor—the same indan racemate (14), which is therefore of necessity of the C^1/C^2-*cis*,C^2/C^3-*cis* configuration (8, 15).[2] Apparently, the hydrogen adds to these indenes from that side of the planar ring system on which its entrance is less hindered by the bulk of the substituent present on the already saturated carbon.

The C^3-epimerism of the α- and the γ-racemate. The bromodiisohomogenol of Haraszti and Széki offers information on the configuration of the two other racemates. The halogen in this substance is secondary, since on dehydrobromination a semicyclic, rather than alicyclic, double bond is formed. The resulting dehydrodiisohomogenol is not identical with 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (X), and affords on ozone or chromic acid degradation the

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number of recrystallizations from alcohol to the form melting at 106°. Bromination of even lower-melting samples gives directly the bromo derivative of the α-racemate, m.p. 125°. Only dimerization with anhydrous zinc chloride in conc'd HCl produced a dimer that, after recrystallizations, still melted consistently at 96°. The product gave no coloration in the bromine test and also no depression of the melting point with the α-racemate. Bromination gives the bromo derivative of the α-racemate. Therefore this form must, at least for the present, be regarded as being perhaps a dimorphic form of the α-racemate, and not a further racemate of indan I.

[2] Meanwhile, 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^1indene also has been prepared, and found to yield the β-racemate of indan I upon hydrogenation.

known 1-veratryl-2-methyl-5,6-dimethoxyindanone (IV).[3] The above bromodiisohomogenol is therefore a 1-veratryl-2-methyl-3-α-bromoethyl-5,6-dimethoxyindan (VI) which, dehalogenated directly with an alcoholic suspension of zinc dust, forms the α-racemate of indan I, evidently without change of configuration at carbon 3. Indirect dehalogenation—dehydrobromination and subsequent catalytic hydrogenation—produces mainly the γ-racemate, by suspension of the asymmetry and creation of the opposite configuration on carbon 3 in the respective phases of the process.

The C^1/C^2-configuration of the two C^3-epimeric racemates is therefore identical, and the same as in 3-α-bromodiisohomogenol, being either *cis* or *trans*. The C^2/C^3-configuration is in the one epimer *cis*, and in the other *trans*. Actually, the C^1/C^2-configuration cannot be other than *trans*, since in the contrary case for the one epimer a *cis*, *trans* and for the other a *cis*, *cis* configuration would follow, in which case the latter would have to be identical with the β-racemate.

The respective C^2/C^3-configurations of the α- and the γ-racemate. The characteristic differences in the bromine test already suggest that of the two racemates it is the γ-racemate which seems to be more closely related to the *cis,cis* configurated β-racemate, and therefore to represent the *cis* alternative of the C^2/C^3-configurations. In view of the little known nature of the color reaction in the bromine test at the present time, this argument alone is not sufficient and requires additional support.

Fortunately, the desired information can be obtained from the 3-hydroxy derivatives of the α- and the β-racemate.

Upon reacting 3-α-bromodiisohomogenol (VI) in anhydrous acetic acid with silver acetate an oily acetate was obtained which, on subsequent acid hydrolysis produced a crystalline carbinol in 50% yield (9). Since the iodoform reaction of this product is negative, and the usual methods fail to effect O-acylation, the hydroxyl appears to be tertiary. This is a demonstration that the reaction with silver acetate involves a retropinacolic rearrangement analogous to the similar conversion of primary isobutyl bromide to tertiary butyl acetate (17). Since neither the reaction with silver acetate nor the subsequent acid hydrolysis are likely to affect the respective asymmetric centers of 3-α-bromodiisohomogenol, the crystalline 3-indanol is evidently C^1/C^2-*trans* configurated.

On reacting *trans*-1-veratryl-2-methyl-5,6-dimethoxyindanone (IV) with ethylmagnesium bromide, and decomposing the magnesium haloid complex with due care, an oily 3-indanol racemate results. The structure and the C^1/C^2-*trans* configuration of this product are already obvious from the mode of its formation.

Consequently, the two 3-indanol racemates are C^3-epimers, the C^2-hydrogen and the C^3-hydroxyl being collateral in the one and antilateral in the other. As expected, the crystalline racemate proved to be quite stable toward dehy-

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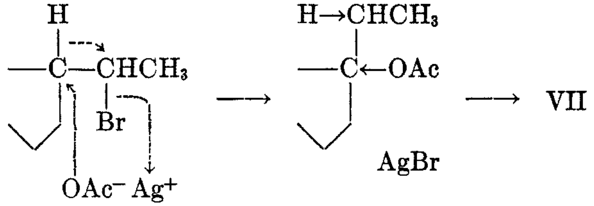
[3] This degradation product is the *trans*-configurated racemate, since it is identical in every respect with the cyclization product of 3,4-dimethoxy-α-methylcinnamic acid (6). In addition, the hydrogenation of 1-veratryl-2-methyl-5,6-dimethoxy-Δ^1-indenone (V) was found to produce this racemate (6), the 1,4-addition of hydrogen being followed by ketonization (*Cf.* 16).

dration by dilute mineral acids, while the oily racemate under same conditions gave 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (X) at a rate that is distinctly dependent upon the concentration of the mineral acid in the reaction mixture. This proves (*cf.* 18) that, of the two epimers, it is the crystalline racemate which has the *trans,cis* (VII), and the oily racemate which has the *trans, trans* (IX) configuration (with respect to the positions of the aryl and the alkyl groups).

