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Cyclodehydration of *o*-Phenoxyphenylacetic Acids to Dihydrodibenz(b,f)oxepinones

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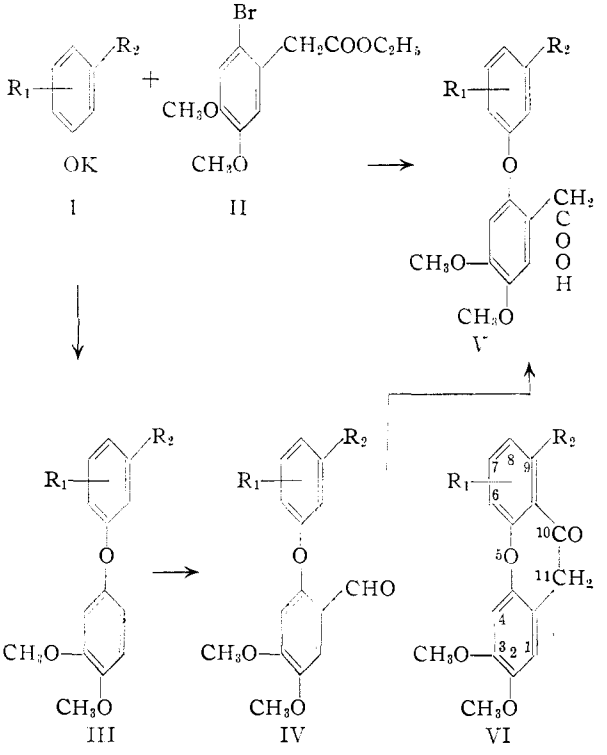
A series of *o*-phenoxyphenylacetic acids have been prepared and cyclized to the corresponding 10,11-dihydrodibenz(b,f)-oxepin-10-ones. The effect of substituents on the cyclodehydration reaction has been noted. Attempts to synthesize the alkaloid cularine did not meet with success.

The presence of the dibenz(b,f)oxepin system in the alkaloid cularine[1] has prompted a study of these little known polycyclic compounds. Two dihydrodibenz(b,f)oxepinones have already been synthesized.[2] The purpose of this investigation was to study the effect of substituents on the cyclodehydration of *o*-phenoxyphenylacetic acids (V) to the substituted dihydrodibenz(b,f)oxepinones (VI) and to explore the possibility of synthesizing the alkaloid cularine.

2-Phenoxy-4,5-dimethoxyphenylacetic acid (V, $R_1 = R_2 = H$) underwent cyclization to 2,3-dimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one (VI, $R_1 = R_2 = H$) in the presence of anhydrous hydrogen fluoride in 50–60% yield. The ease with which 2-(methoxyphenoxy)-phenylacetic acids (V, $R_1 = OCH_3$, $R_2 = H$) cyclized depended to some extent upon the position of the methoxyl group (R_1); 2-(3- and 4-methoxyphenoxy)-4,5-dimethoxyphenylacetic acids (V, $R_2 = H$, R_1 = 3- and 4-OCH_3) each gave the corresponding dibenz(b,f)oxepinone (VI, $R_2 = H$, R_1 = 7- and 8-OCH_3) in 50–60% yield. On the other hand, 2-(2-methoxyphenoxy)-4,5-dimethoxyphenylacetic acid (V, R_1 = 2-OCH_3, $R_2 = H$) underwent ring closure to VI, (R_1 = 6-OCH_3, $R_2 = H$) in the presence of hydrogen fluoride in only 15% yields. Still greater difficulty was experienced in the cyclization of 2-(2-methoxy-5-methylphenoxy)-4,5-dimethoxyphenylacetic acid (V, R_1 = 2-OCH_3, $R_2 = CH_3$), and 2,3,6-trimethoxy-9-methyl-10,11-dihydrodibenz(b,f)oxepin-10-one (VI, R_1 = 6-OCH_3, $R_2 = CH_3$) could only be prepared in 3% yield after drastic treatment of the former with hydrogen fluoride.

