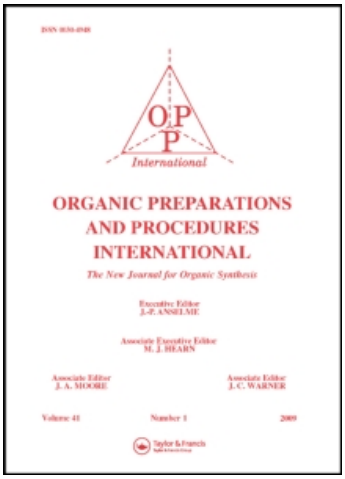

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SYNTHESIS OF ANTIFUNGAL ISOCOUMARINS (I)

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SYNTHESIS OF ANTIFUNGAL ISOCOUMARINS (I)

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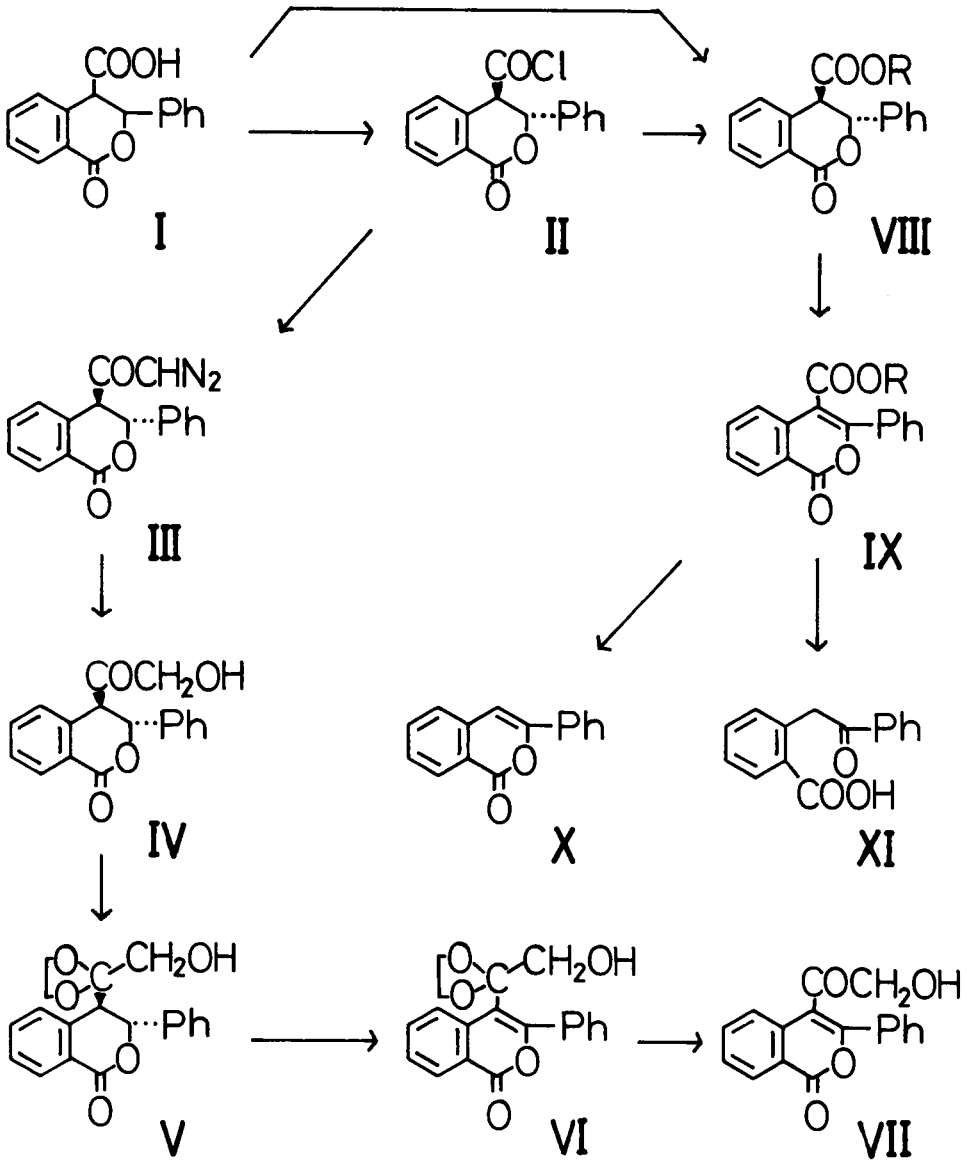
We recently reported that oosponol(8-hydroxy-4-ω-hydroxyacetylisocoumarin) and oospolactone(8-hydroxy-3,4-dimethylisocoumarin), isolated from a wood-rotting basidiomycete *Glocophyllum sepiarium*(Wulf. ex Fr.) Karst, have antifungal activities.[1,2] Later we discovered that phyllodulcin(3,4-dihydro-8-hydroxy-3-(3'-hydroxy-4'-methoxyphenyl)-isocoumarin), a sweetening component of *Hydrangea serrata* SERINGE var. *thunbergii*, which is structurally similar to the above two antifungal isocoumarins, was also antifungal; however, it is completely harmless when taken orally in contrast to the above two isocoumarins which are quite toxic. In an effort to make an antifungal isocoumarin, which is as strongly active as oosponol and as harmless as phyllodulcin, we synthesized 3,4-dihydro-4-ω-hydroxyacetyl-3-phenylisocoumarin (IV), 4-ω-hydroxyacetyl-3-phenylisocoumarin (VII), and some other new 3-arylisocoumarins.

