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

DIMERIC PROPENYL PHENOL ETHERS. XII.[1] THE SYNTHETIC STEREOISOMER OF DIISOHOMOGENOL, DIISOEUGENOL DIETHYL ETHER, AND METANETHOLE

ALEXANDER MÜLLER, LAJOS TOLDY, GÁBOR HALMI, AND MIOMIR MÉSZÁROS

Received August 16, 1949

The synthesis of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindan (Ia) (1) from 1-veratryl-2-methyl-5,6-dimethoxy-Δ^1-inden-3-one (IIa)—by reaction of the latter with ethylmagnesium bromide and subsequent reduction of the resulting intermediate—produced a substance that strongly resembles diisohomogenol of m.p. 106°. Cartwright and Haworth (2), having prepared the same compound from 1-veratryl-2-methyl-5,6-dimethoxyindan-3-one by the same method, find that diisohomogenol of m.p. 106° (3) and synthetic indan Ia are not identical, as the melting point of a mixture of the two substances shows considerable depression. In demonstration that the synthetic indan is an isomer of individual existence, and not a crystal modification of diisohomogenol of m.p. 106°, the substance reappears unchanged after prolonged refluxing with methanolic hydrogen chloride. Structural isomerism appearing in the light of our investigations on the structure of diisohomogenol (4, 5) improbable, the difference between the two substances was attributed to stereoisomerism. Confirming the statements of above authors, we find now in addition that the synthetic stereoisomer gives—in contradistinction to diisohomogenol of m.p. 106°—an instantly developing color reaction with bromine in glacial acetic acid.

Diisohomogenol—like diisochavibetol (6)—has been reported to exist in several forms (7, 8), although the interrelation of these forms is not exactly known. Crude diisohomogenol, as obtained in usual acid-catalyzed dimerizations of isohomogenol, is apparently a mixture of closely related forms which has to be recrystallized several times until the melting point will rise to 106°, while the crude dimerizate of isoeugenol is more uniform, yielding on one recrystallization from alcohol pure diisoeugenol of m.p. 180–181°. So we became interested in the question, whether in an analogous synthesis of a 1-(3-methoxy-4-ethoxyphenyl)-2-methyl-3-ethyl-5-methoxy-6-ethoxyindan (Ib) the known form of m.p. 131° (9) or a hitherto unknown isomer of diisoeugenol diethyl ether will arise. Should the latter unpredictable situation be the case it would be a further demonstration that the above synthetic method leads to a stereoisomer different from that resulting from dimerization. The difference between dimerization and synthesis in respect to stereospecificity might be even indicative of the actual configurations of the respective products.

We have prepared 1-(3-methoxy-4-ethoxyphenyl)-2-methyl-5-methoxy-6-ethoxy-Δ^1-inden-3-one (IIb) by oxidative degradation of diisoeugenol diethyl ether, since the alternative of a synthesis promised to be tedious and impractical. The degradation of diisohomogenol has been studied extensively in previous papers

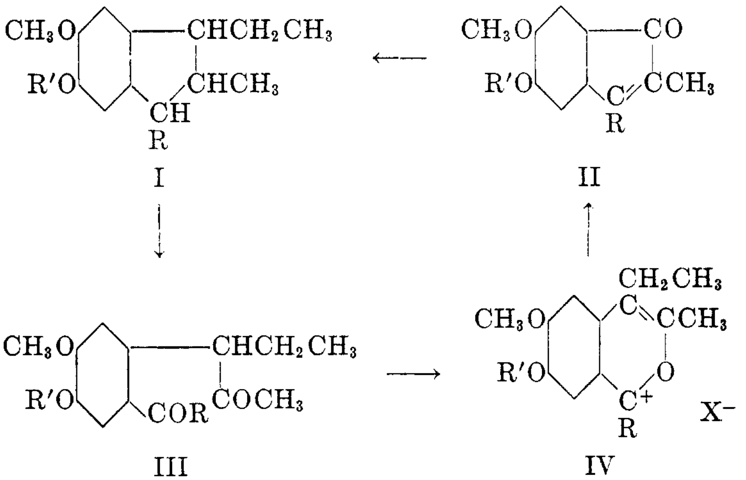
---

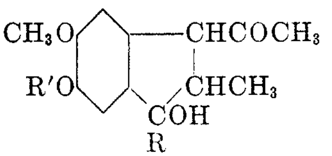
[1] Preceding paper, Part XI, *J. Org. Chem.*, **12**, 815 (1947).

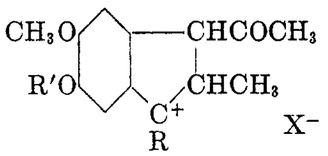
(4, 5, 10). In the light of a report just published by von Doering and Berson (11), the previous formulation of the primary product of the oxidation with chromic acid, as a hydroxyketodiisohomogenol of the structure III′, requires correction.[2] These authors offer conclusive evidence that oxidation will cleave the alicyclic ring of diisohomogenol in the initial phase, the primary product being a diketone of structure IIIa that would form with mineral acids isobenzopyrylium (IVa) (12), rather than as we have been formulating the reaction (13), indanium (IV′) salts.

