[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF INDIANA UNIVERSITY AND STATE UNIVERSITY OF IOWA]

ISOCOUMARIN

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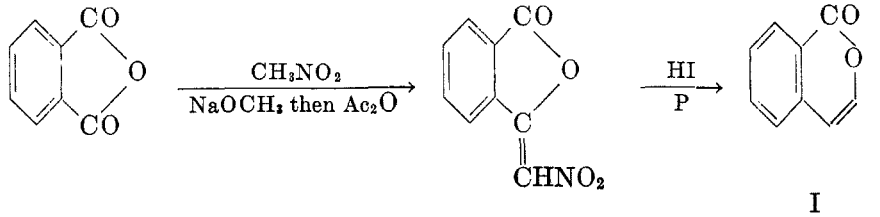
Isocoumarin (I) is an unusual unsaturated lactone, but its use has been limited by the fact that it is difficult to obtain in quantities suitable for research. The present report describes studies made on four methods of preparation.

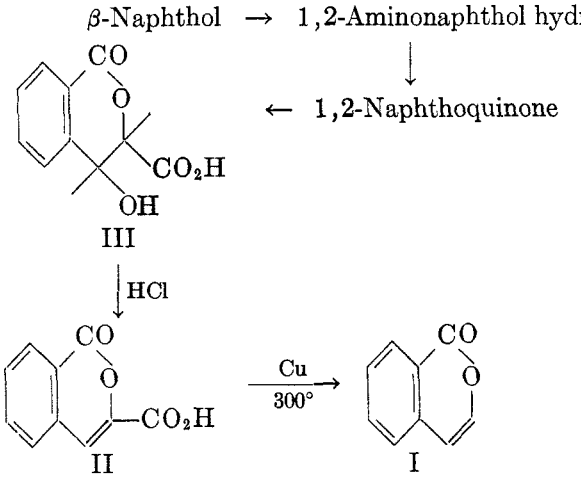
One of the shortest syntheses is the following described by Gabriel (1).



I

The yield of nitromethylenephthalide is about 8% and the reduction gives only 22% yield so that the over-all yield is less than 2%. We have checked the yields reported by Gabriel but have been unable to improve them.

Bamberger and Frew (5) obtained low yields of isocoumarin (I) by heating the silver salt of 3-carboxyisocoumarin (II). The latter had been synthesized by Bamberger and Kitschelt (2) by the following sequence of reactions.



Since improved procedures have been described by Fieser (3) for the preparation of 1,2-naphthoquinone, the remaining steps in this synthesis were studied. It was found that calcium hypochlorite (4) was a better reagent for converting the 1,2-naphthoquinone to the δ-lactone of *o*-carboxyphenylglyceric acid (III) than sodium hypochlorite. If the temperature of the oxidation reaction was

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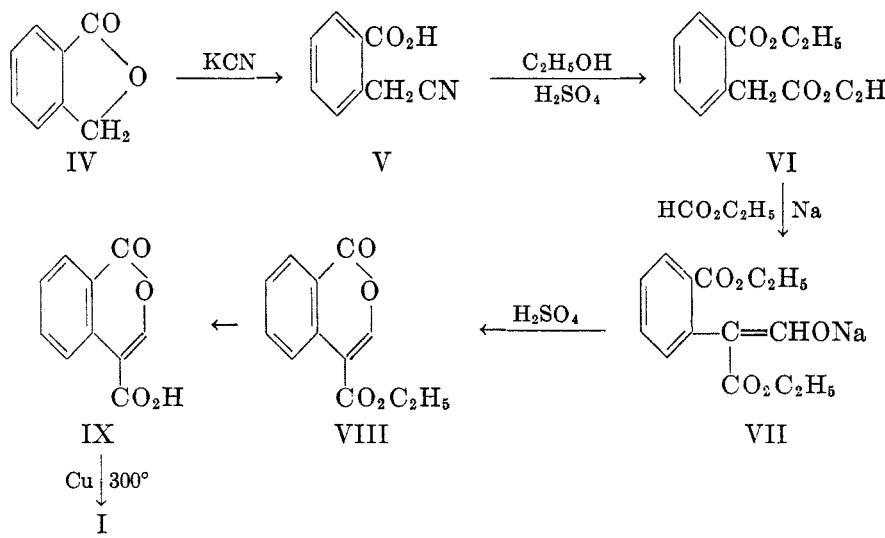
kept at 5 to 10°, the lactone could be isolated as the calcium salt and so removed from the oxidizing medium by filtration. This salt was dissolved in hot hydrochloric acid solution and the desired lactone obtained in 46% yield. The conversion of the δ-lactone of *o*-carboxyphenylglyceric acid into 3-carboxyisocoumarin (II) was accomplished in 82% yields by heating the lactone with concentrated hydrochloric acid in a sealed tube at 160°.