In the course of the total synthesis of phyllodulcin, Naoi *et al.*[3] prepared 3-aryl-3,4-dihydro-8-hydroxy-4-isocoumarincarboxylic acids in three steps from dimethyl homophthalate *via* 2-carboxy-α-carbomethoxy-3-hydroxystilbenes and α-2-di-



carboxy-3-hydroxystilbenes. In the present paper, we could prepare both *trans* and *cis* isomers of 3,4-dihydro-3-phenyl-4-isocoumarincarboxylic acid (I) (78 and 9% respectively), in one step from homophthalic anhydride merely by mixing and shaking for 10 hours with powdered sodium carbonate and benzaldehyde at room temperature. The configurations were determinded by J values of the hydrogen(8 Hz for *trans* and 3 Hz for *cis*) located at the 3- and 4-positions. The compound of the same structural formula,[4] obtained from dimethyl homophthalate in two steps, is the *trans* isomer.

One of target compound *trans*-3,4-dihydro-4-ω-hydroxyacetyl-3-phenylisocoumarin (IV) was derived from the *trans* acid (I) *via* the acid chloride (II) and the diazoketone (III). Attempts to convert IV into 4-ω-hydroxyacetyl-3-phenylixocoumarin (VII) directly either by heating with 10% palladised charcoal in boiling tetralin or treatment with N-bromosuccinimide in the persence of benzoyl peroxide, were unsuccessful. This failure led us to attempt the convertion of 3-phenyl-4-iso coumarincarboxylic acid to VII by a similar route. Thus acid chloride II was converted into *trans*-3,4-dihydro-3-phenyl-4-isocoumarincarboxylic acid methyl ester (VIII, R ◘ Me) which was heated with N-bromosuccinimide in the presence of benzoyl peroxide in benzene to give dehydro compound IX(R = Me). The UV absorption spectrum was remarkably different from that of VIII(R ◘ Me). However, treatment of IX(R = Me) with a mixture of acetic and hydrochloric acids with heating resulted a subsequent decarboxylation after hydrolysis to yield 3-phenylisocoumarin (X). Attempted hydrolysis with acetic acid at room temperature of the tertiary butyl ester of IX(R = *t*-Bu), pre-

pared from I *via* the dihydro derivative VIII(R ▫ *t*-Bu), led to decarboxylation along with hydrolysis and ring opening to give *o*-phenacylbenzoic acid (XI). The mass spectrum of XI was identical to that of X, indicating ring-closure at the mass measurement temperature. Recrystallization of tertiary butyl esters VIII(R ▫ *t*-Bu) and IX(R = *t*-Bu) from methanol gave crystals not of *t*-butyl esters but the corresponding methyl esters, appaently as a result of ester interchange.