The chromic acid oxidation of diisoeugenol diethyl ether is, as would be expected, entirely analogous to that of diisohomogenol and results in the formation of an α-[6-(3-methoxy-4-ethoxybenzoyl)-3-methoxy-4-ethoxyphenyl] propyl methyl ketone (IIIb). This was oxidized with permanganate in the form of its water-soluble isobenzopyrylium salt formed with sulfuric acid. The product was found to be a mixture of related substances that, on being treated with warm methanolic alkali, yields directly the expected indenone IIb. The latter forms a phenylhydrazone and gives on oxidation a mixture of 6-pyruvyl-3′,4-dimethoxy-3,4′-diethoxybenzophenone and 2-(3-methoxy-4-ethoxybenzoyl)-4-ethoxy-5-methoxybenzoic acid.

In the reaction with ethylmagnesium bromide, indenone IIb gave an oily




III′


IV′

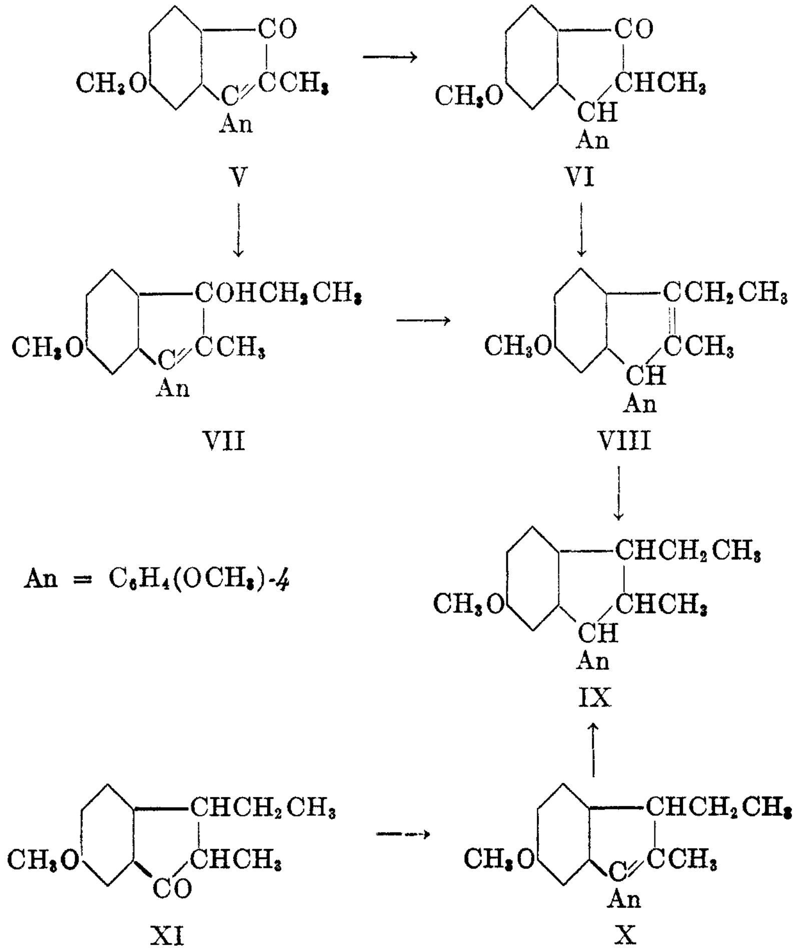
a. $R = C_6H_3(OCH_3)_2\text{-}3,4,\ R' = CH_3$
b. $R = C_6H_3(OCH_3)\text{-}3\text{-}(OC_2H_5)\text{-}4,\ R' = C_2H_5$

---

[2] Structural reinvestigation of the degradation products of diisohomogenol is under progress and will be the subject of a subsequent paper.

indenol that produced on subsequent hydrogenation a 1-(3-methoxy-4-ethoxyphenyl)-2-methyl-3-ethyl-5-methoxy-6-ethoxyindan (Ib) of m.p. 115.5° which is definitively different from diisoeugenol diethyl ether. The synthetic product also exhibits a purple-violet coloration with a dilute solution of bromine in glacial acetic acid. Oxidation with chromic acid produced IIIb, excluding thereby a possible 1,4-addition of the Grignard reagent to IIb in the synthesis, and definitively establishing the stereoisomeric interrelation of synthetic Ib and diisoeugenol diethyl ether.

The formation of a similar stereoisomer has been reported recently by van der Zanden and de Vries (14) in the attempted synthesis of metanethole. 1-*p*-Anisyl-2-methyl-3-ethyl-6-methoxyindan (IX) was prepared from 1-*p*-anisyl-2-methyl-6-methoxyindanone (VI) with ethylmagnesium bromide and subsequent hydrogenation of the resulting Δ^2-indene VIII. An identical product was obtained when 2-methyl-3-ethyl-6-methoxyindanone (XI) was treated with *p*-anisyl magnesium bromide and the resulting Δ^1-indene X was hydrogenated. The samples



were found in both instances to melt at 99°, alone or mixed with each other, and to reappear unchanged from saturated solutions, or the melt, previously seeded with crystals of metanethole of m.p. 135°.

We can confirm this observation, having obtained the same indan in 1944 (15), when a synthesis of the neutral oxidation products of metanethole (16) was undertaken and then extended to an eventual synthesis of metanethole itself. Our method was only a slight variance with one of the routes indicated by van der Zanden and de Vries. From synthetic 1-*p*-anisyl-2-methyl-6-methoxy-Δ^1-inden-3-one (V) and ethylmagnesium bromide an oily indenol VII was obtained that was hydrogenated directly, without isolation of intermediate VIII, to indan X. The product had m.p. 100–101°. The same metanethole isomer was observed also in the hydrogenation of 1-*p*-anisyl-2-methyl-3-ethyl-6-methoxy-Δ^1-indene (X). The substance fails to give a color reaction with bromine.

