In a subsequent experiment, in which the excess magnesium was removed from the *di*-Grignard reagent by filtration before the duryl 2-methoxyphenyl ketone was added, the coupling products were isolated in undiminished yields.

Hydrogenation of 2-(γ-butenylphenyl)durylcarbinol (XII). A solution of 0.38 g. (0.0013 mole) of the carbinol in 25 ml. of ethanol was hydrogenated over 0.04 g. of 30% palladium-on-charcoal at atmospheric pressure (748 mm.) and room temperature (31°). The theoretical uptake of hydrogen (0.0026 mole) had occurred after about 1 hr.; however, the treatment was continued for an additional 3 hr. The catalyst was removed by filtration and the solvent by distillation. The product, recrystallized from ethanol, formed colorless needles, m.p. 81–83°, yield 0.31 g. (86%). A pure sample melted at 83–84°.

Anal. Calcd. for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.68; H, 10.04.

The infrared spectrum (CS_2) contains bands at 2905, 1600, 1383, 868, and 757 cm.$^{-1}$ which are consistent with the hydrocarbon structure 2-(*n*-butylphenyl)durylmethane (XIII).

Reduction of 2-n-butylphenyl duryl ketone (XIV) *with sodium and ethanol.* To a boiling solution of 0.1 g. (0.00034 mole) of the ketone in 10 ml. of absolute ethanol was added, slowly with stirring, 1.0 g. of sodium in small pieces. After all the sodium had reacted, the hot solution was poured into a mixture of 15 ml. of concentrated hydrochloric acid and 30 g. of ice. The organic material was extracted from the cloudy aqueous solution with benzene. The benzene solution was washed, dried, and concentrated; the residual yellow oil crystallized from an ethanol-water mixture in slightly yellow crystals, yield 0.0264 g. (28%), m.p. 77–80°. A mixture melting point with the product of the previous reaction was 78–81°. In addition, the infrared spectrum (CS_2) is identical with that of the product of the previous reaction.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

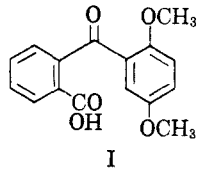
The Synthesis of Some Linear Tetracyclic Substances*[1]

MARSHALL GATES AND CLIFFORD L. DICKINSON, JR.[2]

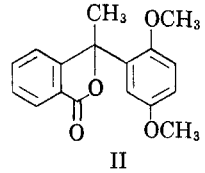
Received July 29, 1957

Several synthetic paths leading to linear tetracyclic substances have been investigated, and a dihydroxydioxomethylhexahydronaphthacene has been prepared.

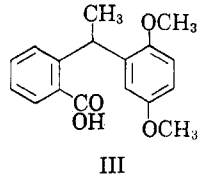
With a view toward assembling large molecules which might have some of the chelating properties associated with the tetracyclines, we have prepared some linear tetracyclic substances bearing several oxygenated functional groups. Our approach has been through *o*-(2,5-dimethoxybenzoyl)benzoic acid (I),[3] readily available by the condensation of *o*-carbomethoxybenzoyl chloride with hydroquinone dimethyl ether.[4] This substance was converted to 3-methyl-3-(2,5-dimethoxyphenyl)phthalide (II) in high yield by the action of methyl magnesium iodide. Reduction of the phthalide II with zinc and ammonia[5] yielded the corresponding acid III which readily cyclized in high yield on treatment with sulfuric acid to give 1,4-dimethoxy-10-methyl-9-anthrone (IV).



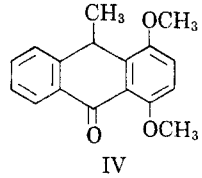
I



II



III



IV

We had hoped to extend the linear annulation of IV by the addition of butadiene or substituted butadienes to the 1,4-quinone corresponding to IV. This approach has the merit of converting the aromatic hydroquinone ring of IV to a hydroaromatic ring corresponding to ring B of the tetracyclines. The deep red quinone VI was readily prepared in high yield from IV by demethylation with aluminum bromide followed by oxidation with ferric chloride, but proved to be too unstable for successful use in the Diels-Alder reaction.

On the assumption that the instability of the quinone was largely the result of the acyl substituent, an attempt to prepare the ethylene thioketal of V prior to its oxidation to the quinone was made, but only unreacted starting material was obtained.

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

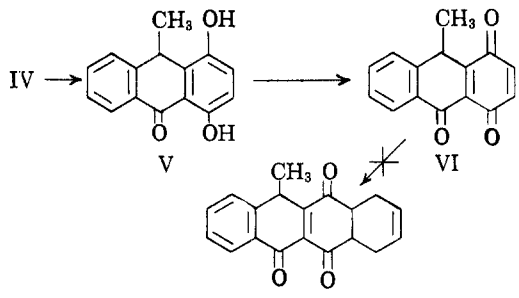
(1) Taken from the Ph.D. dissertation of Clifford L. Dickinson, Jr., the University of Rochester, 1955.