Bamberger and Frew (5) prepared the silver salt of 3-carboxyisocoumarin (II), which was then mixed with a large amount of powdered clay and distilled. When this method was tried it was difficult to isolate the silver salt in even a reasonably pure state and the yield of isocoumarin was very poor (<1%). Hence a study of other procedures for decarboxylation of II was made, and it was found that heating the free acid with copper-bronze powder at 300°, followed by a flash distillation under reduced pressure gave a 65% yield of isocoumarin. The over-all yield from β-naphthol on the five steps was 11.6%.

A third synthesis, described by Dieckmann and Meiser (6), depended on the decarboxylation of 4-carboxyisocoumarin (IX). This acid was obtained by a condensation of ethyl homophthalate (VI) with ethyl formate, cyclization to ethyl isocoumarin-4-carboxylate (VIII), and hydrolysis to the acid (IX). The ethyl homophthalate was made by oxidation of naphthalene to phthalonic acid, reduction of this intermediate with hydriodic acid and red phosphorus to homophthalic acid, and esterification of the latter. The yields were low.

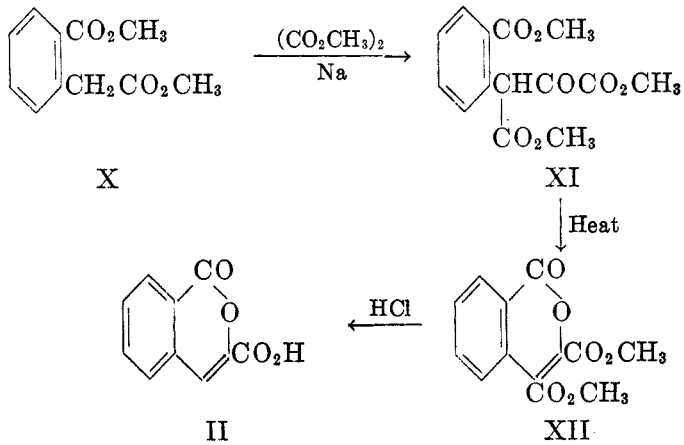
Two alternative methods are available for obtaining the intermediate ethyl homophthalate. Oxidation of indene by sulfuric acid and potassium dichromate gives a 58% yield of homophthalic acid (7), which can be esterified to VI. Also, *o*-carboxyphenylacetonitrile (V) is readily prepared (8) in 89% yields by the action of potassium cyanide on phthalide (IV). The nitrile (V) can be converted directly to ethyl homophthalate (VI). A combination of these reactions with those of Dieckmann above represented the best method for the preparation of 4-carboxyisocoumarin (IX).



In order to avoid losses, the intermediates, VII and VIII, were not isolated. Again, it was found that the 4-carboxyisocoumarin could be decarboxylated in 75% yields by heating it with metallic copper at 300°; a procedure and yield much better than heating the silver salt of IX or refluxing IX with sulfuric acid or phosphoric acid as mentioned by Dieckmann (6).

