

this ring closure can take place either ortho or para to a hydroxyl yielding an aporphine related to corydine or to glaucine. *Dicentra eximia* (Ker) Torr. the source plant of coreximine yields not only cularine, indicating a 7,8-dihydroxybenzylisoquinoline as a precursor, but also corydine as well as glaucine, the related glaucenrine, and dicentrine.<sup>6</sup> Furthermore, III can undergo condensation and ring closure with formaldehyde to yield compounds of type II<sup>3</sup> or a mixture of type I and II.<sup>4</sup> It had generally been assumed that in the plant this ring closure is possible only in a position ortho to a hydroxyl. The present example of coreximine supplies an example of such a ring closure para to a hydroxyl and lends very convincing proof to the theory that the protoberberines are formed in the plant from the benzylisoquinolines. It should be noted that the balance between the two types of ring closure must be a delicate one. Instead of yielding coreximine the closely related *D. oregana* Eastwood yields corypalmine (type I)<sup>7,8</sup> as well as cularine, corydine, glaucine, etc.

### Experimental

A solution of 50 mg. of coreximine O,O-dimethyl ether in 10 cc. of dilute acetic acid was heated on a steam-bath for five hours with an excess of mercuric acetate. The

(6) Manske, *Can. J. Research*, **8**, 592 (1933).

(7) Manske, *ibid.*, **10**, 765 (1934).

(8) Manske, *ibid.*, **B14**, 348 (1936).

resultant deep yellow solution containing mercurous acetate in suspension was treated with an excess of zinc dust and a little hydrochloric acid and digestion on a steam-bath continued until the solution was colorless. The mixture was filtered and the clear filtrate shaken with ether in the presence of an excess of ammonia. The washed ether extract was freed of solvent, rapidly dried *in vacuo* and redissolved in a little dry ether. There was an almost immediate separation of nearly colorless fine prismatic crystals which when washed with a little ether and dried melted sharply at 157°. Small portions of this were mixed with various amounts of norcoralydine<sup>2</sup> similarly crystallized and in all cases the mixture melted at 157°.

The picrate of the base of natural origin melted either alone or in admixture with that of synthetic coralydine at 140° with some previous shrinking at 138°.

### Summary

1. The alkaloid previously recorded as F29, and now termed coreximine, has been shown to be a dihydroxydimethoxyprotoberberine which when O-methylated and racemized yields norcoralydine.

2. This is the first recorded example of a natural base of this type.

3. It is pointed out that the natural occurrence of an alkaloid of the type of norcoralydine is in harmony with, and in substantiation of, the theory that the benzylisoquinolines are biosynthetic intermediates in the formation of alkaloids of more complex types such as cularine, the aporphines, the protoberberines, etc.

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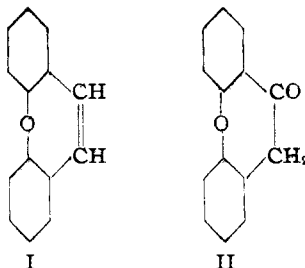
RECEIVED APRIL 7, 1950

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## Synthesis and Reactions of Some Dibenzoxepins

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It has been shown<sup>1</sup> that a portion of the molecular structure of cularine includes the 10,11-dihydrodibenz[*b,f*]oxepin nucleus and on exhaustive methylation yields a derivative of dibenz[*b,f*]oxepin (I). Oxidation of the latter



yielded the expected dibasic acid but there was also obtained about 10% of a compound formulated as a xanthone derivative. Since there came to mind no simple syntheses of a highly substituted xanthone it was of interest to prepare model substances and observe their behavior on oxidation. For this purpose it was desirable

(1) Manske, *THIS JOURNAL*, **71**, 55 (1950).

to have *o*-phenoxybenzaldehyde readily available. It had already been prepared by Lock and Kempter<sup>2</sup> but the reactions were involved, gave low yields, and were not adaptable to highly substituted derivatives. A Stephen's reaction on *o*-phenoxybenzoxonitrile<sup>3</sup> gave some of the material but this method did not seem adaptable to highly substituted derivatives either. It was observed, however, that the copper salt of salicylaldehyde when boiled with iodobenzene or when heated in an autoclave with bromobenzene to 220° gave a 25% yield of *o*-phenoxybenzaldehyde. Similarly *o*-bromoanisole gave a 40% yield of *o*-(2-methoxyphenoxy)-benzaldehyde. Both of these aldehydes were converted to the corresponding arylacetic acids via their azlactones and the arylpyruvic acids. When the chloride of *o*-phenoxyphenylacetic acid was reacted upon by aluminum chloride in nitrobenzene it gave a good yield of 10,11-dihydrodibenz[*b,f*]oxepin-10[11 *H*]one (II). Reduction of the ketone (II) to the corresponding carbinol was readily

(2) Lock and Kempter, *Monatsh.*, **67**, 24 (1935).