The cyclodehydration difficulty caused by the presence of substituents in the *o*-methoxyphenoxyphenylacetic acids (V, R_1 = 2-OCH_3, $R_2 = H$ and R_1 = 2-OCH_3, $R_2 = CH_3$) could perhaps be explained on steric grounds. However, it is surprising that the methoxyl group para and meta to the point of expected ring closure in V (R_1 = 3- and 4-OCH_3, $R_2 = H$) should have so little influence on the cyclodehydration. Incidentally the ring-closed product of V, (R_1 = 3-OCH_3, $R_2 = H$) must be 2,3,7-trimethoxy-(VI, R_1 = 7-OCH_3, $R_2 = H$) and not 2,3,9-trimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one (VI, R_1 = 9-OCH_3, $R_2 = H$) since it has already been shown that a substituent ortho to the point of expected ring closure hinders cyclodehydration.

The *o*-phenoxyphenylacetic acids (V) were prepared by the Ullmann condensation of the appropriate phenol (I) and ethyl 4,5-dimethoxy-2-bromophenylacetate (II) followed by saponification.



However the potassium salt of guaiacol (I, R_1 = 2-OCH_3, $R_2 = H$) condensed with II only in poor yield so that another method for the preparation of 2-(2-methoxyphenoxy)-4,5-dimethoxyphenylacetic acid (V, R_1 = 2-OCH_3, $R_2 = H$) had to be sought. Potassium guaiacolate was first condensed with 3,4-dimethoxybromobenzene and the resulting 2′,3,-4-trimethoxydiphenyl ether (III, R_1 = 2-OCH_3, $R_2 = H$) subjected to the Gattermann reaction to yield the aldehyde IV, (R_1 = 2-OCH_3, $R_2 = H$). The side chain of this was then lengthened through the azlactone to give V (R_1 = 2-OCH_3, $R_2 = H$). 2-(2-Methoxy-5-methylphenoxy)-4,5-dimethoxyphenylacetic acid (V, R_1 = 2-OCH_3, $R_2 = CH_3$) was similarly prepared from 2-methoxy-5-methylphenol and 3,4-dimethoxybromobenzene.

The difficulty with which the model compound V (R_1 = 2-OCH_3, $R_2 = CH_3$) underwent cyclodehydration left little hope for the synthesis of cularine by this method. Nevertheless, several attempts were made and these failed unexpectedly in the early stages. Neither the potassium salt of isovanillin nor of 2-methoxy-5-phthalimidoethylphenol (I, R_1 = 2-OCH_3, R_2 = -$CH_2CH_2N(CO)_2C_6H_5$) would condense with ethyl 4,5-dimethoxy-2-bromophenylacetate (II) to yield V (R_1 = 2-OCH_3, R_2 = CHO and -$CH_2CH_2N(CO)_2$-

(1) R. H. F. Manske, THIS JOURNAL, **72**, 55 (1950).

(2) R. H. F. Manske and A. E. Ledingham, *ibid.*, **72**, 4797 (1950).

C_6H_5, respectively). In each case only resinous materials were obtained. The reaction of 2-methoxy-5-phthalimidoethylbromobenzene with either the potassium salt of 3,4-dimethoxyphenol or of 3,4-dimethoxy-6-hydroxybenzaldehyde at 200° in the presence of copper acetate catalyst resulted only in debromination and 1-methoxy-4-phthalimidoethylbenzene was formed in 60% yield.

The authors are indebted to A. E. Ledingham and R. Mills for the microanalyses.

