[Contribution from the Chandler Laboratory, Columbia University]

A Re-examination of the Diisohomogenol Structure[1]

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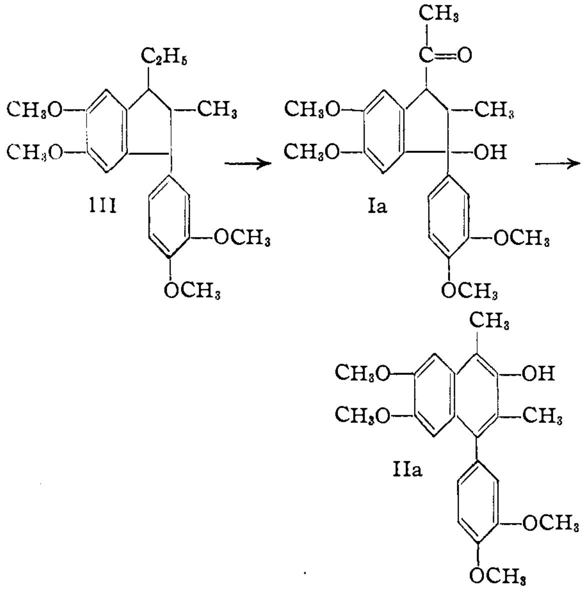
In connection with the projected study of base-catalyzed rearrangements of tertiary α-ketols,[3] we have reinvestigated Müller's curious and apparently unique formulation of the transformation of hydroxyketodiisohomogenol (Ia) to 1,3-dimethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthol-2 (IIa) as a base-catalyzed rearrangement of a tertiary γ-ketol.[4] The result of our work in having shown that the expression Ia for hydroxyketodiisohomogenol is itself untenable, has made the rearrangement non-existent and has occasioned re-evaluation of the experimental basis for the formulation of the parent substance, diisohomogenol (III).



III

Ia

IIa

The key oxidative degradation products of diisohomogenol (III), $C_{22}H_{28}O_4$, the dimer of isoeugenol methyl ether (isohomogenol),[5] are I, $C_{22}H_{26}O_6$, formulated[6] as hydroxyketodiisohomogenol (Ia); IV, $C_{20}H_{20}O_5$, the so-called "red oxidation-product"[7,8,9]; its precursor, V, $C_{20}H_{22}O_6$, to which Müller assigned structure Va[9]; and *o*-veratroylveratric acid, VI.[6,7,10]

It is on the formulation of these oxidation products that the structure of diisohomogenol depends.

I exhibits no absorption maximum in the oxygen–hydrogen stretching region (3500–3700 cm.$^{-1}$) and shows maxima at 1720 cm.$^{-1}$ and 1662 cm.$^{-1}$ in the carbonyl region. (3,3′,4,4′-Tetramethoxybenzophenone shows a carbonyl maximum at 1660 cm.$^{-1}$.) In the Zerewitinoff determination, I liberates 0.30 mole of methane and consumes an additional 1.51 moles of Grignard reagent. These facts, clearly inconsistent with Müller's formula Ia for I, are consistent with the presence of two keto groups in I.[11]

Chemical confirmation of the presence of two keto groups, denied by the failure of I to form more than a mono semicarbazone[10] and a mono-*p*-nitrophenylhydrazone, is obtainable from a consideration of the reactions of I, $C_{22}H_{26}O_6$, both with ammonia and with hydroxylamine in which, by the elimination of *two* molecules of water, there are formed a tertiary *base*, $C_{22}H_{25}O_4N$ (VII), and an amine oxide, $C_{22}H_{25}O_5N$ (VIII), respectively.[12] Interconversion of these two substances is effected from VII by oxidation with perbenzoic acid and from VIII by reduction with zinc and acetic acid.

While the cornerstone of Müller's structural hypothesis[6] for diisohomogenol is the supposed demonstration of the presence of a five-membered ring in I (expressed as Ia), our finding of *two* keto groups in I does not permit the presence of an alicyclic ring.

Closely related to I is the substance V, the precursor of the "red oxidation-product," IV. Müller has obtained V by the oxidation of IX, one of the halochromic salts of I, with chromic acid or potassium permanganate and has converted it to IV by treatment with acid or base.[9] These substances can also be obtained from IX by the action of perbenzoic acid, V being obtained after a short time and IV after a longer time. While the structure of the less directly related substance, IV, has been established by synthesis,[13] the structure assigned to V (Va) has been invalidated by the following synthesis.

4-Propylveratrole (X, dihydrohomogenol) condenses with veratroyl chloride in the presence of

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[3] The example of 3,17-dihydroxypregnen-5-one-20 has been studied extensively: Ruzicka, *et al.*, *Helv. Chim. Acta*, **22**, 626, 707 (1939); **23**, 364, 513 (1940); Shoppee and Prins, *ibid.*, **26**, 185, 201, 1004 (1943); Stavely, This Journal, **62**, 489 (1940); **63**, 3127 (1941).

[4] Müller and Patka, *Ber.*, **77**, 325 (1944).