In the reaction of 3-α-bromodiisohomogenol (VI) with silver acetate, the reversal of the configuration at carbon 3 is highly probable, although not directly evident. The numerous studies on similar rearrangements, where instead of hydrogen an alkyl or aryl is the migrating species, give no information on the behavior of that carbon *from which* the migration occurs (19, 20). Current views on the mechanism of these rearrangements (21), and in particular the accepted concerted or almost concerted nature of the steps involved (22), leave little doubt that an inversion would occur on the carbon furnishing the migrating atom or group (23). In the only instance in the literature directly devoted to this particular question, Cram (24) has actually demonstrated through the acetolysis of *p*-toluenesulfonated 3-phenyl-2-butanols that in fact complete inversion occurs on the carbon from which the phenyl migrates. It is therefore extremely unlikely that in the present reaction, which however is distinctly bimolecular, carbon 3 could retain its original configuration. The *trans,cis* configurated crystalline 3-indanol racemate (VII) would seem therefore to have been formed from a *trans,trans* configurated 3-α-bromoindan racemate (VI).



The observed reduction of the *trans,trans* configurated oily 3-indanol racemate (IX) appears to proceed likewise by inversion on carbon 3, suggesting for the resulting γ-racemate of indan I a *trans,cis* configuration, quite in agreement with the inferences just made. Since the crystalline 3-indanol racemate (VII) is fairly stable to catalytic hydrogenation at room temperature, the actual position of the C^2-methyl must be responsible for the difference. This group is, in the crystalline racemate collateral with, in the oily racemate antilateral to, the C^3-ethyl. The concentration of the two adjacent alkyls on the same side of the ring plane appears to present an obstacle to the displacement of the C^3-hydroxyl by precluding a rearward attack upon carbon 3.[4] Since with the C^2-methyl in the inverted position the mechanism is actually operative, the displacement involves either an inversion (S_N2) mechanism in which hydrogen enters at the face opposite that occupied by the simultaneously-departing hydroxyl, or it involves an S_N1 mechanism in which the approach of hydrogen to the flattened carbonium

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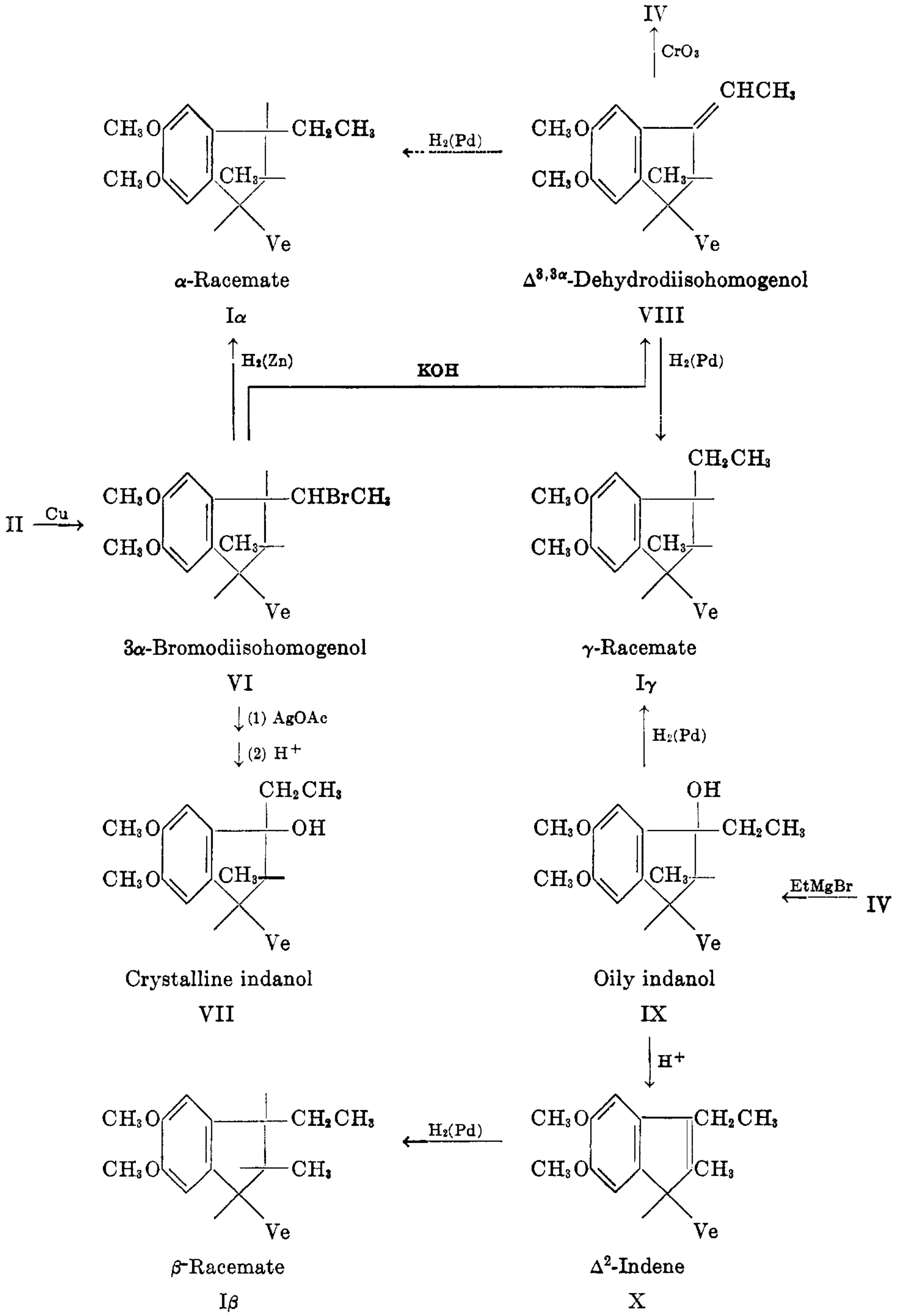
[4] This interpretation is not unlike that offered for the low reactivity of 1-hydroxy- and 1-chloro-apocamphane (25).