Experimental

Preparation of the 2-Phenoxy-4,5-dimethoxyphenylacetic Acids (V).—To a solution of potassium metal (0.7 g.) in absolute ethanol (5 cc.) was added the phenol (I, 5.0 g.) and the solvent removed *in vacuo*. To the residue was added ethyl 2-bromo-4,5-dimethoxyphenylacetate (II, 5.0 g.), copper acetate (0.1 g.) and copper powder (0.1 g.) and the reaction mixture heated at 200° in an atmosphere of nitrogen for 3 hours. The resulting crude ester was saponified by heating under reflux with 2 *N* sodium hydroxide (75 cc.). The alkaline solution was acidified, extracted with ether and the ether solution shaken with aqueous sodium bicarbonate. The bicarbonate solution was acidified, extracted with ether, the solvent removed and the residue distilled collecting the fraction boiling at 180–220° (0.3 mm.), which consisted mainly of the acid V. All the acids V crystallized from ether or from benzene as white prisms.

(a) **2-Phenoxy-4,5-dimethoxyphenylacetic acid** (V, R_1 = R_2 = H) was prepared from phenol and II; yield 50%, m.p. 124–125°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55. Found: C, 66.27; H, 5.86.

(b) **2-(2-Methoxyphenoxy)-4,5-dimethoxyphenylacetic acid** (V, R_1 = 2-OCH_3, R_2 = H) was prepared from guaiacol and II; yield 6%, m.p. 115–116°. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 64.19; H, 5.71.

(c) **2-(3-Methoxyphenoxy)-4,5-dimethoxyphenylacetic acid** (V, R_1 = 3-OCH_3, R_2 = H) was prepared from *m*-methoxyphenol and II; yield 42%, m.p. 129–130°. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 63.95; H, 5.65.

(d) **2-(4-Methoxyphenoxy)-4,5-dimethoxyphenylacetic acid** (V, R_1 = 4-OCH_3, R_2 = H) was prepared from *p*-methoxyphenol and II; yield 46%, m.p. 142–143°. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 64.63; H, 5.81.

(e) **2-(2-Methoxy-5-methylphenoxy)-4,5-dimethoxyphenylacetic acid** (V, R_1 = 2-OCH_3, R_2 = CH_3) was prepared from 2-methoxy-5-methylphenol and II; yield 20%, m.p. 106–107°. *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.07; H, 6.02. Found: C, 65.36, 65.54; H, 6.08, 6.12.

2',3,4-Trimethoxydiphenyl Ether (III, R_1 = 2-OCH_3, R_2 = H).—This was prepared by the Ullmann condensation of guaiacol with 3,4-dimethoxybromobenzene[3] as described above. The dark reaction mixture was dissolved in ether, the ether solution washed with dilute hydrochloric acid, with dilute sodium hydroxide and with water. The solvent was removed and the residue distilled collecting the fraction boiling at 170–190° (12 mm.) and crystallizing first from carbon tetrachloride and then from methanol; white needles, m.p. 73–74°, yield 20%. *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.28. Found: C, 69.54, 69.58; H, 6.21, 6.16.

2',3,4-Trimethoxy-5'-methyldiphenyl Ether (III, R_1 = 2-OCH_3, R_2 = CH_3).—This was prepared from 2-methoxy-5-methylphenol and 3,4-dimethoxybromobenzene as described above. The colorless distillate, b.p. 200–230° (12 mm.), which was obtained in 25% yield would not crystallize and the crude material was used directly in the Gattermann reaction below.

2',3,4-Trimethoxy-6-formyldiphenyl Ether (IV, R_1 = 2-OCH_3, R_2 = H).—To a cooled solution of 2',3,4-trimethoxydiphenyl ether (21 g.) in dry benzene (100 cc.) was added aluminum chloride (50 g.) keeping the temperature below 10°. The reaction mixture was cooled to 0°, dry hydrogen cyanide (35 cc.) added and then saturated at 0° with dry hydrogen chloride. The temperature of the reaction mixture was gradually raised to 40°, and maintained at 40° with stirring for two hours. After allowing to stand overnight, the dark mixture was treated with dilute hydrochloric acid at 60–70° for one hour in order to hydrolyze the imine. The benzene layer was washed with water, the solvent removed and the residue distilled, b.p. 180–185° (0.2 mm.) bath temperature. The light-yellow distillate (20 g.) would not crystallize even after purification through aqueous sodium bisulfite extraction.