[5] (a) Francesconi and Puxeddu, *Gazz. chim. ital.*, **39 I**, 206 (1909); (b) Szeki, *Ber.*, **39**, 2422 (1906); (c) Müller, Raltschewa and Papp, *ibid.*, **75**, 692 (1942).

[6] Müller and Horvath, *ibid.*, **76**, 855 (1943).

[7] Haworth and Mavin, *J. Chem. Soc.*, 1363 (1931).

[8] Müller and Richl, *Ber.*, **76**, 1119 (1943).

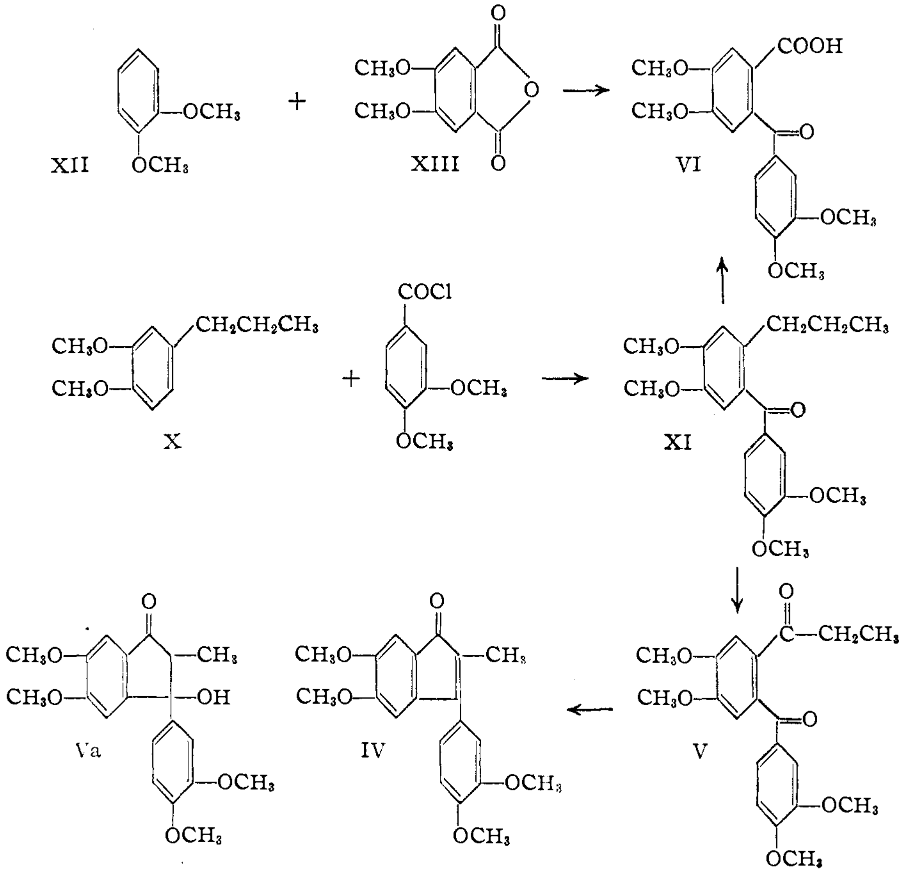
[9] Müller, *ibid.*, **77**, 159 (1944).

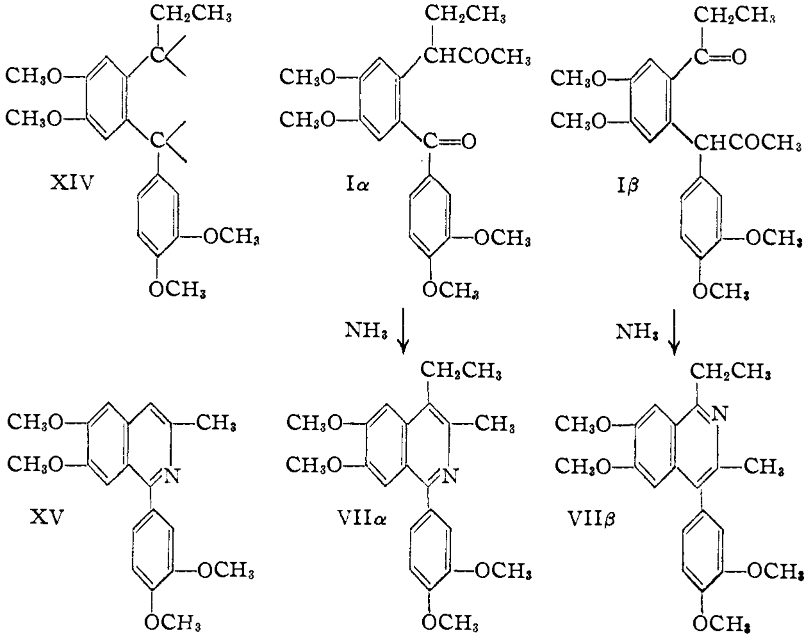
[10] Müller and Hartai, *ibid.*, **75**, 891 (1942).