(2) E. I. du Pont de Nemours Fellow, 1954–1955.

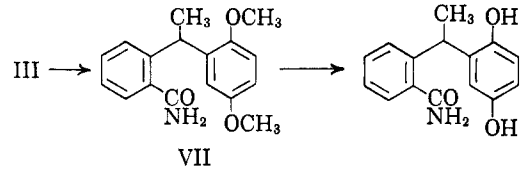
(3) K. Lagodzinski, *Ber.*, **28**, 116 (1895).

(4) C. Dufraisse and A. Allais, *Bull. Soc. Chim.*, [5], **11**, 531 (1944). This method was preferred to the simpler one using phthalic anhydride since it would allow structural specificity with substituted phthalic acid derivatives, *e.g.* the 3-methoxy derivative, whose use was contemplated in extending this synthesis to more highly oxygenated substances.

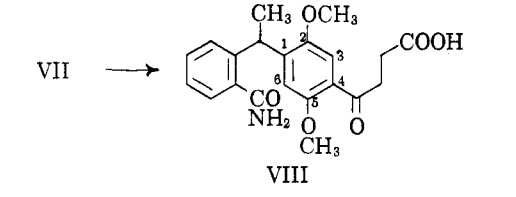
(5) The procedure was based on that of Bergmann for the similar reduction of 3-methyl-3-phenyl phthalide. *cf.* E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).



An attempt to convert the acid III or one of its derivatives into the corresponding quinone with a view toward carrying out the Diels-Alder reaction before ring closure (This would be the equivalent of establishing ring A before ring C of the tetracyclines.) also failed. Demethylation of III with hydrobromic acid led not to the corresponding hydroquinone but to V, and attempts to convert III into its acid chloride also resulted in cyclization. The corresponding amide VII was successfully prepared by the mixed anhydride method, however, and could easily be demethylated. Successful hydrolysis of the refractory amide



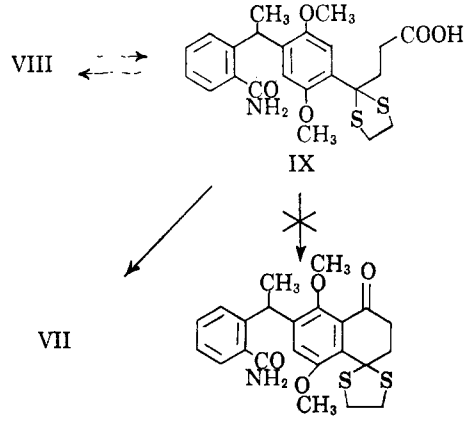
group at a later stage in the presence of reactive groups seemed remote, however, so the amide VII was used in an alternative scheme. Condensation with β-carbomethoxypropionyl chloride in the presence of polyphosphoric acid led to a single substance in 45% yield. This was assumed to have structure VIII on the basis of the following argument: Of the three positions available



for substitution in the substituted dimethoxybenzene ring, the 6 position can be eliminated. It is di-*o*-substituted, and the hindrance produced by the *ortho*-substituted 1-phenylethyl group must be very large. Of the other two positions, both the aliphatic substituent and the steric effect[6] favor position 4. This structural assignment was confirmed by certain characteristics of the completely cyclized compound to be discussed herewith.

We wished, if possible, to retain the carbonyl group of VIII in the final product, but for easy cyclization its deactivating effect on the aromatic ring had to be reduced or eliminated. The action of ethanedithiol and boron fluoride etherate in acetic acid[7] produced the thioketal IX in nearly quantitative yield. Its infrared spectrum shows carbonyl absorption at 5.86 and 6.01 μ. That of VIII shows three bands in this region, at 5.84, 6.01, and 6.05 μ. The common bands at 5.84 and 6.01 μ can be assigned to the carboxyl and carbamide groups, respectively, leaving that at 6.05 μ, somewhat longer than the usual aromatic carbonyl band, assignable to the ketonic group of VIII.

All attempts to cyclize the thioketal IX failed. Hydrogen fluoride gave only starting material, as did concentrated sulfuric acid at room temperature. At higher temperatures complete decomposition took place. Boron fluoride etherate gave either no reaction or resulted in cleavage to VIII[8] depending on conditions. In polyphosphoric acid VIII was again obtained, but in addition to an unidentified sulfur-containing compound containing no aromatic ring, VII was also obtained. This reversal of the Friedel-Crafts reaction, while unexpected, is not abnormal if cleavage of the thioketal takes place first, since Rosenmund and Schurr[9] have reported a number of instances of deacylations of acyl phenols and phenol ethers. These results suggest that an equilibrium is established between VII, a β-carbomethoxypropionylpolyphosphoric acid complex, and VIII, and this suggestion receives support from the observation that in the acylation of VII, some unchanged starting material is invariably recovered.[10]



Although IX could not be cyclized, the corresponding hydroquinone might be expected to be sufficiently active for cyclization with, *e.g.*, hydrogen fluoride. Accordingly, VIII was demethylated to yield the corresponding hydroquinone X, but all

(6) The "buttressing effect" [M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.*, **72**, 19 (1950)] clearly produces more hindrance at position 3 than at 4.

