[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF BUDAPEST]

DIMERIC PROPENYLPHENOL ETHERS. XVIII. HYDROGEN PEROXIDE CLEAVAGE OF ISOCHROMENIUM DERIVATIVES OF THE PRIMARY OXIDATION PRODUCT OF DIISOHOMOGENOL

ALEXANDER MÜLLER, MIOMIR MÉSZÁROS, AND KÁROLY KÖRMENDY

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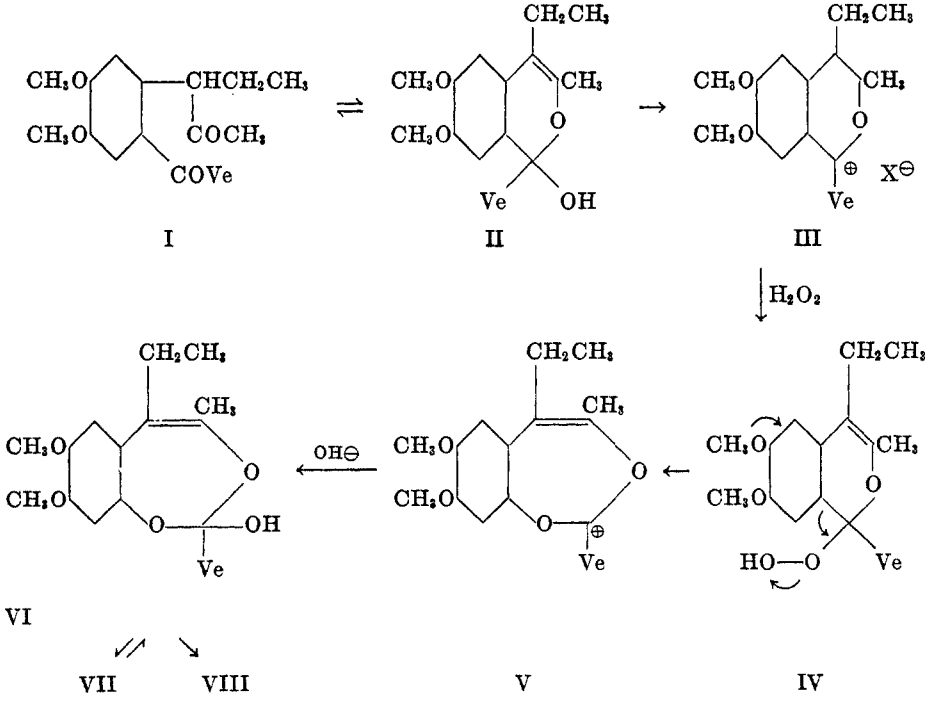
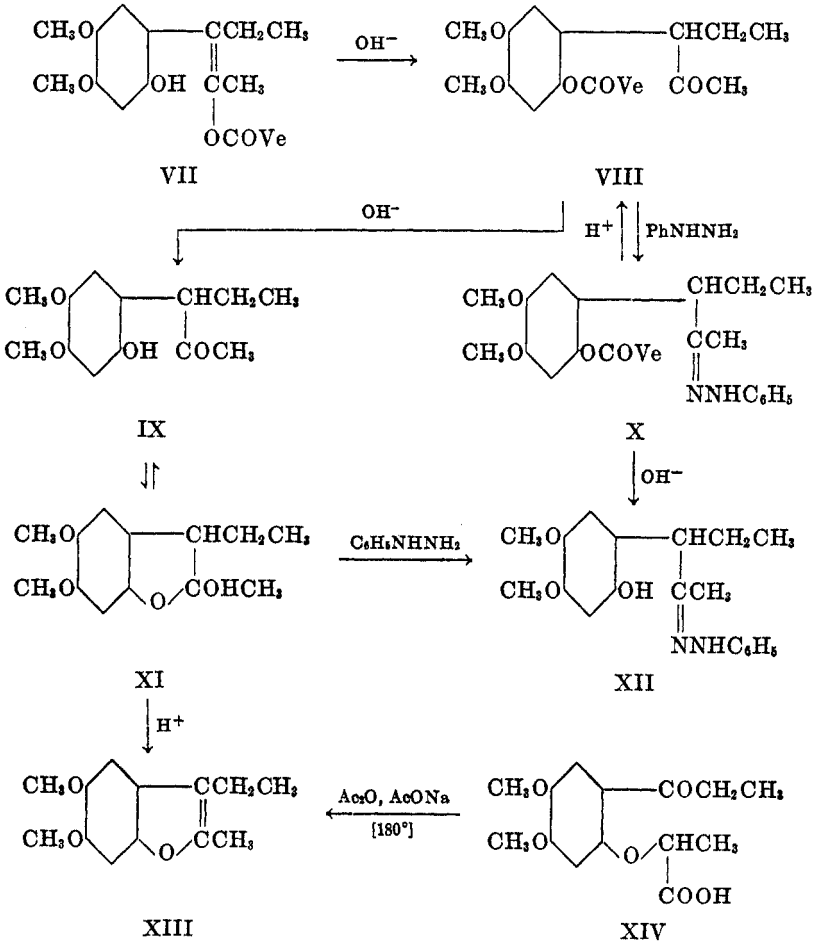
It was reported several years ago that the halochromic salts, formed by the primary oxidation product $C_{22}H_{26}O_6$ (I) of diisohomogenol (*cf.* 1, 2) with mineral acids, are readily oxidized by chromic acid or permanganate (3), with cleavage of the C^3—C^4 bond of an—as is now known—isochromenium structure III. Hydrogen peroxide attacks the system at a different point, cleaving the bond between the carbenium carbon and the higher substituted aromatic ring. The product of this latter reaction was found to be a phenol, $C_{22}H_{26}O_7$, readily decomposed by conc'd alkalies and mineral acids into veratric acid and 2-methyl-3-ethyl-5,6-dimethoxycoumarone (XII) (4). Now that the starting material is known to have structure III the phenolic oxidation product would be expected to represent the enol O-veratroate of a 2-(α-acetopropyl)-4,5-dimethoxyphenol (VII), formed by the indicated steps of the route III → VII (*cf.* 5). Doering and Berson (1), however, formulate the product as the isomeric phenol ester VIII. The present paper offers evidence in favor of structure VII.



