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

DIMERIC PROPENYL PHENOL ETHERS. XIX. THE PRODUCTS OBTAINED FROM DIISOHOMOGENOL BY OXIDATION WITH CHROMIC ACID

ALEXANDER MÜLLER, MAGDA LEMPERT-SRÉTER, AND
ADRIENNE KARCZAG-WILHELMS

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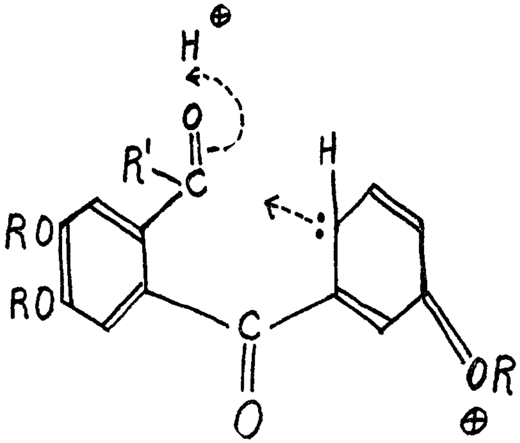
Diisohomogenol (IV) (1) upon degradation with chromic acid affords considerable quantities of 2,3,6,7-tetramethoxyanthraquinone (2). Metanethole (3) and diisosafrole (4) under the same conditions produce the respectively substituted *o*-benzoylbenzoic acid (*cf.* 5). It was demonstrated several years ago that in the case of diisohomogenol the intermediates produced the anthraquinone, not *o*-veratroylveratric acid (6). The approximate scheme of the degradation process, tentatively proposed at that time to demonstrate the compatibility of the indan structure of diisohomogenol with the anthraquinone formation, now requires correction on several points, since Doering and Berson (7) have shown that the primary product of the oxidation is 3,4,3′,4′-tetramethoxy-6α-acetopropylbenzophenone (III), rather than the cyclic hydroxyketone which figured in our scheme.[1]



The present reinvestigation of the structures of the various degradation products has demonstrated that chromic acid cleaves the indan system of diisoho-

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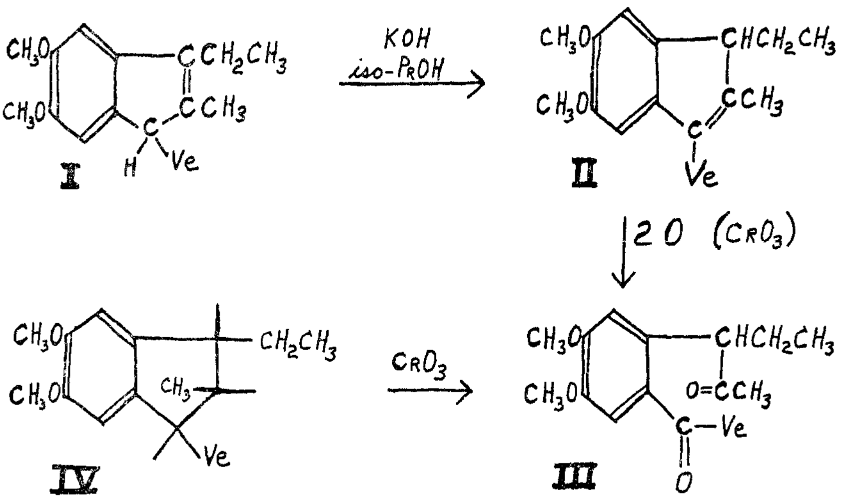
[1] The chromic acid degradation of diisohomogenol to a primary oxidation product which (*a*) contains one methyl ketone group on a *tertiary* carbon of an Ar—CHR—$COCH_3$ grouping (1), (*b*) is oxidizable to 1-veratryl-2-methyl-5,6-dimethoxy-Δ^1-indenone (XIV) (6), and (c) is almost quantitatively reconvertible from its halochromic salts (13), *permits at once without any ambiguity* a decision to be made between an indan IV or an isomeric tetralin structure for the starting material (*cf.* 7). Furthermore, the synthetically established presence of a phenylindan residue in the degradation product XVI *is evidence* concerning the existence of the same nucleus in diisohomogenol. This has been demonstrated by the reported *direct* formation of XVI in the chromic acid oxidation of Δ^3-dehydrodiisohomogenal (8), and the formation of dihydro XVI in the ozonolysis of the same substance (9).

mogenol at the C^1, C^2 bond [*cf.* (10, 11)] which might lead *via* the diketone III to the formation of an isochromenium salt (IX). Consecutive rupture of the C^3, C^4 bond produces an intermediate which then will undergo cyclization, as the result of an acid-catalyzed intramolecular attack by the *strongly* nucleophilic veratroyl group upon the adjacent carbonyl, in one of the subsequent phases of the degradation. Chiefly for this reason, those methronole derivatives, in which the 1-aryl group is *less* nucleophilic, are less liable to produce anthracene derivatives in the degradation with chromic acid.

The structure put forward by Doering and Berson for the primary oxidation product was confirmed by the following synthesis. 1-Veratryl-2-methyl-3-ethyl-5,6-dimethoxy-Δ^2-indene (I) (9), characterized by a bluish-green coloration with bromine in glacial acetic acid and by the ready formation of a picrate, was isomerized in a potassium hydroxide-propanol-2 solution to the corresponding Δ^1-indene (II) which gave a purple-violet color in the bromine test and did not form a solid picrate.[2] Upon opening the double bond of the latter with the required quantity of chromic acid, 3,4,3′,4′-tetramethoxy-6α-acetopropylbenzophenone (III) was obtained which proved to be identical with the primary oxidation product of diisohomogenol.



Ve = 3,4-Dimethoxyphenyl

Simultaneously, a conventional Bischler-Napieralski synthesis of the isoquinoline VII removed all uncertainty concerning the structure tentatively assigned by Doering and Berson to the condensation product of III with ammonia on basis of the ultraviolet spectrum. Veratrylacetone (Va)—prepared from isohomogenol by the method recently described for the preparation of *p*-anisylacetone from anethole (12)—has been C-ethylated to α-veratrylpropyl methyl

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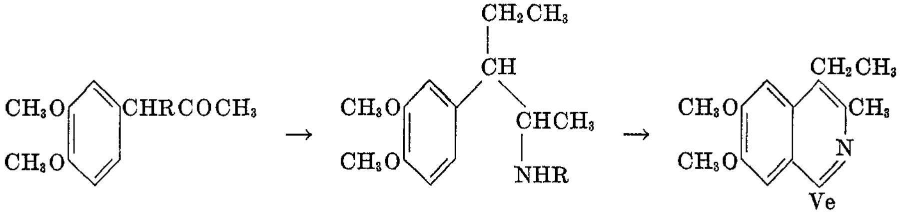
[2] On being hydrogenated in the presence of palladium-charcoal, I and II produce the same indan IV racemate. This presents the hitherto missing *direct* evidence that the β-racemate of IV is the *cis*, *cis* configurated racemic form.

ketone (Vb), and then converted to the corresponding methyl ketoxime. Reduction with sodium in alcoholic solution gave β-amino-γ-veratrylpentane (VIa) without difficulty. The amine was N-veratroylated to VIb, and then subjected to ring-closure in the presence of phosphorus oxychloride. Dehydrogenation of the resulting dihydroisoquinoline gave 1-veratryl-3-methyl-4-ethyl-6,7-dimethoxyisoquinoline (VII) identical in every respect with that prepared from the primary oxidation product of diisohomogenol (*a*) with hydroxylamine by the sulfur dioxide reduction of the N-oxide intermediate, or (*b*) by dissolving the halochromic sulfate IX in alcoholic ammonia.