(7) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

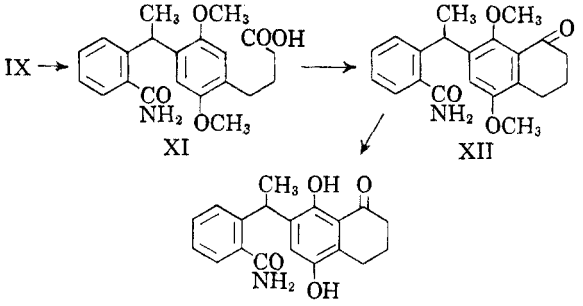
(8) Possibly through an intermediate enol thioether, *cf.* A. Sporzynski, *Arch. Chem. Farm.*, **3**, 59 (1936).

(9) K. W. Rosenmund and W. Schurr, *Ann.*, **460**, 56 (1928).

(10) A possible explanation of the failure of IX to cyclize may be that the sulfur atoms, functioning as Lewis bases, form complexes with the condensing agent which inductively deactivate the ring.

attempts to prepare its thioketal, even under forcing conditions, failed. This failure, coupled with the similar failure of V to form a thioketal strongly suggests that the strong hydrogen bonding present in V and X presents thioketal formation.

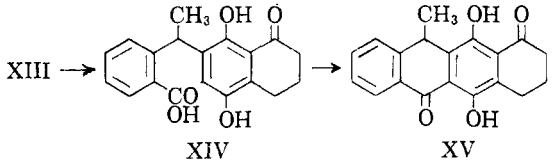
At this point we reluctantly abandoned our efforts to retain the carbonyl of VIII and removed it by desulfurization of IX with Raney nickel to give the butyric acid XI, which was easily cyclized with polyphosphoric acid to the tetralone XII.[11]



XI XII XIII

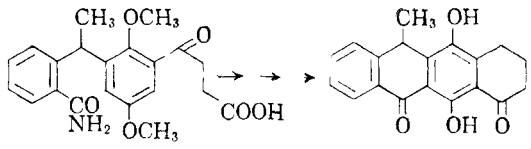
Demethylation with hydrobromic acid-hydriodic gave the hydroquinone XIII in high yield, and this substance was hydrolyzed to the free acid XIV with oxygen-free sodium hydroxide under nitrogen.[12]

Cyclization of XIV with fresh polyphosphoric acid proceeded satisfactorily to give the dark orange 5,12-dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene XV.



XIV XV

Although this substance cannot be extracted from benzene with 10% sodium hydroxide, it is readily extracted with Claisen's alkali to give a deep blue solution. Its infrared spectrum shows bands at 6.08, 6.13, and 6.16 μ, assignable to the hydrogen-bonded tetralone carbonyl, the aromatic ring, and the hydrogen-bonded diarylketo groups, respectively, and no absorption in the 3.0 μ region. The absence of hydroxyl absorption in the latter region confirms the assignment of structure to VIII, since if acylation had taken place in the 3 position the spectrum of the tetracyclic substantance resulting from the further transformations described (XVI) should show hydroxyl absorption in the 3.0 μ region.



XVI

The oxime of XV, which carries a nitrogen atom in the position occupied by the dimethylamino group of the tetracyclines, was also prepared.

EXPERIMENTAL[13]

o-(2,5-Dimethoxybenzoyl)benzoic acid (I). The procedure of Dufraisse and Allais[4] for the preparation of the methyl ester was modified for large-scale use and the ester was saponified to the acid without purification, yield 64%, m.p. 159.5–161.5° (reported[3] 162°).

3-Methyl-3-(2,5-dimethoxyphenyl)phthalide (II). To a solution of methyl magnesium iodide prepared from 12.1 g. (0.525 mole) of magnesium, 75.0 g. (0.525 mole) of methyl iodide and 250 ml. of ether was added 60.0 g. (0.21 mole) of finely divided *o*-(2,5-dimethoxybenzoyl)benzoic acid in small portions with mechanical stirring during the course of an hour. The resulting mixture was heated under reflux for 1 hr., cooled, and decomposed with 200 ml. of cold 3*N* hydrochloric acid. The aqueous layer was extracted with two 200-ml. portions of ether. The combined ethereal solution was washed successively with 200 ml. of 5% sodium bicarbonate solution, 200 ml. of about 1*N* sodium thiosulfate solution, then water, and dried over anhydrous sodium sulfate. Removal of the solvent left 50.0 g. (85%) of yellow-brown oil.