The over-all yield from phthalide by this series of reactions was 16.4%; a yield not much better than the second sequence. However, this third series does not require any sealed tube reactions, hence the quantities used can be increased so that satisfactory amounts of isocoumarin can be obtained.

Instead of using ethyl formate in the third step of the above synthesis, Vorozhtsov and Bogusevich (9) condensed methyl homophthalate (X) with methyl oxalate to produce the keto ester (XI). When heated at 100° the latter was cyclized to methyl isocoumarin-3,4-dicarboxylate (XII) which is hydrolyzed and decarboxylated by hot concentrated hydrochloric acid to isocoumarin-3-carboxylic acid (II).



Since Vorozhtsov and Bogusevich (9) reported a 48% yield of the isocoumarindicarboxylic ester, but gave no yield for the conversion to the 3-carboxyisocoumarin, this synthesis was also evaluated. Condensation of methyl homophthalate with methyl oxalate gave a 20% yield of the keto ester (XI), which when heated at 100° gave a 49% yield of XII. Refluxing XII with hydrochloric acid gave a 45% yield of isocoumarin-3-carboxylic acid (II) which was identical with the product obtained in the second series above. It was decarboxylated to isocoumarin in 65% yields. The over-all yield of isocoumarin calculated for the five steps from phthalide would be 7.0% and for the five steps from indene would be 7.3% using the highest yields reported for preparation of methyl isocoumarin-3,4-dicarboxylate. Lower yields were obtained when ethyl homophthalate and ethyl oxalate were used.

Through the courtesy of Dr. K. K. Chen of The Lilly Research Laboratories some pharmacological tests were made. The isocoumarin-3-carboxylic acid was about one-half as effective as dicoumarol in retarding clotting of the blood and isocoumarin caused only a transient fall in blood pressure in anesthetized cats.

EXPERIMENTAL

1,2-Aminonaphthol hydrochloride and 1,2-naphthoquinone. The procedures of Fieser (3) were used for the preparation of 1,2-aminonaphthol hydrochloride and its oxidation to 1,2-naphthoquinone. The over-all yield for these two steps was 51%.

δ-Lactone of o-carboxyphenylglyceric acid. The procedure given by Zincke (4) was modified as follows:—Five hundred grams of calcium hypochlorite (U.S.P.X. grade) was triturated with 500 ml. of distilled water and the undissolved solid material was collected on a Büchner funnel with suction. This residue was triturated in the same manner with 750 ml. of distilled water. After removal of the solid residue and repetition of the trituration with another 750-ml. portion of distilled water, the filtrates were combined and used. Forty-five grams (0.28 mole) of 1,2-naphthoquinone was mixed with enough water to form a thick paste, the mixture was chilled to 10° in an ice-salt bath, and 1 liter of the above calcium hypochlorite solution previously chilled to 0–5° was added in small portions with stirring.

A creamy white precipitate separated from the reaction mixture after a short time, which was collected on a filter with suction. The filtrate was discarded and the solid was dissolved in 250 ml. of hot water to which enough concentrated hydrochloric acid had been added to decompose the solid and effect complete solution (about 20 ml.). The clear amber solution was filtered to remove a small amount of gum and allowed to cool slowly. Yellow blades of the δ-lactone of *o*-carboxyphenylglyceric acid separated out. The product was dried at 100°, yield 27 g. (46%).

The product was sufficiently pure to be used in the next step. It may be purified by dissolving 53 g. of the yellow crystals in 500 ml. of hot water. Decolorizing carbon was added and the mixture was filtered with suction while hot. The treatment with decolorizing carbon was repeated and the clear filtrate was allowed to cool slowly. The product was obtained as white needles which were recrystallized three times from 250-ml. portions of hot water to yield colorless crystals of m.p. 207–209°. Bamberger (2) reported the melting point 204.5°. The recovery was 35 g.