V
(a) R = H
(b) R = C_2H_5

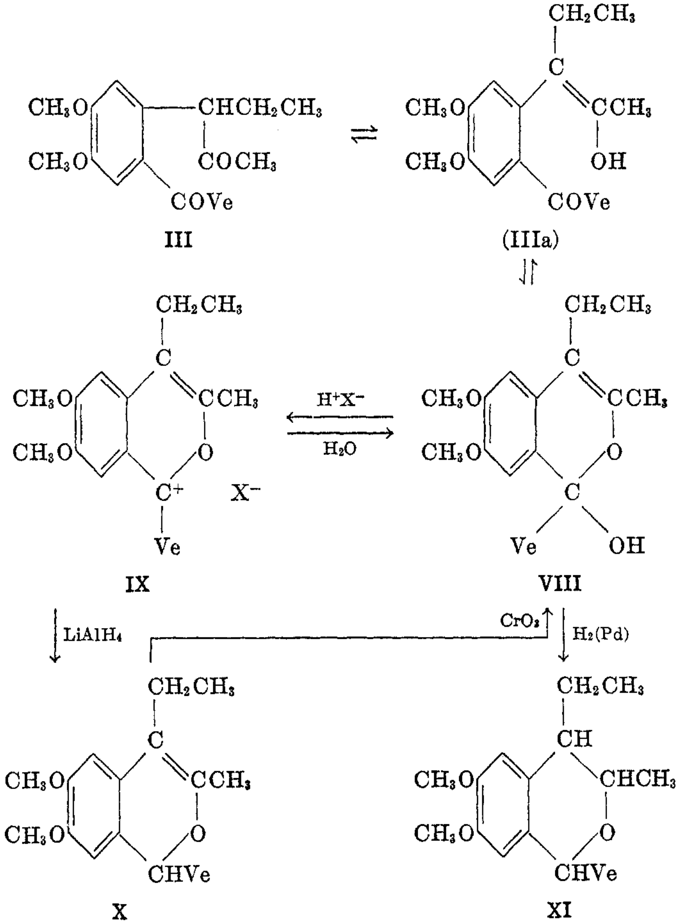
VI
(a) R = H
(b) R = COVe

VII

With the structure of the oxidation product established as III, there can be little doubt that the halochromic salts which are formed from this product with mineral acids (13), are isochromenium derivatives (IX) formed by the prototropic cyclization of a 1,4-diketone (7). This has been demonstrated by hydrolysis of IX to an isomer of III containing 1 atom of active hydrogen. The isomer—which readily rearranges to III in warm organic solvents—is believed to represent the isochromenol VIII, rather than the enol IIIa. Structure VIII is in conformity with the evidence that catalytic hydrogenation of III affords a product that is indifferent toward carbonyl or hydroxyl reactants, as would be expected for an isochromane XI. On reducing IX with lithium aluminum hydride (*cf.* 14) to X, and subjecting this product to hydrogenation, a diastereoisomeric racemate of XI was obtained (*cf.* 15). The formation of XI upon direct hydrogenation of III is suggestive of an equilibrium III $\rightleftharpoons$ IIIa $\rightleftharpoons$ VIII, which however in view of the reported absence of hydroxyl absorption in hexane solutions of III appears to be shifted in non-polar solvents very much toward the form III.

At low temperature the chromic acid oxidation of diisohomogenol stops at the formation of the diketone III. Under the conditions employed by Haworth and Mavin in the degradation, *viz.* with excess oxidant in warm glacial acetic acid, diketone III forms IX•chromate. It is this readily oxidizable derivative which undergoes degradation in a number of collaterally occurring reaction sequences to give 2,3,6,7-tetramethoxyanthraquinone in some 10% yield.

In the controlled oxidation of IX salts (sulfate, chloride) with 4 or 5 equivalents of chromic acid at room temperature 3,4,3′,4′-tetramethoxy-6-propionylbenzophenone (XV) can be isolated from the reaction mixture in about 20% yield (6). The cyclic aldol formula which originally we assigned to the product has been replaced by Doering and Berson by XV on infrared spectral evidence and the formation of traces of the same product in the chromic acid oxidation of 3,4,3′,4′-tetramethoxy-6-propylbenzophenone. We now add the further evidence that the substance readily forms a phthalazine (XIII) with hydrazine hydrate.[3]



(XVI). Chromic acid converts this indenone to 3,4,3′,4′-tetramethoxy-6-

With conc'd sulfuric acid in glacial acetic acid XV deposits deep red needles of a carbenium salt. In water this salt undergoes decomposition to 2,3,6,7-tetramethoxy-9-hydroxy-9-ethylanthrone (XVIII), thus providing evidence that in the degradation XV might contribute directly to the formation of anthracene derivatives. Under the actual conditions of the degradation however, the greater