There can be little doubt that diisohomogenol of m.p. 106°, diisoeugenol diethyl ether of m.p. 131°, and metanethole of m.p. 135°, judging from the analogous way of their formation, represent identical configurations of a 1-phenyl-2-methyl-3-ethylindan structure. The same applies to the synthetic indans Ia, Ib, and IX which represent one other, in all three cases likewise identical, racemic configuration of the same structure.

As to which of the four theoretically possible racemates corresponds to the form arising in dimerization (α-form) and to that obtained by the present synthetic method (β-form), the present information and the experiences in the stereochemistry of hydrogen addition in other fields (17) offer no reliable answer. However, it will be recognized that the last step of the synthesis will be responsible for the configurational difference between the α- and the β-racemates. The addition of hydrogen to the Δ^2-indene precursor (or, as in the case of IX, to the Δ^1-indene) is under the described conditions highly stereospecific and leads uniformly to a configuration of the resulting indan that is characteristically different from that represented by the, likewise stereospecifically formed, dimerizates.

The question is under further investigation.

EXPERIMENTAL

THE STEREOISOMER OF DIISOHOMOGENOL. IMPROVED SYNTHESIS (1)

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxy-Δ^1-inden-3-ol. A solution of 8 g. (0.022 mole) of 1-(3,4-dimethoxyphenyl)-2-methyl-5,6-dimethoxy-Δ^1-inden-3-one (IIa) (1, 5) in 150 ml. of anhydrous dioxane was run while still warm into a solution prepared from 1.6 g. (0.066 g.-atom) of magnesium foil and 8 g. (0.066 mole) of ethyl bromide in 70 ml. of ether. Instant decoloration and formation of a colorless precipitate followed. After 40 minutes' refluxing, the mixture was poured into ice-water containing 10 g. of ammonium chloride, extracted with several portions of ether, and the combined extracts were washed with water, dried over calcium chloride, and evaporated. The remaining pale yellow oil, mixed with 2 ml. of alcohol and left standing overnight at room temperature, partly crystallized. The solid was twice recrystallized from ethyl acetate-petroleum ether, yielding 1.6 g. (18%) of colorless needles, m.p. 128°. [Previously, on material not recrystallized the low m.p. 75–76° was observed (1).] The solution in glacial acetic acid acquires a purple violet color on addition of bromine.

Anal. Calc'd for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1.
Found: C, 71.6, 71.5; H, 7.5, 7.6.

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindan (Ia), β-form. For the preparation of this compound the above indenol was not isolated, the product of the Grignard reaction having been dissolved in 120 ml. of alcohol and then hydrogenated at atmospheric pressure, in the presence of 0.6 g. of a not particularly active 10% palladium-charcoal catalyst and a few drops of a 10% palladous chloride solution. In four hours 900 ml. of hydrogen was absorbed. The solution, which deposited crystals overnight, was warmed to boiling, filtered, and evaporated. The semisolid residue readily crystallized from alcohol. Two subsequent recrystallizations gave 2.7 g. (31%) of long colorless needles, m.p. 105–106°. A 1:1 mixture with a sample prepared by Cartwright and Haworth (2) from 1-(3,4-dimethoxyphenyl)-2-methyl-5,6-dimethoxyindan-3-one[3] was found to be melting likewise at 105–106°.

Anal. Calc'd for $C_{22}H_{28}O_4$: C, 74.1; H, 7.9.
Found: C, 74.3; H, 8.1.

The substance crystallizes from saturated alcoholic solutions in separate or loosely aggregated lancets, while Széki's diisohomogenol of m.p. 106° forms compact clusters of very fine long needles. The melting point suffers depression on 1:1 admixture of (*a*) diisohomogenol of m.p. 106°, to 90–95°, (*b*) diisohomogenol of m.p. 94–96°, to 78–88°, (*c*) diisohomogenol isomer of m.p. 100–101°, to 88–100°. A 1% solution in glacial acetic acid turns purple violet on addition of a 5% solution of bromine in the same solvent, the color appearing dark blue in a thin layer and fading away on standing. From a solution of 1 g. of the substance in 30 ml. of methyl alcohol containing 20% dry hydrogen chloride, and refluxed for two hours, 0.9 g. of unchanged material was recovered [*cf.* (2)].

1-(6-Bromo-3,4-dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindan, β-form. To a solution of 0.2 g. of above indan (Ia) in 10 ml. of ether, 10 ml. of a 10% solution of bromine in ether was added by drops. After the first few drops the mixture acquired a purple-violet color (the same coloration being observed in a parallel bromination of a sample of Ia prepared by Cartwright and Haworth, while diisohomogenol gave no color reaction under the same conditions). After 30 minutes at room-temperature, the solution was shaken with a 10% sodium hydrogen sulfite solution, dried with calcium chloride, and evaporated. The colorless oily residue was crystallized from alcohol, two consecutive recrystallizations yielding 0.18 g. of stout colorless prisms, m.p. 125–126°. A 1:1 mixture with bromodiisohomogenol of m.p. 126° had m.p. 102–105°.