Dehydrogenation of V with N-bromosuccinimide in the presence of benzoyl peroxide yielded the dehydro compound VI which was finally converted into the desired compound, 4-ω-hydroxyacetyl-3-phenylisocoumarin (VII).

The antifungal tests of the products synthesized above, and the preparation of corresponding 8-hydroxy-derivatives are in progress.

EXPERIMENTAL

All mps were uncorrected. The IR spectra were obtained in KBr pellets on a Hitachi model 215 spectrophotometer. The UV spectra were determinded in ethanol on a Hitachi model 124 spectrophotometer. Mass spectra were obtained on a Hitachi model RMS-4 spectrometer. The NMR spectra were obtained on a JEOL model FX-100 spectrometer, with tetramethylsilane as internal standard.

3,4-Dihydro-3-phenyl-4-isocoumarincarboxylic acid (I).— A mixture of 4 g. (0.025 mole) of homophthalic anhydride, 3.7 g. (0.030 mole) of benzaldehyde and 30 ml. of benzene was vigorously shaken for 10 hrs. at room temperature. Fifty ml. of water was added and the mixture was extracted with 20 ml. of benzene to remove excess benzaldehyde, and the aqueous layer was acidified with conc. hydrochloric acid to give a *cis-trans* mixture of I(6.0 g., 89.5%) after washing and drying, as a colorless precipitate. Recrystallization from methanol gave

the *cis* isomer as colorless leaves, mp. 204°, 0.6 g. (9.0%), from the mother liquor the *trans* isomer, 5.2 g. (78%), was obtained as colorless cubes of mp. 189°, lit.[4] 186-187°.

cis isomer of mp. 204°:

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63 ; H, 4.51

Found : C, 71.50 ; H, 4.76

IR; ν= 1700-1720 cm^{-1} (COOH and lactone), 1498 and 1600 cm^{-1} (benzene)

NMR (DMSO-d_6); δ= 4.29 (1H-3, d, J= 3 Hz), 5.96 (1H-4, d, J= 3 Hz), 7.35-8.07 (9H, benzene, m)

Molecular ion: m/e value; 268 (M+).

trans isomer of mp. 189°:

NMR (DMSO-d_6); δ= 4.62 (1H-3, d, J= 8 Hz), 5.97 (1H-4, d, J= 8 Hz), 7.36 (5H, benzene, s), 7.40-8.02 (4H, benzene, m)

Molecular ion: m/e value; 268 (M+).

trans-4-diazoacetyl-3,4-dihydro-3-phenylisocoumarin (III).— Compound I, 5 g. (0.019 mole), was boiled with thionyl chloride for 1.5 hrs. The yellow crystals left after removal of excess reagent by evaporation, was shown to be the 4-chlorocarbonyl-3,4-dihydro-3-phenylisocoumarin (II) by its IR absorption at 1788 cm^{-1}. This acid chloride (II) was dissolved in 30 ml. of dried acetone, and the acetone solution was dropped into an etheral solution of diazomethane (from 50 g. of nitrosomethylurea), cooled to 0°, and kept overnight at room temperature. After removal of acetone by evaporation and crystallization from small amount of acetone, 4.5 g. (82%) of yellow cubes, mp. 137°, were obtained.

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.85 ; H, 4.14 ; N, 9.59

Found : C, 70.09 ; H, 4.45 ; N, 9.44

IR; ν = 2105 cm^{-1} (diazoketone), 1720 cm^{-1} (lactone), 1500 and 1600 cm^{-1} (benzene)

NMR ($CDCl_3$); δ = 4.73 (1H-3, d, J= 8 Hz), 5.97 (1H-4, d, J= 8 Hz), 6.27 (1H, diazomethine,s), 7.20-8.10 (9H, benzene, m)

Mass spectrum m/e value; 264 (M+-28).