(3) Suter, *THIS JOURNAL*, **51**, 2581 (1929).

achieved by heating with aluminum isopropoxide in isopropyl alcohol and the carbinol was quantitatively dehydrated to I when gently warmed with *p*-toluenesulfonic acid.

Oxidation with permanganate in moist acetone converted I into diphenylether-2,2'-dicarboxylic acid in about 90% yield but there was also formed a neutral substance from which xanthone was readily obtained in 6-7% yield. It is therefore quite evident that the anomalous oxidation product obtained from cularine has the structure already assigned to it.

The 6-methoxy derivative of II was also prepared from the corresponding arylacetic acid. It is intended to utilize it as a model compound to study the possible synthesis of cularine.

A number of derivatives of the compounds mentioned above have been prepared and they are described in the experimental section.

### Experimental

***o*-Phenoxybenzaldehyde.**—A mixture of the copper salt of salicylaldehyde (86 g.) and bromobenzene (200 g.) was heated in an autoclave at 200-210° for 5 to 6 hr. Alternately the same amount of copper salt was boiled under reflux with iodobenzene (170 g.) in an atmosphere of nitrogen for 12 hr. In either case the separated cuprous salt was removed by filtration and the excess reagent removed by distillation *in vacuo*. The residue was then dissolved in benzene, washed with dilute hydrochloric acid, with alkali, and then with water. Removal of the benzene and distillation of the residue yielded *ca.* 50 g. of a pale yellow oil, b. p. 150-180° at 2 mm. This product consisted of a mixture of *o*-phenoxybenzaldehyde and parasalicylaldehyde. Some of the latter could frequently be crystallized by long standing. A practically quantitative separation was effected by dissolving the oil in an equal volume of ether and shaking in a machine for several hours with a solution of sodium bisulfite made by dissolving 50 g. of the salt in 150 cc. of water and passing some more sulfur dioxide into the solution. The clear aqueous layer was separated, washed once with fresh ether, acidified with an excess of hydrochloric acid, and gently heated while the liberated sulfur dioxide was drawn off under reduced pressure. The separated oil on distillation gave 29-30 g. of colorless *o*-phenoxybenzaldehyde boiling at 150-153° at 1 mm.

A small portion was oxidized in aqueous emulsion with potassium permanganate and yielded colorless needles of *o*-phenoxybenzoic acid melting at 113-114°<sup>4</sup> when recrystallized from hot water.<sup>4</sup> The semicarbazone was obtained in stout elongated plates when recrystallized from dilute methanol; m. p. 215°. Found: N, 16.25, 16.34. Calcd. for C<sub>14</sub>H<sub>13</sub>O<sub>2</sub>N<sub>3</sub>: N, 16.47.

***o*-Phenoxy-cinnamic Acid.**—A mixture of the aldehyde was heated in pyridine solution with two moles of malonic acid and a trace of piperidine on the steam-bath for several hours and then brought just to boiling. The addition of water and dilute hydrochloric acid gave an almost quantitative yield of the cinnamic acid which when recrystallized from methanol was obtained in fine plates melting at 179°. Found: C, 74.60, 74.77; H, 4.92, 4.70. Calcd. for C<sub>15</sub>H<sub>12</sub>O<sub>3</sub>: C, 75.00; H, 5.00.

A small portion of the above acid was reduced in aqueous solution with an excess of sodium amalgam to *o*-phenoxyhydrocinnamic acid. It was recrystallized from hexane to yield stout polyhedra which melted at 62°. Found: C, 74.76, 74.35; H, 5.76, 5.81. Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>: C, 74.38; H, 5.79.

***o*-Phenoxybenzaldehyde.**—*o*-Phenoxybenzotrile<sup>3</sup> was characterized by hydrolysis with methanolic potassium

hydroxide to the corresponding acid (m. p. 113-114°). During this hydrolysis there was also obtained a small amount of a neutral nitrogen containing compound which when recrystallized from methanol melted at 131°. A nitrogen determination indicates that it is *o*-phenoxybenzamide. Found: N, 6.43. Calcd. for C<sub>13</sub>H<sub>11</sub>O<sub>2</sub>N: N, 6.57.

