

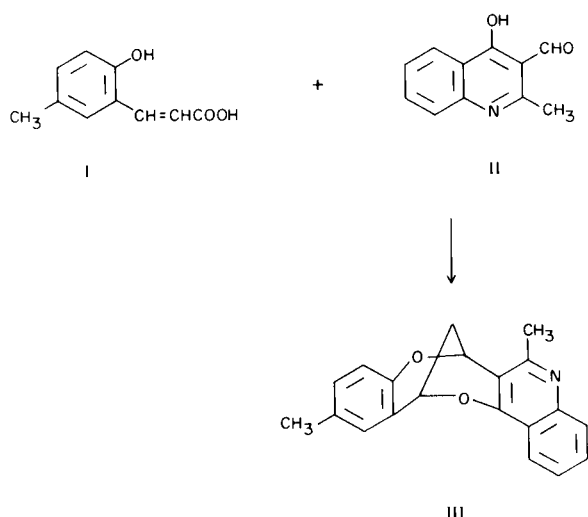
Synthesis of 6*H*,12*H*-6,12-Methanodibenzo[*b,f*][1,5]dioxocin Nitrogen Heteroaromatic Analogs

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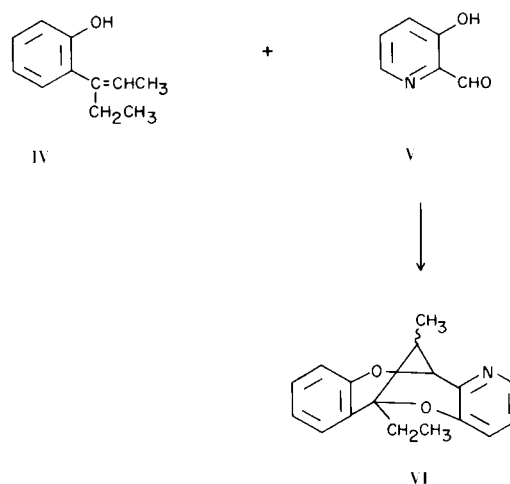
Nair, *et al.*, (2-3) recently concluded that cyanomacurin, a natural product isolated from *Artocarpus integrifolia*, was 1,3,9,13-tetrahydro-6*H*,12*H*-6,12-methanodibenzo[*b,f*][1,5]dioxocin. These same investigators and others (4) synthesized similar compounds by cyclization of 2,2'-dihydroxychalcones to 2'-hydroxyflavones, sodium borohydride reduction of the flavones to flavan-4-ols, and then a second cyclization to the final heterocycle. Last year Hennis and Wang (5) reported that this ring was obtainable from the acid catalyzed reaction of salicylaldehydes with either *o*-vinylphenols or *o*-coumaric acids. A logical extension of this work was the attempted synthesis of analogs with a heteroaromatic ring in place of a benzene ring. This note reports the successful incorporation of the pyridine and quinoline rings.

The reaction of 2-hydroxy-5-methylcinnamic acid (I) and 2-methyl-4-hydroxyquinoline-3-carboxaldehyde (II) in a dilute hydrobromic acid medium at reflux conditions yielded 6,11-dimethyl-7*H*,13*H*-7,13-methano[1,5]benzodioxocino[3,4-*e*]quinoline (III) in 13% yield.



Only tars were obtained from the reaction of *o*-coumaric acid and 3-hydroxypyridine-2-carboxaldehyde (V) under these reaction conditions. The high temperature required to decarboxylate *o*-coumaric acid to *o*-vinylphenol, the active intermediate, appeared to decompose

V. The use of 2-(1-ethylpropenyl)phenol (IV) and more moderate reaction conditions, a glacial acetic acid-hydrobromic acid medium at room temperature, culminated in the successful synthesis of 6-ethyl-13-methyl-6*H*,12*H*-6,12-methano[1,5]benzodioxocino[3,4-*b*]pyridine (VI) in 18% yield. The configuration of the 13-methyl group was not determined in this study.



Work is continuing in an attempt to prepare other heteroaromatic analogs.

EXPERIMENTAL

Elemental analyses were done by the staff of Dr. Paul Boyd, The Dow Chemical Company. Melting points were determined in a "Melt Pointer" (Scientific Glass Apparatus Company, Inc.) and are uncorrected.

Starting Materials.

o-Coumaric acid (6), 2-hydroxy-5-methylcinnamic acid (I) (7), 2-methyl-4-hydroxyquinoline-3-carboxaldehyde (II) (8), 2-(1-ethylpropenyl)phenol (IV) (9), and 3-hydroxypyridine-2-carboxaldehyde (V) (10), were prepared by published procedures. Physical properties and yields were consistent with those reported.

6,11-Dimethyl-7*H*,13*H*-7,13-methano[1,5]benzodioxocino[3,4-*e*]quinoline (III).

A mixture of 8.0 g. (0.045 mole) of 2-hydroxy-5-methylcinnamic acid (I), 4.0 g. (0.021 mole) of 2-methyl-4-hydroxyquinoline-3-carboxaldehyde (II), 100 ml. of water and 10 ml. of

48% hydrobromic acid was heated at the reflux temperature for 16 hours. Sodium hydroxide solution (10%, 150 ml.) was added to the reaction mixture and heating at the reflux temperature was continued for one hour. The yellow solid which remained undissolved was collected in a filter, washed with water, dissolved in an ethanol-water mixture, treated twice with Norite, and recrystallized from the same solvent to yield 0.83 g. (13%) of product (III) as white needles, m.p. 173-175°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.64; N, 4.62. Found: C, 79.4; H, 5.72; N, 4.52.

6-Ethyl-13-methyl-6H,12H-6,12-methano[1,5]benzodioxocino[3,4-b]pyridine (VI).

A mixture of 4.0 g. (0.032 mole) of 3-hydroxypyridine-2-carboxaldehyde, 6.0 g. (0.037 mole) of 2-(1-ethylpropenyl)phenol, 20 ml. of glacial acetic acid, and 10 ml. of 48% hydrobromic acid was stirred at room temperature for four hours. Then 10% aqueous sodium hydroxide solution was added until the mixture was strongly alkaline. The alkaline insoluble material was removed by filtration, washed with water, and recrystallized from ethanol to give white cubic crystalline product (VI), m.p. 196-197°. An additional amount of product was made by a chloroform extraction of the alkaline solution, evaporation of the chloroform solution to dryness and recrystallization of the residue from ethanol. Infrared and elemental analyses indicated that the

product contains one mole of water of crystallization. The yield was 1.6 g. (18%).

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot H_2O$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.8; H, 6.71; N, 4.89.

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