A small portion of this oil was purified by chromatography on alumina with a 50–50 benzene–petroleum ether mixture as the eluent. The colorless oil that resulted crystallized on long standing and was recrystallized from hexane, m.p. 83.0–84.0°. The crude oil, on seeding, crystallized and melted at 78.0–80.5°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.70; H, 5.70.

o-[1-(2,5-Dimethoxyphenyl)ethyl]benzoic acid (III). To a solution of 50.0 g. (0.170 mole) of 3-methyl-3-(2,5-dimethoxyphenyl)phthalide in 200 ml. of alcohol was added 1 l. of 15% ammonium hydroxide solution, 120 g. of zinc dust, and 50 ml. of normal copper sulfate solution. The mixture was heated under reflux for 20 hr., cooled, and filtered. The filter cake was heated on a steam bath with 250 ml. of 10% sodium hydroxide solution until only the suspended zinc dust was undissolved, cooled, and filtered. The combined aqueous filtrates on acidification yielded 42.0 g. (83%) of solid, m.p. 155–161°. Recrystallization from benzene gave 36.0 g. (71%), m.p. 163.5–165°. Several further recrystallizations from benzene gave material of m.p. 164.0–165.5°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.44; H, 6.28.

Its methyl ester, prepared by the action of an excess of diazomethane, melted after several crystallizations from alcohol, at 109.5–110.5°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.12; H, 6.80.

1,4-Dimethoxy-10-methyl-9-anthrone (IV). A solution of 8.00 g. (0.028 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]-benzoic acid in 50 ml. of concentrated sulfuric acid was allowed to stand for 30 min., then slowly poured into ice and

(11) The infrared spectrum of XII exhibits only one band in the carbonyl region (6.00 μ) indicating that the ketonic and amide carbonyl bands coincide. The presence of the amide group is confirmed by the characteristic —N—H bands at 2.98 μ and 3.18 μ, that of the ketonic group by the formation of a 2,4-dinitrophenylhydrazone.

(12) Neither XIV nor XIII shows the bathochromic shift in carbonyl stretching frequency expected as a result of strong hydrogen bonding with the adjacent phenolic hydroxyl.

(13) All melting points are corrected. Analyses were carried out by Miss Annette Smith and by the Micro-Tech Laboratories. Infrared spectra were determined by Mr. Carl Whiteman on a Perkin-Elmer Model 12c Infrared Spectrophotometer equipped with a sodium chloride prism using Nujol mulls.

water. A viscous yellow solid separated and was taken into chloroform. The aqueous solution was extracted with two 100 ml. portions of chloroform, and the combined chloroform solutions were washed with 5% sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. Removal of solvent left 6.00 g. (80%) of pale yellow solid with a melting point of 135.0–136.5°. Recrystallization from ethyl acetate gave a colorless material, m.p. 138.0–139.0°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.01; H, 6.01.

1,4-Dihydroxy-10-methyl-9-anthrone (V). *A. From 1,4-dimethoxy-10-methyl-9-anthrone.* A solution of 1.08 g. (0.0040 mole) of 1,4-dimethoxy-10-methyl-9-anthrone in 15 ml. of dry benzene was added to a solution of 3.30 g. (0.0123 mole) of anhydrous aluminum bromide in 15 ml. of dry benzene, and the mixture was heated under reflux for 2 hr. Hydrochloric acid (20 ml. of 6*N*) was added and the two phase system was heated under reflux until the insoluble red complex disappeared. The layers were separated and the aqueous layer was extracted with 20 ml. of benzene. The combined benzene solution was washed with water and concentrated to yield 0.90 g. (93%) of bright yellow needles, m.p. 186.0–188.5°. Several further recrystallizations from benzene raised the melting point to 190.0–191.0°. Infrared max. 6.16 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.14; H, 5.23.

B. From o-[1-(2,5-dimethoxyphenyl)ethyl]benzoic acid. A solution of 1.00 g. (0.0035 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]benzoic acid in 20 ml. of 48% hydrobromic acid and 10 ml. of glacial acetic acid was heated under reflux for 2 hours, cooled, and diluted with 25 ml. of water. The dark brown precipitate was collected and recrystallized from benzene to give 0.40 g. of yellow needles, m.p. 189.0–191.5°, not depressed by mixture with the sample described above.

1,4-Diacetoxy-10-methyl-9-anthrone was prepared from the dihydroxy compound by acetylation with acetic anhydride and potassium acetate. It was purified by chromatography on alumina and crystallization from benzene-hexane. The colorless product melted at 68.5–70.5° when heated rapidly. When heated slowly from 65–71°, the compound softens but does not melt, and if then heated rapidly above 71° it melts at 112.0–113.5°. However, if heated slowly to 108–114° the final melting point is 127.0–128.5°.