A mixture of anhydrous stannous chloride (57 g.) and dry ether (200 cc.) was saturated with dry hydrogen chloride and then treated with 37 g. of *o*-phenoxybenzotrile. Passage of hydrogen chloride was continued for several hours longer and the mixture then set aside. In the course of several days a small amount of a crystalline deposit was formed which when decomposed with water yielded 16 g. of the aldehyde. When a sample of this was oxidized it yielded *o*-phenoxybenzoic acid. The phenylhydrazone crystallized from methanol in yellow plates melting at 149°. Lock and Kempter<sup>2</sup> record 147°.

***o*-Phenoxybenzaldehyde Azlactone.**—A mixture of the aldehyde (30 g.), hippuric acid (30 g.), anhydrous sodium acetate (12 g.), and acetic anhydride (80 cc.) was heated on a steam-bath for 2.5 hours.<sup>2</sup> The originally homogeneous solution rapidly deposited the azlactone in lemon yellow prisms which were filtered off (33 g.), washed with ether and with water. A portion recrystallized from acetic acid melted at 186°. Found: C, 77.06, 77.07; H, 4.27, 4.27. Calcd. for C<sub>22</sub>H<sub>16</sub>O<sub>3</sub>N: C, 77.42; H, 4.40.

***o*-Phenoxyphenylacetic Acid.**—The above azlactone (33 g.) was gently boiled with potassium hydroxide (50 g.) in water (165 cc.) until the evolution of ammonia had almost ceased (1.5 hr.). The solution was cooled, diluted with water (500 cc.) and saturated with a stream of sulfur dioxide. The mixture was warmed slightly to dissolve the bisulfite addition product, filtered from the benzoic acid, acidified with hydrochloric acid and gently heated *in vacuo* to expel the sulfur dioxide. The oily keto acid crystallized readily. After filtering, washing and drying (19 g.) a portion was recrystallized from benzene but melted not quite sharply at 146-150°.

The crude keto acid (19 g.) was dissolved in 5% sodium hydroxide solution (800 cc.) cooled to 0° and maintained at this temperature while 3% hydrogen peroxide solution (88 cc.) was added. The mixture was then allowed to come to room temperature and after 24 hr. it was filtered and acidified with hydrochloric acid. The separated oil crystallized readily. After filtering, washing and drying (16 g.) a portion of the *o*-phenoxyphenylacetic acid was recrystallized from benzene-hexane and obtained in colorless fine prisms which melted at 91°. Found: C, 73.69; 73.58; H, 5.30, 5.12. Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>: C, 73.68; H, 5.26.

**10,11-Dihydrodibenz[b,f]oxepin-10[11H]-one (II).**—A mixture of *o*-phenoxyphenylacetic acid (10 g.) in chloroform (15 cc.) and thionyl chloride (20 g.) was heated under gentle reflux for 3 hr. and the excess solvents then removed *in vacuo*. The residual acid chloride was dissolved in nitrobenzene (15 cc.) and gradually added at a temperature which was maintained below 20° to a suspension of aluminum chloride (8 g.) in nitrobenzene (25 cc.). After remaining at room temperature for 24 hr. the mixture was decomposed with ice and steam distilled to remove the nitrobenzene. The insoluble oil was taken up in ether and the extract washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and with water. Removal of the ether and distillation of the residue yielded a pale yellow oil (8 g.) boiling at 160-163° at 2 mm. The oil gradually solidified and when recrystallized from hexane the cyclic ketone was obtained in stout polyhedra which melted at 56°. Found: C, 79.71; H, 4.63. Calcd. for C<sub>14</sub>H<sub>10</sub>O<sub>2</sub>: C, 80.00; H, 4.76.

The oxime, when recrystallized from dilute methanol, was obtained in stout prisms melting at 137°. Found: C, 74.10, 74.43; H, 4.89, 4.83. Calcd. for C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>N: C, 74.22; H, 4.88.

**Dibenz[b,f]oxepin (I).**—A mixture of the above cyclic ketone (5.7 g.) and aluminum isopropoxide (11 g.) in isopropyl alcohol (100 cc.) was slowly distilled through a

(4) All melting points are corrected.