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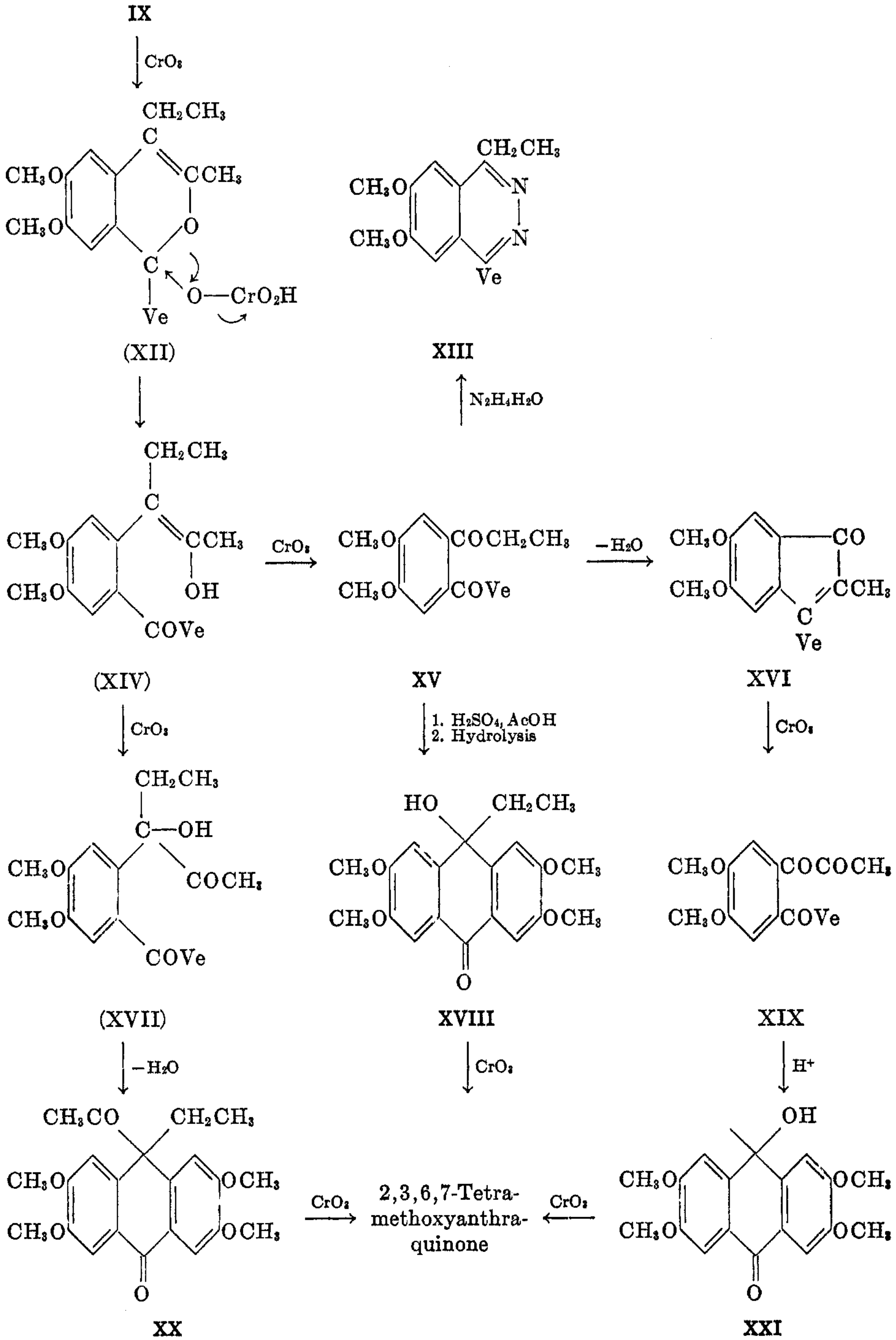
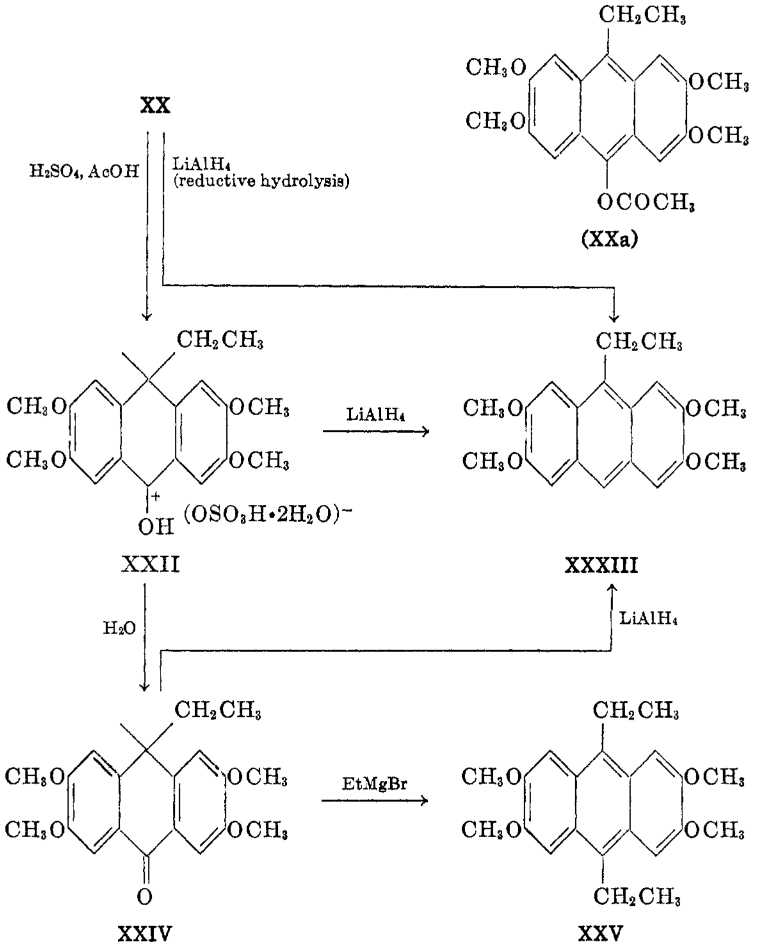
[3] The colorless degradation product $C_{18}H_{18}O_4$ of the chromic acid oxidation of metanethole $C_{20}H_{24}O_2$ (3) likewise forms a phthalazine (see Experimental), giving evidence that the product is a 3,4′-dimethoxy-6-propionylbenzophenone (the analog of XV), rather than the originally (3) suggested isomeric isomeric cyclic hydroxy ketone.



The serial numbers in bold-face type represent isolated compounds, those in italics denote postulated intermediates.

part of XV is converted to 1-veratryl-2-methyl-5,6-dimethoxy-Δ^1-indenone pyruvylbenzophenone (XIX) which, in the presence of excess oxidant, readily undergoes acid-catalyzed cyclization, with a foregoing or concomitant loss of its methyl ketone group, to give 2,3,6,7-tetramethoxy-9-hydroxyanthrone (XXI) (6), and ultimately is oxidized to tetramethoxyanthraquinone. Perhaps this is the path responsible in the main for the bulk of the tetramethoxyanthraquinone that is formed in the Haworth-Mavin degradation.



When IX sulfate was oxidized in strongly diluted acetic acid with one equivalent of chromic acid with the intention that possibly an intermediate less degraded than XV could be separated, a product $C_{22}H_{26}O_6$ was obtained. This could not be converted to veratric acid nor to *o*-veratroylveratric acid by oxidation with permanganate in acetone. Therefore the product already appeared to contain an anthracene skeleton (16).

The presently available information on this product is the following: (*a*) Acid or alkaline hydrolysis (with access of air to the reaction mixture) removes an acetyl group from the molecule which in consequence undergoes an oxidative condensation; (*b*) Reductive hydrolysis with lithium aluminum hydride in not strictly anhydrous ether or dioxane affords—among other products—2,3,6,7-tetramethoxy-9-ethylanthracene (XXIII) identical with a specimen prepared by synthesis from diveratrylmethane and propionaldehyde; (*c*) Conc'd sulfuric acid in glacial acetic acid effects deacetylation with the formation of a carbenium sulfate (XXII) that on reduction with lithium aluminum hydride likewise affords XXIII.