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98. Found: C, 70.80; H, 5.17.

10-Methyl-1,4,9,10-tetrahydro-1,4,9-triketoanthracene (VI). To a solution of 0.200 g. (0.00084 mole) of 1,4-dihydroxy-10-methyl-9-anthrone in 10 ml. of ethanol was added 1 ml. of 2*N* ferric chloride solution. After 10 min., 30 ml. of water containing 5 drops of concentrated hydrochloric acid was added and the mixture was allowed to stand in the refrigerator overnight. The precipitate was collected to give 0.196 g. (98%) of bright red crystals, m.p. 176.5–179.5°. Although this compound appeared to be stable in the solid state or when suspended in the acid solution, all attempts to recrystallize it resulted in decomposition.

The compound was reduced with sodium hydrosulfite solution to give 1,4-dihydroxy-10-methyl-9-anthrone as shown by melting point and mixed melting point.

Attempted condensation of 10-methyl-1,4,9,10-tetrahydro-1,4,9-triketoanthracene with 1,3-butadiene. A mixture of 0.050 g. (0.00021 mole) of the quinone, 3 ml. of pure dioxane, and a large excess of 1,3-butadiene was heated in a pressure bottle at 50–60° for 15 hours. The cooled contents were removed by solution in acetone, and the acetone was evaporated to give a dark brown tarry residue. This residue was treated with dilute hydrochloric acid, dissolved in benzene, and extracted with 10% sodium hydroxide solution. No material was extracted into the sodium hydroxide solution.

Attempted preparation of the ethylene thioketal of 1,4-dihydroxy-10-methyl-9-anthrone. A solution of 0.100 g. (0.00042 mole) of 1,4-dihydroxy-10-methyl-9-anthrone, 5 drops of ethylene dithioglycol, and 5 drops of boron trifluoride etherate in 2 ml. of glacial acetic acid was allowed to stand at room temperature for 24 hr. Dilution with water gave only starting material as shown by mixed melting point.

When ethylene dithioglycol was used as the solvent as well as the reactant, the result was the same.

o-[1-(2,5-Dimethoxyphenyl)ethyl]benzamide. VII. *A. Attempted preparation through the acid chloride.* A solution of 0.500 g. (0.00175 mole) of *o*-[1-(2,5-dimethoxyphenyl)-ethyl]benzoic acid and 0.380 g. (0.00180 mole) of phosphorus pentachloride in 25 ml. of dry benzene was heated under reflux for 1 hr. Ammonia gas was then bubbled through the solution for 10 min. and 20 ml. of 15% ammonium hydroxide solution was added. The benzene layer was separated, washed with water, and evaporated to dryness. The remaining solid was shown to be 1,4-dimethoxy-10-methyl-9-anthrone by a mixed melting point.

B. By the mixed carbonic anhydride procedure. A solution of 20.00 g. (0.0070 mole) of *o*-[1-(2,5-dimethoxyphenyl)-ethyl]benzoic acid and 14.40 g. (0.137 mole) of triethylamine in 300 ml. of chloroform (Reagent Grade) was cooled to −10° in an ice-salt mixture and 15.10 g. (0.137 mole) of ethyl chlorocarbonate was added slowly with vigorous mechanical stirring so that the temperature did not rise above −5°. The solution was allowed to stand for 30 min. after the addition of the ethyl chlorocarbonate. A stream of gaseous ammonia was then passed in at a rate such that the temperature did not rise above 0°. After 2 hr. 150 ml. of water was added. The layers were separated and the chloroform layer was washed with 100 ml. of water. The combined aqueous layers on acidification gave 1.80 g. of starting material.

The dried chloroform solution was concentrated and the semisolid residue was dissolved in 100 ml. of methanol, 100 ml. of 10% sodium hydroxide solution was added, and the resulting mixture was heated to boiling on a steam bath until colorless crystals began to separate. The solution was diluted with 100 ml. of water and cooled. The crystalline precipitate was collected to give 12.20 g. (61%), m.p. 156–158°. After recrystallization from ethyl acetate the melting point was 158.5–159.0°. The filtrate on acidification gave 4.20 g. of additional starting material. The yield of amide based on unrecovered starting material was 87%.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 71.76; H, 6.87.