3-Carboxyisocoumarin. Ten grams of the δ-lactone of *o*-carboxyphenylglyceric acid was placed in a 600 x 25 x 18 mm. Pyrex bomb-tube with 50 ml. of concentrated hydrochloric acid. The bomb was sealed and heated in a furnace at 160° for 16 hours. The large massive crystals were washed well with water. The yield was 7.5 g. (82%) of orange colored crystals, m.p. 242–244°. The product is pure enough for use in the preparation of isocoumarin, but it may be recrystallized from about 500 ml. of hot water. Two such recrystallizations yielded a crystalline product, m.p. 245–246°. Since Bamberger and Kitschelt (2) reported the melting point 237° and Vorozhtsov and Bogusevich (9) a value of 236°, the compound was analyzed.

Anal. Calc'd for $C_{10}H_6O_4$: C, 63.16; H, 3.18.
Found: C, 62.95; H, 3.16.

o-Carboxyphenylacetonitrile. The procedure of Price and Rogers (8) was followed with modifications. A mixture of 200 g. of phthalide and 200 g. of powdered potassium cyanide was placed in a 5-l. round-bottomed flask fitted with a stirrer having four wire paddles so placed that the sides of the flask were well scraped as the stirrer was rotated. From time to time stirring was stopped and a thermometer pushed down so that the tip was immersed in the reaction mixture and the temperature observed. The entire surface of the flask was heated in an electric heating mantle, and vigorous stirring was maintained. It was found that a good yield was obtained by controlling the rate of heating so that a maximum temperature of no more than 200° was reached over a period of one hour. The reaction temperature is critical. Stirring was continued at 200° for two to three hours. The solid mass was dissolved in 1 liter of water and a small amount of insoluble material removed by filtration. Concentrated hydrochloric acid was added with vigorous stirring until *p*H about 5 was obtained, and the solution became quite turbid. The acidity is determined with test paper and the solution should never become acid to Congo Red. If too much acid is added, the main product separates out as an oil in addition to the residue of homophthal-

imide which precipitates at this point. The mixture was filtered and decolorizing carbon (Norit) was added to the filtrate which was stirred for several minutes and again filtered.

The product was precipitated by the rapid addition of 50 ml. of concentrated hydrochloric acid. The mixture was chilled in an ice-bath and crystallized; yield 213 g. (89%) of white crystals which melted at 113–117°.

Ethyl homophthalate. In a 1-liter three-necked flask equipped with a mechanical stirrer, reflux condenser, and a dropping-funnel were placed 161 g. (1 mole) of *o*-carboxyphenylacetonitrile and 400 ml. of 95% ethanol. The mixture was cooled in an ice-bath and stirred while 196 g. (2 moles, 109 ml.) of concentrated sulfuric acid was added dropwise over a period of about one-half hour.

After complete addition of the acid, the stirrer and dropping-funnel were replaced by a reflux condenser and the mixture was refluxed for 12 hours. It was poured into 1 liter of water and a small amount of insoluble material was removed by filtration. The aqueous solution was extracted with 1 liter of ether and then with two 500-ml. portions of ether. The ether extracts were combined and washed four times with 200-ml. portions of water, three times with 100-ml. portions of 10% sodium carbonate, and, finally, twice with 200-ml. portions of distilled water. The ether solution of the product was dried over magnesium sulfate and the ether was distilled. The residue was distilled under reduced pressure. After separating a small amount of forerun up to 164°/19 mm. the main fraction of ethyl homophthalate was collected at 164–169° at 19 mm. The yield was 133 g. (56%) of a product having an index of refraction, n_D^{20} 1.5072.

4-Carboxyisocoumarin. In a 1-liter three-necked round-bottomed flask was placed 23 g. of powdered sodium which was covered with 100 ml. of absolute ether. A reflux condenser protected by a calcium chloride drying tube, a mechanical stirrer and a dropping-funnel were fitted to the flask which was immersed in an ice-salt bath.