The presence of a free phenolic hydroxyl in the oxidation product was demonstrated previously by the preparation of a crystalline O-methanesulfonate (4). Moreover, it was reported that the oxidation product melting at 130°, on being contacted with warm dilute alkali, was transformed to an isomer of m.p. 95° which no longer reacted with hydroxyl reagents, while its reactivity with carbonyl reagents was distinctly enhanced. This observation finds ready interpretation in that the enol ester VII reacts with carbonyl reagents only after rearrangement —presumably through the *ortho* ester intermediate VI—to the phenol ester VIII which contains a free carbonyl group.

The identical insolubility of both isomers in cold aqueous 10 % alkali indicates a rather hindered phenolic hydroxyl even in VII (*cf.* 6). On addition of some alcohol, however, VII soon passes into solution; the resulting solution then deposits crystals of VIII on standing.



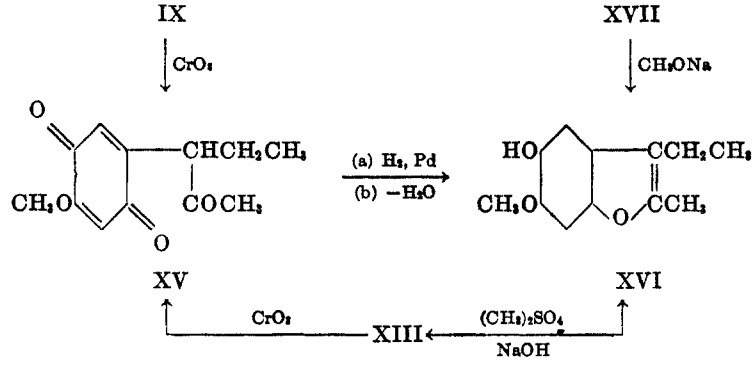
In conc'd alcoholic alkali this difference disappears, and in both cases quantitative hydrolysis occurs. The products of hydrolysis are veratric acid and a

phenolic methyl ketone (IX). The latter seems to exist in tautomeric equilibrium with α-coumaranol (XI), since its phenolic hydroxyl proves to be rather hindered (no O-acyl derivatives). Its phenylhydrazone (XII) is identical with that of VIII after deveratroylation of the latter with alkali. Mineral acids dehydrate the methyl ketone (IX) to 2-methyl-3-ethyl-5,6-dimethoxycoumarone (XIII) (4) which has been prepared from α-(3,4-dimethoxy-6-propionylphenoxy)propionic acid (XIV).

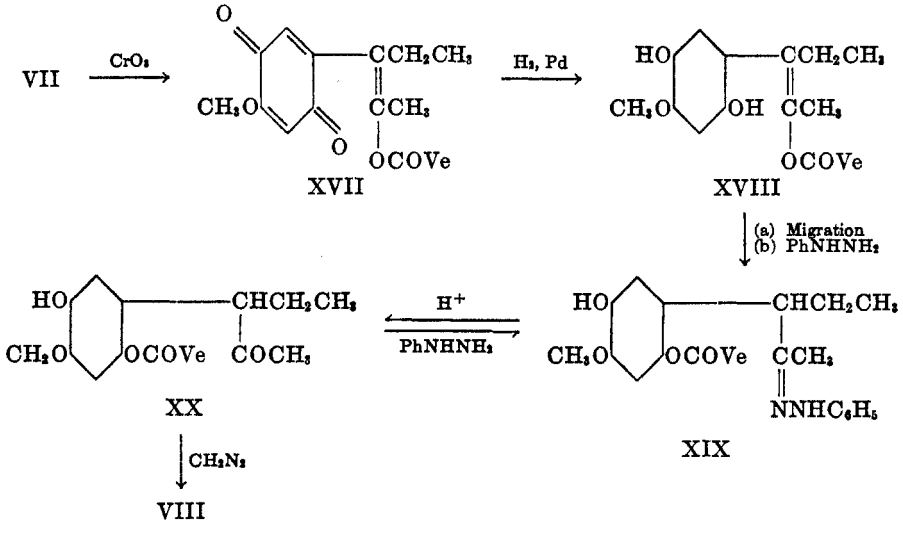
The most conspicuous difference between the two isomers VII and VIII is in their respective behavior towards oxidants. Phenol ester VIII, or the O-acetate or O-methanesulfonate of VII, are fairly stable toward chromic acid at room temperature. Under the same conditions, enol ester VII undergoes oxidation to a highly crystalline, golden-yellow product.

Alcoholic alkali was found to cleave this product with rapid darkening of the reaction mixture, to one mole of veratric acid and small amounts of a coumarone of m.p. 101–102° containing one carbon atom less than coumarone XIII. The non-identity of this product with either the 2,3-dimethyl- or the 3-ethyl- derivative of 5,6-dimethoxycoumarone suggested that the missing carbon atom must have been lost from the aromatic ring.

Further investigation of this cleavage was greatly simplified by the occasional observation that the methyl ketone (IX) ($C_{13}H_{18}O_4$) undergoes similar oxidation. The golden-yellow oxidation product so obtained proved to be identical with the substance already described (4) as being obtained from coumarone XIII with chromic acid. Repeated analyses of exhaustively purified samples have shown that the previously suggested formula $C_{11}H_{12}O_4$ is to be replaced by $C_{12}H_{14}O_4$. Consequently, the oxidation of IX involves the loss of one carbon atom and of four hydrogen atoms. The liberation of iodine from hydrogen iodide solutions, or of nitrogen from phenylhydrazine, suggested a quinone character for $C_{12}H_{14}O_4$. Catalytic hydrogenation proceeded with great rapidity with the absorption of exactly one mole of hydrogen. The resulting alkali-soluble product of m.p. 101–102° was not a hydroquinone, however, but a courmarone identical with the coumarone which was formed in the alkaline hydrolysis of the yellow oxidation product of the enol ester VII.



Alkaline methylation gave a methyl ether identical with coumarone XIII thus presenting proof that the oxidation product of the methyl ketone (IX) is a 2-α-acetopropyl-5-methoxyquinone (XV), formed by oxidation and simultaneous demethylation of the aromatic ring (*cf.* 7). Hydrogenation to the hydroquinone then results in the immediate loss of water with formation of a 2-methyl-3-ethyl-5-hydroxy-6-methoxycoumarone XVI (*cf.* 8). Such information already establishes the structure of the oxidation product of the enol ester (VII), purely from analogy, as that of a quinone (XVII). Sodium methoxide then not only hydrolyzes this quinone but effects to some extent a concomitant reduction and subsequent dehydration to XVI. Catalytic hydrogenation converts quinone XVII to a hydroquinone (XVIII) which—with the enolic hydroxyl protected—cannot undergo subsequent dehydration. At room temperature this hydroquinone is indifferent also toward phenylhydrazine. On prolonged heating, however, just as in the reaction of enol ester VII with phenylhydrazine, migration of the O-veratroyl group from the enolic to the phenolic hydroxyl occurs which makes subsequent condensation with phenylhydrazine possible. Acid hydrolysis of the resulting phenylhydrazine (XIX) affords an isomer XX of hydroquinone XVIII, which readily yields with diazomethane the phenol ester VIII.