o-[1-(2,5-Dihydroxyphenyl)ethyl]benzamide. A solution of 2.85 g. (0.01 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]-benzamide (VII) in 40 ml. of dry thiophene-free benzene was added to a solution of 8.70 g. (0.031 mole) of aluminum bromide in dry thiophene-free benzene. The resulting mixture was heated under reflux for 1.5 hr., diluted with 50 ml. of 6*N* hydrochloric acid, and again heated for 30 min., the benzene being allowed to boil away. The solution was cooled in ice and the precipitate collected to give 2.50 g., m.p. 193.0–195.0°. After recrystallization from dilute alcohol and treatment with Norite, the yield was 1.90 g., m.p. 209.0–210.0°. Several further recrystallizations raised the melting point to 217.5–218.5°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.04; H, 5.93.

o-[1-(2,5-Diacetoxyphenyl)ethyl]benzamide. A mixture of 1.00 g. (0.0039 mole) of *o*-[1-(2,5-dihydroxyphenyl)ethyl]-benzamide, 6.0 g. of acetic anhydride, and 0.25 g. of sodium acetate was heated on a steam bath for 30 min. and diluted with water. The precipitate was collected to give 0.80 g. (60%), m.p. 135.0–144°. After several recrystallizations from benzene, the melting point was 149.5–150.0°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61. Found: C, 66.80; H, 5.72.

8-{2,5-Dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}-propionic acid (VIII). A mixture of 10.00 g. (0.0352 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]benzamide, 7.00 g.

(0.0467 mole) of β-carbomethoxypropionyl chloride,[14] and 150 g. of polyphosphoric acid was heated at 45–50° with mechanical stirring until the brown mixture became orange. The time required varied from 45 min. to 2 hr., depending upon the freshness of the polyphosphoric acid. The reaction mixture was diluted with water and a viscous yellow material separated. The organic material was taken into chloroform (two extractions), and the chloroform solution was washed with water, dried, and concentrated. The oily solid residue was taken into 75 ml. of methanol, treated with 150 ml. of 10% sodium hydroxide solution, and heated on a steam bath (open flask) for 45 min., cooled, diluted with 100 ml. of water, and filtered. The 4.00 g. of material collected was shown to be unreacted starting material by a mixed melting point. Acidification of the filtrate gave 7.50 g., m.p. 194.0–196.0°. Recrystallization from alcohol gave 6.00 g. (45%), m.p. 199.0–200.5°. Infrared maxima 5.84, 6.01, 6.05 μ.

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.41; H, 5.91.

Ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (IX). A solution of 3.80 g. (0.0099 mole) of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid, 4.00 g. of ethylene dithioglycol in 40 ml. of glacial acetic acid containing 4 ml. of boron fluoride etherate was allowed to stand for 18 hr. at room temperature and then diluted with 150 ml. of water. The colorless precipitate was collected, dissolved in 125 ml. of 5% sodium bicarbonate solution, extracted with three portions of benzene to remove the ethylene dithioglycol, and acidified with dilute hydrochloric acid. The precipitate was collected to give 4.39 g. (98.5%), m.p. 201.5–203.0°. After several recrystallizations from ethyl acetate the melting point was 202.5–203.3°. Infrared maxima 5.86, 6.01 μ.

Anal. Calcd. for $C_{23}H_{27}O_5S_2N$: C, 59.84; H, 5.90. Found: C, 59.62; H, 6.10.

Attempted cyclization of the ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid. A. With anhydrous hydrogen fluoride. A solution of 0.200 g. (0.00043 mole) of the ethylene thioketal in 4.0 g. of anhydrous hydrogen fluoride was allowed to stand until the hydrogen fluoride had evaporated. The residue was completely soluble in 5% sodium bicarbonate solution, and acidification of this solution yielded only starting material (mixed melting point).

B. With sulfuric acid. A solution of 0.100 g. (0.00022 mole) of the ethylene thioketal in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 1 hr. and then diluted. The precipitate was shown to be unchanged starting material by mixed melting point.

C. With boron trifluoride etherate. A solution of the ethylene thioketal in 1 ml. of boron trifluoride etherate was heated at 60° for 1 hr., cooled, and decomposed with 10 ml. of water. A viscous oil separated and the odor of ethylene dithioglycol was pronounced. The oil was taken into benzene and extracted with 5% sodium bicarbonate solution. Acidification of the bicarbonate solution gave a colorless precipitate that was collected and recrystallized from alcohol. This compound was shown to be β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (VIII) by mixed melting point.

The remaining benzene solution was evaporated to dryness leaving an amorphous tan powder. Attempts to induce this material to crystallize were unsuccessful.

D. With polyphosphoric acid. A mixture of 1.00 g. (0.0022 mole) of the ethylene thioketal and 20 g. of polyphosphoric acid was heated at 45–50° with stirring for 1 hr., diluted with water, and extracted several times with chloroform. The chloroform solution was washed with water, extracted with 50 ml. of 5% sodium bicarbonate solution, and dried. The sodium bicarbonate solution on acidification gave 0.100 g. of tan precipitate which after recrystallization from alcohol melted at 199.0–200.0°. It did not depress the melting point of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)-ethyl]benzoyl}propionic acid (VIII).

