

DIMERIC PROPENYL PHENOL ETHERS. XI. THE FORMATION  
OF ANTHRAQUINONE DERIVATIVES IN THE CHROMIC  
ACID DEGRADATION OF DIISOHOMOGENOL (1)

ALEXANDER MÜLLER

*Received June 2, 1947*

In view of the identity of diisohomogenol (diisoeugenol 0-dimethyl ether) with 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindane (2) (I), the formation of 2,3,6,7-tetramethoxyanthraquinone (XI) in the oxidation of diisohomogenol with chromic acid (3) was made the subject of a detailed investigation.

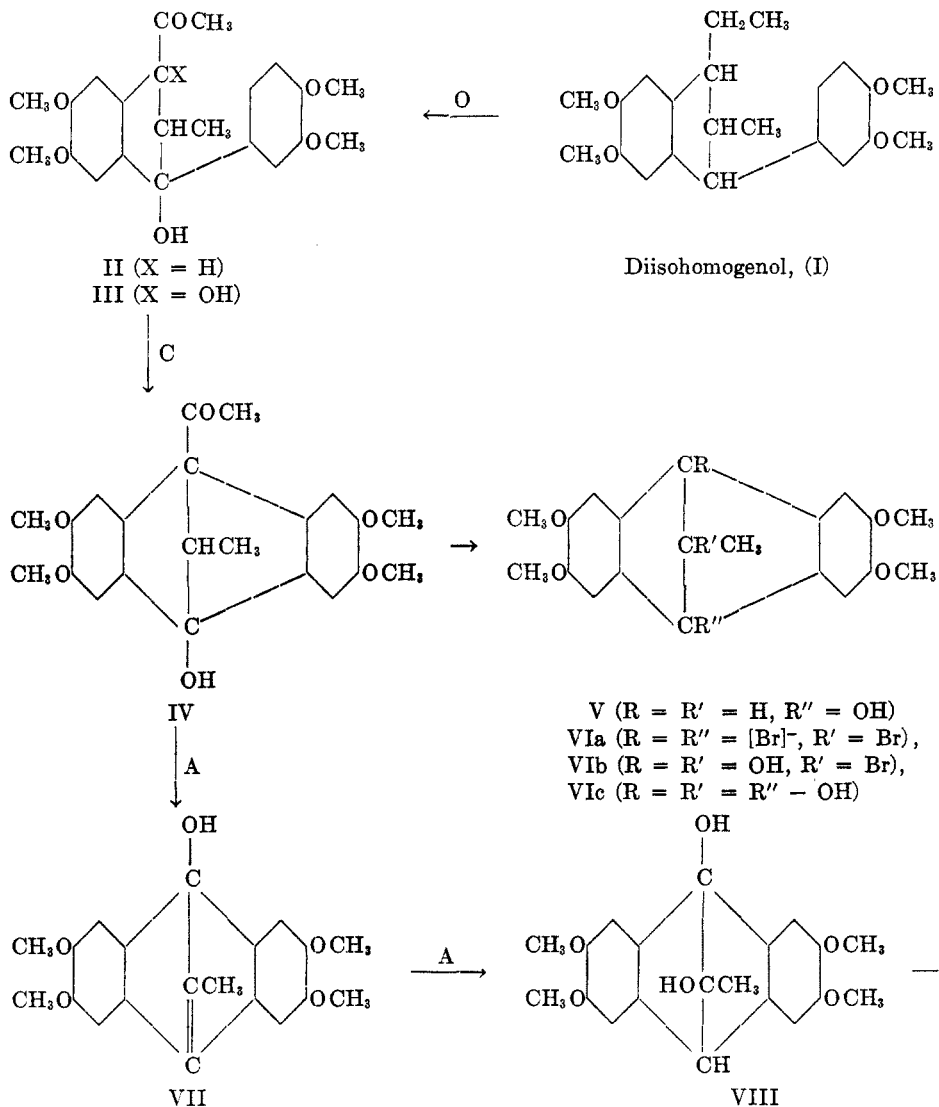
On account of this reaction, Haworth and Mavin rejected the cyclobutane structure originally introduced by Tiemann (4), and strongly advocated by Puxeddu (5), assigning to diisohomogenol a 2,3,6,7-tetramethoxy-9,10-diethyl-9,10-dihydroanthracene formula. Our investigations, beginning in 1942, have shown both structures to be untenable (6). The formation of *o*-veratroylveratric acid in the oxidation of diisohomogenol indicated a phenyltetralin or phenylindane structure, the conversion of hydroxy-keto-diisohomogenol into a phenylnaphthol derivative being first interpreted in favor of the phenyltetralin structure (7). However, continued investigations soon proved that diisohomogenol is actually a phenylindane of the structure (I) (2). On the basis of the established formula, the so-called "red oxidation-product" (XIV) and a diisohomogenol stereomeride were synthesized (1).