Hydrolysis of the sulfate XXII with aqueous solvents produces pale yellow blocks of 2,3,6,7-tetramethoxy-9-ethylanthrone (XXIV) which with lithium aluminum hydride produces XXIII. Ethylmagnesium bromide converts the substance to 2,3,6,7-tetramethoxy-9,10-diethylanthracene (XXV) identical with a synthetic (17) specimen. With alcoholic alkalies or on being treated with acetic anhydride and sodium acetate XXIV, like its parent substance, undergoes oxidative condensation.

From (*b*) the anthracene system in the oxidation product $C_{22}H_{26}O_6$ appears to be proved. Therefore, in the oxidation of IX sulfate under the stated conditions the anthracene skeleton is formed already before further degradation. The best expression of the structure of the resulting product would seem to be XX. The tautomeric structure XXa, although likewise compatible with the transformations (*a*)–(*c*), is less readily reconcilable with an oxidative formation from IX. A shift XX → XXa appears unlikely. The infrared spectrum would easily discriminate between these two structures; this facility, however, at present is not at our disposal.

EXPERIMENTAL

SYNTHESIS OF THE PRIMARY OXIDATION PRODUCT III

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxy-Δ²-indene (I) (9) forms glistening black needles of a *dipicrate*, m.p. 109–111° (from alcohol).

Anal. Calc'd for $C_{22}H_{26}O_4 \cdot 2C_6H_3N_3O_7$: C, 50.0; H, 3.9; N, 10.7.
Found: C, 50.1, 50.1; H, 4.0, 4.1; N, 10.7, 10.4.

1-(3,4-Dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxy-Δ¹-indene (II). A solution of 10 g. of I in 100 ml. of isopropyl alcohol containing 6 g. of potassium hydroxide was refluxed for four hours, then 500 ml. of water was added, and the mixture was extracted with ether. The extract, washed with water and dilute hydrochloric acid, on evaporation left a deep brown oil which was crystallized from a small amount of alcohol. The solid was collected and extracted with warm alcohol, leaving behind a sparingly soluble by-product. The product separated from the filtrate in long, slightly colored needles which, after one recrystallization from the same solvent, melted at 97–98° (yield, 3 g.). It gave a reddish-violet coloration on addition of bromine to its solution in glacial acetic acid. On addition of an alcoholic picric acid solution a deep brown color resulted but no separation of a solid picrate was observed.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.4; H, 7.4; OCH_3, 35.1.
Found: C, 74.6, 74.7; H, 7.5, 7.5; OCH_3, 34.8.

On hydrogenation, 2 g. of the substance (in 80 ml. of alcohol-ethyl acetate 3:1, with 0.2 g. of a 5% palladium-charcoal catalyst) absorbed 132 ml. of hydrogen in 50 minutes. Evaporation of the filtrate gave an oil which crystallized readily from alcohol, yielding

1.4 g. of the *β-racemate of 1-(3,4-dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindan* (IV with the CH_3 inverted) which melted at 105–106° alone or mixed with an authentic specimen. The bromine test gave an intense purple-violet color.

3,3′,4,4′-Tetramethoxy-6-α-acetopropylbenzophenone [α-(*o*-veratroylveratryl)propyl methyl ketone] (III). To a cooled and vigorously stirred solution of 1.4 g. of II in 40 ml. of glacial acetic acid a solution of 0.9 g. of chromium trioxide in 2 ml. of water and 8 ml. of glacial acetic acid was added by drops (two hours). After two days at room temperature, water was added, followed by extraction with benzene. The extract, washed with dilute sodium carbonate solution and with water, on evaporation left a reddish oil which crystallized readily from alcohol. Two consecutive recrystallizations from ethyl acetate gave 0.9 g. of large glistening cubes identical in every respect with the primary oxidation product of diisohomogenol. M.p. 155–157°, alone or mixed with an authentic specimen.

SYNTHESIS OF ISOQUINOLINE VII

3,4-Dimethoxyphenylacetone (Va). To a vigorously stirred solution of 188 g. (1 mole) of isohomogenol, b.p. 140°/14 mm., in 700 ml. of glacial acetic acid—kept constantly at 50–55°—675 g. (1 mole) of red lead was added in small portions, each batch being allowed time for complete dissolution before adding a further quantity (three hours). Stirring and warming was continued for one more hour, then water was added and the mixture was extracted with benzene. The extract, washed repeatedly with sodium carbonate solution and with water, on evaporation left a yellow oil which, on distillation after a forerun of 50 g. of unchanged isohomogenol, gave 153 g. of a mobile yellow liquid, b.p. 170–190°/3 mm. This liquid was refluxed with 500 ml. of 25% sulfuric acid for six hours under vigorous stirring, and then was extracted with benzene. Distillation of the washed benzene extract produced 89 g. (43%) of a moderately viscous oil, b.p. 165–170°/8 mm. (*cf.* 18). Samples of the *oxime*, small silky needles, m.p. 62.5–63°, and of the *semicarbazone*, slender colorless needles, m.p. 176–177°, have been prepared.

α-(3,4-Dimethoxyphenyl)propyl methyl ketone (Vb). To a solution of 16.1 g. (0.7 g.-atom) of sodium in 580 ml. of absolute alcohol, 114 g. (0.66 mole) of Va was added. The solution was cooled in ice-water and mixed dropwise with 132 g. (0.7 mole) of ethyl bromide. After two hours at room temperature, the mixture was refluxed on the steam-bath for three hours, then about 300 ml. of alcohol was removed by distillation. Water was added, followed by thorough extraction with ether. The extract was washed with water and with dilute hydrochloric acid. The residue obtained by evaporation on subsequent distillation gave a pale yellow oil, b.p. 141°/0.6 mm., while considerable quantities of an orange-colored clear resin remained behind. Redistillation produced 57 g. (39%) of an almoss colorless liquid, b.p. 110–113°/0.05 mm.

Anal. Calc'd for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1.
Found: C, 69.8, 69.9; H, 8.0, 8.1.

The *semicarbazone* formed silky colorless needles, m.p. 151–152° (from alcohol).

Anal. Calc'd for $C_{14}H_{23}N_3O_3$: C, 60.0; H, 7.5; N, 15.0.
Found: C, 60.3; H, 7.8; N, 15.3.

α-Dimethoxyphenylpropyl methyl ketoxime. A solution, prepared from 20 g. (0.3 mole) of hydroxylamine hydrochloride and 40 g. of cryst. sodium acetate in 550 ml. of alcohol, was refluxed with 57 g. (0.26 mole) of Vb for five hours. After the removal of about 300 ml. of the solvent by distillation, 800 ml. of water was added. The mixture was extracted with benzene; on evaporation a pale brown oil was left which on distillation afforded 55 g. (90%) of a slightly colored, highly viscous oil, b.p. 150–156°/0.06 mm. that crystallized in long colorless needles, m.p. 78–80° from ethyl acetate.

Anal. Calc'd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9.
Found: C, 66.1; H, 8.1; N, 5.8, 6.0.