The chloroform solution was concentrated under reduced pressure to give 0.650 g. of viscous brown oil which was chromatographed on 40 g. of silica with a 75–25 benzene-ethyl acetate mixture as the eluent. The first fractions yielded 0.114 g. of an unidentified colorless crystalline sulfur-containing material, melting point, after several recrystallizations from benzene, 243.5–244.5°.

The following fractions yielded 0.125 g. of tan solid, m.p. 140–150°. After several recrystallizations from benzene, it melted at 158.5–160.0°, and did not depress the melting point of o-[1-(2,5-dimethoxyphenyl)ethyl]benzamide (VII).

Further elution with 50–50 benzene–ethyl acetate yielded a yellow oil that could not be induced to crystallize.

β-{2,5-Dihydroxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}-propionic acid (X). A solution of 4.00 g. (0.015 mole) of aluminum bromide in 50 ml. of dry thiophene-free benzene was treated with stirring with 1.06 g. (0.00275 mole) of finely divided β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (VIII). The mixture was heated under reflux for 1.5 hr., then diluted with 30 ml. of 6*N* hydrochloric acid. Heating was continued for 30 min., during which the benzene boiled away. The mixture was then cooled in an ice bath to yield 0.96 g. (97%) of solid, m.p. 175.0–180.0°. After recrystallization from dilute alcohol and treatment with Norit, it melted at 187.0–187.5°.

Anal. Calcd. for $C_{19}H_{19}O_6N$: C, 63.86; H, 5.36. Found: C, 63.98; H, 5.61.

Attempted preparation of the ethylene thioketal of β-{2,5-dihydroxy-4-[1-(o- carboxamidophenyl)ethyl]benzoyl}propionic acid. A. In acetic acid. A solution of 0.200 g. (0.00056 mole) of the hydroquinone X, 5 drops of boron trifluoride etherate, and 5 drops of ethylene dithioglycol in 10 ml. of glacial acetic acid was allowed to stand 48 hr. at room temperature. The precipitate was collected and shown to be unchanged starting material by a mixed melting point.

B. In ethylene dithioglycol. A solution of 0.200 g. of the hydroquinone X, 5 drops of boron trifluoride etherate was allowed to stand for 24 hr., diluted with chloroform, and extracted with 30 ml. of 5% sodium bicarbonate solution. The bicarbonate solution on acidification gave only starting material (mixed melting point).

γ-{2,5-Dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]phenyl}-butyric acid. (XI). A solution of 9.50 g. (0.0206 mole) of the ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl] benzoyl}propionic acid in 100 ml. of ethyl alcohol was treated with 110 g. of Raney nickel and heated under gentle reflux for 19 hr. The catalyst was removed and extracted with alcohol in a Soxhlet extractor for 48 hr. The combined alcoholic solutions on concentration gave an oily solid which was heated on the steam bath for 15 min. with 100 ml. of 10% sodium hydroxide. The cooled solution was treated with Norit, filtered, and acidified with dilute hydrochloric acid to give 6.50 g. (89%) of a solid, m.p. 174.0–178.0°. After several recrystallizations from ethyl acetate the melting point was 178.5–179.5°.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78. Found: C, 67.66; H, 7.05.

5,8-Dimethoxy-7-[1-(o-carboxamidophenyl)ethyl]-1-tetralone (XII). A mixture of 3.00 g. (0.0081 mole) of the butyric acid XI and 40 g. of polyphosphoric acid was heated at 45–50° with stirring for 1.5 hr. and then diluted with water. The organic material was taken into chloroform (three extractions), washed with 5% sodium bicarbonate solution, water, and dried. Removal of the chloroform left a yellow-brown solid that was treated with Norit and recrystallized from ethyl acetate. The yield was 2.14 g. (75%), m.p. 170.5–173.0°. After several recrystallizations from benzene the melting point was 174.5–175.5°. Infrared maxima 2.98, 3.18, 6.00 μ.

Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.37; H, 6.56. Found: C, 71.12; H, 6.88.

(14) J. Cason, *Org. Syn.*, **25**, 19 (1945).

Its *2,4-dinitrophenylhydrazone* melted at 254.5–255.5° when crystallized from ethyl acetate.

Anal. Calcd. for $C_{27}H_{27}O_8N_5$: C, 60.78; H, 5.10. Found: C, 60.73; H, 5.23.

5,8-Dihydroxy-7-[1-(o-carboxamidophenyl)ethyl]-1-tetralone (XIII). A solution of 5.25 g. of the tetralone XII in 30 ml. of glacial acetic acid was treated with 30 ml. of 48% hydrobromic acid and 30 ml. of 57% hydroiodic acid and heated under reflux for 2 hr. Dilution with ice and water gave a bright yellow precipitate, 4.20 g. (87%), m.p. 246.5–247.5°. Several recrystallizations from alcohol did not raise the melting point. Infrared maxima 2.96, 3.08, 5.96 μ.

