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Furocoumarins. Synthesis of 2,3-Dihydropsoralene

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The chief physiological activity usually associated with the coumarin system is a narcotic and toxic effect which is demonstrated with greatest effectiveness in the case of cold-blooded animals. This effect is presumably due to the unsaturated lactone structure present in such compounds, and variations in degree of toxicity are ascribed to variations in lipoid solubility resulting from changes in side chain or substituent groups.[2] The best known of these compounds are the various fish-poisons of the furocoumarin group. At the same time, coumarins may show a sedative action in warm-blooded animals, particularly when certain functional groups are introduced; derivatives of coumarin-3-carboxylic acid usually show sedative or hypnotic activity.[3]

To obtain additional information on the effect of structural changes on activity, with particular regard to the changes which may be involved in warm-blooded activity *versus* cold-blooded activity, a study of certain furocoumarins has been initiated. The first part of this work has been concerned with the development of a route to derivatives of 2,3-dihydropsoralene. A synthesis of the parent compound (V) has been described previously by Späth,[4] along with its conversion to psoralene by catalytic dehydrogenation with a palladium catalyst.

A new method of synthesis is shown in the figure. The condensation of chloroacetonitrile with resorcinol was carried out in the usual way, and resulted (after hydrolysis of the intermediate imine) in a mixture of 4-chloroacetoresorcinol and 6-hydroxycoumaran-3-one. A treatment of the mixed product with potassium acetate in alcohol brought about cyclization of the haloketone, and gave 6-hydroxycoumaran-3-one (I) as the product in good yield. The conversion of this compound to 6-hydroxycoumaran (IV) has been accomplished previously only by the method of Sonn,[5] which involved formation of the oxime, reduction to the corresponding amine, deamination of the amine or its acetyl derivative by boiling in concentrated aqueous solution, and reduction of the resulting benzofuran to the dihydro compound.

A better and more direct method for converting I to IV was developed through a study of the catalytic reduction of the carbonyl group of I to a methylene group. A single-step reduction of I to IV could not be carried out successfully with a palladium catalyst, but acetylation of the phenolic group changed the picture completely. It was found that 6-acetoxycoumaran-3-one (II) could be reduced easily in acetic acid solution at 65° with a palladium–carbon catalyst to 6-acetoxycoumaran (III) in nearly quantitative yield. Alkaline hydrolysis of the product gave 6-hydroxycoumaran (IV) as a colorless, viscous oil. This compound was reported as an oil by Sonn,[5] and as a solid melting at 61° by Späth.[4]

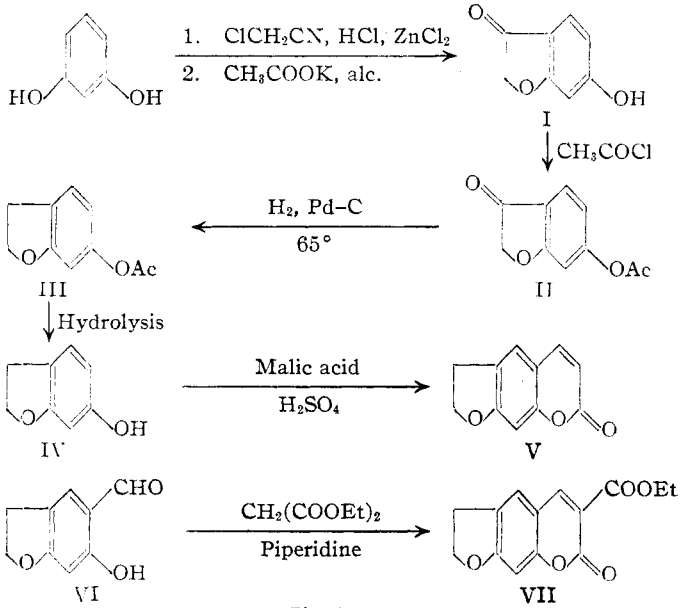

Fig. 1.

Condensation of 6-hydroxycoumaran with malic acid in concentrated sulfuric acid gave 2,3-dihydropsoralene, although the yield of pure material was low. To allow the preparation of coumarins substituted in the 3-position of the coumarin ring, 6-hydroxycoumaran was converted into 5-formyl-6-hydroxycoumaran (VI) by the zinc cyanide–hydrogen chloride method. Condensation of the aldehyde with ethyl malonate, using piperidine as a catalyst, led to 6-carbethoxy-2,3-dihydrofuro[3,2-g]coumarin (VII).