β-Amino-γ-(3,4-dimethoxyphenyl)pentane (VIa). Into a boiling-hot solution of 4.6 g. (0.02 mole) of above ketoxime in 40 ml. of absolute alcohol 5 g. (0.2 g.-atom) of thin slices of sodium were introduced in three portions. Dissolution was completed by warming the mixture for 15 minutes. The mixture then was poured onto ice and extracted with ether. The ethereal extract was re-extracted with 5% hydrochloric acid which subsequently was made alkaline. The ethereal extract of the alkaline mixture on evaporation and subsequent distillation gave 2.3 g. (50%) of a mobile colorless liquid, b.p. 98–101°/0.1 mm.

Anal. Calc'd for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.3.
Found: C, 69.9; H, 9.6; N, 6.2, 6.3.

The *hydrochloride*, colorless rosettes of needles, m.p. 143°, separated on saturation of an ethereal solution of VIa with hydrogen chloride, and was recrystallized from ether.

Anal. Calc'd for $C_{13}H_{22}ClNO_2$: N, 5.4. Found: N, 5.7, 5.7.

β-(3,4-Dimethoxybenzoylamino)-γ-(3,4-dimethoxyphenyl)pentane (VIb). To a mixture of 10 g. of finely powdered anhydrous potassium carbonate and a solution of 6 g. (0.026 mole) of VIa in 25 ml. of dry acetone, refluxed on the steam-bath, a solution of 6 g. (0.026 mole + 33%) of veratroyl chloride in 30 ml. of dry acetone was added by drops with vigorous stirring (30 minutes). After dilution with water, the mixture was extracted with ethyl acetate. The extract, washed with dilute hydrochloric acid and with water, on evaporation left an oil which crystallized slowly from gradually diluted alcohol as highly solvated, interlacing colorless needles. The rather indefinite melting point gradually rose to 137–139° on two subsequent recrystallizations from 50% alcohol and consecutive drying at 56°/10 mm. over phosphorus pentoxide. Yield, 9.2 g. (91%).

Anal. Calc'd for $C_{22}H_{29}NO_5$: C, 68.2; H, 7.6; N, 3.6.
Found: C, 68.3; H, 7.6; N, 3.4.

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline. A solution of 3.85 g. (0.01 mole) of VIb in 80 ml. of dry toluene was mixed with 8 ml. of phosphorus oxychloride and was refluxed for 90 minutes. Upon adding ice to the cooled solution, a gelatinous precipitate separated, which dissolved again in the warm hydrochloric acid that formed. The toluene layer repeatedly was extracted with warm conc'd hydrochloric acid, the extracts being added to the original acid layer from which on cooling greenish-yellow needles of the hydrochloride separated. These were collected and mixed with 10% sodium hydroxide solution. The mixture was extracted with ether, and the ethereal solution subsequently was re-extracted with 10% hydrochloric acid, from which dilute ammonia precipitated colorless flocks which crystallized from 50% alcohol in colorless needles, m.p. 109° (2.2 g., 60%). For analysis the product was dried over phosphorus pentoxide at 100°/13 mm.

Anal. Calc'd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8.
Found: C, 71.6, 71.5; H, 7.4, 7.5; N, 3.8, 3.7.

The *hydrochloride*, separating from a conc'd solution of the base in 20% hydrochloric acid, forms greenish-yellow needles melting at 219–220° after one recrystallization from 15% hydrochloric acid and subsequent drying over phosphorus pentoxide at 100°/13 mm.

Anal. Calc'd for $C_{22}H_{28}ClNO_4$: C, 65.1; H, 7.0.
Found: C, 64.9; H, 7.3.

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisoquinoline (VII). (*a*) From the dihydroisoquinoline: An intimate mixture of 1.4 g. of the above sharply dried dihydroisoquinoline and 0.4 g. of 5% palladium-charcoal was slowly brought to 200° (two hours), then kept at this temperature for 45 minutes. The mixture was ground, when cold again, with ether; the extract on evaporation left 1.1 g. of a semicrystalline residue. This was dissolved in 5 ml. of alcohol, and 0.9 g. of picric acid was added. The yellow crystalline cake was washed with some alcohol, then it was dissolved in chloroform and decomposed by shaking the solution with a 2% sodium hydroxide solution. On evaporation of the organic layer, an oil was obtained which crystallized readily from ethyl acetate in large colorless wedge-shaped crystals (0.9 g.). After one recrystallization from the same solvent, the product melted at 156–157°, alone or mixed with a specimen prepared under (*b*).

Anal. Calc'd for $C_{22}H_{25}NO_4$: C, 71.9; H, 6.7; N, 3.8.
Found: C, 72.0, 72.1; H, 7.0, 7.1; N, 3.9.

From an alcoholic solution mixed with water until incipient turbidity the substance reappeared in long silky needles, which melted at 157° after being air-dried. This is a *semihydrate.*

Anal. Calc'd for $C_{22}H_{25}NO_4 + 0.5H_2O$: C, 70.2; H, 7.0.
Found: C, 70.0; H, 7.3.

The *picrate*, prepared from an alcoholic solution of the base mixed with the calculated quantity of picric acid, afforded bright yellow needles which—after one recrystallization from glacial acetic acid—had m.p. 220–221° [reported (7): 226–227°]. No depression with a specimen prepared from sample (*c*).

Anal. Calc'd for $C_{22}H_{25}NO_4 \cdot C_6H_3N_3O_7$: N, 9.4. Found: N, 9.5, 9.6.

(*b*) From the N-oxide: Passing a moderate current of sulfur dioxide through a solution of 5 g. of VII N-oxide (prepared from III with hydroxylamine) in 200 m. of glacial acetic acid warmed on the steam-bath (four hours), followed by the addition of 200 g. of ice and an adequate quantity of conc'd ammonia precipitated the base. The solid was collected, air-dried, and then twice recrystallized from ethyl acetate to give large colorless prisms (3.2 g.), m.p. 155–156°. There was no depression with a sample prepared under (*a*).

(*c*) From IX salts: Upon dissolving 2 g. of IX chloride (or sulfate) (13) in 50 ml. of absolute alcohol saturated with ammonia at 0°, the dark orange color of the solution rapidly changed to canary yellow. After 12 hours, 30 ml. of alcohol was removed by distillation, then ice was added and the mixture was extracted with ether. The ethereal solution was re-extracted with dilute hydrochloric acid, and from the latter ammonia precipitated colorless flocks. These were removed and then dissolved in an alcoholic solution of picric acid saturated at room temperature. From the picrate 1.4 g. of the isoquinoline was obtained which, after one recrystallization from ethyl acetate, melted at 155–156°. There was no depression with sample (*a*).

When samples of the base were dissolved in the just sufficient quantity of approximately 3 *N* solutions of acids, eventually with gentle warming, the resulting salts crystallized on standing. These were freely soluble in alcohol and rather less soluble in water.

Oxalate: Nearly colorless clusters of small needles, m.p. 110°, decomp.