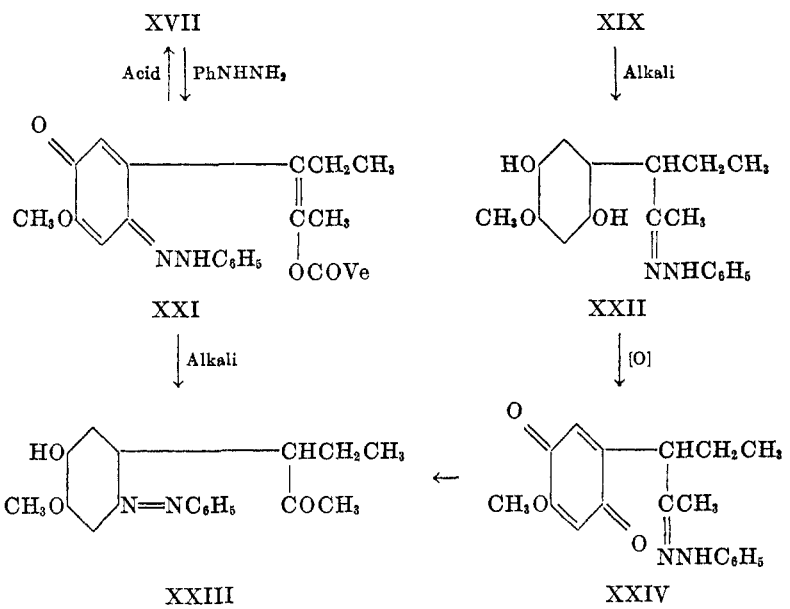


At low temperatures the quinone (XVII) reacts smoothly with phenylhydrazine to the quinone phenylhydrazone (XXI) of m.p. 190° (*cf.* 9). Acid hydrolysis of this product recovers quinone XVII in about 50 % yield, while alkaline hydrolysis effects deveratroylation and subsequent rearrangement to an orange-colored alkali-soluble benzeneazo derivative (XXIII) (*cf.* 10).

At elevated temperatures, however, quinone XVII reacts with phenylhydrazine with considerable vigor to give a dihydro phenylhydrazone of m.p. 203° identical in every respect with XIX. Obviously, under these conditions

phenylhydrazine first reduces quinone XVII to XVIII (*cf.* 11), which, after rearrangement to XX, reacts to form the phenylhydrazone (XIX).

Noteworthy enough, the phenylhydrazo group could be shown to share the tendency of the O-veratroyl group toward internal migration from the side chain into the aromatic ring. On removing the veratroyl group from XIX with alkali, the resulting hydroquinone phenylhydrazone (XXII) underwent dehydrogenation during recrystallization producing the benzeneazo derivative XXIII which was obtained also directly from XXI with alcoholic alkali. Phenylhydrazones and semicarbazones react with reactive carbonyl compounds (benzaldehyde, acetone, pyruvic acid etc.) with recovery of the original carbonyl group. In the present case, this reaction occurs intramolecularly, the quinone part of XXIV cleaving the phenylhydrazone grouping with subsequent transposition of the phenylhydrazo group to the aromatic ring.



Although it was not feasible for us to take infrared spectra of these compounds, these reactions leave no reasonable doubt that the product obtained from the isochromium salt (III) with hydrogen peroxide has structure VII. The fact that in the stable isomer VIII the phenolic hydroxyl had become protected by transesterification of the O-veratroyl from the enolic hydroxyl, and the methyl ketone part of the molecule had been, in consequence, uncovered, was further demonstrated by the selenium dioxide oxidation of this substance, whereby a dicarbonyl compound was formed without concomitant change on the alicyclic ring.

EXPERIMENTAL

The enol veratroate of 2-(α-acetopropyl)-4,5-dimethoxyphenol (VII) was prepared from the isochromenium sulfate (chloride, nitrate) (III) as described previously (4). The substance was recrystallized three times from alcohol, slender colorless needles, m.p. 130°.

Anal. Calc'd for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5; Active H, 0.258.
Found: C, 65.8, 65.9; H, 6.7, 6.7; Active H, 0.221, 0.209.

The substance was insoluble in 20% sodium hydroxide solution at room temperature. Upon adding a little alcohol to the suspension gradual solution took place, and on the next day the solution deposited sturdy prisms of VIII. Upon adding diazomethane to a methanol-ether solution of the substance, followed by subsequent evaporation of the filtered solution on the next day, a colorless oil was formed which slowly crystallized from a small amount of alcohol. Two subsequent recrystallizations from alcohol produced colorless prisms, m.p. 95–96°, identical with VIII. Yield, 32%.

Upon mixing the substance with an equal weight of phenylhydrazine, and then dissolving the mixture in warm alcohol, after a few hours at room temperature colorless flat needles, m.p. 203–204°, separated. One recrystallization from alcohol raised the melting point to 207–208°, which remained undepressed on the admixture of the phenylhydrazone prepared from VIII.

After oxidizing 3 g. of the O-methanesulfonate (4) (small colorless needles of m.p. 151–152°), in 250 ml. of glacial acetic acid with 1.2 g. of chromium trioxide at room temperature for 48 hours, the mixture was poured into ice-water and extracted with benzene. The benzene extract contained no alkali-soluble products. From the extract unchanged material (2.2 g.) was isolated, which melted after one recrystallization from alcohol at 151–152°, alone or in mixture.

Anal. Calc'd for $C_{23}H_{28}O_9S$: C, 57.5; H, 5.9.
Found: C, 57.6; H, 6.1.

2-(α-Acetopropyl)-4,5-dimethoxyphenol veratroate (VIII) was prepared from VII as described (4), and was recrystallized three times from ethyl or butyl alcohol, stout colorless prisms, m.p. 95–96°. It was insoluble in aqueous or 90% alcoholic 20% sodium hydroxide solution.