[11] The stability of I to chromic acid at room temperature for forty-eight hours is inconsistent with the presence of an aldehyde group.[10]

[12] Analogously, homophthalaldehyde reacts directly with hydroxylamine to give isoquinoline-N-oxide [(a) Schöpf, Hartmann and Koch, *Ber.*, **69**, 2766 (1936)] and as its isobenzopyrylium salt with ammonia to give isoquinoline [(b) Blount and Robinson, *J. Chem. Soc.*, 555 (1933)].

[13] Müller and Gal, *Ber.*, **77**, 343 (1944).





aluminum chloride to give a product (XI) which may be 2-, 5- or 6-veratroyl-3,4-dimethoxypropylbenzene. Oxidation of XI with permanganate gives the same veratroylveratric acid (VI) that is obtained by the nitric acid oxidation of I[10] and by acylation of veratrole (XII) with metahemipinic anhydride (XIII).[7,14] Since this latter synthesis can lead either to 6-veratroylveratric acid or to 6-(2,3-dimethoxybenzoyl)-veratric acid and the oxidation of XI can lead to 2-, 5- or 6-veratroylveratric acid, it follows unequivocally that the acid VI must be 6- (*i. e.*, *o*)-veratroylveratric acid.[15] Consequently XI is 6-veratroyl-3,4-dimethoxypropylbenzene.

When XI is oxidized with chromic acid under carefully controlled conditions, two hydrogens are replaced by one oxygen giving a compound, identical with V and characterized by quantitative conversion to the "red oxidation product" IV on treatment with acid. Further oxidation of V having given *o*-veratroylveratric acid,[9] only three structures for V need be considered: $R{-}CH_2{-}CH_2{-}CHO$, $R{-}CH_2{-}COCH_3$ and $R{-}CO{-}CH_2CH_3$. The first, demanding aldehyde properties which are not shown by V, and the second, which would undergo condensation to an *acidic* β-naphthol, are untenable. Only the third is consistent with the usual course of chromic acid side-chain oxidations and conversion to a *red, neutral, ketonic* condensation product. The possibility that V has the structure of its aldol tautomer Va, as proposed on a different basis by Müller,[9] can be excluded by the fact

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(14) Vanzetti and Oliverio, *Gazz. chim. ital.*, **60**, 620 (1930).

(15) While this structure has always been assumed to be correct by analogy with the generally observed reactivity of the 4-position in veratole, the present piece of evidence places the structural assignment on a firmer experimental basis.

that V shows no infrared absorption in the oxygen–hydrogen stretching region.

Recognition of 6-veratroyl-3,4-dimethoxypropiophenone as the more satisfactory expression for V, first, invalidates the simple, direct inference made by Müller that the synthetically established presence of a phenylindane residue in IV is evidence for the existence of the same nucleus in diisohomogenol, and, second, indicates XIV as a partial structure for I. The problem of devising a complete expression for I now consists in choosing between the two possible ways, Iα and Iβ, of adding two carbons, four hydrogens and two keto groups to XIV.

The virtual congruency of the ultraviolet absorption spectra of the known 1-(3,4-dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (XV)[16] and the isoquinoline VII (Fig. 1) allows the suggestion that of the two formulations VIIα and VIIβ, derivable from the structural hypotheses Iα and Iβ, respectively, VIIα is the more probably correct.

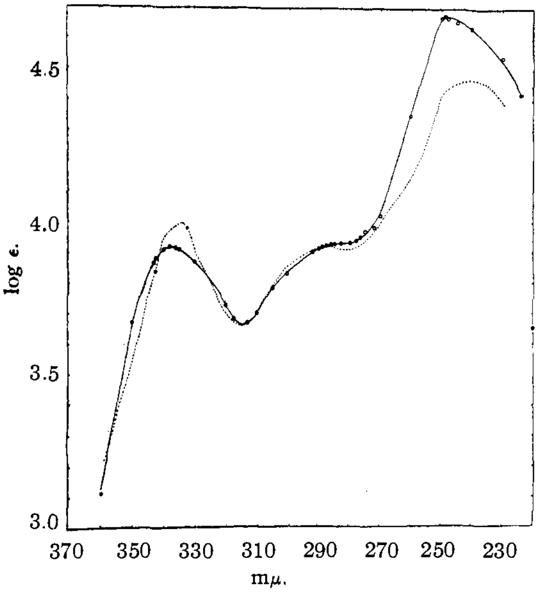
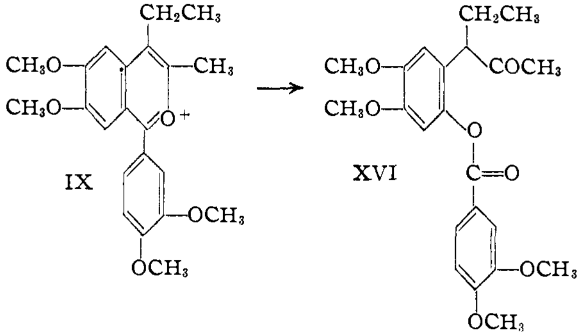
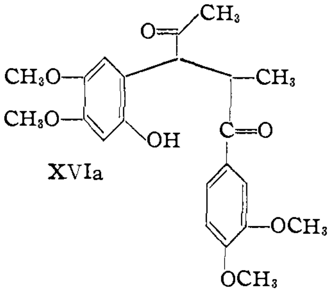


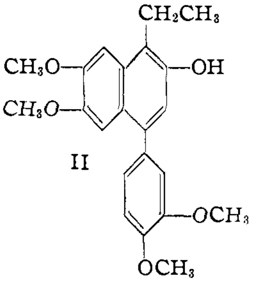
Fig. 1.— —∘—∘—VII (experimental points shown); ------ XV.