Anal. Calc'd for $C_{22}H_{27}BrO_4$: C, 60.7; H, 6.3.
Found: C 60.8, 60.8; H, 6.6, 6.3.

THE STEREOISOMER OF DIISOEUGENOL DIETHYL ETHER

3-Methoxy-4-ethoxy-α-methylcinnamic acid. A mixture of 7.5 g. of vanillin ethyl ether (18), 5.6 g. of propionic anhydride, and 3.7 g. of anhydrous sodium acetate was warmed to 180–190° under reflux for 24 hours and then extracted with a warm 10% sodium carbonate solution. The filtered extract on acidification with 20% hydrochloric acid gave a crystalline solid. Recrystallization from alcohol produced 3.4 g. of colorless needles, m.p. 131–132°.

Anal. Calc'd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8; Neut. equiv., 236.
Found: C, 65.9; H, 7.1; Neut. equiv., 242, 235.

Diisoeugenol diethyl ether (The α-form of Ib). (*a*) A mixture of 3 g. of the foregoing acid, 30 ml. of water, and 15 ml. of conc'd sulfuric acid was kept boiling under reflux and stirred energetically for two hours. The supernatant oil solidified on cooling; it was washed with water and dried at room temperature. Recrystallization from ethyl acetate-alcohol gave 2.2 g. of fibrous colorless needles, m.p. 130°. (*b*) Diisoeugenol of m.p. 180–181° was ethylated

---

[3] We are indebted to Professor R. D. Haworth for a specimen of this substance, kindly sent over for direct comparison.

with ethyl bromide and alkali (9) and the product twice recrystallized from ethyl acetate-alcohol; m.p. 130–131°, alone or mixed with a sample prepared by method (*a*).

α-[6-(3-Methoxy-4-ethoxybenzoyl)-3-methoxy-4-ethoxyphenyl]propyl methyl ketone (IIIb). Eighty grams of diisoeugenol diethyl ether (9) was dissolved on the water-bath in 400 ml. of glacial acetic acid and then cooled under stirring to room temperature. With cooling and vigorous stirring a solution of 133 g. of sodium dichromate dihydrate (corresponding to 6 g.-atom of active oxygen per mole) in a mixture of 60 ml. of water, 260 ml. of glacial acetic acid, and 21 ml. of conc'd sulfuric acid was added by drops in about 60 minutes. Stirring was continued for another six hours. After standing at room temperature for two days, the mixture was poured into 4 liters of water. Repeated extractions with benzene followed. The deep orange-colored extract was washed consecutively with water, with 5% sodium carbonate solution, and again with water, then dried over calcium chloride and evaporated, finally under reduced pressure. The quickly solidifying residue crystallized from a mixture of 150 ml. of ethyl acetate and 150 ml. of alcohol. After two days, 52 g. of crystalline material, m.p. 144–145°, was collected, the mother-liquor containing about 10 g. of uncharacterized, slowly crystallizing oxidation products.

Recrystallization of the first crop of crystals from ethyl acetate produced 40 g. of colorless spheroids, m.p. 148°. The substance dissolves in warm alcoholic sodium hydroxide with a pale yellow coloration. Its solution in alcohol or in chloroform is faintly yellow, in glacial acetic acid pale yellow, turning to orange on addition of methanolic hydrogen chloride. From a solution in pyridine-acetic anhydride 1:1, kept at room temperature for two days or warmed on the water-bath for two hours, unchanged material was recovered.

Anal. Calc'd for $C_{24}H_{30}O_6$: C, 69.5; H, 7.3.
Found: C, 69.5, 69.5; H, 7.2, 7.3.

1-(3-Methoxy-4-ethoxyphenyl)-3-methyl-4-ethyl-6-methoxy-7-ethoxyisoquinoline N-oxide. A solution of 2 g. of IIIb in 5 ml. of dry pyridine was mixed with 0.4 g. of hydroxylamine hydrochloride, and kept on the water-bath for 30 minutes. On successive dilution with water a product of light blue color separated from the dark green solution. This was recrystallized from 50% alcohol, yielding 0.8 g. of a faintly colored crystalline powder, m.p. 143–144°.

Anal. Calc'd for $C_{24}H_{29}NO_5$: N, 3.0. Found: N, 3.3, 3.2.

1-(3-Methoxy-4-ethoxyphenyl)-4-ethyl-6-methoxy-7-ethoxy-3-naphthol. A solution of 1.5 g. of IIIb in 30 ml. of alcohol was mixed with 15 ml. of 20% aqueous sodium hydroxide, and warmed on the water-bath for ten minutes. The yellow solution was then diluted with water until incipient turbidity and acidified with 3 ml. of conc'd hydrochloric acid. After standing, the oily precipitate solidified to a mass of crystals. Recrystallization from dilute alcohol or from ethyl acetate-petroleum ether gave 1.2 g. of slightly colored plates, m.p. 143°. The colorless solution in glacial acetic acid turns to deep red-brown when mixed with conc'd sulfuric acid.

Anal. Calc'd for $C_{24}H_{28}O_5$: C, 72.7; H, 7.1.
Found: C, 72.9, 73.0; H, 7.4, 7.2.

The *picrate* was prepared by dissolving 0.2 g. of the naphthol derivative in 3 ml. of a saturated alcoholic solution of picric acid; instantly separating long brown-violet needles, m.p. 143–144° (0.25 g.).