trans-3,4-dihydro-4-ω-hydroxyacetyl-3-phenylisocoumarin (IV).— The diazoketone (III), 1 g. (0.003 mole), was dissolved in 20 ml. of acetone, and the acetone solution was added dropwise to a mixture of sulfuric acid, acetone and water (1:3:30) at room temperature. After all the acetone had been removed by heating in a boiling water bath for 20 min., the yellow oil which separated, crystallized on cooling. Purification by recrystallization from aqueous ethanol gave 0.63 g. (60%) of yellow cubes, mp. 142°.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33 ; H, 5.00

Found : C, 72.51 ; H, 5.43

IR; ν= 1700-1740 cm^{-1} (ketone and lactone), 1500 and 1600 cm^{-1} (benzene)

NMR ($CDCl_3$); δ= 4.34 (1H-3, d, J= 8 Hz), 5.86 (1H-4, d, J= 8 Hz) 7.22 (5H, benzene, s), 7.0-8.2 (4H, benzene, m)

Molecular ion: m/e value; 282 (M+).

trans-3,4-dihydro-3-phenyl-4-isocoumarincarboxylic acid methyl ester (VIII, R = Me).— One g. (0.0037 mole) of I was converted to II and the residue was heated with 20 ml. of methanol for 1 hr.; concentration yielded 0.9 g. (91%) of colorless cubes, mp. 139°.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33 ; H, 5.00

Found : C, 72.49 ; H, 5.26

IR; ν= 1720 cm^{-1} (ester and lactone), 1500 and 1600 cm^{-1}

(benzene)

NMR ($CDCl_3$); δ= 3.72 (3H, Me, s), 4.32 (1H-3, d, J= 8 Hz), 5.87 (1H-4, d, J= 8 Hz), 7.0-8.2 (9H, benzene, m)

UV; λ_{max}^{EtOH} = 237 (log ε, 3.87), 282 (log ε, 3.06), 293 (log ε, 3.00)

Molecular ion: m/e value; 282 (M+).

3-Phenyl-4-isocoumarincarboxylic acid methyl ester (IX, R = Me).— Compound VIII(R = Me), 1.9 g. (0.0067 mole), was dissolved in 25 ml. of carbon tetrachloride, and 1.2 g. (0.0067 mole) of N-bromosuccinimide and 0.02 g. (0.08 mmole) of benzoyl peroxide were added, and boiled under ilumination of fluorescent light. After 1 hr., when the color of bromine had disappeared, an additional 0.02 g. of benzoyl peroxide was added and boiling was continued for another hour. The precipitated succinimide was removed by filtration, and the filtrate was evaporated *in vacuo* to remove solvent. The residual crystals were purified by recrystallization from methanol to afford 1.3 g. (68%) of colorless feather-like crystals, mp. 119°, lit.[5] mp. 117°.

NMR ($CDCl_3$); δ= 3.76 (3H, Me, s), 7.1-8.4 (9H, benzene, m)

UV; λ_{max}^{EtOH} = 233 (log ε, 4.32), 292 (log ε, 4.22), 325 (log ε, 3.94)

Molecular ion: m/e value; 280 (M+).

3-Phenylisocoumarin (X).— The methyl ester (IX, R ▫ Me), 1.9 g. (0.0067 mole), was mixed with 1 ml. of acetic acid and 5 ml. of hydrochloric acid, and was heated on a boiling water bath for 10 hrs.. The crystalline residue which deposited after evaporation, was purified by recrystallization from ethanol to give 0.5 g. (33%) of IX as colorless needles, mp. 90°, lit.[6] 90°.