Hypotheses Iα and Iβ differ unambiguously with respect to consistency with an observation of Müller,[17] which we have confirmed: oxidation of IX, a halochromic salt of I, with hydrogen peroxide leads to a substance, $C_{22}H_{26}O_6$ (XVI), which is hydrolyzed in quantitative yield to veratric acid. Iα, but not Iβ, is hypothetically convertible by the insertion of a *single* oxygen atom to a molecule which may easily be hydrolyzed to veratric acid.[18]


IX

XVI


XVIa


II

With Iα, 3-(2-veratroyl-4,5-dimethoxyphenyl)-pentanone-2, rather than Ia, hydroxyketodiisohomogenol, as the correct expression for I, the halochromic salts of I become 1-(3,4-dimethoxyphenyl) - 3 - methyl - 4 - ethyl - 6,7 - dimethoxyisobenzopyrylium salts (IX) by analogy with the isobenzopyrylium salt of homophthalaldehyde[12b] instead of carbonium ions derived from Ia by the loss of a tertiary hydroxyl group. The "base-catalyzed rearrangement" of Ia to the β-naphthol IIa is presumably to be interpreted as an intramolecular aldol condensation of Iα with dehydration leading to 1-ethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthol-2 (II).[19]

With a large part of the experimental basis for assigning structure III to diisohomogenol having been invalidated,[21] it is amusing that the new evidence leads to the same formulation as before. On the assumption that the two carbonyl groups of I represent the termini of a carbon–carbon bond in diisohomogenol, both structures Iα and Iβ lead unequivocally to III for diisohomogenol, although the oxidation of III to I is more plausible in terms of Iα.[22]

On the basis of modern mechanistic concepts, III is the expected product from the acid-induced dimerization of isohomogenol (XVII).[23]

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[16] Gerendas and Varga, *J. prakt. Chem.*, **149**, 175 (1937).

[17] Müller and Richter, *Ber.*, **77**, 12 (1944).

[18] Müller's expression XVIa for XVI is not reconcilable with the facile hydrolysis to veratric acid.

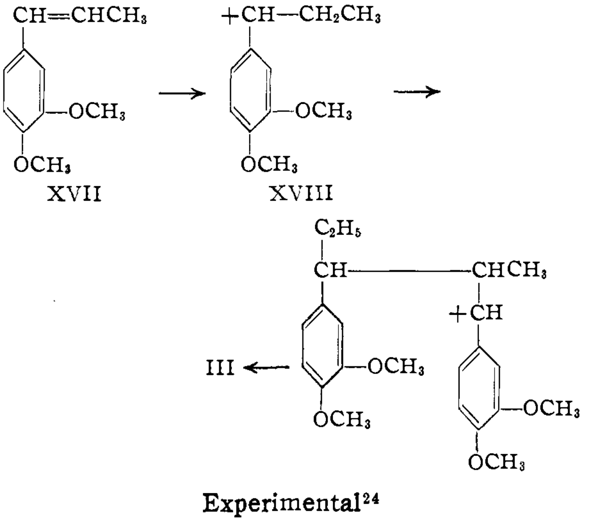
[19] Although it is not planned to re-examine the other diisohomogenol degradation products in the light of the new structure for I, we wish to indicate that the recent formulation of a chromic acid oxidation product of IX as a 9,10-endoethylidene-9,10-dihydroanthracene[20] is not tenable.

[20] Müller, *J. Org. Chem.*, **12**, 815 (1947).

[21] The synthesis of III[13] has been questioned [Cartwright and Haworth, *Chem. and Ind.*, 117 (1947), *J. Chem. Soc.*, 948 (1947)], and admitted to have been illusory.[20]

[22] Muller's representation of the transformation of III to Ia by chromic acid oxidation finds no analogy in the literature.

[23] The occurrence of small yields of other dimers is not precluded. Thus, Pailer [*Monatsh.*, **77**, 45 (1947)] has demonstrated the presence in the reaction mixture of less than 1% of 2,3,6,7-tetramethoxy-9,10-diethyl-9,10-dihydroanthracene. This product presumably arises through attack of the benzyl carbonium ion (XVIII) at the 6-position of isohomogenol (XVII) followed by ring closure of the Friedel–Crafts type.



Experimental[24]

Diisohomogenol (III).[7]—The dimer, prepared by methylation of diisoeugenol[7] with methyl sulfate, was obtained as white needles from hexane, m. p. 102.4–104.6° (reported 105–106°).

3-(2-Veratroyl-4,5-dimethoxyphenyl)-pentanone-2 (I α).[10]—I, prepared by chromic acid oxidation of III, was obtained as white cubes from ethyl acetate, m. p. 156.2–157.0° (reported 156°).

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.11; H, 6.85.