Quite recently, Cartwright and Haworth (8), while accepting the phenylindane formula (I), drew attention to the fact that the product of the above mentioned synthesis may not be identical with the diisohomogenol stereomeride, m.p. 106°, obtained by repeated recrystallization from dimerized isohomogenol, the mixture of the two specimens giving a depression in melting point. Repeating earlier determinations of the melting points (1), a mixture of synthetic diisohomogenol, m.p. 105.5–106°, and diisohomogenol, m.p. 106°, from dimerized isohomogenol, was found to melt at 92–95°, while the mixture of the corresponding bromo derivatives, m.p. 125° and 126° respectively, melted at 109–112°. Synthetic diisohomogenol is therefore, quite in agreement with Cartwright and Haworth, not necessarily identical with the stereomerides present in dimerized isohomogenol, four racemic forms of diisohomogenol (*cis-cis*, *cis-trans*, *trans-cis*, *trans-trans*) being possible. The phenylindane formula (I), however, leaving open the question of the particular spatial arrangement in individual stereomers, remains unaffected by this fact.

In a previous study of the formation of 2,3,6,7-tetramethoxyanthraquinone (XI) from diisohomogenol, evidence was presented (9) that in the oxidation with chromic acid, among other products, 4-pyruvyl-5-veratroylveratrol is formed, this derivative being responsible for the subsequent cyclization (XIII → XI) yielding XI as the final oxidation product. Such a cyclization, however, may occur under appropriate conditions in an earlier step of the degradation,

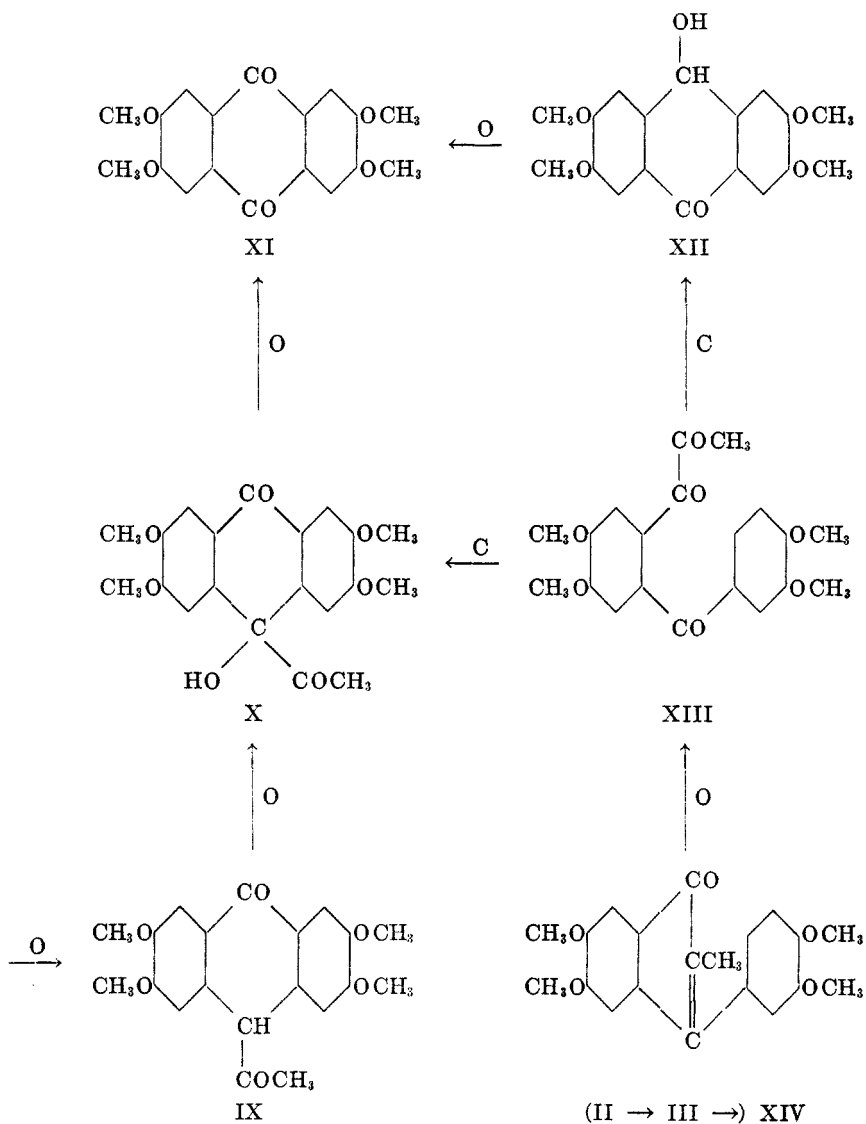
leading to the formation of 9,10-endoethylidene-9,10-dihydroanthracene derivatives.