A mixture of 236 g. (1 mole) of ethyl homophthalate and 81.4 g. (1.1 mole) of freshly distilled dry ethyl formate was dissolved in an equal volume of absolute ether and placed in the dropping-funnel. A small amount of ethyl formate was added to the reaction flask through the condenser to start the reaction and the mixed esters in the dropping-funnel were then added at a slow rate. The start of the reaction was indicated by the formation of gas bubbles and the development of a red color in the mixture. The reaction was vigorous but it was easily controlled in the cold. The reaction mixture was stirred three hours at room temperature after complete addition of the reagents. A small amount of ethyl formate was then added to use up a little unreacted sodium. The reaction mixture was allowed to stand overnight at room temperature, treated with 100 ml. of water and 200 ml. of ether, and extracted. The red aqueous layer was washed twice with 100-ml. portions of ether, which were discarded. Dilute sulfuric acid (6 *N*) was added with stirring to the aqueous mixture until it was acid to Congo Red. The product was a yellow oil which was removed and the acid aqueous layer was extracted twice with 100-ml. portions of ether which were added to the main product. The ether solution of the product was washed three times with 150-ml. portions of water to remove excess mineral acid, after which the ether was removed by distillation. To the residual oil were added 150 ml. of glacial acetic acid and 150 ml. of concentrated hydrochloric acid and the mixture was heated at reflux temperature for sixteen hours. A yellow granular solid separated out during the heating period. The flask was allowed to cool slowly to room temperature and the 4-carboxyisocoumarin was recrystallized twice from 2 l. of hot 95% ethanol. Short needles, slightly yellow in color, were obtained, m.p. 250–252°. The yield was 84 g. (44%). This product was sufficiently pure for the preparation of isocoumarin.

A 10-g. portion was purified further by dissolving it in 250 ml. of hot ethanol and adding Norit. The hot filtrate was allowed to cool slowly to room temperature, and gave 6 g. of white needles melting at 249–251°. A second crystallization raised the melting point to 251–252°. Since Dieckmann and Meiser (6) reported the melting point 244° the acid was analyzed.

Anal. Calc'd for $C_{10}H_6O_4$: C, 63.16; H, 3.18.
Found: C, 63.21; H, 3.03.

Methyl isocoumarin-3,4-dicarboxylate. The procedure described by Vorozhtsov and Bogusevich (9) was followed. A mixture of 20 g. of methyl homophthalate, 11.9 g. methyl oxalate, 2.3 g. powdered sodium in 100 ml. absolute ether was stirred at 25° for 46 hours. The mixture was decomposed by addition of 150 ml. of water and acidified with 5% sulfuric acid. Extraction with four 50-ml. portions of ether gave 5.9 g. (20.8%) of the keto ester. In order to avoid losses this was not purified but was heated at 100° for two hours to give 5.2 g. of crude ester. This was recrystallized from 75 ml. of hot methanol to give 2.6 g. (49%) of methyl isocoumarin-3,4-dicarboxylate which melted at 130.5–131.7°, (lit. value 134°).

3-Carboxyisocoumarin. Two grams of the above di-ester was refluxed for two hours with 100 ml. of concentrated hydrochloric acid. When cooled, 0.8 g. of crude 3-carboxyisocoumarin separated, which melted at 238–240°. It was purified by solution in dilute alkali, filtration, and acidification. This product was twice recrystallized from hot water, yielding 0.6 g. (45%) of white crystals which melted at 246–247° and did not depress the melting point of the 3-carboxyisocoumarin prepared from the δ-lactone of *o*-carboxyphenylglyceric acid. When mixed with 4-carboxyisocoumarin (m.p. 251–252°) a marked depression in melting point of the mixture to 211–216° occurred. This confirms the structure of the product obtained by hydrolysis and decarboxylation of methyl isocoumarin-3,4-dicarboxylate as the 3-carboxyisocoumarin.