The infrared spectrum was determined in chloroform solution (0.03 g./cc.).

The **semicarbazone** melted at 188.5–189° (reported[10] 188°).

The **p-nitrophenylhydrazone**, obtained by refluxing 1 g. of I, 1.6 g. of p-nitrophenylhydrazine and two drops of acetic acid in 25 cc. of ethanol for thirty minutes, was recrystallized from methanol or ethanol to give a light-yellow powder, m. p. 177.8–178.8°.

Anal. Calcd. for $C_{28}H_{31}O_7N_3$: C, 64.48; H, 5.99; N, 8.06. Found: C, 64.34; H, 6.07; N, 8.25.

Refluxing 475 mg. of the p-nitrophenylhydrazone and 450 mg. of p-nitrophenylhydrazine in 30 cc. of ethanol containing three drops of acetic acid for ninety-six hours afforded 30 mg. of a brick-red powder, m. p. 190–191°.

Anal. Found: N, 8.02, 7.92.

When I was allowed to react with periodic acid in acetic acid solution for forty and one-half hours at room temperature, 89% of the periodic acid was consumed and 41% of the starting material was recovered.[25]

3,3',4,4'-Tetramethoxybenzophenone, prepared from veratrole and veratroyl chloride,[26] crystallized as white needles from methanol, m. p. 146.0–147.2° (reported 145°). The infrared spectrum was measured in chloroform solution (0.025 g./cc.).

Reaction of I with Methylmagnesium Iodide. A.—The quantitative Grignard determinations were carried out in anisole solution in a modified Lauer[27] apparatus.

In three runs, I evolved 0.32, 0.36 and 0.21 mole of methane, consumed 1.95, 1.70 and 1.78 moles of reagent and thus added 1.63, 1.34 and 1.57 moles of reagent.

B.—The Grignard reaction was carried out on a preparative scale by adding a solution of 3 g. of I in 50 cc. of dry benzene to a stirred solution of methylmagnesium iodide (from 1 g. of magnesium) in 100 cc. of ether over a period of thirty minutes. The resulting yellow slurry was refluxed thirty minutes, hydrolyzed with ice-ammonium chloride and extracted with ether. After being dried over magnesium sulfate, the ethereal solution was distilled to dryness and the residual oil crystallized from toluene-hexane to give 2.0 g. (62%) of pale-yellow solid, softening at 112° and melting over a range up to 134°. Recrystallization from toluene-hexane (Norit-A) gave rosettes of prisms, m. p. 134.6–138.2°. Further recrystallization from toluene-hexane and from dilute ethanol gave material of m. p. 139.7–141.4°, but subsequent recrystallization caused the m. p. to drop to 131–134°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.37; H, 8.19. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 69.13; H, 8.04.

1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisoquinoline (VII). A. Reaction of I with Ammonia.—A solution of 2.0 g. of I in 20 cc. of benzene and 40 cc. of ethanol was saturated with ammonia gas at −5° and autoclaved at 70–80° for four and one-half hours. The dark-brown residue obtained on removal of the solvents and excess ammonia by distillation was dissolved in 2 N hydrochloric acid, washed with benzene, made alkaline and extracted with benzene. The benzene solution was extracted with 2 N acid, and the aqueous layer made alkaline and extracted with ether. On evaporation of the dried (magnesium sulfate) ether extract, 1.68 g. of a pink powder, m. p. 133–140° was obtained. Recrystallization from toluene-hexane and from ethyl acetate afforded white, glistening plates, m. p. 156.9–157.6°. A mixed m. p. with I was depressed about 20°.

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.87; N, 3.81. Found: C, 71.79; H, 6.92; N, 3.73.

The **picrate**, 480 mg. of glistening, canary-yellow needles, prepared by warming a solution of 325 mg. of VII in 6 cc. of 95% ethanol with 4 cc. of a saturated solution of picric acid, was recrystallized from acetic acid and melted at 225–227°.

Anal. Calcd. for $C_{28}H_{28}O_{11}N_4$: C, 56.37; H, 4.73; N, 9.39. Found: C, 56.18; H, 4.81; N, 9.66.

B. **Reduction of the N-Oxide of VII.**—A mixture of 500 mg. of the N-oxide of VII (*vide infra*) and 1 g. of zinc dust in 25 cc. of acetic acid was refluxed for one hour, cooled, filtered from excess zinc and the filtrate made alkaline and extracted with ether. Evaporation of the dried (magnesium sulfate) solution afforded a pale-yellow oil which crystallized from toluene-hexane as 280 mg. of white plates, m. p. 152–155°. Recrystallization from toluene-hexane and from ethyl acetate raised the melting point to 156.5–157.5°. A mixed m. p. with material prepared by method A was not depressed.

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.87; N, 3.81. Found: C, 72.08; H, 6.95; N, 3.82.

The base failed to react with benzenesulfonyl chloride in the Hinsberg test.