Anal. Calc'd for $C_{22}H_{26}NO_4 \cdot HC_2O_4$: N, 3.1; $H_2C_2O_4$, 17.3.
Found: N, 3.1; $H_2C_2O_4$, 17.1.

Nitrate: Yellow needles, m.p. 195–197°, decomp.

Anal. Calc'd for $C_{22}H_{26}NO_4 \cdot NO_3 \cdot HNO_3$: N, 7.1. Found: N, 7.0.

Hydrochloride: Elongated prisms of a light greenish-yellow color and of somewhat varying composition, melting at about 85° when air-dried. Sampled dried at 100°/14 mm. over phosphorus pentoxide melted at 208°.

Sulfate: Light greenish-yellow needles, m.p. 131–132°, decomp. (air-dry), 237–238°, softening at 162° (dried at 100°/14 mm. over phosphorus pentoxide).

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisoquinoline-N-oxide was prepared by the following simple method (*cf.* 7). A mixture of 19 g. of III, 23 g. of hydroxylamine hydrochloride, and 23 g. of cryst. sodium acetate was dissolved in 150 ml. of 60% alcohol on the steam-bath (30 minutes), and was refluxed for another 90 minutes. Then 200 ml. of water was added, the solid being removed after two days in the ice-box. The air-dry product (21 g., m.p. 203–205°) was recrystallized from ethyl acetate to give small colorless needles, m.p. 221–223°.

The *hydrochloride* crystallized on standing in pale yellow large prisms, m.p. 203°, from a solution of the N-oxide in the ten-fold weight of ethyl acetate saturated with hydrogen chloride.

Anal. Calc'd for $C_{22}H_{26}ClNO_5$: N, 3.3; HCl, 8.6.
Found: N, 3.2; HCl, 8.9.

HYDROLYSIS AND REDUCTION OF THE ISOCHROMENIUM SALTS IX

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisochromenol (VIII). Upon warming a solution of 5 g. of the isochromenium sulfate IX (13) in 100 ml. of water on the steam-bath, 3.9 g. of long flat blades gradually crystallized from the solution (one hour). The solid was collected and washed with water until it gave no reaction to litmus, then it was dissolved in 80 ml. of cold (2–6°) acetone, and brought to crystallization in the ice-box by the gradual addition of cold water. The product formed long colorless flat prisms (3.1 g.), m.p. 156°. There was no m.p. depression with diketone III, and no coloration was observed with methanolic ferric chloride solution. For analysis the samples were dried at 20°/0.01 mm. over phosphorus pentoxide (two days).

Anal. Calc'd for $C_{22}H_{26}O_6$: C, 68.4; H, 6.8; Active H, 0.261.

Found: C, 68.5, 68.3; H, 7.0, 7.0; Active H, 0.265, 0.255.

Recrystallization of a 0.5-g. sample from 5 ml. of ethyl acetate produced big cubes, m.p. 156°, of diketone III.

Anal. Calc'd for $C_{22}H_{26}O_6$: Active H, none. Found: Active H, 0.071, 0.074.

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisochromene (X). To a vigorously stirred suspension of 0.8–1.0 g. of lithium aluminum hydride in 100 ml. of absolute ether 2.0 g. of finely powdered IX sulfate or chloride was added in portions (30 minutes). No reaction was observed to occur with sharply dried (56°/20 mm., phosphorus pentoxide) material, whereas on addition of 2–3 ml. of moist ether, or using samples previously exposed to air, decoloration took place within 10 to 15 minutes. After decomposing the excess reagent with moist ether, 5% aqueous hydrochloric acid was added, which caused an intense canary-yellow coloration. The colorless ethereal layer, washed with dilute hydrochloric acid and with water, on subsequent evaporation left a pale yellow oil which crystallized readily from 6 ml. of alcohol diluted gradually with water to incipient turbidity. After three consecutive recrystallizations from small quantities of alcohol, 0.9 g. of stout colorless blocks, m.p. 105°, were obtained. The solution in glacial acetic acid was yellow and (*a*) instantly decolorized bromine, (*b*) turned purple-red with a slight blue reflex, and then to cherry-red, if mixed with a few drops of conc'd sulfuric acid. The solution in dilute alcohol acquired an intense pale yellow color on addition of mineral acid. Alcoholic picric acid dissolved the substance with a deep red-brown color, but no solid picrate was obtained.

Anal. Calc'd for $C_{22}H_{26}O_5$: C, 71.5; H, 7.0.

Found: C, 71.3, 71.3; H, 7.0, 7.1.

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisochromane (XI). *Diastereoisomer A.* The yellow solution of 0.5 g. of X in 20 ml. of glacial acetic acid, hydrogenated in the presence of 0.05 g. of a 10% palladium-charcoal catalyst, absorbed 38 ml. of hydrogen in two hours. Evaporation of the filtrate gave a greenish-yellow oil which crystallized from a little alcohol on the gradual addition of water. One recrystallization from alcohol afforded 0.2 g. of colorless needles, m.p. 108–109°, depressed to 92–96° on admixture of the starting material.

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 71.0; H, 7.6.

Found: C, 71.2, 71.3; H, 7.8, 7.8.

Diastereoisomer B. A solution of 7.7 g. of diketone III in 160 ml. of glacial acetic acid, hydrogenated in the presence of 0.5 g. of a 10% palladium-charcoal catalyst, absorbed 920 ml. of hydrogen in four hours. On evaporation of the filtrate a practically colorless oil was obtained that slowly crystallized from alcohol upon gradual dilution with water. It formed short stout prisms, m.p. 89–92° (3.0 g.). Repeated recrystallizations from 50% alcohol gave 2.0 g. of flat colorless needles, m.p. 97–98° (occasionally, 104–106°). From the mother liquors addition of water precipitated considerable quantities of oily material.

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 71.0; H, 7.6; OCH_3, 33.4.

Found: C, 71.1, 70.9, 70.0; H, 7.6, 7.5, 7.6; OCH_3, 33.9, 34.0.

No difference was found between the two diastereoisomers in the following tests: (*a*) Each did not decolorize bromine in glacial acetic acid, (*b*) Each gave a purple-violet coloration in glacial acetic acid on addition of conc'd sulfuric acid, and separation on prolonged standing of colorless cottony needles, m.p. 173°, (*c*) Each failed to react with acetic anhydride or semicarbazide hydrochloride (in the presence of sodium acetate) on the steam-bath, (*d*) Each formed diketone III in 53 and 55% yield (addition of 0.66 g. of chromium trioxide dissolved in 3 ml. of 90% acetic acid to the 0.5-g. samples in 15 ml. of glacial acetic acid, followed by the usual isolation). M.p. 155–156°, undepressed by an authentic specimen.