ion is predeterminated as to its direction by the position of the C^2-methyl and this circumstance will lead to the reversal of the configuration on carbon 3 (*cf.* 26).



The inferred mechanism would then suggest that, of the C^3-epimeric α-and γ-racemates of indan I, it is the α-racemate to which the *trans*- and the γ-racemate to which the *cis*-alternative of the C^2/C^3-configurations are to be assigned. This seems to agree completely with the observation that in this particular series of compounds the maximum color in the bromine test is associated with an all-*cis* configuration, since then a negative test would appear quite reasonable for an all-*trans*, and a partial coloration for an intermediate configuration which, a C^1/C^2-*cis* configuration having been excluded, can be only *trans,cis*.

From the available evidence we tentatively assign to the α-, the β-, and the γ-racemates of indan I the configurations Iα, Iβ, and Iγ, respectively. (In each case but one of the two enantiomorphs is represented.)

It will be then concluded that in the acid-catalyzed dimerization of isohomogenol, and presumably also in that of other propenylphenol ethers, the formation of the all-*trans* configurated racemate seems to be the preferred alternative.

EXPERIMENTAL

THE PREPARATION OF THE α- AND THE γ-RACEMATES OF INDAN I FROM ISOHOMOGENOL

α-(3,4-Dimethoxyphenyl)-α,β-dibromopropane (II) (27). A solution of 30 g. (0.17 mole) of isohomogenol in 150 ml. of absolute ether was cooled to −20°, and mixed dropwise with 27 g. (0.17 mole) of bromine in 200 ml. of ice-cold absolute ether, with exclusion of direct light. From the mixture colorless small needles separated which, after about 30 minutes, were removed from the reaction mixture, as otherwise later byproducts would appear (*cf.* 28). The product was washed with some cold ether until completely colorless; 26–32 g. (45–55%) of a crystalline powder, m.p. 99–100°, were obtained. This can be stored in a desiccator over calcium oxide for about two days without perceptible deterioration.

trans,trans-1-(3,4-Dimethoxyphenyl)-2-methyl-3-(α-bromoethyl)-5,6-dimethoxyindan, 3α-bromodiisohomogenol (VI). Haraszti and Széki's procedure (9) was used with some modifications, as indicated by previous unfavorable experiences. To a well stirred suspension of 16 g. (0.04 mole) of II in 25 ml. of dry benzene, 22 g. (0.36 g.-atom) of copper dust (Lackbronz Sirius, Doppelschliff No. 60) was added in two or three portions at room temperature. Reaction set in within 5–15 minutes. If it did not, the mixture was warmed gently. After the reaction was under way, the mixture was kept at 40°, this temperature being maintained for 90 minutes. Then the solid was removed and washed repeatedly on the filter with warm chloroform. Evaporation of the filtrate gave a pale yellow oil, crystallizing from 40 ml. of alcohol within a few hours. In parallel preparations very regularly 3.0 g. (29%) of slender interlacing silky colorless needles, m.p. 142°, have been obtained. Recrystallization from alcohol raised the melting point to 147°, giving 2.4 g. of material adequate for the subsequent conversion. Haraszti and Széki report m.p. 153°, and a yield of 70%. This was in no case attained, the probable reason being the lower quality of the copper used in place of the Naturkupfer C Kahlbaum recommended originally.

trans,cis-1-(3,4-Dimethoxyphenyl)-2-methyl-3-hydroxy-3-ethyl-5,6-dimethoxyindan, crystalline 3-indanol (VII). To a solution of 4.2 g. (0.01 mole) of VI in 50 ml. of anhydrous acetic acid, 5 g. (0.03 mole) of freshly prepared and finely powdered dry silver acetate was added with vigorous stirring, the mixture being then placed into a bath at 60°, and kept there with continuous stirring for three hours. Upon removing the solid by filtration, and pouring the filtrate into 300 ml. of water, an oil separated. This was extracted with ether, and the extract washed with water and dried over sodium sulfate, leaving on subsequent evaporation a light brown oil. This was refluxed with 80 ml. of methyl alcohol containing 2% dry hydrogen chloride (one hour), and then 100 ml. of water was added. The solid (2.0 g.) was collected after 24 hours, and more water was added until incipient turbidity. On standing, 0.9 g. of additional material was obtained. The product was dried, and then dissolved in