(5) Barger and Silberschmidt, *J. Chem. Soc.*, 2925 (1928).

short column until acetone could no longer be detected in the distillate. Most of the isopropyl alcohol was then removed by distillation and the residue extracted with ether after dilution with dilute hydrochloric acid. Removal of the ether yielded a viscous oil which was heated to 120–140° for ca. 10 min. with 1 g. of *p*-toluenesulfonic acid. Water was rapidly eliminated and the mixture on slight cooling crystallized rapidly. The resultant dibenzoxepin thus obtained in quantitative yield was washed with water, dried, and recrystallized by adding hot methanol to its concentrated solution in acetone. It was obtained in colorless plates melting at 111°—readily soluble in warm acetone but sparingly soluble even in boiling methanol. Found: C, 86.19, 86.32; H, 5.03, 5.21. Calcd. for  $C_{14}H_{10}O$ : C, 86.60; H, 5.16.

**Diphenylether-2,2'-dicarboxylic Acid and Xanthone.**—The above unsaturated cyclic hydrocarbon (2 g.) in acetone (50 cc.) was treated with a few drops of water and then finely powdered potassium permanganate was added from time to time in small portions until the pink color remained for 2 hr. The solid manganese dioxide and potassium salt was separated by filtration and washing with fresh acetone (filtrate—below), and then extracted with hot water. The clear filtrate on acidification yielded the dibasic acid (1.9 g.) which when recrystallized from acetone–benzene was obtained in colorless stout prisms melting at 231°. It was sparingly soluble in boiling water, and crystallized in stout needles from the cooled solution. Found: C, 65.19, 65.24; H, 3.89, 3.67. Calcd. for  $C_{14}H_{10}O_6$ : C, 65.12; H, 3.89.

The acetone filtrate (above) was freed of solvent and the residual oil washed several times with hot water. It was then dissolved in acetone, evaporated to a small volume, and treated with a little methanol. A mixture of two crystalline products separated in the course of several days. When this mixture was washed with several portions of cold acetone, one of the crystalline species, which was not further investigated, dissolved very quickly. The substance of lesser solubility was recrystallized from hot methanol and then obtained in pale yellow stout prisms melting sharply at 175°. When this was admixed in various proportions with a specimen of xanthone similarly recrystallized the mixture also melted at 175°. The yield of purified xanthone was ca. 0.1 g.

***o*-(2-Methoxyphenoxy)-benzaldehyde.**—A suspension of the copper salt of salicylaldehyde (86 g.) in *o*-bromoanisole (200 g.) was heated under reflux in an oil-bath at 210–220° for 2 to 3 hr. by which time the original bulky green copper salt had changed to the dense reddish brown cuprous bromide. An atmosphere of nitrogen was maintained throughout the heating. The mixture was filtered and the excess bromoanisole distilled off under reduced pressure. The residue was extracted with ether and the extract washed with dilute hydrochloric acid, with aqueous alkali, and with water. Removal of the solvent and distillation of the residue yielded a solid distillate (39 g.); b. p. 160–185° at 2 mm. This distillate was redissolved in ether (75 cc.) and shaken on the machine with a solution of sodium bisulfite (40 g.) in water (100 cc.) which had been treated with a little sulfur dioxide. The aqueous phase was acidified with hydrochloric acid, gently warmed under reduced pressure, and cooled. The aldehyde which readily solidified (22 g.) when recrystallized from ether–hexane consisted of colorless pyramidal prisms melting at 81°. Found: C, 73.57, 73.79; H, 5.28, 5.22. Calcd. for  $C_{14}H_{12}O_2$ : C, 73.68; H, 5.26. The ether solution from which the bisulfite complex had been separated yielded *para*-salicylaldehyde (m. p. 131° from methanol).

The semicarbazone when recrystallized from hot methanol, in which it is sparingly soluble, was obtained in colorless fine needles melting at 213°. Found: N, 14.61. Calcd. for  $C_{14}H_{12}O_2N_3$ : N, 14.74.

***o*-(2-Methoxyphenoxy)-benzoic acid** was obtained when the above aldehyde was oxidized in diluted acetone with potassium permanganate. It was recrystallized from ether–hexane and consisted of colorless stout prisms melting at 115°. Found: C, 69.05, 69.15; N, 4.84, 5.00. Calcd. for  $C_{14}H_{12}O_4$ : C, 68.85; H, 4.92.