The oxime which was obtained in 60% yield crystallized from benzene as white needles and melted at 121–122°. *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.37; H, 5.61; N, 4.62. Found: C, 63.60, 63.24; H, 5.48, 5.58; N, 4.64.

A small portion of the aldehyde IV, (R_1 = 2-OCH_3, R_2 = H) was oxidized by warming with potassium permanganate in moist acetone. **The 2',3,4-trimethoxy-6-carboxydiphenyl ether** which was obtained in quantitative yield melted at 185–186°. *Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.14; H, 5.26. Found: C, 62.90; H, 5.76.

2',3,4-Trimethoxy-5'-methyl-6-formyldiphenyl Ether (IV, R_1 = 2-OCH_3, R_2 = CH_3).—This was prepared from crude III (R_1 = 2-OCH_3, R_2 = CH_3) by the Gattermann reaction as described above. The distillate crystallized from methanol as light-yellow prisms, m.p. 108–109°, yield 50%. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.55; H, 5.96. Found: C, 67.32; H, 6.16.

Oxidation of this with potassium permanganate in acetone at room temperature yielded (80%) **2',3,4-trimethoxy-5'-methyl-6-carboxydiphenyl ether** which crystallized from benzene as white needles and melted at 186–187°. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 64.31, 64.43; H, 6.12, 5.63.

The Azlactone of 2',3,4-Trimethoxy-6-formyldiphenyl Ether (IV, R_1 = 2-OCH_3, R_2 = H).—Crude 2',3,4-trimethoxy-6-formyldiphenyl ether (IV, R_1 = 2-OCH_3, R_2 = H) (21 g.), hippuric acid (20 g.), acetic anhydride (40 cc.) and potassium acetate (12 g.) were heated on the steam-bath for two hours. The acetic anhydride was removed *in vacuo*, the residue washed with methanol and water and crystallized from benzene–methanol, orange needles (16.0 g.), m.p. 185–187°. *Anal.* Calcd. for $C_{25}H_{21}O_6N$: C, 69.60; H, 4.87; N, 3.25. Found: C, 69.75; H, 4.93; N, 3.24.

The Azlactone of 2',3,4-trimethoxy-5'-methyl-6-formyldiphenyl ether (IV, R_1 = 2-OCH_3, R_2 = CH_3).—This was prepared in 45% yield from IV (R_1 = 2-OCH_3, R_2 = CH_3) as above. It crystallized from benzene–methanol as orange needles melting at 184–185°. *Anal.* Calcd. for $C_{26}H_{23}O_6N$: C, 70.12; H, 5.17; N, 3.15. Found: C, 69.75; H, 5.19; N, 3.42.

2-(2-Methoxyphenoxy)-4,5-dimethoxyphenylacetic Acid (V, R_1 = 2-OCH_3, R_2 = H) **from the Azlactone.**—The azlactone of IV, (R_1 = 2-OCH_3, R_2 = H) (16 g.) and 10% potassium hydroxide solution (300 cc.) were heated under reflux for eight hours and filtered. The cooled filtrate was treated with 30% hydrogen peroxide (35 cc.) in small portions and then allowed to stand overnight. This was now filtered, the filtrate acidified with hydrochloric acid and extracted with ether. The solvent was removed and the benzoic acid was separated from the residue by sublimation at 150° and 0.3 mm. pressure. The required acid V (R_1 = 2-OCH_3, R_2 = H) distilled at 200–230 (0.3 mm.) and on crystallization from benzene melted at 115–116° alone or in admixture with the compound prepared from guaiacol and II above. The yield was 60%.