Anal. Calc'd for $C_{24}H_{28}O_5 \cdot C_6H_3N_3O_6$: N, 6.9. Found: N, 6.6, 6.7.

1-(3-Methoxy-4-ethoxyphenyl)-3-methyl-4-ethyl-6-methoxy-7-ethoxyisobenzopyrylium hydrogen sulfate (IVb). Thirty-one grams of IIIb, m.p. 144–145°, was dissolved on the water-bath in a mixture of 30 ml. of glacial acetic acid and 10 ml. of conc'd sulfuric acid. The dark orange solution was heated for an additional period of ten minutes, during which 100 ml. of ethyl acetate was added. Crystallization of the warm mixture was completed by cooling in ice-water. The crude salt was washed with alcohol and recrystallized from 100 ml. of alcohol with the gradual addition of 100 ml. of ethyl acetate. Golden-yellow needles, m.p. 227–228° (28 g). The salt is readily soluble in water. With crude material turbid solutions are obtained, the insoluble part being chiefly the indenone IIb (about 3–4 g).

Anal. Calc'd for $C_{24}H_{29}O_5 \cdot HSO_4$: H_2SO_4, 19.6. Found: H_2SO_4, 20.4, 20.5.

A clear, or if necessary filtered solution of 0.75 g. of IVb in 30 ml. of water was warmed on the water-bath for two hours. The separating crystalline solid was removed from time to time; total, 0.45 g. Recrystallization from 8 ml. of alcohol produced 0.39 g. of large colorless spheroids of IIIb, melting at 148°, alone or mixed with a sample directly obtained from diisoeugenol diethyl ether. Another way of preparing very pure IIIb is warming IVb with an equal weight of crystalline sodium acetate in glacial acetic acid.

Anal. Calc'd for $C_{24}H_{30}O_6$: C, 69.5; H, 7.3.

Found: C, 69.5, 69.6; H, 7.3, 7.3.

The *nitrate* was prepared by adding 10% nitric acid by drops to a 5% solution of the hydrogen sulfate IVb in water. Orange-yellow clusters immediately separated. These were washed with water and air-dried. When recrystallized from alcohol, the orange clusters reappear and must be removed from the mixture within a few minutes; silky needles, m.p. 121–122°. On standing with the mother liquor, the crystals change their color, without apparent major change in composition, to bright yellow, forming silky needles of m.p. 123°.

Anal. Calc'd for $C_{24}H_{29}O_5 \cdot NO_3$, N, 3.0; NO_3, 13.5.

Found: (a) N, 2.7 (micro-Dumas); NO_3, 13.5, 13.3 (titrimetric). (b) N, 2.6 (micro-Dumas); NO_3, 13.2 (titrimetric).

(a) = sample of orange needles (recrystallized from alcohol). (b) = sample of yellow needles.

1-(3-Methoxy-4-ethoxyphenyl)-2-methyl-5-methoxy-6-ethoxy-Δ^1*-inden-3-one* (IIb). To a solution of 20 g. of IVb, m.p. 227°, in 300 ml. of water, 25 g. of potassium permanganate in 600 ml. of water was added by drops at room temperature, with vigorous stirring. Addition was regulated so that no appreciable excess of oxidant was present in the reaction mixture. Initially yellow flakes of the manganate salt separated that gradually turned to brown as the oxidation proceeded. The reaction was considered to be complete when a filtered sample remained crimson red after ten minutes' standing. Then the managanese dioxide was dissolved by the dropwise addition of a 40% sodium hydrogen sulfite solution. A tan-colored substance remained undissolved; it was washed with water, transferred to a separatory-funnel and dissolved by shaking in a mixture of 150 ml. of benzene and 100 ml. of 5% hydrochloric acid. The yellow benzene layer was washed with water, with 10% sodium carbonate solution, and again with water. Freed from the solvent, the quickly solidifying residue slowly crystallized from 50 ml. of alcohol, yielding 2.4–3.2 g. of a faintly colored substance of indefinite melting point 125–140°. [Acidification of the sodium carbonate washings gave an oily precipitate that was isolated by extraction with chloroform and crystallized from toluene: slightly colored needles, m.p. 193°, of 3-methoxy-4-ethoxybenzoic acid (19)].

For the preparation of IIb the above crude oxidation product was used without further purification. (*a*) Eight grams of the substance was dissolved in 30 ml. of ethyl acetate containing 10% dry hydrogen chloride. On gentle warming on the water-bath, a cherry-red solution was obtained that solidified on subsequent cooling to a thick paste of crystals. After the addition of 30 ml. of alcohol, the solid was removed and washed several times alternately with alcohol and with water and was finally recrystallized from 150 ml. of alcohol, yielding 4.5 g. of thin red needles, m.p. 132–133°. (*b*) On dissolving 4 g. of the crude oxidation product in 50 ml. of 5% methanolic sodium hydroxide on the water-bath, in 10 minutes a red-brown solution was obtained. This solidified, when brought to room temperature, to a mass of crystals that was washed as above, yielding 2.05 g. of red needles, m.p. 130–131°. Two consecutive recrystallizations from about a fifty-fold weight of alcohol produced big clusters of long slender needles, m.p. 135°, that are cherry-red while moist and a dull red-brown color when completely dry.

Anal. Calc'd for $C_{22}H_{24}O_5$: C, 71.7; H, 6.6.