On oxidizing 1-hydroxy-3'-keto-diisohomogenol (7) (II) in the form of its water-soluble sulfate (10) with no more than two equivalents of chromic acid,



loss of but two atoms of hydrogen takes place, accompanied by simultaneous hydrolysis of the carbenium salt. The resulting product can no longer be converted into *o*-veratroylveratric acid or into veratric acid, while oxidability to 2,3,6,7-tetramethoxyanthraquinone remains preserved. The following reactions characterize this substance as being a 2,3,6,7-tetramethoxy-9-acetyl-9,10-endoethylidene-9,10-dihydroanthracenol-10 (IV).

(A) The new degradation product forms deeply colored carbenium salts with mineral acids, owing to the anionotropy of the carbon linking the two methoxy-



A = action of alkali  
 C = condensation  
 H = hydrolysis  
 O = oxidation

lated aromatic rings. The salt formation is connected with loss of the acetyl group, the salts (V, R'' = e.g. HSO<sub>4</sub><sup>-</sup>) yielding the corresponding 9-deacetyl carbinol (V) on hydrolysis.

(B) In alkaline medium the acetyl group is equally unstable, and is readily replaced by a hydroxyl group. At the same time anhydridization seems to take place, prolonged interaction of the alkali resulting in readdition of one mole of water, and giving as the final product a "monobasic" diol (VIII).

(C) The acetyl and hydroxyl groups and the tertiary hydrogen are replaced by bromine to yield a highly unstable bromo-dibromide (VIa). Careful hydrolysis of this salt gave a monobromo-diol (VIb), while more energetic conditions resulted in the formation of a triol (VIc) or of an unsaturated diol.

Following the degradation of IV in the presence of chromic acid, the next step was found to be the oxidative fission of the endo-bridge and the formation of a compound which is regarded as 2,3,6,7-tetramethoxy-9-acetylanthrone (IX), since it forms carbenium salts with loss of the 9-acetyl group, the sulfate yielding on hydrolysis 2,3,6,7-tetramethoxyanthrone. Further oxidation converts IX into 2,3,6,7-tetramethoxy-9-hydroxy-9-acetylanthrone (X), which was actually prepared by oxidizing IX with hydrogen peroxide. This hydroxyanthrone represents the last step before the formation of 2,3,6,7-tetramethoxyanthraquinone (XI), the conversion to the latter taking place with loss of acetaldehyde.

The cyclization of diisohomogenol in a comparatively early step of its oxidation is a reaction quite analogous to the cyclization of 4-pyruvyl-5-veratroyl-veratrol (XIII) to 2,3,6,7-tetramethoxy-9-hydroxyanthrone (XII) (9) and, presumably, to 2,3,6,7-tetramethoxy-9-hydroxy-9-acetylanthrone (X). It seems to be due to the intermediate formation of a 1,3-dihydroxy-3'-keto-diisohomogenol (III), whose 3-hydroxyl reacts under the influence of the adjacent 3-acetyl with considerable readiness. On the other hand, 1-veratryl-2-methyl-5,6-dimethoxyindenone-3 (XIV) or its hydrate, which possesses no acetyl at carbon 3, does not undergo ring closure under the same conditions, unless oxidative fission of the linkage C<sup>2</sup>—C<sup>3</sup> produces such a group.