***o*-(2-Methoxyphenoxy)-cinnamic acid** prepared in the usual manner was recrystallized from hot benzene in which it is sparingly soluble, and obtained in colorless plates melting at 199°. Found: C, 71.37, 71.07; H, 5.00, 4.92. Calcd. for  $C_{16}H_{14}O_4$ : C, 71.11; H, 5.18. When reduced in aqueous solution with sodium amalgam it yielded  $\beta$ -*o*-2-methoxyphenylphenyl-propionic acid which when recrystallized from benzene–hexane consisted of colorless plates melting at 83°. Found: C, 70.47, 70.26; H, 5.86, 5.56. Calcd. for  $C_{16}H_{16}O_4$ : C, 70.59; H, 5.88.

***o*-(2-Methoxyphenoxy)-benzaldehyde Azlactone.**—A mixture of the aldehyde (20 g.), hippuric acid (20 g.), anhydrous sodium acetate (8 g.) and acetic anhydride (52 cc.) was heated on a steam-bath for 3 hr. The azlactone (24 g.) which separated was filtered off, washed with ether and with water, and a portion recrystallized from hot benzene. The lemon yellow wedge shaped prisms thus obtained melted at 206°. Found: C, 74.74, 74.39; H, 4.48, 4.61. Calcd. for  $C_{23}H_{17}O_4N$ : C, 74.40; H, 4.58.

***o*-(2-Methoxyphenoxy)-pyruvic Acid.**—When the above azlactone (33 g.) was boiled with a solution of potassium hydroxide (50 g.) in water (165 cc.) for 1 hr., evolution of ammonia had practically ceased. The addition of hydrochloric acid to the diluted and filtered mixture yielded a precipitate of a mixture of the keto acid and benzoic acid which was separated by dissolving in ether and shaking with sodium bisulfite solution. The benzoic acid remained in the ether and the sparingly soluble bisulfite compound which crystallized was filtered off, dissolved in alkali, and the solution acidified with hydrochloric acid. The oily precipitate crystallized readily (12 g.) and when recrystallized from acetone–benzene, the pyruvic acid consisted of fine needles which melted at 165°. Found: C, 67.08, 67.26; H, 4.84, 4.72. Calcd. for  $C_{16}H_{14}O_4$ : C, 67.13; H, 4.90.

The aqueous layer, from the sparingly soluble bisulfite compound, from which the ether layer had been separated, on acidification with hydrochloric acid yielded a further small amount of the pyruvic acid (2 g.).

***o*-(2-Methoxyphenyl)-acetic Acid.**—The above methoxy-pyruvic acid (14 g.) in 10% sodium hydroxide solution (400 cc.) was cooled to 5° and treated with 30% hydrogen peroxide (7 cc.). The mixture was allowed to come to room temperature and then acidified after 24 hr. The acid (12 g.) which readily crystallized, was recrystallized from ether–hexane and obtained in colorless stout prisms melting at 93°. Found: C, 69.60, 69.72; H, 5.44, 5.48.  $C_{16}H_{14}O_4$  requires: C, 69.77; H, 5.43.

**6-Methoxy-10,11-dihydrodibenz[b,f]oxepin-10[11H]-one.**—When the above acid was converted to its chloride and the latter condensed with aluminum chloride as described for the ketone (II) there was formed a large amount of resinous condensation product from which ether removed about 10–20% of a substance which largely crystallized. This when recrystallized from ether–hexane yielded the ketone in colorless stout prisms melting at 85°. Found: C, 74.60, 74.69; H, 4.91, 4.93. Calcd. for  $C_{16}H_{12}O_2$ : C, 75.00; H, 5.00.

The oxime was obtained in stout prisms melting at 196° when recrystallized from methanol. Found: N, 5.27. Calcd. for  $C_{16}H_{13}O_2N$ : N, 5.49.

### Summary

1. Dibenzoxepin has been prepared by dehydrating the carbinol obtained from a dihydrodibenzoxepinone. When it is oxidized it yields the expected diphenyletherdicarboxylic acid along with a small amount of xanthone.

2. The diphenylether cyclic ketones were prepared from diphenylether acetic acids which in turn were prepared from *o*-phenoxybenzaldehydes.

3. *o*-Phenoxybenzaldehydes may be obtained by treating the copper salt of salicylaldehyde with aryl halides at elevated temperatures.

GUELPH, ONTARIO, CANADA RECEIVED MAY 15, 1950