1-(3-Methoxy-4-acetoxyphenyl)-3-methyl-4-ethyl-6-methoxy-7-acetoxyisochroman. A solution of 4.4 g. of the primary oxidation product of diisoeugenol diacetate (1) in 50 ml. of glacial acetic acid was hydrogenated until 570 ml. of hydrogen was absorbed. The solution was filtered, solvent was removed, and the residue was crystallized from alcohol upon gradual dilution with water, yielding 2.1 g. of colorless slender needles, m.p. 114°. The material did not decolorize bromine and gave a purple-violet coloration with conc'd sulfuric acid in glacial acetic acid. A solution in 5% aqueous sodium hydroxide produced no iodoform on being mixed with crystals of iodine.

Anal. Calc'd for $C_{24}H_{28}O_7$: C, 67.3; H, 6.6.
Found: C, 67.5; H, 6.8.

THE PRODUCTS OBTAINED BY OXIDATION OF IX WITH CHROMIC ACID

2,3,6,7-Tetramethoxy-9-hydroxy-9-ethylanthrone (XVIII). A solution of 1 g. of 3,3′,4,4′-tetramethoxy-6-propionylbenzophenone (XV) [prepared from IX as described (6)] in 3 ml. of glacial acetic acid was mixed with 0.5 g. of conc'd sulfuric acid dissolved in 1 ml. of the same solvent. In a few minutes the mixture became a mass of deep red needles. These were removed by filtration and suspended in 10 ml. of water. The turbid solution was filtered quickly. On standing small yellow needles separated from the filtrate. These were recrystallized from 30% acetic acid, and then melted at 143° (yield 0.1 g.). The solution in glacial acetic acid gave no coloration with bromine. Conc'd sulfuric acid led to the slow crystallization of a dark red carbenium sulfate which, on addition of a few drops of water, quickly passed into solution with a yellow color.

Anal. Calc'd for $C_{20}H_{22}O_6$: C, 67.0; H, 6.2.
Found: C, 67.0; H. 6.4.

Upon warming a solution of 30 mg. of the substance in 0.5 ml. of 50% acetic acid and 2 drops of 30% hydrogen peroxide on the steam-bath for 30 minutes, needles of 2,3,6,7-tetramethoxyanthraquinone (19 mg.) separated, m.p. 339–342°, which dissolved with a deep green color in conc'd sulfuric acid.

1-(3,4-Dimethoxyphenyl)-4-ethyl-6,7-dimethoxyphthalazine (XIII). After adding 0.8 ml. of hydrazine hydrate to a solution of 1 g. of XV in 20 ml. of warm alcohol, 0.9 g. of colorless needles separated on standing which, after one recrystallization from alcohol, had m.p. 200–201°. The product readily dissolved in dilute solutions of mineral acids, and reappeared in fine needles on subsequent alkalization with ammonia.

Anal. Calc'd for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.2; N, 7.9.
Found: C, 67.7, 67.9; H, 6.3, 6.4; N, 7.8, 7.8.

The *picrate*, canary-yellow needles, readily crystallized on dissolving the base in an alcoholic solution of picric acid, and—after one recrystallization from alcohol—had m.p. 199–201°, decomp.

Anal. Calc'd for $C_{20}H_{22}N_2O_4 \cdot C_6H_3N_3O_7$: N, 12.3. Found: N, 12.1, 12.2.

1-(p-Methoxyphenyl)-4-ethyl-7-methoxyphthalazine. A solution of 0.3 g. of 3,4′-dimethoxy-6-propionylbenzophenone, m.p. 117° [obtained by the chromic acid degradation of metanethole (3)] and 0.2 g. of hydrazine hydrate in 2 ml. of alcohol was refluxed for five minutes. The product, which crystallized from the reaction mixture on standing overnight, was dissolved in 5 ml. of aqueous 5% hydrochloric acid. Some unchanged starting material was removed by filtration. On cooling colorless rosettes of long slender needles of the *hydrochloride* separated, m.p. 93°, after one recrystallization from alcohol.

Anal. Calc'd for $C_{18}H_{18}N_2O_2 \cdot HCl$: HCl, 11.0, Found: HCl, 11.2.

The *base*, which separated from the aqueous solution of the hydrochloride on the addition of dilute ammonia, formed long colorless needles. These were recrystallized from 40% alcohol, m.p. 136°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.4; H, 6.2; N, 9.5.
Found: C, 73.3, 73.6; H, 6.3, 6.2; N, 9.9, 9.7.

The *picrate*, obtained from an alcoholic picric acid solution of the base, formed canary yellow needles and was recrystallized from alcohol, m.p. 179°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$: C, 55.1; H, 4.0; N, 13.4.
Found: C, 55.0, 55.2; H, 4.2, 4.1; N, 13.3, 13.2.

2,3,6,7-Tetramethoxy-9-acetyl-9-ethylanthrone (XX or, less probably, the isomer XXa). [Improved preparation (*cf.* 16)]. To a solution of 25 g. (0.075 mole) of isochromenium sulfate IX in 140 ml. of warm glacial acetic acid 350 ml. of water was added. To this mixture, warmed on the steam-bath and stirred vigorously, 7 g. of chromium trioxide in 50 ml. of water was added by drops. After each drop time was allowed for the resulting precipitate to dissolve before the next drop was added. The quantity of the oxidant used represented 0.075 g.-atom + 30% of active oxygen. A 50–60% excess was not detrimental. After the addition was completed, stirring was continued for ten minutes, and then further reaction was stopped by chilling. The pale yellow solid (11.2 g.) which separated was collected, washed with some alcohol, and then was five times recrystallized from the same solvent, yielding 10 g. (35%) of colorless sturdy prisms, m.p. 199–201°.

Alkaline hydrolysis of 0.2 g. of the substance with 10 ml. of 5% alcoholic potassium hydroxide solution (one hour at 60°) gave—after removal of the yellow needles which separated in the cold—a yellow filtrate. This was evaporated, the residue being subsequently distilled with 20 ml. of 25% phosphoric acid with the gradual addition of 20 ml. of water. The first 15 ml. of the distillate contained acetic acid corresponding to 14.5% of the starting material (calc'd, 17.3%), identified as acetanilide (colorless plates, melting at 115° alone or mixed).

After oxidizing 1.0 g. of XX in 30 ml. of acetone with 4.8 g. of finely powdered potassium permanganate on the steam-bath, the solvent was removed subsequently by distillation. The residue was mixed with a sodium hydrogen sulfite solution and dilute sulfuric acid, and then extracted with chloroform. Upon washing the extract repeatedly with 5% sodium hydroxide solution, no water-insoluble acidic degradation product was obtained from the latter.