The ultraviolet absorption spectrum (Fig. 1) of a 1.34×10^{-5} M solution in ethanol was determined with a Beckman ultraviolet spectrophotometer, model DU. Maxima at 249 mμ ($\log \epsilon = 4.68$) and at 338 mμ ($\log \epsilon = 3.91$) and an inflection point at 285 mμ ($\log \epsilon = 3.92$) were observed. Maxima for 1-(3,4-dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (XV) at 240 mμ ($\log \epsilon = 4.47$), 287 mμ ($\log \epsilon = 3.93$) and 334 mμ ($\log \epsilon = 4.00$) are reported.[16]

N-Oxide of VII (VIII). A. Reaction of I with Hydroxylamine.—A solution of 1.0 g. of I and 1.175 g. of hydroxylamine hydrochloride in 4.4 cc. of absolute ethanol and 4.4 cc. of dry pyridine was refluxed for three hours, the solvent removed *in vacuo*, and the green, viscous residue crystallized from water to yield 0.8 g. of a white powder, m. p. 220–222°. Several recrystallizations from dilute methanol gave material softening at 205° and melting at 221.7–222.9°. Further recrystallization from

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[24] All melting points are corrected. The microanalyses were performed by Clark Microanalytical Laboratories, Elek Microanalytical Laboratories, and Miss Lois May.

[25] This is in accord with the observation of Pennington and Ritter, THIS JOURNAL, **69**, 187 (1947), that many phenols and phenol ethers decompose periodate without apparent stoichiometric consistency.

[26] Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1661 (1906).

[27] Fieser and Fieser, "Organic Chemistry," D. C. Heath and Company, Boston, Mass., 1944, p. 212.

benzene–hexane gave a somewhat hygroscopic product, m. p. 222.5–223.5°. The analytical sample was dried to constant weight at 110° *in vacuo* immediately before analysis.

Anal. Calcd. for $C_{22}H_{25}O_5N$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.63; H, 6.45; N, 3.89.

B. **Oxidation of VII.**—A solution of 700 mg. of VII (prepared by either method above) in 8 cc. of chloroform was treated at 0–10° with 8 cc. of a 0.46 *M* chloroform solution of perbenzoic acid.[28] After standing in the refrigerator for two hours and at room temperature for three hours, a drop of the solution produced only a faint orange color with starch–potassium iodide solution. The reaction mixture, after being washed with 10% potassium hydroxide and water, was dried over magnesium sulfate and concentrated to dryness. The oily, yellow-brown residue crystallized from hexane, yielding 480 mg. of a white powder, m. p. 217–221°, which when mixed with VIII (from A) did not cause a depression in its melting point.

Reaction of I with Ethyl Mercaptan.—A solution of 1.0 g. of I, 5 cc. of ethyl mercaptan and three drops of concentrated hydrochloric acid in 40 cc. of acetic acid was allowed to stand at room temperature for twenty-four hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue taken up in methanol. On cooling, the solution deposited 130 mg. of white cubes, m. p. 155–157°, which on admixture with I did not cause a depression in the melting point. The mother liquor was evaporated to dryness, leached with boiling methanol and filtered hot. The insoluble material consisted of 100 mg. of blood-red prisms, m. p. 195–198°. On recrystallization from acetic acid–ethyl acetate, the red crystals had m. p. 199–201°, alone or mixed with IV (*vide infra*). The phenylhydrazone had m. p. 168–170°, and caused no depression in the m. p. of the phenylhydrazone of IV[9] on admixture.

The methanol filtrate from the leaching operation was evaporated to dryness and the residue recrystallized from methanol to give white needles, m. p. 97.8–99.2°.

Anal. Calcd. for $C_{30}H_{46}O_4S_4$ (bis-thioketal of I): C, 60.16; H, 7.73; S, 21.41. Calcd. for $C_{26}H_{36}O_5S_2$ (thioketal of I): C, 63.38; H, 7.37; S, 13.01. Found: C, 67.96; H, 6.87; S, 8.42.

When I was allowed to stand at room temperature in acetic acid containing a trace of hydrochloric acid for one hundred and six hours, the solution evaporated to dryness, the residue suspended in methanol and stirred with a few crystals of anhydrous sodium acetate, I was recovered unchanged.

4-Propylveratrole (X).—A solution of 50 g. of isoeugenol in 50 cc. of 95% ethanol was shaken in the presence of 330 mg. of Adams catalyst under 2 atm. pressure of hydrogen. The theoretical quantity of hydrogen was consumed in thirty minutes, whereupon the catalyst was filtered off, the alcohol removed by distillation and the liquid residue methylated directly by treating its solution in 500 cc. of 10% potassium hydroxide with 39 cc. of dimethyl sulfate. The reaction mixture was extracted with ether, the extract concentrated and the residue distilled *in vacuo* to give 40 g. of a colorless liquid, b. p. 146° (30 mm.), n^{29}_D 1.5136, d^{20} 1.0125 (reported b. p. 246°,[29] d^{20} 1.0105[30]).

The product was characterized by nitration to **1-propyl-3,4-dimethoxy-6-nitrobenzene**,[31] which was obtained as shimmering buff flakes from ethanol, m. p. 79–80° (reported m. p. 81–82°).