Found: C, 71.6, 71.8; H, 6.9, 6.9.

The phenylhydrazone, from 0.5 g. of IIb and 1 ml. of phenylhydrazine in 5 ml. of alcohol containing two drops of glacial acetic acid, forms bright orange prisms of m.p. 188° (from *n*-butyl alcohol); yield, 0.65 g.

Anal. Calc'd for $C_{28}H_{30}N_2O_4$: N, 6.1. Found: N, 6.2, 6.1.

6-Pyruvyl-3',4-dimethoxy-3,4'-diethoxybenzophenone. A solution of 3.5 g. of IIb in 60 ml. of glacial acetic acid was mixed with cooling with a solution of 2.3 g. of chromium trioxide in 5 ml. of water and 40 ml. of glacial acetic acid. After ten minutes at room-temperature, the mixture was warmed on the water-bath for 15 minutes, diluted with 300 ml. of water, and extracted several times with a total of 250 ml. of benzene. The extract was washed with 10% sodium carbonate solution and freed from the solvent. The pale yellow solid residue (2.6 g.) obtained was recrystallized from *n*-butyl alcohol; long yellow lancets, m.p. 173–174° (cherry-red).

Anal. Calc'd for $C_{22}H_{24}O_7$: 66.0; H, 6.0.
Found: C, 66.3; H, 6.3.

The quinoxaline derivative, prepared from a mixture of 0.5 g. of above product and 0.5 g. of *o*-phenylene diamine in 5 ml. of glacial acetic acid by warming on the water-bath for 30 minutes and subsequent dilution with 5 ml. of alcohol, formed a mass of interlacing fine yellow needles. After one recrystallization from ethyl acetate, 0.3 g. of golden yellow silky needles, m.p. 217–219°, were obtained.

Anal. Calc'd for $C_{28}H_{28}N_2O_5$: N, 5.9. Found: N, 5.2, 5.5.

2-(3-Methoxy-4-ethoxybenzoyl)-4-ethoxy-5-methoxybenzoic acid. To a suspension of 0.5 g. of the foregoing benzophenone in 100 ml. of 20% sodium hydroxide was added 5 ml. of a 20% solution of hydrogen peroxide. The mixture was shaken until practically all solid dissolved. Acidification of the filtrate with dilute hydrochloric acid gave a voluminous flocky precipitate that was recrystallized from alcohol, yielding 0.36 g. of stout colorless prisms, m.p. 215°. The same acid was isolated also from the sodium carbonate washings obtained in the above preparation of the foregoing benzophenone: 0.4 g. of small slightly colored prisms, m.p. 213–214°, alone or mixed with the sample obtained with hydrogen peroxide (20).

Anal. Calc'd for $C_{21}H_{22}O_8$: Neut., equiv. 402. Found: Neut. equiv., 394, 396.

1-(3-Methoxy-4-ethoxyphenyl)-2-methyl-3-ethyl-5-methoxy-6-ethoxyindan (Ib), β-form. Adding 8 g. (0.022 mole) of indenone IIb in 120 ml. of warm anhydrous dioxane to a solution prepared from 1.7 g. (0.07 g.-atom) of magnesium turnings and 8 g. (0.07 mole) of ethyl bromide in 70 ml. of ether, produced a rather energetic reaction with the formation of a tan-colored precipitate. The mixture was refluxed for one hour on the water-bath, poured into ice-water containing 10 g. of ammonium chloride, and extracted repeatedly with a total of 400 ml. of ether. The extract, washed with water and dried over calcium chloride, on evaporation left an orange-colored oil containing minute amounts of a colorless solid. The latter was removed by dissolving the oil in 120 ml. of alcohol and filtration. The filtrate absorbed, in the presence of 1 g. of a 5% palladium-charcoal catalyst and a few drops of 10% palladous chloride solution, 810 ml. of hydrogen at atmospheric pressure, with simultaneous separation of long colorless needles. The solution was warmed to boiling, filtered, and evaporated. Recrystallization of the solid residue from alcohol (charcoal) gave 3.2 g. (39%) of slender prisms that, after two recrystallizations from ethyl acetate-alcohol, had m.p. 115.5°. A 1:1 mixture with diisoeugenol diethyl ether of m.p. 131° melted at 107–108°.

Anal. Calc'd for $C_{24}H_{32}O_4$: C, 75.0: H, 8.4.
Found: C, 74.7, 74.9; H, 8.5, 8.6.

A 1% solution of the substance in glacial acetic acid acquires purple-violet color on addition of a dilute solution of bromine in the same solvent. The color fades away in a few minutes, returning on further addition of bromine and changing finally to green and then to red-brown.

The substance (0.5 g.) was oxidized with sodium dichromate dihydrate and conc'd sulfuric acid in glacial acetic acid, as described above for the stereoisomeride of m.p. 131°, 0.2 g. of IIIb, colorless plates of m.p. 147–148° being obtained. No depression with IIIb prepared from diisoeugenol diethyl ether.