8 ml. of benzene. On the addition of 4 ml. of petroleum ether (b.p. 60–80°) long needles separated, followed by rosettes of a different appearance. The two forms of crystals have the identical m.p., 122–123°, and the melting point of the mixture is not depressed. The evidence points to crystal dimorphism, since on recrystallization from ethyl acetate compact clusters of an homogeneous appearance were obtained. Repeated recrystallizations from alcohol yielded clusters composed of long feathery colorless needles, m.p. 132–133°, and the mother liquor on gradual dilution with water yielded identical material, of which a total of 2.1 g. was obtained. (Haraszti and Széki report m.p. 133°). This did not give a color reaction with a 1% solution of bromine in anhydrous acetic acid. The iodoform reaction was negative. With methanesulfonyl chloride or with *p*-nitrobenzoyl chloride in pyridine no change was observed at room temperature. Upon refluxing an alcoholic solution with zinc dust, with the gradual addition of 10% aqueous hydrochloric acid, or with this acid alone, unchanged material was recovered after two hours. An attempted catalytic hydrogenation in alcoholic solution at room temperature at atmospheric or at 8 atm. pressure left the substance unaltered.

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 70.9; H, 7.6.

Found: C, 71.0, 70.9, 71.1; H, 7.8, 7.8, 7.7.

trans-1,(3,4-Dimethoxyphenyl)-2-methyl-3-ethylidene-5,6-dimethoxyindan,$\Delta^{3\text{-}3\alpha}$*-dehydrodiisohomogenol* (VIII) (3, 9). A solution of 7.2 g. of VI in 70 ml. of 6% methyl alcoholic potassium hydroxide and 2 ml. of water gave, after being refluxed for one hour, 4.7 g. (80%) of glistening long colorless needles, m.p. 117°, on cooling. Recrystallization from 85% methyl alcohol raised the melting point to 122° (reported, 122°), while the yield decreased to 3.8 g. (65%). A dilute solution in anhydrous acetic acid instantly decolorized bromine (1% solution in the same solvent), giving a transitory pure emerald-green coloration. If the reagent is added in excess, the color will persist a while longer.

Oxidation: (*a*) A current of a 1% ozone-air mixture was bubbled through an ice-cooled solution of 2.0 g. of VIII in 60 ml. of dry ethyl acetate until the potassium iodide test indicated the end of the reaction (25 minutes). After adding 10 ml. of water and 2 g. of zinc dust, the mixture was warmed on the steam-bath for 10 minutes, and then filtered. The filtrate was washed with water, then with 2% hydrochloric acid, and again with water, and dried over sodium sulfate. Evaporation left a reddish-brown oil, that crystallized readily on being triturated with a small quantity of ice-cold alcohol. The solid, 0.6 g. of m.p. 117–118°, crystallized from alcohol in stout colorless polyhedra, yielding 0.45 g. of *trans-(3,4-dimethoxyphenyl)-2-methyl-5,6-dimethoxyindan-3-one* (IV), m.p. 118–119°, alone or mixed with an authentic (6) specimen.

(*b*) To an ice-cold and vigorously stirred solution of 2.0 g. (0.0056 mole) of VIII in 80 ml. of anhydrous acetic acid, 0.72 g. (0.011 mole) of chromium trioxide in 20 ml. of 90% acetic acid was slowly added from a dropping-funnel (three hours), stirring being continued at 4–10° for an additional period of three hours. The next day, the greenish-purple solution was diluted with 300 ml. of water and then extracted with ether. The extract, washed and dried as usual, left an oil which readily crystallized from alcohol. After one recrystallization from the same solvent, 0.9 g. (46%) of stout colorless polyhedra, m.p. 119–120°, was obtained. There was no depression of the m.p. on admixture with sample (*a*), or with an authentic specimen of IV.

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindan (I). (*a*) *From 3-α-bromodiisohomogenol. The α-racemate* (Iα). A mixture of 2 g. of VI and 4 g. of zinc dust was refluxed with 40 ml. of alcohol for one hour (*cf.* 3, 9). The filtrate on evaporation left a colorless oil, which crystallized from alcohol. After recrystallization from the same solvent, 1.3 g. of slender colorless needles, m.p. 105–106°, were obtained, identical in every respect with five-times recrystallized diisohomogenol of m.p. 105–106°. This gave no coloration in the bromine test. The bromination product melts at 125° alone or mixed with 6′-bromodiisohomogenol.

The γ-racemate (Iγ). A solution of 4 g. of VIII in 200 ml. of ethyl acetate on being hydrogenated in the presence of 0.8 g. of 10% palladium-charcoal absorbed 240 ml. of hydrogen in 90 minutes. Evaporation of the filtrate gave a colorless oil crystallizing from 5 ml. of alcohol in hard small cubes. Three consecutive recrystallizations from the same solvent gave 2.1 g. of sturdy translucent bricks, m.p. 100–102°, which gave a purple-violet coloration in the bromine test.

The combined mother liquors were evaporated, and the residue was redissolved in a small volume of alcohol. After prolonged standing in the ice-box, crystallization occurred on seeding with diisohomogenol and frequent scratching. The product was a mixture of slender needles and small cubes, melting indefinitely at 83–94°. Repeated recrystallizations gave 0.4 g. of fine slender needles of the α-racemate, m.p. 104–105° alone or mixed with an authentic specimen. These gave no coloration in the bromine test. (An intentional mixture 1:1 of pure α- and γ-racemate displayed a similar reluctance towards crystallization from alcohol.)