Anal. Calc'd for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5; Active H, 0.
Found: C, 65.9, 65.9; H, 6.6, 6.6; Active H, 0.

A solution of 3 g. of the substance in 100 ml. of glacial acetic acid was mixed with 1.2 g. of chromium trioxide in 40 ml. of glacial acetic acid, and kept at room temperature for 48 hours. Upon working up the mixture as above, 1.9 g. of unchanged material was recovered which melted after two recrystallizations from alcohol at 95°, alone or in mixture.

The *phenylhydrazone* (X) instantly crystallized from an alcoholic solution of VIII on addition of phenylhydrazine (4). After one recrystallization from alcohol, colorless flat needles were obtained, m.p. 208–209°, alone or mixed with a sample prepared from VII. The solution in conc'd sulfuric acid was pale yellow with an intense green fluorescence.

Anal. Calc'd for $C_{28}H_{32}N_2O_6$: C, 68.3; H, 6.5; N, 5.7.
Found: C, 68.2, 68.3; H, 6.7, 6.7; N, 5.5, 5.8.

A solution of 0.7 g. of the substance in 25 ml. of alcohol was mixed with 6 ml. of conc'd hydrochloric acid and kept at 60° for one hour. After addition of 200 ml. of water, the mixture was extracted with benzene. On evaporation, the extract left a reddish oil which slowly crystallized from 4 ml. of methyl alcohol. This gave colorless prisms (0.37 g.) of VIII, which melted after two recrystallizations from alcohol at 94–95° alone or in mixture.

The *semicarbazone*, from 1 g. of VIII or VII and 0.4 g. of semicarbazide acetate in 5 ml. of alcohol refluxed for 30 minutes, separated in long colorless needles, which, after one recrystallization from alcohol, melted at 127–128°. The air-dry product contained water of hydration.

Anal. Calc'd for $C_{23}H_{29}N_3O_7 \cdot H_2O$: C, 58.1; H, 6.5; N, 10.3.
Found: C, 58.3, 58.3; H, 6.6, 6.6; N, 9.7, 9.4.

Drying at 80°/14 mm. for six hours over phosphorus pentoxide afforded anhydrous material, m.p. 127–128°.

Anal. Calc'd for $C_{23}H_{29}N_3O_7$: C, 60.1; H, 6.4.
Found: C, 60.3, 60.1; H, 6.5, 6.5.

2-(α-Acetopropyl)-4,5-dimethoxyphenol (IX). A solution of 5 g. of VII or VIII in 100

ml. of methyl alcohol containing 2 g. of previously dissolved sodium was kept at room temperature for 20 hours, then mixed with 300 ml. of water and extracted with a total of 300 ml. of benzene. (From the benzene extract 1.1 g. of VIII was recovered quite regularly.) The aqueous methyl alcoholic layer was next concentrated to 180 ml. at reduced pressure and then saturated with carbon dioxide. Extraction of the resulting mixture with benzene produced 2.0 g. of a slowly solidifying oil. This was distilled at 11 mm., and the colorless liquid quickly solidified on being seeded with the crude. Recrystallizing the product from ether-petroleum ether in an ice-salt mixture gave small colorless needles which melted at 75–77° after undergoing softening at 72°. The substance was readily soluble in organic solvents, except petroleum ether, and insoluble in water; it quickly dissolved, however, on addition of alkali. It gave a faint green coloration with methanolic ferric chloride solution and conc'd sulfuric acid dissolved it with formation of a yellow color, the solution displaying a green fluorescence. There was no reaction with acetic anhydride-pyridine 1:1 at room temperature.

Anal. Calc'd for $C_{13}H_{18}O_4$: C, 65.8; H, 7.6.
Found: C, 65.6, 65.7; H, 7.8, 7.8.

Phenylhydrazone (XII). (*a*) A mixture of 2 g. of IX and 1 ml. of phenylhydrazone in 10 ml. of alcohol containing two drops of glacial acetic acid, kept at room temperature for one day, deposited a mass of flat needles (1.5 g.) which, after two recrystallizations from alcohol, melted at 123–124°. (*b*) Upon refluxing a mixture of 2.0 g. of X and 200 ml. of alcohol containing 20 ml. of 20% sodium hydroxide solution, a clear orange-colored solution was obtained in six hours. After removal of the alcohol at reduced pressure, the remaining solution was saturated with carbon dioxide. The oily precipitate was then isolated by extraction with ether. The residue of the extract was crystallized from alcohol, two recrystallizations from the same solvent yielding 0.9 g. of stout colorless prisms of m.p. 122–124°. There was no depression on admixture with sample (*a*). On standing both samples (*a*) and (*b*) acquired a buff color with lowering of the melting point. Conc'd sulfuric acid dissolved the substance giving a pale yellow color and a green fluorescence.

Anal. Calc'd for $C_{19}H_{24}N_2O_3$: C, 69.6; H, 7.3; N, 8.5.
Found: (*a*): C, 69.7, 69.8; H, 7.6, 7.5; N, 8.6, 8.4.
(*b*): N, 8.4, 8.5.

Semicarbazone. A mixture of 2 g. of IX and 2 g. of semicarbazide acetate in 25 ml. of 70% methyl alcohol, kept at 50° for one hour and then mixed gradually with water, precipitated a rapidly solidifying oil. This formed colorless needles from alcohol, 2.1 g. melting at 161–163°.

Anal. Calc'd for $C_{14}H_{21}N_3O_4$: C, 56.9; H, 7.2; N, 14.2.
Found: C, 56.7; H, 7.3; N, 14.4.

2-Methyl-3-ethyl-5,6-dimethoxycoumarone (XIII). (*a*) The preparation starting with VII or VIII has been described (4). (*b*) After dissolving 1.0 g. of XII in 20 ml. of alcohol containing 1 ml. of conc'd sulfuric acid, the red-brown solution was diluted in 12 hours with water, and subsequently extracted with benzene. Upon removing the solvent, the remaining mobile oil, on being dissolved in 10 ml. of a 10% alcoholic solution of picric acid, afforded 0.9 g. of a red-brown picrate, m.p. 94–96°. There was no depression in m.p. with the picrate of sample (*a*). (*c*) A mixture of 3 g. of α-(3,4-dimethoxy-6-propionylphenoxy)-propionic acid (XIV), 3 g. of anhydrous sodium acetate, and 20 ml. of acetic anhydride was gently refluxed in an oil-bath for five hours. Then the mixture was cooled and water was added. After decomposition of the anhydride, the mixture was extracted with chloroform. The extract, washed with 10% potassium hydrogen carbonate solution, dried with calcium chloride, and evaporated, gave a straw-colored oil. This product, on being dissolved in 5 ml. of a saturated alcoholic solution of picric acid, gave 2.6 g. of red-brown needles, m.p. 93–94°. Recrystallization from alcohol raised the melting point to 95–96°, without substantial loss of material. There was no depression in m.p. with the picrate of sample (*a*). This material was analyzed.