1-(6-Bromo-3-methoxy-4-ethoxyphenyl)-2-methyl-3-ethyl-5-methoxy-6-ethoxyindan, β-form. To a solution of 0.5 g. of above synthetic indan Ib in 50 ml. of ether, 0.10 ml. of bromine in

30 ml. of ether was added. The solution turned greenish blue with intense blue reflection (diisoeugenol diethyl ether gives under the same conditions light yellow solutions). After 30 minutes at room-temperature, the solution was washed with 5% sodium hydrogen sulfite solution, dried with calcium chloride, evaporated, and the residue crystallized from alcohol; colorless plates, m.p. 111°. A 1:1 mixture with bromodiisoeugenol diethyl ether, m.p. 116° (9), melts at 101–102°.

Anal. Calc'd for $C_{24}H_{31}BrO_4$: C, 62.2; H, 6.7.
Found: C, 62.1, 61.9; H, 7.0, 6.8.

THE STEREOISOMER OF METANETHOLE

1-p-Anisyl-2-methyl-3-ethyl-6-methoxyindan (IX), *β-form.* (a) *From 1-p-Anisyl-2-methyl-6-methoxy-Δ¹-indenone* (V). To a chilled solution, prepared from 0.36 g. (0.015 g.-atom) of magnesium turnings and 1.6 g. (0.015 mole) of ethyl bromide in 25 ml. of ether, 2.0 g. (0.007 mole) of twice recrystallized and finely powdered solid V was added. Instant solution, with formation of a colorless precipitate, followed. The mixture was poured without delay into ice-cold 1% ammonium chloride solution and was repeatedly extracted with ether. The extract, washed with ammonium chloride solution and with water, dried with calcium chloride, left on evaporation a pale yellow oil. This was dissolved in 50 ml. of alcohol and hydrogenated at atmospheric pressure in the presence of 0.3 g. of 5% palladium-charcoal catalyst to absorb 175 ml. of hydrogen in about 90 minutes. Evaporation of the filtered solution left a colorless oil readily crystallizing from 4 ml. of alcohol. Recrystallized twice from alcohol and once from glacial acetic acid, gave m.p. 98–99° and then 100–101°; yield, 1.2 g. (57%) of long colorless needles. (b) *From 2-methyl-3-ethyl-6-methoxyindanone* (XI). The starting material was prepared by essentially the method of van der Zanden and de Vries (14, 21). Addition of 18 g. (0.09 mole) of the pale yellow oil, b.p. 164–165°/14 mm., dissolved in 100 ml. of ether, to a solution prepared from 4.8 g. (0.2 g.-atom) of magnesium turnings and 37.4 g. (0.2 mole) of *p*-bromoanisole in 200 ml. of ether, caused a dark oil to separate. After ten minutes at room temperature, the mixture was poured into ice-cold 2% hydrochloric acid and was repeatedly extracted with ethyl acetate. The extract, washed with 1% hydrochloric acid and with water, left on evaporation an oily residue. From this a partly crystallizing pale yellow oil of b.p. 160–170°/0.01 mm. was isolated by distillation. On dissolving this product in 100 ml. of alcohol, 0.9 g. of thin colorless plates of *p,p'*-dianisyl (22), m.p. 174–176°, separated and were removed. The substance subsequently crystallizing from the filtrate had m.p. 64–66°. Two consecutive recrystallizations from alcohol raised the melting point to 67–68°; 7.0 g. (27%) of *1-p-anisyl-2-methyl-3-ethyl-6-methoxy-Δ¹-indene* (X) (14), colorless slender needles, were obtained. A solution of the substance in glacial acetic acid (a) rapidly decolorizes bromine and (b) turns on addition of a few drops of conc'd nitric acid to a cherry red that is quickly changed to deep orange.

Anal. Calc'd for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5.
Found: C, 81.8, 81.8; H, 7.8, 7.9.

A solution of 5 g. of this substance (X) in 100 ml. of alcohol absorbed at atmospheric pressure, in the presence of 0.5 g. of a 5% palladium-charcoal catalyst, 408 ml. of hydrogen rather sluggishly, the process being completed in about ten hours. The filtrate readily crystallized on cooling, yielding 4.0 g. of long colorless needles, m.p. 96–98°. Recrystallization from alcohol, and then from glacial acetic acid, raised the melting point to 100–101°, which remained undepressed on admixture of a sample prepared by method (a).

Anal. Calc'd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2.
Found: (a) C, 80.6, 80.6; H, 8.4, 8.4.
(b) C, 80.8, 80.6; H, 8.3, 8.3.

The product is distinctly more soluble in alcohol, glacial acetic acid and in ether than is metanethole. A 1:1 mixture with metanethole, m.p. 135°, melts at 116–118°, after previous softening at 100°. It gave no coloration with bromine in glacial acetic acid. Seeding the saturated solution in glacial acetic acid with crystals of metanethole of m.p. 135°, or refluxing the substance in methyl alcohol containing 20% hydrogen chloride for two hours, had no effect upon the melting point. Upon adding 0.8 ml. of conc'd nitric acid to a suspension of 0.1 g. of the substance in 1.0 ml. of glacial acetic acid, within a few minutes a reddish yellow solution was obtained which remained perfectly clear on standing at room temperature, while metanethole in a parallel nitration precipitated yellow needles of the dinitro derivative, m.p. 191° (23), within eight minutes.

A *monobromo derivative* was obtained by adding 2 ml. of a 5% solution of bromine in glacial acetic acid to 0.2 g. of the synthetic indan IX in 5 ml. of the same solvent. After three hours at room temperature, the separated crystals were recrystallized from glacial acetic acid; small colorless needles, m.p. 90–92°.