2-(2-Methoxy-5-methylphenoxy)-4,5-dimethoxyphenylacetic Acid (V, R_1 = 2-OCH_3, R_2 = CH_3) **from the Azlactone.**—The azlactone of IV (R_1 = 2-OCH_3, R_2 = CH_3) was treated as above. The required acid V (R_1 = 2-OCH_3, R_2 = CH_3) which was obtained in 44% yield melted at 106–107° alone or in admixture with the compound obtained from 2-methoxy-5-methylphenol and II above.

Preparation of the 9,10-Dihydrodibenz(b,f)oxepin-10-ones (VI).—To liquid anhydrous hydrogen fluoride (about 50 cc.) was added the *o*-phenoxyphenylacetic acid (1.2 g.) stirred for a few minutes and the solution allowed to stand at room temperature overnight. The residual product was dissolved in ether and the solution washed with aqueous sodium hydroxide and water and the solvent removed. The residue distilled at about 200° at 0.3 mm. and crystallized from methanol as white prisms. The alkaline washings contained no starting material.

(a) **2,3-Dimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one** (VI, R_1 = R_2 = H).—This was prepared from V (R_1 =

(3) R. Y. Moir and C. B. Purves, *Can. J. Research*, **26B**, 694 (1948).

R_2 = H) in 52% yield, m.p. 115–116°. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.18. Found: C, 71.13; H, 5.41.

(b) **2,3,6-Trimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one** (VI, R_1 = 6-OCH_3, R_2 = H).—This was prepared from V (R_1 = 2-OCH_3, R_2 = H) in 15% yield, m.p. 133–134°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33. Found: C, 68.23; H, 5.46.

(c) **2,3,7-Trimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one** (VI, R_1 = 7-OCH_3, R_2 = H).—This was prepared from V (R_1 = 3-OCH_3, R_2 = H) in 60% yield, m.p. 138–139°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33. Found: C, 68.45; H, 5.67.

(d) **2,3,8-Trimethoxy-10,11-dihydrodibenz(b,f)oxepin-10-one** (VI, R_1 = 8-OCH_3, R_2 = H).—This was prepared from V (R_1 = 4-OCH_3, R_2 = H) in 53% yield, m.p. 119–120°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33. Found: C, 67.74; H, 5.59.

(e) **2,3,6-Trimethoxy-9-methyl-10,11-dihydrodibenz(b,f)oxepin-10-one** (VI, R_1 = 6-OCH_3, R_2 = CH_3).—The preparation of this required treatment of V (R_1 = 2-OCH_3, R_2 = CH_3) with hydrogen fluoride for two days; yield 3%, m.p. 106–107°. *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.80; H, 5.73. Found: C, 68.94; H, 6.10.

2-Methoxy-5-methylphenol.—This was prepared from 3-nitro-4-methoxytoluene by reduction, diazotization and decomposition of the diazonium salt. Reduction with tin and hydrochloric acid[4] was not satisfactory since 3-amino-4-methoxy-6-chlorotoluene (m.p. 104–105°) was formed. The reduction with iron powder and 50% aqueous acetic acid at 90–100° followed by basification and steam distillation gave an 80% yield of 3-amino-4-methoxytoluene, m.p. 52–53°, literature[5] 52°. This product (100 g.) in water (300 cc.) and concentrated sulfuric acid (150 g.) was diazotized at 0° with sodium nitrite (50 g.) in water (100 cc.). The diazonium salt solution was then added in a thin stream to a vigorously boiling solution of copper sulfate pentahydrate (500 g.) and water (500 g.) allowing the phenol to steam distil out through a condenser as soon as it was formed. The crude product (57 g.) melted 36–38° after distillation, literature[6] 37–39°.