Anal. Calc'd for $C_{13}H_{16}O_3 \cdot C_6H_3N_3O_7$: C, 50.8; H, 4.3; N, 9.4.
Found: C, 51.0; H, 4.3; N, 9.1.

A solution of 0.3 g. of picrate (*c*) in 30 ml. of chloroform, decolorized by shaking with 300 ml. of a 1% aqueous sodium hydroxide solution, on subsequent evaporation left 0.13 g. of an almost colorless oil. This, on being chilled in ice, solidified to colorless serrated plates, m.p. 28–29°. There was no depression in m.p. with a sample prepared under (*a*).

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3; OCH_3, 28.2.
Found: C, 70.8, 70.9; H, 7.4, 7.3; OCH_3, 28.2.

2-(α-Acetopropyl)-5-methoxyquinone (XV). (*a*) A solution of 4.3 g. (0.018 mole) of 2-(α-acetopropyl)-4,5-dimethoxyphenol (IX) in 50 ml. of glacial acetic acid was slowly mixed under ice-cooling with 4 g. (0.04 mole) of chromium trioxide in 20 ml. of 90% acetic acid. When kept at room temperature for 16 hours, the mixture occasionally crystallized. It was diluted, regardless of a precipitate, with water and extracted with benzene. Evaporation of the extract left a crystalline residue, which crystallized from water or from alcohol in shining golden-yellow plates (2.0 g., 50%) and, after one recrystallization from alcohol, melted at 129–130°. (*b*) An ice-cold solution of 1.5 g. (0.0035 mole) of 2-(α-acetopropyl)-4,5-dimethoxyphenol-1-veratroate (VIII) in 20 ml. of glacial acetic acid, mixed with 0.6 g. (0.006 mole) of chromium trioxide in 6 ml. of 90% acetic acid, was kept at room temperature for 48 hours. Then water was added, followed by extraction with benzene. By washing the extract with 5% sodium carbonate solution, 0.6 g. (90%) of veratric acid, m.p. 177–178°, was isolated. Evaporation of the benzene extract produced a solid residue which, after one recrystallization from alcohol, gave 0.45 g. (54%) of golden-yellow leaflets, m.p. 128–130°, alone or mixed with sample (*a*). (*c*) Oxidation of the coumarone (XIII) as already described (4). The melting point, 128–130°, was undepressed on admixture with the samples (*a*) and (*b*).

When phenylhydrazine or semicarbazide acetate was added to the alcoholic solution of the above, nitrogen was evolved. No crystalline condensation products have been obtained. An alcoholic solution liberates iodine from an acidified potassium iodide solution (starch-test).

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4; OCH_3, 13.9.
Found: (*a*): C, 65.0, 65.0; H, 6.6, 6.5; OCH_3, 13.9, 14.0.
(*b*): C, 65.2; H, 6.5.
(*c*): C, 64.8; H, 6.6.

Enol veratroate of 2-(α-acetopropyl)-5-methoxyquinone (XVII). (*a*) A solution of 10 g. (0.025 mole) of VII in 60 ml. of glacial acetic acid was mixed with ice-cooling with 6 g. (0.06 mole) of chromium trioxide in 5 ml. of water and 20 ml. of glacial acetic acid. After 24 hours at room temperature, the mixture (often depositing a solid mass of crystals) was diluted with water and then extracted with benzene. The extract, washed with 5% sodium carbonate solution, on evaporation left a semisolid residue which crystallized from alcohol. Three subsequent recrystallizations from the same solvent produced 4.9 g. of golden-yellow prisms, m.p. 149°. (*b*) In a mixture of 20 ml. of glacial acetic acid and 4 ml. of 60% nitric acid, 2 g. of VII was dissolved by shaking at room temperature. After 30 minutes, the red-brown solution was gradually diluted with water. The voluminous crystal mass which separated was collected, washed thoroughly with water, and recrystallized from alcohol to give stout golden-yellow prisms (1.2 g.), m.p. 148–149°, alone or mixed with sample (*a*).

Anal. Calc'd for $C_{21}H_{22}O_7$: C, 65.3; H, 5.7; OCH_3, 24.1.
Found: C, 65.6, 65.4; H, 5.9, 5.9; OCH_3, 24.1, 24.1.

The substance is slightly soluble in alcohol and in glacial acetic acid, more readily in chloroform, acetone, or ethyl acetate. Alcoholic alkali or mineral acid induce rapid darkening of the alcoholic solution.

The substance quickly decolorizes bromine in chloroform, or destroys permanganate in acetone. It liberates iodine from acidified potassium iodide solutions (starch test). The solution in pure methyl alcohol, mixed with aqueous sodium hypobromite solution and then steam-distilled, produced yellow plates, m.p. 119°, of iodoform.

Semicarbazone. In an alcoholic solution of semicarbazide acetate the substance dissolves with gentle evolution of nitrogen, the resulting solution on standing depositing lemon-

yellow cottony needles which, after being recrystallized from dilute alcohol, melted at 198–200°.

Anal. Calc'd for $C_{22}H_{25}N_3O_7$: C, 59.6; H, 5.7; N, 9.5.

Found: C, 59.3, 59.4; H, 5.7, 5.8; N, 9.6, 9.6.

Phenylhydrazone (XXI). To a suspension of 4.0 g. of the substance in 60 ml. of alcohol, cooled in ice, 4 ml. of phenylhydrazine was added by drops. There was a gradual dissolution with vigorous evolution of nitrogen and heat. In a few hours practically colorless flat polyhedrons separated (4.4 g. 90%), melting at 190–191°.

Anal. Calc'd for $C_{27}H_{28}N_2O_6$: C, 68.0; H, 5.9; N, 5.9; OCH_3, 19.5.

Found: C, 68.0, 68.3; H, 6.1, 6.0; N, 5.7, 5.7; OCH_3, 19.7, 19.8.