Anal. Calc'd for $C_{20}H_{23}BrO_2$: C, 64.0; H, 6.2.

Found: C, 64.2, 64.0; H, 6.2, 6.4.

A second crop of colorless prisms, m.p. 143–146°, separated from the filtrate on standing; recrystallized once from alcohol and then from glacial acetic acid, this proved to be a mixture containing the monobromo and the dibromo derivative in the proportion 1:4. Metanethole gave in a parallel bromination a dibromo derivative, m.p. 137° (23).

Acknowledgment. The authors wish to express their sincere thanks to Mrs. M. Lempert-Sréter, Z. Rácz, and Gy. Kalocsai for helpful assistance with preparative work, and to Mrs. Dr. A. Karczag-Györy (Wilhelms) for microanalyses.

SUMMARY

The synthesis of 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindan (Ia), 1-(3-methoxy-4-ethoxyphenyl)-2-methyl-3-ethyl-5-methoxy-6-ethoxyindan (Ib), and 1-*p*-anisyl-2-methyl-3-ethyl-6-methoxyindan (IX) was investigated. The synthetic indans are stereoisomeric with diisohomogenol of m.p. 106°, diisoeugenol diethyl ether of m.p. 131°, and metanethole of m.p. 135°, respectively. For this the last step of the synthesis, addition of hydrogen to the corresponding indenes, appears to be responsible, leading to a relative steric disposition of the substituents on the alicyclic ring of the resulting indan which is different from that present in the above dimeric propenylphenol ethers.

VÁCI UT 34. III. 1.
BUDAPEST XIII, HUNGARY

REFERENCES

(1) Part X, *Ber.* **77,** 343 (1944).
(2) CARTWRIGHT AND HAWORTH, *J. Chem. Soc.*, 1094 (1947).
(3) SZÉKI, *Ber.*, **39,** 2422 (1906).
(4) Part III, *Ber.*, **76,** 855 (1943).
(5) Part VIII, *Ber.*, **77,** 159 (1944).
(6) *Cf.* FUNAKUBO, *J. Chem. Soc. Japan*, **63,** 1361 (1942) [*Chem. Abstr.*, **41,** 3441 (1947)].
(7) CIAMICIAN AND SILBER, *Ber.*, **42,** 1390 (1909); FRANCESCONI AND PUXEDDU, *Gazz. chim. ital.*, **39,** 208 (1909); BRUCKNER, *Ber.*, **75,** 2035 (1942); FUNAKUBO, KUWASAKI, AND HOSHIMOTO, *J. Chem. Soc. Japan*, **63,** 1555 (1942); FUNAKUBO AND KIKKAWA, *J. Chem. Soc. Japan*, **63,** 1558 (1942) [*Chem. Abstr.*, **41,** 3441 (1947)].
(8) Part I, *Ber.*, **75,** 692 (1942).
(9) PUXEDDU, *Rend. accad. nazl. Lincei*, **21,** 124 (1912); PUXEDDU AND RATTU, *Gazz. chem. ital.*, **66,** 700 (1936).
(10) Part II, *Ber.*, **75,** 891 (1942); Part XI, *J. Org. Chem.*, **12,** 815 (1947).
(11) VON DOERING AND BERSON, *J. Am. Chem. Soc.*, **72,** 1118 (1950).
(12) *Cf.* BLOUNT AND ROBINSON, *J. Chem. Soc.*, 555 (1933).

(13) Part VI, *Ber.*, **77**, 6 (1944).

(14) VAN DER ZANDEN AND DE VRIES, *Rec. trav. chim.*, **68**, 261, 407 (1949).

(15) TOLDY, Thesis submitted to the Faculty of Philosophy, University of Budapest, 1944. {We are not prepared to take responsibility for, or to take reference to (a) Müller, Hauer, Toldy, and von Rácz, *Ber.*, **77**, 766 (1944); (b) Müller, Toldy, and von Rácz, *Ber.*, **77**, 777 (1944) [*Chem. Abstr.*, **44**, 3477 (1950)], these papers having been issued while in a preparatory state, without our final authorization.}

(16) Part V, *Ber.*, **76**, 1119 (1943).

(17) *Cf.* OTT, *Ber.*, **61**, 2124 (1928); SKITA AND FAUST, *Ber.*, **64**, 2878 (1931).

(18) KANEWSKAJA, *Arch. Pharm.*, **271**, 464 (1933).

(19) WASSERMANN, *Ann.*, **179**, 379 (1875); TIEMANN, *Ber.*, **8**, 1130 (1875); PUXEDDU, *Rend. accad. nazl. Lincei*, **20**, 722 (1911); NOMURA, *J. Chem. Soc.*, **111**, 774 (1917).

(20) ERDTMAN, *Svensk Kem. Tid.*, **46**, 229 (1934); VANZETTI AND DREYFUSS, *Gazz. chim. ital.*, **64**, 381 (1934); VANZETTI, *Mem. reale acad. Italia, Classe sci. fis., mat. e nat.*, **8**, 411 (1937).

(21) MÉSZÁROS, Thesis submitted to the Faculty of Philosophy, University of Budapest, 1948.

(22) GILLMEISTER, *Ber.*, **30**, 2849 (1897); ULLMANN AND LÖWENTHAL, *Ann.*, **332**, 67 (1904).

(23) BAKER AND ENDERBY, *J. Chem. Soc.*, 1094 (1940).