6-Veratroyl-3,4-dimethoxypropylbenzene (XI).—A mixture of 1.0 g. of veratric acid and 1.3 g. of phosphorus pentachloride in 5 cc. of carbon disulfide was refluxed for one hour and fifteen minutes. The residue remaining after removal of the solvent and phosphorus oxychloride *in vacuo* was dissolved in 10 cc. of carbon disulfide, treated with 0.8 g. of X and 1.15 g. of anhydrous aluminum chloride, refluxed one hour and thirty minutes, hydrolyzed with ice-dilute hydrochloric acid and extracted with benzene. The benzene solution, after being washed with 10% potassium hydroxide and water, was dried over magnesium sulfate, and distilled to dryness. The residue crystallized from ether to give 1.15 g. of material of m. p. 79–82° (two crops). Recrystallization from ethanol and from ethyl acetate-hexane afforded the pure ketone as hexagonal plates, m. p. 83.5–84.5°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.79; H, 6.83.

6-Veratroylveratric Acid (IV). A. **Oxidation of XI.**—A mixture of 350 mg. of XI and 200 mg. of potassium permanganate in 8 cc. of water was refluxed for thirty minutes, acidified, treated with sodium bisulfite until milky-white and extracted with ether–benzene (50%). The extract was concentrated to 70 cc., extracted with 10% potassium hydroxide, and the aqueous layer again acidified, treated with sodium bisulfite and extracted with ether.

Evaporation of the dried (magnesium sulfate) ethereal solution afforded a residue which crystallized from ether as 25 mg. of white plates, m. p. 206–217°. Recrystallization from ethanol raised the m. p. to 218–220°, alone or mixed with a sample of VI prepared by method B.

B. **Oxidation of I.**[6]—Oxidation of I with nitric acid afforded a mixture of 2,3,6,7-tetramethoxyanthraquinone, golden needles, m. p. 342–343° (reported[6] 336°) and VI, white plates, m. p. 221–222° (reported[6] 221°). The acid VI was characterized (1) by cyclization to the anthraquinone with 80% sulfuric acid (m. p. 341–343°, reported[7] 344°) according to reference 7; (2) by reduction according to reference 14 with zinc and acid to 6-veratrylveratric acid, clustered, feathery needles from ethanol, m. p. 165–166° (reported[14] 165–166°); and (3) by cyclization of the latter, according to reference 14, to 2,3,6,7-tetramethoxyanthrone, decomposing slowly above 290° (reported[14] m. p. 282–284° with decomposition).

6-Veratroyl-3,4-dimethoxypropiophenone (V). A. **Oxidation of IX.**—A suspension of 440 mg. of IX chloride in 25 cc. of chloroform and 10 cc. of benzene was shaken vigorously with 15 cc. of a 0.4 *M* chloroform solution of perbenzoic acid, allowed to stand for five minutes at 4° and for ten minutes at room temperature, washed with sodium carbonate and water, dried over magnesium sulfate, evaporated, and the residue (60 mg.) recrystallized from ethyl acetate to give buff plates, m. p. 148–150°. A mixed melting point with V (m. p. 151.4–152.7°, reported 151–152°) prepared by permanganate oxidation of IX sulfate according to reference 9 was unchanged.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.77; H, 5.95.

The infrared spectrum of a chloroform solution (0.03 g./cc.) was observed.

2-Methyl-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindanone (IV) was obtained when 1.0 g. of IX chloride was allowed to react with perbenzoic acid for two and one-half hours or sixty-seven hours. The yield was 150 mg. of blood-red prisms, m. p. 196–198°. On admixture with IV (m. p. 201–202°, reported 195°) prepared by treating V with sulfuric acid, the melting point was not depressed.

B. **Synthesis of V.**—A vigorously stirred solution of 0.35 g. of XI, 8 cc. of acetic acid and 0.5 cc. of concentrated sulfuric acid in 20 cc. of acetic anhydride was treated at 0–10° with 0.212 g. of chromic oxide over a period of twenty-five minutes. The mixture was poured into 200 cc. of ice-water, extracted with three 110-cc. portions of ether, and the ether extract washed with ten 20-cc. portions of 10% potassium hydroxide and several portions of water. Evaporation of the dried (sodium sulfate) solution, crystallization of the residue from ether, and recrystallization from ethyl acetate afforded 30 mg. of white plates, m. p. 149.5–150°. Admixture with a sample of V prepared by method A or according to reference 9 caused no change in the melting point. Treatment of the synthetic product with sulfuric acid gave IV, blood-red prisms, which alone or mixed with a sample of IV[9] had m. p. 196–198°.

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(28) Braun, "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p. 431.

(29) Ciamician and Silber, *Ber.*, **23**, 1166 (1890).

(30) Ipatieff, *ibid.*, **46**, 3591 (1913).

(31) Thoms, *ibid.*, **36**, 860 (1903).

3-(2-Veratroyloxy-4,5-dimethoxyphenyl)-pentanone-2.[17] (XVI).—A solution of 8 g. of IX sulfate in 50 cc. of water was treated with 8 cc. of 30% hydrogen peroxide and warmed for one hour on the steam-bath. The mixture was cooled and the aqueous layer decanted from the oil, which was then crystallized from ethanol, to give 3.9 g. of fine, colorless needles, m. p. 125-126.5°. Recrystallization from ethanol afforded material of m. p. 128.5-129° (reported m. p. 129-130°).

Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; OCH_3, 30.85. Found: C, 65.96, 66.05; H, 6.56, 6.65; OCH_3, 30.54.

The **phenylhydrazone**[17] was obtained as hard, glittering needles, m. p. 203-207° with decomposition (reported 208-210°).

A mixture of 2.65 g. of XVI and 55 cc. of 15% aqueous sodium hydroxide was refluxed for two hours, cooled, acidified and extracted with chloroform. The chloroform solution was extracted with 10% sodium carbonate and the extract acidified and extracted with chloroform. Evaporation of the extract gave 1.15 g. (97%) of white needles, m. p. 172-177°. Recrystallization from ethyl acetate gave material of m. p. 180-181° alone or mixed with an authentic specimen of veratric acid.

Treatment of a solution of 100 mg. of XVI in 5 cc. of methanol with 1 cc. of 10% sodium hydroxide and excess iodine-potassium iodide solution gave 30 mg. of a canary-yellow precipitate, m. p. 118-119° alone or mixed with an authentic sample of iodoform. A blank test on the solvent was negative.

Summary

A firm experimental basis for assigning the structure 1-(3,4-dimethoxyphenyl)-2-methyl-3-ethyl-5,6-dimethoxyindane to diisohomogenol (III) has been provided by showing that crucial oxidation products, erroneously formulated as hydroxyketodiisohomogenol and 2-methyl-3-hydroxy-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindanone by Müller, have the structures, 3-(2-veratroyl-4,5-dimethoxyphenyl)-pentanone-2 and 6-veratroyl-3,4-dimethoxypropiophenone, respectively. Other products and reactions have been reformulated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. III. Ring Expansion of Tropinone to R-Homotropinone and its Degradation to 1,3,5-Cycloöctatriene[1]

BY ARTHUR C. COPE, HAROLD R. NACE AND LELAND L. ESTES, JR.

The difficulty with which pseudopelletierine is obtained has led us to investigate the synthesis of eight-membered cyclic polyolefins from tropinone, which is more readily available. This paper describes the preparation of R-homotropinone (IV), an isomer of pseudopelletierine, from tropinone (I) by application of the Tiffeneau method of ring expansion.[2] R-Homotropinone has been degraded to 1,3,5-cycloöctatriene (X) by a series of reactions analogous to the sequence used by Willstätter in the synthesis of 1,3,5-cycloöctatriene (and cycloöctatetraene) from pseudopelletierine.[3,4]

The hydrogenation of tropinone cyanohydrin (II) to 3-aminomethyl-3-tropanol (III) gave satisfactory, reproducible yields only when II was reduced immediately after purification. Recrystallization of II from ethyl acetate required large volumes of solvent and resulted in excessive losses, and it was preferable to wash the crude cyanohydrin with water, alcohol and ether, dry it briefly under reduced pressure, and then hydrogenate it at once in the presence of Adams platinum catalyst in glacial acetic acid at 40°. Initially, III was isolated as the free base by treating its hydrochloride with a strongly basic ion exchange resin in aqueous solution. Subsequently it proved to be unnecessary to isolate III, for addition of hydrochloric acid to the acetic acid solution obtained by hydrogenation of II, followed by concentration and treatment with sodium nitrite in aqueous acetic acid, gave R-homotropinone (IV) in 57% yield (43% over-all from tropinone). R-Homotropinone was isolated as a colorless, hygroscopic liquid, which darkened on exposure to air. It was characterized by preparation of the 2,4-dinitrophenylhydrazone. Catalytic hydrogenation of IV in the presence of W-7 Raney nickel[5] gave R-homotropanol (V) in 70% yield as a stable, viscous liquid.

Dehydration of V by treatment with sulfuric acid in glacial acetic acid yielded 64% of R-homo-2(or 3)-tropidine (VIa or VIb). It was expected that dehydration would yield a mixture of the two isomers, but the liquid product crystallized readily, m. p. 17.2-18°, and consequently was probably a single isomer. No evidence was obtained concerning the location of the double bond. A sample of VI was hydrogenated quantitatively to R-homotropane (XI), which was characterized as the picrate and perchlorate.

Reaction of R-homo-2(or 3)-tropidine with methyl iodide gave the methiodide (VII) in 99% yield, which was converted to the quaternary base with silver hydroxide. Distillation gave a dimethylaminocycloöctadiene (VIII) in 77% yield. The product had a constant boiling point and refractive index, and appeared to be a single compound rather than a mixture of isomers. It gave a picrate and a methiodide which did not depress the m. p. of the corresponding derivatives

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(2) Tiffeneau, Weill and Tchoubar, *Compt. rend.*, **205**, 54 (1937).

(3) Willstätter and Waser, *Ber.*, **44**, 3423 (1911); Willstätter and Heidelberger, *ibid.*, **46**, 517 (1913).

(4) Cope and Overberger, THIS JOURNAL, **70**, 1433 (1948).

(5) Adkins and Billica, *ibid.*, **70**, 695 (1948).