#### EXPERIMENTAL

*2,3,6,7-Tetramethoxy-9-acetyl-9,10-endoethylidene-9,10-dihydroanthranol-10 (IV)*  
Five grams of the carbenium sulfate prepared from 1-hydroxy-3'-keto-diisohomogenol (10) was dissolved in 70 ml. of acetic acid containing 70% of water. The solution was cooled by ice and mixed with 1 g. of chromic acid dissolved in 5.5 ml. of water. An amorphous chromate precipitate was formed which, on heating the mixture on the steam-bath, slowly dissolved. The solution was warmed for another ten minutes. On cooling, a crystalline solid was obtained which was washed thoroughly with water and purified by three recrystallizations from alcohol (or dioxane-water), yielding 1.5 g. of colorless stout prisms, m.p. 196–197°. (From the filtered reaction mixture, 0.5 g. of IX was obtained by extraction with benzene.).

*Anal.* Calc'd for C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>: C, 68.7; H, 6.3; C—CH<sub>3</sub>, 7.8.

Found: C, 68.5, 68.7, 68.7; H, 6.4, 6.6, 6.5; C—CH<sub>3</sub>, 7.7.

The substance is readily soluble in chloroform, acetone, ethyl acetate, and dissolves in glacial acetic acid with a yellow color. On oxidation with concentrated nitric acid-glacial acetic acid (3:1), 2,3,6,7-tetramethoxyanthraquinone, m.p. 344° (80% yield), and some V, but no acid degradation product was obtained.

*Mineral Acids*

*2,3,6,7 - Tetramethoxy - 9,10 - endoethylidene - 9,10 - dihydroanthranyl sulfate (V, R" = HSO<sub>4</sub>-) trihydrate.* One gram of IV in 10 ml. of glacial acetic acid was mixed with 1 ml. of concentrated sulfuric acid. Orange plates with bright green reflections separated (1.1 g.). The salt, m.p. 178–179°, being sensitive towards moisture, should be kept in a desiccator.

*Anal.* Calc'd for C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>·HSO<sub>4</sub> + 3H<sub>2</sub>O: C, 50.4; H, 5.9.

Found: C, 51.0, 51.2; H, 5.8, 5.8.

The tetrahydrate was obtained by mixing 1 g. of IV in 10 ml. of glacial acetic acid with no more than 0.5 ml. of concentrated sulfuric acid. Slender prisms of a brighter orange, m.p. 172°, were obtained.

*Anal.* Calc'd for C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>·HSO<sub>4</sub> + 4H<sub>2</sub>O: C, 48.6; H, 6.1; HSO<sub>4</sub>, 19.6.

Found: C, 48.6, 48.8; H, 6.3, 6.4; HSO<sub>4</sub>, 20.0.

The chloride was formed by dissolving IV in glacial acetic acid saturated with dry hydrogen chloride or containing acetyl chloride; it consisted of stout needles of deep violet color, which quickly decomposed on exposure to moist air.

*2,3,6,7 - Tetramethoxy - 9,10 - endoethylidene - 9,10 - dihydroanthranol - 10 (V).* On triturating 5.6 g. of the above sulfate trihydrate with 5 ml. of methyl alcohol at room temperature, a faintly colored powder was obtained. This was dissolved in 30 ml. of dioxane (some XI remaining undissolved) and the filtered solution was mixed with 30 ml. of boiling water giving stout greenish-yellow prisms, m.p. 185°; yield 3.2 g.

*Anal.* Calc'd for C<sub>20</sub>H<sub>22</sub>O<sub>5</sub>: C, 70.1; H, 6.5; C—CH<sub>3</sub>, 4.4.

Found: C, 70.0, 70.1; H, 6.6, 6.6; C—CH<sub>3</sub>, 4.3.

*Alkali*

*2,3,6,7 - Tetramethoxy - 9,10 - (10,11 - dehydro - endoethylidene) - 9,10 - dihydroanthranol - 9 (VII).* Five grams of IV in 15 ml. of dioxane was mixed with 15 ml. of a 2 *N* solution of sodium methoxide. A bright yellow solid separated almost immediately. The mixture was kept at room temperature for twelve hours and then diluted with 100 ml. of water. The resulting clear solution soon deposited pale yellow needles when boiled gently. These were recrystallized from *n*-propyl alcohol, m.p. 210–214°; yield 3.0 g.

*Anal.* Calc'd for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>: C, 70.6; H, 5.9.

Found: C, 70.2; H, 6.2.

Often, without apparent alteration of the above conditions, a product melting between 215–225° and of composition corresponding to a hemihydrate was obtained. This is probably a mixture of the above and the following compound.