(*b*) *From isohomogenol. The α-racemate* (Iα). A mixture of 100 g. of isohomogenol, b.p. 140°/14 mm., and 400 ml. of 40% sulfuric acid was kept at reflux with vigorous stirring for 6 hours (3). The next day, the dilute acid was removed by decantation, and the remaining semisolid was dissolved in 400 ml. of alcohol under reflux. After 2 days, 78 g. of colorless crystals forming peculiar mushroom-like colonies, m.p. 74–90°, were collected. The product was 5 times recrystallized, each time from a fourfold weight of alcohol, to yield small adherent tough rosettes, and later big clusters of slender colorless needles, m.p. 105–106° (48 g.) These did not give a color reaction in the bromine test. The bromo derivative (3, 4) forms, after recrystallization from alcohol, thin needles of m.p. 125–126°.

The γ-racemate (Iγ). The mother liquor of preceding first crystallization, which is of a dark yellow or brown color with a slight violet reflex, deposits in about 1 week at room temperature a thin, hard, mostly coherent, crust on the bottom of the flask. The liquor was removed by decantation, together with some later appearing natant needles or clusters of a different appearance. The remaining solid, on recrystallization from alcohol, forms hard translucent cubes or polyhedra, m.p. 100–102°, the yield after 2 recrystallization being 1.7–2.0 g. The cubes give a purple-violet coloration in the bromine test. The substance was recovered unchanged from a methyl alcoholic solution containing 20% hydrogen chloride after refluxing for 6 hours. No depression of melting point was observed upon melting the mixture prepared with a sample obtained in above catalytic hydrogenation of VIII, while the mixture with Iα or Iβ melted at 89–98°, and 88–100°, respectively. The bromo derivative (3, 8), colorless flat prisms of m.p. 110–111° from alcohol was found upon melting in admixture with the bromination product of Iα, or of Iβ, to melt at 97–102°, and at 99–105°, respectively.

The combined mother liquors resulting from above crystallizations were freed from the bulk of the solvent, and then water was added and the mixture was extracted with benzene. The extract was washed with 5% sodium hydroxide solution and with water, and was then evaporated. The residue distilled at 180–182°/0.01 mm., or at 220–222°/0.06 mm., as a highly viscous yellow oil solidifying at room temperature to a glass (35. g), about 8 g. of a polymeric resin being left behind. The glass was dissolved in 50 ml. of alcohol; after weeks of standing 15 g. of fairly pure α-racemate crystallized, m.p. 96–99°. The substance remaining in solution gives a rather intense purple-violet coloration in the bromine test. Oxidation of the non-crystalline material with chromic acid gave III in the usual yield of 50%.

SYNTHETIC PREPARATION OF THE β- AND THE γ-RACEMATES OF INDIN I

α-Methyl-3,4-dimethoxycinnamic acid. The preparation of this acid by the Claisen condensation (29) is superior to the previously used Perkin condensation (6). To 8.7 g. (0.38 g.-atom) of thin slices of sodium, 50 g. (0.30 mole) of veratraldehyde and 150 ml. of ethyl propionate were added at room temperature, with vigorous stirring. The mixture gradually became warm and turbid. After about 1 hour, the flask was transferred to a steam-bath and warmed for 8 hours under reflux, the contents turning to a homogeneous thick brown paste

The next day this was decomposed with ice and dilute acetic acid. After separation of the upper layer, the aqueous layer was extracted with ethyl acetate. The residue of the combined ethyl acetate and ethyl propionate solution was refluxed for 2 hours with a solution of 33 g. of sodium hydroxide in 200 ml. of 60% alcohol. The solution was then diluted with water, extracted subsequently with ether, and acidified with dilute hydrochloric acid. The acid, separating at a low temperature, was collected, and recrystallized while moist from 30 ml. of anhydrous acetic acid. The crude product (34–38 g., 50–56%), small needles of the color of old gold, melts at 135–139°. Recrystallization from alcohol gave pale yellow needles of m.p. 140–141°. Completely colorless material was obtained *via* the methyl ester, melting then at 142–143°. The acid prepared by the Perkin condensation is colorless already as a crude, melting at 141°. In the literature the substance is reported to form colorless needles of m.p. 144° (29) and 141° (30).

The methyl ester forms small colorless flat prisms, m.p. 65–67°.

Anal. Calc'd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8.

Found: C, 66.0; H, 6.8.

α-Methyl-β,β-bis(3,4-dimethoxyphenyl)propionic acid. The formerly recommended procedure (6) was slightly modified. To a mixture of 118 g. (0.5 mole) of the above acid and 620 g. (4.5 moles) of freshly distilled veratrole, vigorously stirred on the steam-bath, 147 g. (1.5 moles) of conc'd sulfuric acid was added by drops (1 hour). Stirring and heating was continued for an additional period of 5 hours, and ice and then a 20% sodium hydroxide solution was added until there was a strong alkaline reaction. Unchanged veratrole (370 g.) was removed by steam-distillation, the mixture being subsequently acidified with conc'd hydrochloric acid while hot. The precipitated dark oil was removed instantly, since soon after sodium veratrole sulfonate separated. The crude could be crystallized from 100 ml. of 50% acetic acid as light tan-colored needles of m.p. 174–175° (90 g., 50%).