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Experimental

Chloroacetonitrile.—A mixture of 170 g. (1.2 moles) of phosphorus pentoxide, 187 g. (2 moles) of chloroacetamide and 800 ml. of trimethylbenzene (Eastman T 2549) was heated under reflux with vigorous stirring for one hour. The reaction mixture was allowed to cool to about 100°, with continued stirring, and the reflux condenser was replaced with a distilling adapter. Direct distillation of the

(1) Bristol Laboratories Fellow, 1948.
(2) Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).
(3) Werder, *E. Merck's Jahresber.*, **50**, 88 (1936).
(4) Späth, Manjunath, Pailer and Jois, *Ber.*, **69**, 1087 (1936).
(5) Sonn and Patschke, *Ber.*, **58**, 96 (1925).

mixture at atmospheric pressure yielded 131 g. (87%) of crude colorless chloroacetonitrile, b. p. 124–128°. About 200 ml. of the hydrocarbon solvent was recovered by continuing the distillation.

The crude chloroacetonitrile was sufficiently pure for immediate use. Fractionation at atmospheric pressure through a 30-cm. Vigreux column resulted in about 10–15% loss of material; b. p. 123–124°.

This method is more satisfactory than the procedure of Steinkopf[6] in which chloroacetamide and phosphorus pentoxide are heated in the absence of a solvent.

6-Hydroxycoumaran-3-one.—Dry hydrogen chloride was passed for thirty-five minutes through a well-stirred mixture of 6.0 g. (0.055 mole) of resorcinol, 4.0 g. (0.053 mole) of chloroacetonitrile, 4.0 g. of powdered anhydrous zinc chloride, and 40 ml. of dry ether. The precipitated ketimine hydrochloride was separated and washed by decantation with two 10-ml. portions of dry ether. After addition of the solid to 200 ml. of water, the ether which accompanied the solid was removed with the aid of an air stream. The aqueous solution was heated under reflux for ten minutes. On cooling and chilling overnight a mixture of 4-chloroacetoresorcinol (colorless) and 6-hydroxycoumaran-3-one (yellow) was obtained. This was removed by filtration, washed with two 20-ml. portions of cold water, and dried to yield 8.3 g. of mixed crude products. This material was added to a hot solution of 5 g. of potassium acetate in 20 ml. of absolute ethanol; the resulting mixture was heated under reflux for fifteen minutes, cooled, and poured into about 50–60 ml. of cold water. The crude product was separated and treated with about 30 ml. of boiling water; after chilling for some time the glistening yellow flakes of 6-hydroxycoumaran-3-one were separated and dried *in vacuo;* yield 6.8 g. (85%); m. p. 243–243.5° (reported[7] m. p. 243°).

This procedure may be carried out on a larger scale with slightly reduced yield. In this case, it is necessary to cool the initial mixture in ice during passage of the hydrogen chloride, and to cool again during the addition of the ketimine hydrochloride to water.

6-Acetoxycoumaran-3-one.—A mixture of 40.0 g. of 6-hydroxycoumaran-3-one, 80 ml. of acetyl chloride and 200 ml. of ethyl acetate was heated under reflux for three hours. The solvent was removed on a steam-bath with the aid of an air stream, and the residue was triturated with water. The yield of dry crude product was 48.0 g. For purification before catalytic reduction, this material was recrystallized from cyclohexane with the addition of decolorizing carbon to yield 33.2 g. (65%) of colorless product, m. p. 77–78° (reported[8] m. p. 79°).

6-Acetoxycoumaran.—The hydrogenation of 9.54 g. of 6-acetoxycoumaran-3-one in 30 ml. of acetic acid was carried out at 65° in a low-pressure apparatus with 2.5 g. of 5% palladium–carbon catalyst.[9] The absorption of hydrogen was about 95% of the theoretical. The catalyst was removed and washed with ether; the filtrate was added to 200 ml. of water, and solid sodium bicarbonate was added until neutralization was completed. The solution was extracted with two 100-ml. portions of ether, and the combined ether extracts were washed with three 25-ml. portions of saturated sodium bicarbonate solution and 100 ml. of water. The ether solution was dried, and the solvent was removed to yield a residue of 8.27 g. (94%) of colorless material, m. p. 69–71°. Recrystallization from ethanol-water (1:1) raised the melting point to 73.5–74.5°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.30; H, 5.58.