2,3,6,7-Tetramethoxy-9-ethylanthracene (XXIII). (*a*) From XX: A colorless solution of 1 g. of XX in 10 ml. of redistilled dioxane (dried over calcium chloride) was mixed with 0.4 g. of lithium aluminum hydride, under vigorous stirring on the steam-bath. Very gradually an orange color developed. After four hours of heating, the mixture was cooled, and then mixed with moist ether and later with ethyl acetate, and washed with dilute hydrochloric acid. Evaporation of the ether-ethyl acetate solution gave a reddish-brown semi-solid. This substance was extracted with boiling alcohol, when 0.5 g. of a yellow solid (soluble in conc'd sulfuric acid with a deep red color) remained undissolved. The extract deposited colorless crystals that were quickly removed, since sturdy pale yellow prisms, m.p. 183–184°, of anthrone XXIV (0.16 g.) separated from the filtrate. Upon recrystallizing the initial colorless crystals from alcohol, 0.09 g. of flat needles, m.p. 232°, were obtained, which were identical in every respect with samples of the following preparations.

(*b*) From anthrone XXIV. Upon refluxing 1.0 g. of XXIV in 50 ml. of ether (dried over calcium chloride) (incomplete solution) with 0.4 g. of lithium aluminum hydride under vigorous stirring, a colored solution was obtained (four hours). This was decomposed and washed as before. After evaporation the residue was extracted with warm alcohol from which 0.25 g. of partly colored plates crystallized. Sublimation and subsequent recrystallization from alcohol gave 0.17 g. of colorless plates of m.p. 231–232° undepressed by sample (*a*), the picrate melting at 169–172°.

(*c*) From the carbenium sulfate XXII: From 2 g. of XX, dissolved in 6 ml. of glacial acetic acid and mixed subsequently with 1 ml. of conc'd sulfuric acid XXII was prepared (16). The brick-red prisms were collected, washed with 6 ml. of glacial acetic acid, and kept in a vacuum over potassium hydroxide for two hours. The salt was then suspended in 40 ml. of ether (dried over calcium chloride), and 2 g. of lithium aluminum hydride was added in four portions with vigorous stirring at 30° (40 minutes). After two hours decoloration was complete. Moist ether, and then ethyl acetate was added, and the mixture was washed with dilute hydrochloric acid. The residue of the ether-ethyl acetate solution was extracted with boiling alcohol, from which 0.5 g. of naphthalene-like plates separated overnight. Two subsequent recrystallizations from alcohol afforded 0.34 g. of thin colorless plates, m.p. 232°. No depression with samples (*a*) and (*b*). The picrate melted at 171–172°.

(*d*) By synthesis: To an ice-cooled solution of 2.8 g. (0.01 mole) of 3,3′,4,4′-tetramethoxydiphenylmethane in 40 ml. of carbon disulfide with vigorous stirring 0.7 g. (0.0065 mole) of propionaldehyde was added in drops with the simultaneous introduction of 1.4 g. (0.02 mole) of boron trifluoride. After standing at room temperature for one hour, the mixture was warmed on the steam-bath (two hours). Subsequently ice and a conc'd solution of sodium acetate were added, and the oily boron complex then was decomposed upon vigorous shaking of the mixture. The organic layer was removed, and the carbon disulfide was distilled off. A solid residue was obtained that was washed with some alcohol and recrystallized subsequently from dioxane-water and then from alcohol to give colorless flat blades (1.5 melting at 230–231°. There was no depression of m.p. on admixture with samples (*a*), (*b*), and (*c*). The picrate melted at 170–171°.

All samples in organic solvents showed the same, moderately intense, blue fluorescence while, in glacial acetic acid mixed with conc'd nitric acid there was seen the same deep bluish-green color that soon turned to a pure green and faded to a pale yellow on standing.

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8.

Found: (*a*) C, 73.3; H, 6.9; (*c*) C, 73.4; H, 7.1; (*d*) C, 73.7; H, 6.8.

In a warm alcoholic solution of picric acid the substance dissolved with a deep brown color. On standing, unchanged material separated, which changed gradually (in a few days) into almost black cubes of a *dipicrate*, m.p. 171–173°.

Anal. Calc'd for $C_{20}H_{22}O_4 \cdot 2C_6H_3N_3O_7$: C, 49.0; H, 3.6; N, 10.4.

Found: (*a*) N, 9.9, 9.7.
(*c*) C, 49.4, 49.3; H, 3.9, 3.9; N, 9.6, 9.7.
(*d*) N, 9.7, 9.8.

2,3,6,7-Tetramethoxy-9-ethylanthrone (XXIV). Carbenium sulfate XXII, freshly prepared from 5 g. of XX, was dissolved in 100 ml. of 96% methyl alcohol at room temperature. The readily-separating solid was redissolved in 150 ml. of acetone, and the solution then was filtered and mixed with 50 ml. of water. On warming this solution on the steam-bath, acetone slowly evaporated, and long colorless needles crystallized. Upon being dried, the product acquired a pale yellow color and melted at 183–184°, without solidifying on further rise of the temperature. Yield, 3.5 g. (*cf.* 16).

Anal. Calc'd for $C_{20}H_{22}O_5$: C, 70.1; H, 6.5; OCH_3, 36.3.

Found: C, 70.0; H, 6.7; OCH_3, 35.9, 35.9.

After decomposing the carbenium sulfate with water and recrystallizing the product from acetone-water, pale yellow needles melting at 182–183° were formed which resolidified at 190°, and melted again at 225–235°. The product prepared with methyl alcohol is yellow when melted, whereas samples prepared with water are cherry-red when melted.

2,3,6,7-Tetramethoxy-9,10-diethylanthracene (XXV). A mixture, prepared from a solution of 0.4 g. (0.032 g.-atom) of magnesium foil and 3.27 g. (0.032 mole) of ethyl bromide in 15 ml. of ether and from 2.7 g. (0.008 mole) of XXIV in 27 ml. of anhydrous dioxane, was refluxed on the steam-bath with vigorous stirring (40 hours). This mixture was poured onto ice mixed with hydrochloric acid and 2.5 g. of a pale yellow solid, m.p. 220–230°, separated. Three consecutive recrystallizations from ethyl acetate-alcohol 3:1 gave 2.2 g. of long slender needles, m.p. 235–247°. There was no depression with a sample prepared from veratrole and propionaldehyde and recrystallized to the above melting point. [For the latter product m.p. 239° was reported previously (17), whereas Pailer (4) gives m.p. 248–250°]. The substance gives an intense sky-blue fluorescence in alcoholic solutions, and a deep-blue coloration in glacial acetic acid on the addition of conc'd nitric acid.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.6; H, 7.4.

Found: C, 74.9, 74.7; H, 7.5, 7.6.

When dissolved in a warm alcoholic solution of picric acid the substance reappears at first unchanged and then gradually changes to glistening thin black needles of a *picrate*, m.p. 182°. The same picrate was obtained with the samples prepared by synthesis.

Anal. Calc'd for $C_{22}H_{26}O_4 \cdot C_6H_3N_3O_7$: N, 7.2. Found: N, 7.3, 7.4.

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SUMMARY

The intermediates of the chromic acid oxidation of diisohomogenol have been reinvestigated in the light of the correction made by Doering and Berson concerning the earlier formulation of the primary oxidation product. A corrected scheme of the degradation is proposed.

Muzeum körut 4/b,
Budapest VIII, Hungary

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