Isocoumarin. (a) *From 3-carboxyisocoumarin.* A 125-ml. Claisen flask was arranged for distillation with a 125-ml. distilling flask, water cooled, as a receiver. Eight grams (0.042 mole) of 3-carboxyisocoumarin was mixed with 0.128 g. of copper-bronze powder and heated to 300° with a metal-bath. The side arm of the receiver was extended just under the surface of a beaker of water so that the progress of the decarboxylation could be followed by observation of the rate of formation of gas bubbles. The compound melted to a brown liquid which rapidly lost carbon dioxide on continued heating. As soon as a rapid evolution of bubbles ceased, the beaker of water was removed from the side arm of the receiver and an aspirator was attached which reduced the pressure to about 20 mm.

Isocoumarin was rapidly removed in this manner from the hot reaction flask and was collected as a yellow oil which crystallized rapidly when cooled. The solid product was dissolved in 10 ml. of methanol at about 50°. Distilled water was added dropwise to the methanol solution until a turbidity just appeared, a few drops of methanol were added to clarify the solution, and it was rapidly chilled in the refrigerator. Colorless platelets were obtained, m.p. 43–46°. The recrystallization procedure was repeated three times with methanol-water mixtures in the ratio of approximately 5 ml. methanol to 3 ml. water. The yield of isocoumarin of melting point, 44–45° was 4 g. (65%).

(b) *From 4-carboxyisocoumarin.* In a 125-ml. Claisen flask equipped with a thermometer and a 50-ml. distilling flask as a receiver was placed a mixture of 38 g. (0.2 mole) of 4-carboxyisocoumarin and 0.9 g. (0.014 mole) of copper-bronze powder. It was heated to about 270–300° in a metal-bath. A rapid evolution of carbon dioxide took place which was followed as above. After all of the carbon dioxide was driven off at atmospheric pressure, the apparatus was connected to an aspirator and the mixture was flash distilled.

The yellow liquid which collected in the receiving flask was transferred to a 50-ml. boiling-flask connected to a 3-inch Vigreux column. The product was then distilled at 20 mm. pressure and collected at 155–156°. The clear, almost odorless distillate was taken up in 1500 ml. of petroleum ether (b.p. 30–60°) and allowed to crystallize in an ice-box. White needles were obtained having the melting point 44–46°. The mother liquor was evaporated to one-half its original volume to recover another crop of crystals of melting point 43.5–45°. The total yield was 22 g. (75%). The product is sufficiently pure for synthetic purposes but may be recrystallized again from petroleum ether to give isocoumarin of melting point 45–46°. Gabriel (1) has reported the melting point 46° and Bamberger and Frew (5) the value 47°.

SUMMARY

Isocoumarin may be obtained in 65 and 75% yields by decarboxylation of 3- and 4-carboxyisocoumarin respectively using copper powder as a catalyst at 300°.

A comparison of the methods for the preparation of isocoumarin indicates that the most practical sequence involves the condensation of ethyl homophthalate with ethyl formate to ethyl isocoumarin-4-carboxylate, hydrolysis to the acid, and decarboxylation.

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REFERENCES

(1) GABRIEL, *Ber.*, **36**, 571 (1903).
(2) BAMBERGER AND KITSCHELT, *Ber.*, **25**, 893, 1138 (1892).
(3) FIESER, *Org. Syntheses*, Coll. Vol. **2**, 35, 430 (1943).
(4) ZINCKE, *Ber.*, **25**, 405, 1168 (1892).
(5) BAMBERGER AND FREW, *Ber.*, **27**, 207 (1894).
(6) DIECKMANN AND MEISER, *Ber.*, **41**, 3259 (1908).
(7) WHITMORE AND COONEY, *J. Am. Chem. Soc.*, **66**, 1239 (1944).
(8) PRICE AND ROGERS, *Org. Syntheses*, **22**, 30 (1942).
(9) VOROZHTSOV AND BOGUSEVICH, *J. Gen. Chem. (USSR)*, **10**, 2014 (1940); *Chem. Abstr.*, **35**, 4365 (1941).