It was found advantageous to isolate the acid *via* the methyl ester, since the product was then purer. From above crude oily acid 125 g. (67%) of the readily crystallizing colorless methyl ester was obtained. This was hydrolyzed with 500 ml. of 20% methyl alcoholic potassium hydroxide solution on the steam-bath (6 hours). Water was added, and after removal of the methyl alcohol by distillation, the mixture was cooled and extracted with ether. The yellow solution was filtered, and freed subsequently from dissolved ether on the steam-bath. To the hot solution gradually anhydrous acetic acid was added, until the precipitating oil just dissolved. The product reappears from the hot solution in large, entirely colorless needles, m.p. 177° (115 g., 64%).

The methyl ester. The crude oily acid obtained in above preparation was dissolved in 250 ml. of methyl alcohol, the solution being then saturated with dry hydrogen chloride, under cooling with ice. Next day, the mixture was refluxed for 2 hours. On standing, the product soon separated, forming a solid cake of needles. This was collected and washed on the filter with methyl alcohol until completely colorless. For analysis, the product was recrystallized once from methyl alcohol; stout needles, m.p. 106°.

Anal. Calc'd for $C_{21}H_{26}O_6$: C, 67.4; H, 7.0.

Found: C, 67.6; H, 7.1.

trans-1-(3,4-Dimethoxyphenyl)-2-methyl-5,6-dimethoxyindan-3-one (IV). For the cyclization of above acid, stannic chloride was found to give very satisfactory results (*cf.* 31), being distinctly superior in this particular case to the sulfuric acid (6) or aluminum chloride (7) used previously. To 41 g. (0.2 mole) of phosphorus pentachloride a suspension of 70 g. (0.2 mole) of above acid in 350 ml. of dry benzene was added with cooling. On agitation, a blue-colored solution formed in 15 minutes. This was then warmed to 50° for 10 minutes, and cooled subsequently to 0°. Addition of 52 g. (0.2 mole) of stannic chloride in 50 ml. of benzene precipitated a red-violet semisolid. After about 30 minutes, crushed ice, conc'd hydrochloric acid, and 250 ml. of benzene were added, and the mixture was shaken until all solid dissolved (1 to 2 hours). The benzene layer was then separated and washed consecutively with 10% hydrochloric acid, with water, and with 10% sodium carbonate solution.

Evaporation left a pale yellow oil that readily crystallized from alcohol. The faintly colored crystalline powder, m.p. 116–117°, upon 1 recrystallization from alcohol, gave 47 g. (73%) of large colorless polyhedra, m.p. 118–119°. A solution in anhydrous acetic acid produced no coloration with bromine or with conc'd nitric acid. The product is identical in every respect with catalytically hydrogenated 1-veratryl-2-methyl-5,6-dimethoxy-Δ^1-inden-3-one (V) of m.p. 119–120° (6), while the mixture melts at 118–120°.

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (X). To a vigorously stirred solution, prepared from 4.8 g. (0.2 g.-atom) of magnesium foil and 22 g. (0.2 mole) of ethyl bromide in 100 ml. of ether, 34.2 g. (0.1 mole) of IV in 200 ml. of dry benzene was added at room temperature. The mixture was refluxed for 30 minutes. In order to obtain X, the mixture was then poured into ice-water containing 2% sulfuric acid. The benzene-ether layer was separated, washed with water, dried with sodium sulfate, and evaporated at reduced pressure. Upon dissolving the deep orange-colored oily residue in an equal volume of alcohol, slow crystallization occurred, being completed within a few days after occasional scratching. The product was collected and washed with a little ice-cold alcohol on the filter, 25 g. (70%) of an almost colorless crystalline powder, m.p. 76–78° being obtained. For analysis, a 1-g. sample was recrystallized from alcohol-hexane to give 0.49 g. of fine, cotton-like needles, m.p. 82–83°. A second recrystallization from alcohol gave short colorless prisms, m.p. 83–84°. A solution in anhydrous acetic acid showed (a) on addition of conc'd nitric acid, a deep ruby red (intense green reflex) → emerald green → yellow coloration; and (b) on addition of bromine, an instantly vanishing, but with excess reagent, permanent bluish-green color.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.5; H, 7.4.

Found: C, 74.4, 74.3, 74.6; H, 7.4, 7.6, 7.6.

trans, trans-1-(3,4-Dimethoxyphenyl)-2-methyl-3-hydroxy-3-ethyl-5,6-dimethoxyindan, the oily 3-indanol (IX). The procedure was the same as in the above preparation of X, except that the reaction mixture, after being refluxed, was poured onto a large excess of crushed ice mixed with 10% ammonium chloride solution. Washing the benzene-ether layer thoroughly with ice-water and evaporation under reduced pressure at 40° followed. On dissolving the residue in an equal volume of alcohol the solution remained perfectly clear for weeks. This solution was used directly for hydrogenation experiments.

On prolonged standing some crystallization occurred. The separated material (flat prisms, m.p. 83–84°) proved to be the indene X. Upon adding 0.1, 0.3, and 0.5 ml. of methanolic 20% HCl, respectively, to 2-ml. samples of the clear solution, the extent and velocity of crystallization were found to be directly proportional to the quantity of the acid added.