(*a*) *Acid hydrolysis.* A solution of 3 g. of XXI in 150 ml. of alcohol mixed with 25 ml. of 25% hydrochloric acid, and kept at 60° for 30 minutes, was mixed subsequently with water and extracted with benzene. From the extract a semisolid was obtained, that crystallized slowly from alcohol. After one recrystallization from the same solvent, 1.3 g. (52%) of golden-yellow prisms, m.p. 148–149°, of quinone XVII were obtained. There was no depression with an authentic specimen.

(*b*) *Alkaline hydrolysis.* A solution of 6.5 g. of XXI in 60 ml. of alcohol, mixed with 10 ml. of 20% aqueous sodium hydroxide solution and warmed subsequently on the steam-bath for 30 minutes, was diluted with 200 ml. of water and freed from alcohol under reduced pressure. The remaining aqueous alkaline solution was then neutralized with carbon dioxide. The separating dark brown oil was isolated with ether. [The subsequently acidified aqueous layer precipitated 2.3 g. (95%) of veratric acid, m.p. 177–178°]. Upon removing the ether, the residue crystallized from a small amount of alcohol. Two subsequent recrystallizations from the same solvent gave 0.8 g. of orange-colored flat prisms, m.p. 178–179°, of *4-benzeneazo-2-methoxy-5-(α-acetopropyl)phenol* (XXIII). The substance dissolves in aqueous alkali on addition of some alcohol to the suspension. The solution in conc'd sulfuric acid is cherry-red, in glacial acetic acid-sulfuric acid it is deep orange.

Anal. Calc'd for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 8.9; OCH_3, 9.9.

Found: C, 69.5, 69.6; H, 6.7, 6.6; N, 8.8, 8.9; OCH_3, 10.3.

Enol veratroate of 2-(α-acetopropyl)-5-methoxyhydroquinone (XXVIII). A solution of 5 g. of quinone XVII in 100 ml. of alcohol, hydrogenated in the presence of 0.5 g. of a 5% palladium-charcoal catalyst, consumed 305 ml. of hydrogen in 25 minutes. Evaporation of the colorless filtrate left a fibrous, amorphous mass which resisted crystallization.

The *diacetate*, prepared by acetylation of the substance with acetic anhydride and anhydrous sodium acetate on the steam-bath, slowly crystallized from dilute acetic acid. Recrystallized from ethyl acetate-petroleum ether, it formed colorless cubes or sturdy prisms, m.p. 105°.

Anal. Calc'd for $C_{26}H_{28}O_9$: C, 63.5; H, 6.0; OCH_3, 19.7.

Found: C, 63.8, 63.6; H, 6.3, 6.2; OCH_3, 19.7, 19.8.

2-(α-Acetopropyl)-5-methoxyhydroquinone-1-veratroate phenylhydrazone (XIX). (*a*) To a boiling solution of 3 g. of quinone XVII in 40 ml. of alcohol, 2 ml. of phenylhydrazine was added by drops. After the very vigorous reaction, the solution was refluxed for 30 minutes. At room temperature, 2.25 g. of flat colorless needles, m.p. 203–204°, separated. (*b*) From a solution of 1.5 g. of hydroquinone XVIII and 1.5 g. of phenylhydrazine in 10 ml. of alcohol, kept on the steam-bath for 30–40 minutes, 1.2 g. of colorless plates, m.p. 203–204°, separated. There was no depression with a sample prepared under (*a*).

Anal. Calc'd for $C_{27}H_{30}N_2O_6$: C, 67.8; H, 6.3; N, 5.8; OCH_3, 19.4.

Found: C, 68.1; H, 6.5; N, 5.9, 5.9; OCH_3, 19.9, 19.5.

In the alkaline hydrolysis of 5 g. of the substance, as described for phenylhydrazone XXI, the neutralization of the aqueous alkaline solution produced a canary-yellow solid precipitate. This was removed and recrystallized several times from alcohol; the product formed orange-colored thin plates of m.p. 178–179°, identical in every respect with the 4-benzeneazo derivative (XXIII) obtained from the quinone phenylhydrazone (XXI) in the analogous procedure. [From the extracted aqueous alkaline mixture, hydrochloric acid precipitated only 1.2 g. (42%) of veratric acid.]

Anal. Calc'd for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 8.9; OCH_3, 9.9.
Found: C, 69.4, 69.5; H, 6.7, 6.8; N, 8.8, 9.0; OCH_3, 10.4.

2-(α-Acetopropyl)-5-methoxyhydroquinone-1-veratroate (XX). A mixture of 2.2 g. of XIX, 100 ml. of alcohol, and 25 ml. of 20% hydrochloric acid was refluxed on the steam-bath for one hour. After addition of water and benzene, the benzene extract was removed, washed as usual, and evaporated. The remaining dark oil slowly crystallized from alcohol, repeated recrystallizations from the same solvent affording 1.5 g. of colorless small needles, m.p. 150–151°. The substance slowly dissolved in aqueous 10% sodium hydroxide solution. The solution in glacial acetic acid-sulfuric acid was pale yellow with a faint green reflex. Bromine in glacial acetic acid was not decolorized instantly by this material.

Anal. Calc'd for $C_{21}H_{24}O_7$: C, 64.9; H, 6.4; OCH_3, 23.9.
Found: C, 64.6, 65.1; H, 6.4, 6.5; OCH_3, 24.0, 23.7.

The *phenylhydrazone* instantly separated from a warm solution of 0.4 g. of above substance in 4 ml. of alcohol on the addition of 0.2 ml. of phenylhydrazine and two drops of glacial acetic acid. It formed colorless needles, which on recrystallization from alcohol became plates, m.p. 192–194°, identical in every respect with the phenylhydrazone XIX obtained from XVIII or from XVII as described above.

Anal. Calc'd for $C_{27}H_{30}N_2O_6$: N, 5.8. Found: N, 5.9, 5.9.

The *semicarbazone* separated, on cooling from a dilute alcoholic solution of semicarbazide acetate and XX refluxed on the steam-bath for 30 minutes, as long colorless needles, m.p. 126–128°, from alcohol. For analysis the product was dried at 56°/14 mm. over phosphorus pentoxide.

Anal. Calc'd for $C_{22}H_{27}N_3O_7$: C, 59.3; H, 6.1; N, 9.4.
Found: C, 59.6; H, 6.4, 6.3; N, 8.9, 9.2.