*Anal.* Calc'd for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub> + 0.5H<sub>2</sub>O: C, 68.7; H, 6.1.

Found: C, 68.6, 68.8; H, 6.1, 6.2.

*2,3,6,7 - Tetramethoxy - 9,10 - endo - α - hydroxyethylidene - 9,10 - dihydroanthranol - 9 (VIII).* When a solution of 1 g. of IV in 20 ml. of *n*-butyl alcohol containing 1 g. of dissolved sodium was boiled for 30 minutes, yellow needles separated. These were washed with alcohol and recrystallized twice from 30 ml. of acetic acid containing 40% of water. Yellow prisms were obtained, m.p. 226–227°; yield 0.5 g.

*Anal.* Calc'd for C<sub>20</sub>H<sub>22</sub>O<sub>6</sub>: C, 67.0; H, 6.2.

Found: C, 67.0; H, 6.2.

The carbenium sulfate of this product was obtained by adding 5% of concentrated sulfuric acid to the solution of VIII in glacial acetic acid; deep red needles, m.p. 130–135°.

*Bromine*

*2,3,6,7 - Tetramethoxy - 9,10 - endo - α - bromoethylidene - 9,10 - dihydroanthradibromide (VIa).* A solution of 1 g. of IV in 2 ml. of glacial acetic acid was cooled in ice and mixed with 0.5 ml. of pure bromine. The mixture turned into a red-brown mass of crystals, with evolution of hydrogen bromide. The crystals were filtered and washed with about 1 ml. of

cold glacial acetic acid as quickly as possible, and then put into a vacuum desiccator without delay, as they are highly sensitive towards moisture and decompose within a few days even if kept in a desiccator. For analysis the salt was dried 2 hours *in vacuo* over phosphorus pentoxide and potassium hydroxide.

*Anal.* Calc'd for  $C_{20}H_{19}BrO_4 \cdot Br_2$ : Br, 42.4.

Found: Br, 42.8.

*2,3,6,7-Tetramethoxy-9,10-endo- $\alpha$ -bromoethylidene-9,10-dihydroanthradiol-9,10 (VIb).* The bromo-dibromide was prepared and isolated as above, and was dissolved in 10 ml. of cold methyl alcohol. The resulting clear solution, on standing at room temperature for two to three days, deposited a colorless crust of crystals. This was recrystallized from ethyl acetate-petroleum ether, yielding 1.0 g. of small prisms, m.p. 150–153° (with decomposition). The substance undergoes slow decomposition in moist air.

*Anal.* Calc'd for  $C_{20}H_{21}BrO_6$ : C, 54.9; H, 4.8; Br, 18.3.

Found: C, 54.8, 54.7; H, 5.0, 5.1; Br, 18.4, 18.5.

*2,3,6,7-Tetramethoxy-9,10-endo- $\alpha$ -hydroxyethylidene-9,10-dihydroanthradiol-9,10 (VIc).* One gram of the foregoing bromo-diol (VIb), refluxed with 50 ml. of alcohol containing 10% of water yields 0.6 g. of stout, colorless prisms, m.p. 143°.

*Anal.* Calc'd for  $C_{20}H_{22}O_7$ : C, 64.2; H, 5.9; C—CH<sub>3</sub>, 4.0.

Found: C, 64.2, 64.3; H, 6.2, 6.2; C—CH<sub>3</sub>, 4.3.

*2,3,6,7-Tetramethoxy-9,10-endoethenylidene-9,10-dihydroanthradiol-9,10.* One gram of IV was brominated as described above and, without removing the bromo-dibromide (VIa), 0.5 ml. of methyl alcohol was added. The resulting clear brown solution crystallized in a few days, yielding 0.9 g. of small colorless needles containing no bromine. This was recrystallized from ethyl lactate, m.p. 188–189°. The same product was obtained by extracting the bromo-dibromide from the reaction mixture with chloroform and water. The chloroform layer was washed with water and with sodium hydrogen sulfate solution, dried over calcium chloride, and evaporated. The resulting colorless oil crystallized from ether as small prisms (0.2 g.), m.p. and mixed m.p. 188–189°. The substance decolorizes dilute solutions of bromine.

*Anal.* Calc'd for  $C_{20}H_{20}O_6$ : C, 67.4; H, 5.7.

Found: C, 67.2, 67.6; H, 5.9, 6.1.