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindan (I). *The β-racemate* (Iβ). A solution of 18 g. of X in 100 ml. of alcohol, hydrogenated in the presence of 1 g. of a 5% palladium-charcoal catalyst at room temperature and atmospheric pressure, absorbed 1100 ml. of hydrogen in eight hours. From the filtrate, 16.5 g. of colorless needles, m.p. 103–105°, separated. Distillation of the product at 222°/0.06 mm. and subsequent recrystallization from alcohol gave m.p. 106–107° (8).

On concentrating the combined alcoholic mother liquors to 6 ml., the solution gradually became colored and, after several weeks in the ice-box, deposited large, densely packed silky clusters. The product (82 mg.), after four consecutive recrystallizations from alcohol, melted constantly at 104–106°. The melting point of a 1:1 mixture with the β-racemate obtained above was 88–93° (depressed) while a similar mixture with authentic α-racemate of m.p. 105–106° melted at 104–106°. Since the substance gave a distinct violet coloration in the bromine test, one cannot tell whether this results from eventually formed, or still contaminating, α-racemate. It gave the following analysis.

Anal. Calc'd for $C_{22}H_{28}O_4$: C, 74.1; H, 7.9.

Found: C, 74.3, 74.2; H, 8.0, 8.1.

Similar hydrogenation of 1.8-g. (0.005 mole) samples of X in (a) 50 ml. of anhydrous acetic acid, (b) 50 ml. of anhydrous acetic acid containing 2.5 g. of conc'd sulfuric acid, (c)

50 ml. of alcohol containing 2.5 g. of sodium hydroxide, gave 1.4, 1.2, and 1.3 g. respectively, of an easily crystallized β-racemate.

The γ-racemate (Iγ). After dissolving 4 g. of the crude, oily 3-indanol (IX) (as obtained above) in 100 ml. of alcohol, subsequent hydrogenation led to the absorption of 220 ml. of hydrogen in 14 hours. The filtrate was evaporated and the colorless, oily residue was redissolved in 5 ml. of alcohol. In about two hours the solution became a solid mass of translucent polyhedra. Recrystallization from alcohol gave 2.7 g. of colorless, hard cubes, m.p. 101–102°. The m.p. was not depressed by γ-racemate prepared from VIII, or isolated from the crude dimerizate of isohomogenol. Another 0.07 g. of the β-racemate, long needles, m.p. 106°, separated from the mother liquors.

Upon hydrogenating the Δ^2-indene (X) in anhydrous acetic acid containing two molal equivalents of hydrogen bromide, the absorption was greatly retarded and the main product was a bright orange-colored resin, b.p. 220–222°/0.05 mm., which crystallized reluctantly from alcohol. From the crystalline material the γ-racemate was obtained in 20% yield together with the β-racemate, which formed in 8% yield. Hydrogen iodide or hydrogen chloride, although similarly retarding hydrogenation had no similar effect, and the small amount of crystallizable material proved to be almost pure β-racemate.

The relative intensities of the colorations in the bromine test have been measured. From each racemate a 0.125% (0.003 molal) solution in anhydrous acetic acid was prepared. To 15.0 ml. of the solution was added four drops of a 1% solution of bromine in the same solvent, the coloration being examined after five minutes. With the β-racemate, the color instantly developed; with the γ-racemate, color developed only after about one minute; and the α-racemate gave no coloration. The β- and the γ-racemates give between 480 and 620 mμ a single maximum at 560 and 570 mμ, respectively, the ratio of the intensities, β:γ being 1.00:0.46.

Chromic acid oxidation of the indan I racemates. Parallel oxidations have been made with 3.56-g. (0.01 mole) samples of the racemates Iα, Iβ, and Iγ, respectively. The sample was dissolved in 40 ml. of anhydrous acetic acid and, with ice-cooling and vigorous stirring, a solution of 2.4 g. of chromium trioxide (representing 3.5 g.-atom of active oxygen per mole) in 4.0 ml. of water and 20.0 ml. of anhydrous acetic acid was dropped in over a 60-minute period. After being kept at room temperature for 24 hours, the mixture was poured into 400 ml. of water, then extracted four times with a total of 200 ml. of ether. The orange-colored extract, washed twice with water, twice with 5% sodium carbonate solution, dried with magnesium sulfate, and evaporated on the steam-bath, left a quickly solidifying residue. This was redissolved in 25.0 ml. of ethyl acetate and the separated material was collected after 24 hours and washed on the filter with 10.0 ml. of ice-cold alcohol. Recrystallization from 20.0 ml. of ethyl acetate followed, and the stout, colorless cubes of 3,3′,4,4′-tetramethoxy-6-α-acetopropylbenzophenone (III) were examined.

FROM 3.56 G. OF	YIELD OF III, G.	M.P., °C.	FOUND	
			C	H
I	1.86	156–157	68.4	7.1
I	1.92	156–157	68.3	6.9
I	1.79	156–156.5	68.3	6.9
Calc'd for $C_{22}H_{26}O_6$			68.4	6.8

No depression was observed in the melting point upon mixing the oxidation products. The semicarbazone and the naphtholic dehydration product had in all three cases the melting points 197–198° and 175°, respectively.

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SUMMARY

The epimeric inter-relationships of the three presently known diastereoisomeric racemates of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindan have been established. For diisohomogenol the *trans,trans* racemic configuration is suggested.