The *acetate* quickly solidifies when a mixture of 0.5 g. of XX, 0.5 g. of anhydrous sodium acetate, and 5 ml. of acetic anhydride, after being kept on the steam-bath for 20 minutes, was poured into ice. When recrystallized from acetone with the gradual addition of water, it gave colorless, thin quadratic plates, m.p. 132–133°.

Anal. Calc'd for $C_{23}H_{26}O_8$: C, 64.2; H, 6.1; OCH_3, 21.6.
Found: C, 64.2, 64.0; H, 6.3, 6.3; OCH_3, 21.8, 21.3.

The *methyl ether*, prepared by methylation of XX in ethereal solution with diazomethane, crystallized from a small quantity of alcohol in colorless rosettes, in a yield of 50%. Two recrystallizations from alcohol raised the melting point to 94–95° which remained undepressed on admixture of VIII prepared from VII.

Anal. Calc'd for $C_{22}H_{26}O_7$: OCH_3, 30.8. Found: OCH_3, 30.9, 30.6.

2-Methyl-3-ethyl-5-hydroxy-6-methoxycoumarone (XVI). (*a*) *By hydrogenation of quinone* XV. A solution of 5 g. of XV in 30 ml. of alcohol absorbed 620 ml. of hydrogen within eight minutes. Evaporation of the colorless filtrate left a solid residue which crystallized from a concentrated solution in warm alcohol in thin colorless leaflets, m.p. 99–101° (3.8 g.). Recrystallization from 20 ml. of alcohol afforded glassy cubes, m.p. 101–102°. [Previously (4) m.p. 95–96° was reported.] The *picrate* forms deep violet-brown needles, m.p. 112–113° (from alcohol). (*b*) *By reductive alkaline hydrolysis of quinone XVII.* A solution of 3 g. of XVII in 100 ml. of methyl alcohol was mixed with a solution of 1 g. of sodium in 50 ml. of methyl alcohol. The solution acquired a red-brown color on standing for 24 hours at room temperature. The mixture was then diluted with 500 ml. of water, then neutralized with carbon dioxide, and extracted with benzene. The extract, on being evaporated after the usual washing and drying, left a dark semisolid residue which on subsequent distillation at 0.02 mm. solidified to a colorless mass in the receiver. The product was recrystallized from alcohol, 0.9 g. of thin plates being obtained, melting at 101–102°, alone or mixed with specimen (*a*). [From the aqueous alkaline reaction mixture, remaining after the neutralization with carbon dioxide and subsequent extraction, 1.35 g. (96.5%) of veratric acid was isolated].

(*c*) *By acid hydrolysis of hydroquinone veratroate* (XX). Upon dissolving 3.4 g. of XX in 25 ml. of conc'd sulfuric acid by shaking at room temperature, the brown-red solution, which later acquired a green fluorescence, was allowed to stand for 24 hours, and was then

poured into ice-water. The resulting mixture now was extracted with chloroform, the extract being washed repeatedly with 5% sodium carbonate solution which removed 1.48 g. of veratric acid. The extract was then dried with sodium sulfate and evaporated. The residue crystallized from ether in colorless plates, and after two subsequent recrystallizations from methyl alcohol, 0.8 g. of thin leaflets, m.p. 101–102°, were obtained. There was no depression on admixture with specimens prepared under (*a*) and (*b*), respectively. The *picrate* was found to melt at 112–113°, alone or mixed with picrate (*a*).

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8; OCH_3, 15.0.
Found: (*a*): C, 71.10, 69.9; H, 7.1, 7.0; OCH_3, 15.0, 15.0.
(*b*): C, 70.0, 70.0; H, 7.2, 7.1.
(*c*): C, 69.7, 69.9; H, 7.1, 7.1; OCH_3, 15.2.

The substance gave a pale green coloration with methanolic ferric chloride. On being dissolved in just the sufficient quantity of luke warm 10% sodium hydroxide solution, giant rosettes of the *sodium salt* separated that were freely soluble in alcohol.

Anal. Calc'd for $C_{12}H_{13}NaO_3 \cdot H_2O$: Na, 9.4. Found: Na, 9.8.

The *picrate* readily crystallized from a saturated alcoholic solution of picric acid, forming long violet-brown needles which, after one recrystallization from alcohol, melted at 112–113°.

Anal. Calc'd for $C_{12}H_{14}O_3 \cdot C_6H_3N_3O_7$: C, 49.7; H, 4.0; N, 9.7.
Found: (*a*): N, 9.6, 9.7.
(*b*): C, 49.6, 49.9; H, 4.3, 4.3; N, 9.9.

The *acetate*, prepared from XVI with acetic anhydride and sodium acetate by heating the mixture on the steam-bath for 15 minutes, crystallized from aqueous acetone, forming colorless quadratic cubes, m.p. 87–88°.

Anal. Calc'd for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5; OCH_3, 12.5.
Found: C, 67.8, 68.0; H, 6.5, 6.6; OCH_3, 12.6, 12.8.

The *methyl ether* was prepared by the addition of dimethyl sulfate to a solution of XVI in 10% aqueous sodium hydroxide. The oil which separated was isolated by extraction with benzene, the extract leaving a colorless oil that solidified on being chilled to naphthalene-like plates, m.p. 27–29°, identical in every respect with coumarone XIII prepared from VII. The *picrate* separated in red-brown needles, m.p. 95–96°. There was no depression on admixture with an authentic specimen.

The oxidation of 2-(α-acetopropyl)-4,5-dimethoxyphenol veratroate (VIII) *with selenous acid.* A solution of 6 g. of VIII in 60 ml. of alcohol was gently refluxed on the steam-bath for 20 hours, with the gradual addition of 3 g. of powdered selenous acid during the first six hours. After removal of the selenium precipitate, the solution was evaporated, and the residue was repeatedly extracted with benzene under reflux. The combined benzene extracts, washed with water and dried with calcium chloride, left a red-brown oil on subsequent evaporation. This was dissolved in 40 ml. of alcohol, and then mixed with 6 ml. of phenylhydrazine. On the following day, big golden-yellow rosettes separated. By concentration of the mother liquor another crop of the same crystals was obtained. The product was twice recrystallized from butyl alcohol, yielding 3 g. of bright yellow needles, m.p. 203°, of a *bisphenylhydrazone, presumably of 2-(α-glyoxylpropyl)-4,5-dimethoxyphenol veratroate.*

Anal. Calc'd for $C_{34}H_{36}N_4O_6$: C, 68.5; H, 6.1; N, 9.4; OCH_3, 20.6.
Found: C, 68.5, 68.4; H, 6.2, 6.3; N, 9.2, 9.3; OCH_3, 20.7.