Anal. Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89. Found: C, 70.04; H, 5.99.

5,8-Dihydroxy-7-[1-(o-carboxyphenyl)ethyl]-1-tetralone (XIV). A solution of 0.820 g. (0.0025 mole) of 5,8-dihydroxy-7-1-(*o*-carboxamidophenyl)ethyl-1-tetralone (XIII) in 15 ml. of 10% sodium hydroxide solution through which a stream of nitrogen had been passed to remove the oxygen was heated under nitrogen on a steam bath for 11 hr. The solution was carbonated and filtered rapidly, and the filtrate was immediately acidified with 3*N* hydrochloric acid. The precipitate was collected and washed with ether to give 0.650 g. (79%) of a dark yellow solid that did not melt, but decomposed at 255.0–260°. This was recrystallized from ethanol to give 0.450 g. of bright yellow material that decomposed at 265–267°. Infrared maxima broad, 5.96 to 6.00 μ.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.92; H, 6.03.

5,12-Dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene (XV). A mixture of 1.00 g. (0.00307 mole) of crude XIV and 25 g. of freshly opened polyphosphoric acid was heated at 55–60° with stirring for 2 hr., diluted with water, and extracted with three 30-ml. portions of benzene. The benzene solution was extracted with 50 ml. of 5% sodium bicarbonate solution, washed with water, dried, and concentrated to yield 0.800 g. (85%) of dark orange crystalline material, m.p. 139.0–142.0°. Recrystallization from alcohol gave 0.600 g. (63%), m.p. 142.0–144.0°. The analytical sample was recrystallized several times from a very small amount of ethyl acetate and melted at 148.5–149.0°. Infrared max. 6.08, 6.13, 6.16 μ. No absorption in the 3.0 μ region.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.89; H, 5.23.

5,12-Diacetoxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene. A mixture of 0.100 g. (0.000325 mole) of 5,12-dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene and 0.5 ml. of acetic anhydride was treated with a drop of concentrated sulfuric acid. The mixture was stirred for 10 min., during which a yellow solid separated, and then diluted with water. After several recrystallizations from alcohol, the precipitated material melted at 194.0–195.0°. Infrared max. 6.04, 6.13 μ.

Anal. Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.55; H, 5.10.

5,12-Dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene-1-oxime (XXX). A solution of 0.100 g. (0.000325 mole) of XV and 0.025 g. (0.00036 mole) of hydroxylamine hydrochloride in 1 ml. of a 50–50 pyridine-alcohol was heated on a steam bath for 2 hr., and the solvent was then removed with a stream of nitrogen. The product was washed with water, collected, and recrystallized from benzene to give a solid of m.p. 196.0–196.5°. Although the melting point was sharp, two crystalline forms, one pale orange and the other dark orange, persisted through several further recrystallizations.

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.57; H, 5.30. Found: C, 70.82; H, 5.45.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Alkylation and Related Reactions of Dibenzo-*p*-dioxin*

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A number of alkyl derivatives of dibenzo-*p*-dioxin(I) have been prepared. These include the 2-(II), 2,7(8)-di-*t*-butyldibenzo-*p*-dioxin(III); 2-(IV), 2,3-di-(V), 2,3,7,8-tetra-(VI), and a hexaisopropyldibenzo-*p*-dioxin(VII); and 2-benzyldibenzo-*p*-dioxin(VIII). Also obtained in the study were ethyl dibenzo-*p*-dioxin-2-dithiocarboxylate(IX), methyl dibenzo-*p*-dioxin-2-dithiocarboxylate(X), diethyl dibenzo-*p*-dioxin-2,7-bis(dithiocarboxylate)(XI), 2-chloromethyldibenzo-*p*-dioxin (XII), and the dibenzo-*p*-dioxin-2-carboxaldehyde(XIII). A 2,4-dinitrophenylhydrazone was formed from XIII yielding (XIV).

The acylation of dibenzo-*p*-dioxin (I) is known to proceed under normal conditions to a mixture of the 2, the 2,7 and, in one case, the 2,8 substituted compounds.[1,2] It is also fairly easy to obtain exclusively the mono or the di products by employing special conditions.[3]

In an extension of the above work, a study was made of direct alkylation of dibenzo-*p*-dioxin using mainly *t*-butyl chloride and isopropyl chloride since these reagents presented the least possibility of isomerization. Ethyl chloride, ethyl bromide, and methyl iodide were also used, but failed, as has already been reported[4–6] for other compounds, to give the normal alkylation products in carbon disulfide.

A number of solvents were tried before the choice of carbon disulfide was made. *s*-Tetrachloroethane could not be used since it apparently reacted with

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