Any of the above products yields XI on oxidation with concentrated nitric acid-glacial acetic acid (3:1) on the steam-bath. The carbinols form deep red solutions in glacial acetic acid containing 5% of concentrated sulfuric acid.

*The Degradation of 2,3,6,7-Tetramethoxy-9-acetyl-9,10-endoethylidene-9,10-dihydroanthranol-10 (IV)*

*2,3,6,7-Tetramethoxy-9-acetylanthrone (IX).* (a) A solution of 5 g. of IV in 15 ml. of dioxane was mixed with 5 ml. of 2 *N* sodium methoxide solution. On addition of 2.5 ml. of 30% solution of hydrogen peroxide, the yellow precipitate dissolved with simultaneous decoloration, and crystallization of slender long needles. The crystals were washed with water, and recrystallized from dioxane-water and, subsequently, from xylene; the yield was 2.75 g., m.p. 235°.

(b) The same product was obtained by oxidizing 1-hydroxy-3'-keto-diisohomogenol (II) carbenium salts, but the yields were less satisfactory. A solution of 5 g. of the sulfate prepared from II in 65 ml. of acetic acid containing 75% water was cooled in ice, and a solution of 2 g. of chromic acid in 3 ml. of water was added. On heating the mixture on the steam-bath, the yellow precipitate dissolved. The same temperature was kept for forty minutes after solution was complete. On cooling, faintly colored needles (2.6 g., m.p. about 180°) separated. Simultaneously-formed XIV and XI were removed by recrystallizing this product three times from xylene; pale yellow slender prisms, m.p. 234–235°. The filtered reaction mixture yielded on extraction with benzene 0.3 g. of 5,6-dimethoxy-1-hydroxy-1-veratryl-2-methylindanone.

(c) A solution of 20 g. of II in 100 ml. of glacial acetic acid was mixed with 20 ml. of concentrated nitric acid and kept at room temperature for a week. During this period the mixture was successively diluted with increasing portions of a total of 350 ml. of water. The clear solution was warmed on a steam-bath for sixty minutes, and 0.2 g. of XI was removed by filtration. Water (200 ml.) was added, and the resulting clear solution crystallized on being boiled. The product was recrystallized from alcohol, yielding colorless needles, m.p. 236°; when mixed with specimens prepared according to (a) and (b), 235° and 233-234° respectively; yield 1.4 g.

The product prepared by the above methods should be recrystallized from ethyl alcohol for final purification, in order to remove traces of X, which is particularly disturbing in the subsequent reaction. The samples recrystallized from xylene contain hydrate water which is retained with remarkable persistence.

*Anal.* Calc'd for  $C_{20}H_{20}O_6$ : C, 67.5; H, 5.7.

Found: a C, 67.5, 67.8; H, 6.2, 6.2.

b C, 67.7, 67.3; H, 5.9, 5.9.

Calc'd for  $C_{20}H_{20}O_6 + 0.5H_2O$ : C, 65.7; H, 5.8; C—CH<sub>3</sub>, 4.1.

Found: c C, 65.8, 65.9, 65.7, 65.9, 66.0; H, 6.0, 5.9, 5.7, 5.8, 6.0; C—CH<sub>3</sub>, 4.0.

a = sample recrystallized from ethyl alcohol

b = sample recrystallized from xylene and dried at 13 mm. over phosphorus pentoxide at 140°

c = samples recrystallized from xylene and dried at 100°

The colorless crystals acquire a pale yellow color if exposed to light. The substance is insoluble in aqueous alkalis and readily soluble in chloroform, acetone, or ethyl acetate; the solution in glacial acetic acid is pale yellow. No reaction occurs with hydrazine derivatives, acyl halides, or with dilute solutions of bromine.

On oxidizing 0.6 g. of this substance with 6 ml. of concentrated nitric acid in 12 ml. of glacial acetic acid on the steam-bath for ten minutes, 0.3 g. of XI (golden-yellow needles from diamyl phthalate, m.p. 343°) was formed. On adding water to the filtered reaction mixture, a faintly colored powder was obtained, which crystallized from ethyl acetate-petroleum ether or dioxane-water as colorless long needles, m.p. 205°, insoluble in aqueous alkali, soluble in warm alcoholic alkali with deep green color. This product, probably a *dihydrodi-(4,5-dimethoxysalicylide)*, was not further investigated.

*Anal.* Calc'd for  $C_{18}H_{18}O_8$ : C, 59.7; H, 5.0.