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REFERENCES

(1) Part III, Müller and Horváth, *Ber.*, **76**, 855 (1943); Part VII, Müller and Richter, *Ber.*, **77**, 12 (1944); Part VIII, Müller, *Ber.*, **77**, 159 (1944); *Cf.* Pailer, U. Müller, and Porschinski, *Monatsh.*, **79**, 620 (1948).

(2) von E. Doering and Berson, *J. Am. Chem. Soc.*, **72**, 1118 (1950).

(3) *Cf.* Part I, Müller, Raltschewa, and Papp, *Ber.*, **75**, 692 (1942).

(4) Denozza, *Gazz. chim. ital.*, **23**, 556 (1893); Széki, *Ber.*, **39**, 2422 (1906); Francesconi and Puxeddu, *Gazz. chim. ital.*, **39**, 202 (1909); Haworth and Mavin, J. *Chem. Soc.*, 1363 (1931); Puxeddu and Rattu, *Gazz. chim. ital.*, **66**, 700 (1936); *Cf.* Glichitch, *Bull. soc. chim.*, [4], **35**, 1162 (1924); van Duin, *Rec. trav. chim.*, **45**, 351 (1926); Kovács, *J. Org. Chem.*, **15**, 15 (1950).

(5) Part V, Müller and Richl, *Ber.*, **76**, 1119 (1943); *Cf.* Erdmann, *Ann.*, **227**, 249 (1885).

(6) Part X, Müller and Gal, *Ber.*, **77**, 343 (1944).

(7) Cartwright and Haworth, *J. Chem. Soc.*, 1094 (1947).

(8) Part XII, Müller, Toldy, Halmi, and Mészáros, *J. Org. Chem.*, **16**, 481 (1951).

(9) Haraszti and Széki, *Ann.*, **503**, 204 (1933); *Cf. Ann.*, **507**, 197 (1933).

(10) Funakubo, *Ber.*, **74**, 832 (1941).

(11) *Cf.* Boedecker and Volk, *Ber.*, **64**, 61 (1931).

(12) Ciamician and Silber, *Ber.*, **42**, 1390 (1909); *Cf.* Bruckner, *Ber.*, **75**, 2034 (1942).

(13) *Cf.* Weidlich in Criegee, *Katalyse in der Organischen Chemie*, Springer Verlag, Vienna, 1943, pp. 749, 757.

(14) van der Zanden and de Vries, *Rec. trav. chim.*, **68**, 261, 407 (1949).

(15) Part XIII, Müller, Mészáros, Lempert-Sréter, and Szára, *J. Org. Chem.*, **16**, 1003 (1951).

(16) *Cf.* Weidlich and Meyer-Delius, *Ber.*, **74**, 1195, 1213 (1941).

(17) *Cf.* Hückel, *Theoretische Grundlagen der organischen Chemie*, 3rd edition, Vol. 1, p. 282–284, Akademische Verlagsgesellschaft, Leipzig, 1940.

(18) Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J. Chem. Soc.*, 2093 (1948) (See especially p. 2117); *Cf.* Müller, Móricz, and Verner, *Ber.*, **72**, 745 (1939); Price and Karabinos, *J. Am. Chem. Soc.*, **62**, 1159 (1940); Cristol, *J. Am. Chem. Soc.*, **69**, 338 (1947); Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, New York, 1950, p. 118.

(19) Whitmore and Meunier, *J. Am. Chem. Soc.*, **55**, 3721 (1933); Whitmore and Fleming, *J. Chem. Soc.*, 1269 (1934); Whitmore, Wittle, and Popkin, *J. Am. Chem., Soc.*, **61**, 1581 (1939).

(20) Bartlett and Brown, *J. Am. Chem. Soc.*, **62**, 2927 (1940).

(21) Wheland, *Advanced Organic Chemistry*, 2nd edition, John Wiley & Sons, New York, 1949, pp. 451–534.

(22) Swain, *J. Am. Chem. Soc.*, **70**, 1119 (1948) (especially p. 1126); Swain and Eddy, *J. Am. Chem. Soc.*, **70**, 2989 (1948) (especially p. 2991; *Cf.* (24).

(23) Wallis and Bowman, *J. Org. Chem.*, **1,** 383 (1936).

(24) Cram, *J. Am. Chem. Soc.*, **71,** 3863 (1949).

(25) Bartlett and Knox, *J. Am. Chem. Soc.*, **61,** 3184 (1939).

(26) Cowdrey, Hughes, Ingold, Masterman, and Scott, *J. Chem. Soc.*, 1252 (1937); See however, Meer and Polanyi, *Z. physik. Chem.*, [B]**19,** 164 (1932); *Cf.* Hückel, ref. (17), Vol. 1, p. 399.

(27) Ciamician and Silber, *Ber.*, **23,** 1165 (1890); Hell and Portmann, *Ber.*, **28,** 2090 (1895).

(28) von Wacek, *Ber.*, **77,** 85 (1944).

(29) Ide and Buck, *J. Am. Chem. Soc.*, **62,** 425 (1940).

(30) Tiemann and Kraaz, *Ber.*, **15,** 2070 (1882).

(31) *Cf.* Feeman and Amstutz, *J. Am. Chem. Soc.*, **72,** 1526 (1950).