Catalytic Reduction of 6-Hydroxycoumaran-3-one.—Numerous attempts were made to carry out a direct catalytic reduction of 6-hydroxycoumaran-3-one to 6-hydroxycoumaran, using a palladium–carbon catalyst. In acetic acid at 50–65° it was possible to effect a reduction, but usually 30–40% of hydrogen in excess of the calculated amount was absorbed, and a mixture of neutral and acidic (phenolic) products was obtained. Attempts to isolate the desired product after absorption of the calculated quantity of hydrogen were not successful. These studies were discontinued when it was found that reduction of the acetyl derivative proceeded in the desired way in nearly quantitative yield.

6-Hydroxycoumaran.—A mixture of 10.9 g. of 6-acetoxycoumaran, 8.7 g. of sodium hydroxide, and 100 ml. of water was boiled under reflux for twenty minutes, cooled, and extracted with 50 ml. of ether. The aqueous solution was acidified with diluted hydrochloric acid (1:1), and the product extracted with ether. The ether solution was dried over magnesium sulfate and the solvent removed to yield a residue of dark brown oil. Distillation under reduced pressure gave 5.7 g. (69%) of a colorless viscous oil, b. p. 99–104° (0.3 mm.). This material has been reported both as an oil[5] and a solid[4] (m. p. 61°). The material in our hands has not crystallized.

Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.37; H, 6.07.

2,3-Dihydrofuro[3,2-g]coumarin (2,3-Dihydropsoralene).—A mixture of 2.0 g. of 6-hydroxycoumaran, 2.0 g. of malic acid, and 8 g. of concentrated sulfuric acid was heated at 120° with constant stirring until foaming stopped (about five minutes). After cooling, the mixture was poured into 50 ml. of water. The aqueous solution was washed with two 20-ml. portions of chloroform, and the combined organic solutions were washed with two 20-ml. portions of saturated sodium bicarbonate solution and with 20 ml. of water. The chloroform solution was dried and the solvent evaporated to yield 1.4 g. of crude, discolored product. This material was recrystallized twice from methanol with the aid of decolorizing carbon to provide 0.3 g. (11%) of colorless needles of 2,3-dihydropsoralene, m. p. 199.5–201°. The melting point reported by Späth[4] was 204°.

5-Formyl-6-hydroxycoumaran.—Dry hydrogen chloride was passed for thirty minutes through a well-stirred mixture of 3.0 g. (0.022 mole) of 6-hydroxycoumaran, 3.9 g. (0.033 mole) of zinc cyanide and 100 ml. of dry ether. The mixture was allowed to stand for two hours and hydrogen chloride was again passed through the mixture for thirty minutes. The solid aldimine hydrochloride was separated by decantation and washed with dry ether. The salt was hydrolyzed to the aldehyde in 100 ml. of boiling water, and after cooling the aldehyde was removed by filtration. The yield of crude 5-formyl-6-hydroxycoumaran, m. p. 105–108°, was 2.7 g. (75%). By subliming this material at atmospheric pressure colorless needles of the pure aldehyde, m. p. 109–110°, were obtained.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.75; H, 4.99.

6-Carbethoxy-2,3-dihydrofuro[3,2-g]coumarin.—The condensation of 0.51 g. of 5-formyl-6-hydroxycoumaran with ethyl malonate was carried out in ethanol[10] with piperidine as a catalyst. The yield of crude product was 0.58 g. (m. p. 176–187°). Recrystallization from ethanol (95%) gave light yellow needles of the ester, m. p. 200.5–202.5°.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.35; H, 4.80.

Summary

The synthesis of 2,3-dihydrofuro[3,2-g]coumarin and its 6-carbethoxy derivative is described.

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(6) Steinkopf, *Ber.*, **41**, 2540 (1908).

(7) Bruhl and Friedlaender, *Ber.*, **30**, 299 (1897).

(8) Sonn, *Ber.*, **50**, 1262 (1917).

(9) "Organic Syntheses," **26**, 77 (1946).

(10) Horning and Horning, THIS JOURNAL, **69**, 968 (1947).