Found: C, 59.4, 59.4, 59.6; H, 5.3, 5.4, 5.0.

*2,3,6,7-Tetramethoxyanthranyl sulfate.* To 1 g. of IX (repeatedly recrystallized from ethyl alcohol) in 100 ml. of glacial acetic acid, 0.5 ml. of concentrated sulfuric acid was added. The carbenium salt crystallized within forty minutes in large cherry-red clusters. The substance, m.p. 175-178°, is extremely sensitive towards moisture.

*Anal.* Calc'd for  $C_{18}H_{17}O_8 \cdot HSO_4 + 0.5H_2SO_4$ : SO<sub>4</sub>, 31.8.

Found: SO<sub>4</sub>, 31.4.

*2,3,6,7-Tetramethoxyanthrone.* The above carbenium salt (0.6 g.), dissolved in 10 ml. of ethyl alcohol containing 0.2 g. of potassium acetate, gave slender yellow needles, m.p. 175-176°; yield 0.28 g.

*Anal.* Calc'd for  $C_{18}H_{18}O_8$ : C, 68.8; H, 5.8.

Found: C, 68.6; H, 5.7.

*2,3,6,7-Tetramethoxy-9-hydroxy-9-acetylanthrone (X).* A solution of 1 g. of IX in 10 ml. of glacial acetic acid was mixed with 8 ml. of a 10% solution of hydrogen peroxide. The solution, kept at 80° for 30 minutes, deposited small colorless plates, which were recrystallized from ethyl acetate-petroleum ether or dioxane-water. The crystals melt at 325° to a deep cherry-red liquid; yield 0.3 g. The substance is insoluble in aqueous alkali but quickly dissolves on addition of a few drops of alcohol, and is precipitable from the alkaline solution by acetic acid.

*Anal.* Calc'd for  $C_{20}H_{20}O_7$ : C, 64.5; H, 5.4.

Found: C, 64.1, 64.3; H, 5.8, 5.8.

Oxidation of this substance in glacial acetic acid with aqueous chromic acid or potassium permanganate, or addition of hydrazine, phenylhydrazine, 3,5-dinitrophenylhydrazine, hydroxylamine, or semicarbazide to its solution in acetic acid, gave in all cases 2,3,6,7-tetramethoxyanthraquinone (XI) (yellow needles containing no nitrogen, m.p. 343-344°) in fair yield.

*Anal.* Calc'd for  $C_{18}H_{16}O_6$ : C, 65.9; H, 4.9.

Found: a C, 65.6; H, 5.0.

b C, 65.8; H, 5.0.

a = sample obtained with hydroxylamine

b = sample obtained with semicarbazide

The author wishes to express his sincere thanks to Dr. M. Hauer, Dr. Gy. Gál, Dr. Z. Rácz, and Dr. L. Toldy for their assistance with the experimental work.

#### SUMMARY

In the oxidation of diisohomogenol (I) with chromic acid, 2,3,6,7-tetramethoxyanthraquinone (XI) arises from 4-pyruvyl-5-veratroylveratrol (XIII) formed in the reaction mixture. Under altered conditions, 1-hydroxy-3'-ketodiisohomogenol (II), also may undergo ring closure by oxidative cyclization; in this case, 9,10-endoethylidene-9,10-dihydroanthracene derivatives are the immediate products. In both cases the acetyl at carbon 3 seems to induce the formation of the anthracene skeleton.

BUDAPEST, HUNGARY

#### REFERENCES

- (1) Part X, *Ber.*, **77**, 343 (1944).
- (2) Part III, *Ber.*, **76**, 855 (1943).
- (3) HAWORTH AND MAVIN, *J. Chem. Soc.*, 1363 (1931).
- (4) TIEMANN, *Ber.*, **24**, 2870 (1891).
- (5) MARICA AND PUXEDDU, *Gazz. chim. ital.*, **46**, 177 (1916); PUXEDDU, AND RATTU, *Gazz. chim. ital.*, **66**, 700 (1936); PUXEDDU, *Gazz. chim. ital.*, **66**, 710 (1936).
- (6) Part I, *Ber.*, **75**, 692 (1942).
- (7) Part II, *Ber.*, **75**, 891 (1942).
- (8) CARTWRIGHT AND HAWORTH, *Chem. and Ind.*, 117 (1947).
- (9) Part VIII, *Ber.*, **77**, 159 (1944).
- (10) Part VI, *Ber.*, **77**, 6 (1944).