2-Methoxy-5-phthalimidoethylphenol. (a). **From 3-Hydroxy-4-methoxy-ω-nitrostyrene.**—To a suspension of 3-hydroxy-4-methoxy-ω-nitrostyrene[7] (5 g.) in glacial acetic acid (100 cc.) was added Adams catalyst (0.1 g.) and the reaction mixture shaken under 45 lb. hydrogen for one-half hour. The solvent and catalyst were removed and the residue heated with phthalic anhydride (5 g.) at 200° for five minutes. Crystallization of the cooled cake from methanol yielded 1.65 g. (or 20%) of white prisms melting at 156–157°. *Anal.* Calcd. for $C_{17}H_{15}O_4N$: C, 68.46; H, 5.37; N, 4.69. Found: C, 68.72, 68.92; H, 5.26, 5.36; N, 4.59.

(b) **From 3-Benzyloxy-4-methoxy-ω-nitrostyrene.**—Lithium aluminum hydride (8 g.) and dry ether (400 cc.) were heated under reflux for 48 hours allowing the condensed vapors to dissolve out crude 3-benzyloxy-4-methoxy-ω-nitrostyrene[8] (16 g.) from a thimble of a soxhlet apparatus. The reaction mixture was decomposed with wet ether and extracted with dilute hydrochloric acid. The acid solution was concentrated under reduced pressure and allowed to cool. The base (4.0 g.) was freed from the precipitated hydrochloride and fused at 200° with phthalic anhydride (2.5 g.). The resulting **2-methoxy-5-phthalimidoethylbenzyloxybenzene** crystallized from ethanol as light-yellow needles (5.6 g.) and melted at 126–127°. *Anal.* Calcd. for $C_{24}H_{22}O_4N$: C, 74.23; H, 5.67. Found: C, 73.64, 73.78; H, 6.02, 6.16.

This compound (2.1 g.) was debenzylated by shaking with 5% palladium-on-carbon catalyst (0.5 g.) in ethyl acetate (150 cc.) and methanol (50 cc.) at 40° under 45 lb. of hydrogen for 16 hours. After removal of the catalyst and solvent, the residue was crystallized first from benzene and then from methanol. The white prisms (0.5 g.) melted at 155–157° alone or in admixture with those obtained in (a).

Ethyl 2-Bromo-4,5-dimethoxyphenylacetate (II).—This was prepared from 2-bromo-4,5-dimethoxyphenylacetic acid[9] in 90% yield by esterification in absolute ethanol in the presence of concentrated sulfuric acid. It crystallized from aqueous ethanol as white needles melting at 66–67°. *Anal.* Calcd. for $C_{12}H_{15}O_4Br$: C, 47.52; H, 4.98. Found: C, 47.45; H, 5.26.

1-Phthalimidoethyl-4-methoxybenzene.—*p*-Methoxyphenylethylamine (25 g.) and phthalic anhydride (25 g.) were heated at 200° for 10 minutes and the cooled cake was crystallized from ethanol. The white needles which melted at 139–140° were obtained in quantitative yield. *Anal.* Calcd. for $C_{17}H_{15}O_3N$: C, 72.60; H, 5.34; N, 4.98. Found: C, 72.76, 72.78; H, 5.38, 5.19; N, 5.19.

1-Phthalimidoethyl-3-bromo-4-methoxybenzene.—To a solution of 1-phthalimidoethyl-4-methoxybenzene (25 g.) in acetic acid (200 cc.) and dry sodium acetate (25 g.) at 80° was added a solution of bromine (15 g.) in acetic acid (30 cc.). After allowing to stand at room temperature for one hour, the reaction mixture was poured into water. The precipitate was filtered, washed, dried and crystallized from benzene yielding white prisms (22 g.) melting at 162–163°. *Anal.* Calcd. for $C_{17}H_{14}NO_3Br$: C, 56.66; H, 3.88; N, 3.88. Found: C, 56.92; H, 3.90; N, 3.65.

In order to establish the position of the bromine atom in the brominated product, it (10 g.) was hydrolyzed to 3-bromo-4-methoxyphenylethylamine according to the method of Ing and Manske[10] and the latter (6.0 g.) oxidized with aqueous 2% potassium permanganate. This yielded (2.0 g.) of 3-bromo-4-methoxybenzoic acid melting at 218°, literature[11] 217°.

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