SYNTHESIS OF 5,6-DIMETHOXYCOUMARONE HOMOLOGS

Hydroxyhydroquinone trimethyl ether. The following modification of the process recommend in the literature (12, *cf.* 13) proved to be rather satisfactory. Hydroxyhydroquinone triacetate, prepared from 120 g. (1.1 moles) of quinone, was mixed with 480 ml. of methyl alcohol and then 840 ml. (5.5 moles) of freshly distilled dimethyl sulfate was added. Under vigorous stirring in a nitrogen atmosphere, 720 g. (18 moles) of sodium hydroxide in 720 ml. of water was slowly added, the temperature of the mixture being maintained at 30–40°. Then the mixture was diluted with 1 liter of water, and stirring at *room temperature* was continued for one hour. Then 25 ml. of 27% ammonia was added to the mixture and, after

a few minutes, the oily layer was separated and the aqueous alkaline portion was repeatedly extracted with benzene. The extract was combined with the oil, and the whole was washed with water until free of alkali, then dried and evaporated on the steam-bath. The residue was distilled, one redistillation affording a colorless mobile oil, b.p. 137–142°/18 mm. Yield, 174 g. (92%).

Ethyl α-(2-propionyl-4,5-dimethoxyphenoxy)propionate. A mixture of 4.6 g. of 2-hydroxy-4,5-dimethoxypropiophenone of m.p. 124–125° (12), 4.6 g. of ethyl α-bromopropionate, 8 g. of finely powdered anhydrous potassium hydroxide, and 30 ml. of anhydrous acetone was vigorously refluxed on the steam-bath, until the greenish-blue ferric chloride reaction disappeared (six to ten hours). Upon adding water, the separated oil rapidly solidified, subsequent recrystallization from methyl alcohol affording 5.7 g. of glistening flat colorless needles, m.p. 62–63°.

Anal. Calc'd for $C_{16}H_{22}O_6$: C, 61.9; H, 7.1.
Found: C, 61.7, 61.8; H, 7.2, 7.3.

α-(2-Propionyl-4,5-dimethoxyphenoxy)propionic acid (XIV). A suspension of 4 g. of the foregoing ester in 80 ml. of aqueous 10% sodium hydroxide solution was kept on the steam-bath with occasional shaking, until complete dissolution took place. After standing overnight at room temperature, the solution was acidified, the resulting emulsion soon being transformed into a mass of slender colorless needles. Recrystallization from water or from dilute alcohol afforded 3.4 g. of a hydrate, the air-dried product melting at 100–104°. This product was used directly for the above described conversion of the acid to coumarone XIII.

Anal. Calc'd for $C_{14}H_{18}O_6 \cdot O \cdot 5H_2O$: C, 57.7; H, 6.5; Neut. equiv., 291.
Found: C, 57.7, 57.9; H, 6.8, 6.7; Neut. equiv., 288.

Ethyl 2-propionyl-4,5-dimethoxyphenoxyacetate was prepared from 9 g. of 2-hydroxy-4,5-dimethoxypropiophenone and 7.8 g. of ethyl bromoacetate. It formed long colorless needles, from alcohol, m.p. 112–114°. Yield, 12.2 g.

Anal. Calc'd for $C_{15}H_{20}O_6$: C, 60.8; H, 6.8.
Found: C, 61.0, 60.8; H, 7.1, 7.2.

2-Propionyl-4,5-dimethoxyphenoxyacetic acid formed long colorless needles from water or dilute alcohol, m.p. 138–140°.

Anal. Calc'd for $C_{13}H_{16}O_6$: C, 58.2; H, 6.0.
Found: C, 58.3, 58.2; H, 6.4, 6.3.

3-Ethyl-5,6-dimethoxycoumarone was prepared from 4 g. of the foregoing acid, 4 g. of anhydrous sodium acetate, and 40 ml. of acetic anhydride, as described for coumarone XIII by method (*c*). Upon decomposing the excess anhydride, 3.3 g. of a colorless solid was obtained, which crystallized from alcohol in small slightly-colored prisms, m.p. 82°. Distillation at 5 mm., followed by recrystallization from alcohol, afforded stout colorless prisms, m.p. 83°.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.6; H, 6.8.
Found: C, 69.7, 69.6; H, 7.0, 7.0.

The *picrate* forms deep orange-colored, long thin needles from alcohol, m.p. 80–81°.

Anal. Calc'd for $C_{12}H_{14}O_3 \cdot C_6H_3N_3O_7$: N, 10.1. Found: N, 9.9.

Ethyl α-(2-acetyl-4,5-dimethoxyphenoxy)propionate. 2-Hydroxy-4,5-dimethoxyacetophenone was prepared from 2,4,5-trimethoxyacetophenone (14), and this was condensed with ethyl α-bromopropionate to form colorless stout prisms from dilute alcohol, m.p. 70–72°.

Anal. Calc'd for $C_{15}H_{20}O_6$: C, 60.8; H, 6.8.
Found: C, 60.8, 60.8; H, 6.8, 7.0.

α-(2-Acetyl-4,5-dimethoxyphenoxy)propionic acid gave elongated colorless prisms from methyl alcohol or water, m.p. 132–134°.

Anal. Calc'd for $C_{13}H_{16}O_6 \cdot H_2O$: C, 54.6; H, 6.3.
Found: C, 54.6, 54.4; H, 6.7, 6.6.

2,3-Dimethyl-5,6-dimethoxycoumarone appeared as stout colorless prisms, m.p. 90°.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
Found: C, 69.6, 69.8; H, 7.0, 7.0.

A *picrate*, deep violet-brown slender needles (from alcohol), m.p. 108–110°, has been prepared.

Anal. Calc'd for $C_{12}H_{14}O_3 \cdot C_6H_3N_3O_7$: C, 49.7; H, 4.0; N, 10.1.
Found: C, 49.9; H, 4.3; N, 9.9.

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SUMMARY

The isochromenium salts formed by 3,3′,4,4′-tetramethoxy-6-α-acetopropylbenzophenone (the primary oxidation product of diisohomogenol) are cleaved by hydrogen peroxide at the carbenium carbon. The structure of the resulting phenol has been established (thus correcting the previously suggested formula). The base-catalyzed isomerization of the substance presents an intramolecular acyl migration.

MUZEUM KORUT 4/B,
BUDAPEST VII, HUNGARY

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