NMR ($CDCl_3$);δ= 6.96 (1H-4, s), 7.2-8.4 (9H, benzene,m)

Molecular ion: m/e value; 222 (M+)

o-Phenacylbenzoic acid (XI).— A mixture of compound I 1.8 g. (0.0067 mole), dissolved in 400 ml. of methylene chloride containing 1 ml. of sulfuric acid was cooled to 0°. Then gaseous isobutylene, prepared by dropping a total 200 g. of *t*-butanol onto the pre-heated anhydrous oxalic acid, was passed into the solution. Then the solution was washed with 100 ml. of 10% sodium bicarbonate and the same volume of water and dried. After evaporation of solvent, the 3,4-dihydro-3-phenyl-4-isocoumarincarboxylic acid *t*-butyl ester (VIII, R = *t*-Bu) was obtained as colorless crystals (1.9 g., 87%). It had the same UV spectrum as the methyl ester (VIII, R = Me); upon heating in methanol, it changed into the methyl ester (VIII, R = Me). This ester (VIII, R = *t*-Bu) was dissolved in 200 ml. of benzene, and 1.2 g. of N-bromosuccinimide and 0.03 g. of benzoyl peroxide was added. After 1 hrs'boiling under illumination with fluorescent light, the color of bromine had faded and additional 1.2 g. of N-bromosuccinimide and 0.05 g. of benzoyl peroxide were added and continuously boiled for 5 hrs.. The succinimide was removed by filtration, and the filtrate was washed with water, dried over anhydrous sodium sulfate, and the solvent removed by distillation. The brown residue, 1.62 g. (85% on the basis of VIII (R ▫ *t*-Bu)) was shown to be the 3-phenyl-4-isocoumarincarboxylic acid tertiary butyl ester (IX, R ▫ *t*-Bu) by the observation into the UV spectrum which was same as that of the methyl ester (IX, R = Me), and also by the fact that it changed into the methyl ester (IX, R = Me) upon heating with methanol. This tertiary butyl ester was dissolved in 20 ml. of acetic acid and 20 ml. of water was added

and kept overnight at room temperature for 12 hrs. After addition of 50 ml. of water, the whole mixture was kept overnight in a refrigerator. The precipitated powder was collected and mixed with 50 ml. of 10% sodium bicarbonate and 100 ml. of ether. Upon acidification of the aqueous layer, colorless crystals precipitated; recrystallization from acetone gave large prisms of pure *o*-phenacylbenzoic acid (XI), mp. 164°, lit.[7] 164°; yield, 0.6 g. (50% on the basis of IX (R = *t*-Bu)).
NMR (DMSO-d_6); δ= 4.76 (2H, methylene, s), 7.0-8.2 (9H, benzene, m)
Mass spectrum m/e value; 222 (M+-18).

4-ω-Hydroxyacetyl-3-phenylisocoumarin (VII).— Compound IV, 0.38 g. (0.0014 mole), was mixed with 21 ml. of toluene, 4 ml. (0.07 mole) of ethylene glycol, 0.0245 g. (0.00014 mole) of *p*-toluenesulfonic acid, and the mixture was heated to remove the water, produced by the reaction, by co-distillation with toluene. During the distillation, 300 ml. of toluene was continuously added dropwise. All the solvent was evaporated and the residue was treated with ether, and the soluble fraction, after removal of ether, was washed with 5% sodium bicarbonate then water and dried to afford 0.39 g. (90%) of crude ketal V. This ketal (V) was dissolved in 30 ml. of carbon tetrachloride, and 0.26 g. (0.0015 mole) of N-bromosuccinimide and 0.01 g. (0.04 mmole) of benzoyl peroxide were added and refluxed under illumination with fluorescent light. After 1 hr., an additional 0.26 g. of N-bromosuccinimide and 0.01 g. of benzoyl peroxide were added and reflux continued for two hours. The succinimide was removed by filtration, and then the solvent was removed by distillation. The residue was washed with 5 ml.

water, dried, and extracted with ether. After removal of the ether, 0.23 g. (60% on the basis of IV) of crude VII was obtained, which was purified by recrystallization from ethanol to colorless cubes, mp. 116°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85 ; H, 4.32

Found : C, 73.03 ; H, 4.70

IR; ν= 1700-1750 cm^{-1} (ketone and lactone), 1600 cm^{-1} (benzene)

NMR ($CDCl_3$); δ= 3.72 (2H, methylene, s), 7.2-8.4 (9H, benzene, m)

Molecular ion: m/e value; 280 (M+).

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