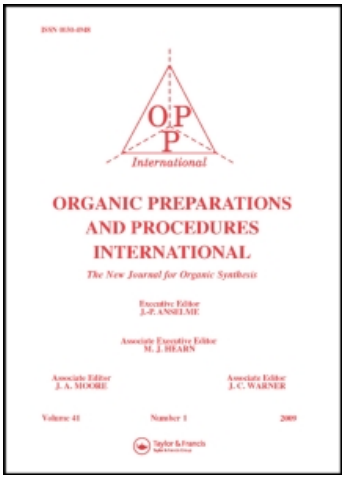

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SYNTHESIS OF ANTIFUNGAL ISOCOUMARINS

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SYNTHESIS OF ANTIFUNGAL ISOCOUMARINS

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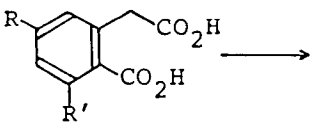
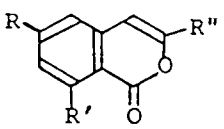
As a continuation of our previous studies,[1-3] we have synthesized various isocoumarin derivatives in an effort to obtain an antifungal isocoumarin as active as 8-hydroxy-4-ω-hydroxyacetylisocoumarin (oosponol)[4] and as harmless as 3,4-dihydro-8-hydroxy-3-(3′-hydroxy-4′-methoxyphenyl)isocoumarin (phyllodulcin).[5]

3-Alkylisocoumarins (2a and 2b), 3-alkyl-8-methoxyisocoumarins (2c-2e), and 3-alkyl-6,8-dimethoxyisocoumarins (2f-2h) were obtained by the procedure described earlier[2] by simple heating of homophthalic (1a), 3-methoxyhomophthalic[6] (1b) or 3,5-dimethoxyhomophthalic[7] acids (1c) in excess hexanoyl, octanoyl or hexadecanoyl chloride. In the cases of the reaction



1

a) R=R′=H
b) R=H, R′=OMe
c) R=R′=OMe

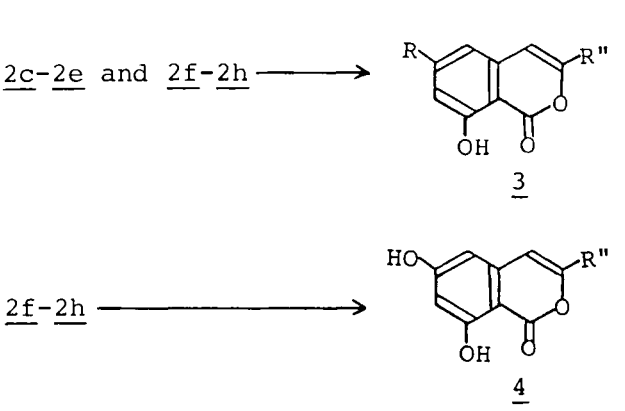


2

a) R=R′=H, R″=C_5H_{11}
b) R=R′=H, R″=$C_{15}H_{31}$
c) R=H, R′=OMe, R″=C_5H_{11}
d) R=H, R′=OMe, R″=C_7H_{15}
e) R=H, R′=OMe, R″=$C_{15}H_{31}$
f) R=R′=OMe, R″=C_5H_{11}
g) R=R′=OMe, R″=C_7H_{15}
h) R=R′=OMe, R″=$C_{15}H_{31}$

of 1b or 1c with octanoyl chloride, demethylation of the 8-methoxyl group occurred concurrently to afford 3-heptyl-8-hydro-

xyisocoumarin (3b) and 3-heptyl-8-hydroxy-6-methoxyisocoumarin



a) R=H, R"=C_5H_{11}
b) R=H, R"=C_7H_{15}
c) R=H, R"=$C_{15}H_{51}$
d) R=OMe, R"=C_5H_{11}
e) R=OMe, R"=C_7H_{15}
f) R=OMe, R"=$C_{15}H_{31}$

a) R"=C_5H_{11}
b) R"=C_7H_{15}
c) R"=$C_{15}H_{31}$

(3e) respectively, along with 3-heptyl-8-methoxyisocoumarin (2d) and 3-heptyl-6,8-dimethoxyisocoumarin (2g). The demethylation of the 8-methoxyl substituent of 3-alkyl-8-methoxyiso-

TABLE 1. 3-Alkylisocoumarins

	Mp (°C)	Yield (%)	Recryst. solvent	Mass(M^+)[a] (m/e)	Analysis Calcd(Found) C	H
2a	201	45	$CHCl_3$	216.1163 (216.1150)		
2b	58	89	MeOH	356	80.65(80.62)	10.18(10.01)
2c	oil	43		246.1263 (246.1256)		
2d	oil	39		274.1567 (274.1563)		
2e	81	62	MeOH	386	77.67(78.01)	9.91(10.05)
2f	96	45	MeOH	276	69.54(69.22)	7.30(7.32)
2g	68	50	MeOH	304.1684 (304.1674)		
2h	101	85	MeOH	416	74.96(74.63)	9.68(9.64)
3a	38	77	MeOH	232	72.39(72.40)	6.94(6.99)
3b	40	17	MeOH	260	73.82(73.44)	7.74(7.91)
3c	80	83	MeOH	372	77.37(77.12)	9.74(9.81)
3d	92	82	MeOH	262	68.68(68.76)	6.92(6.98)
3e	77	20	MeOH	290.1508 (290.1516)		
3f	81[b]	86	MeOH	402	74.59(74.93)	9.52(9.73)
4a	106	84	MeOH	248.1062 (248.1049)		
4b	98	74	MeOH	276	69.54(69.72)	7.30(7.50)
4c	114	78	MeOH	388.2581 (388.2584)		

a) Values in parenthesis are theoretical mass numbers.

b) Lit.[8] 110°.

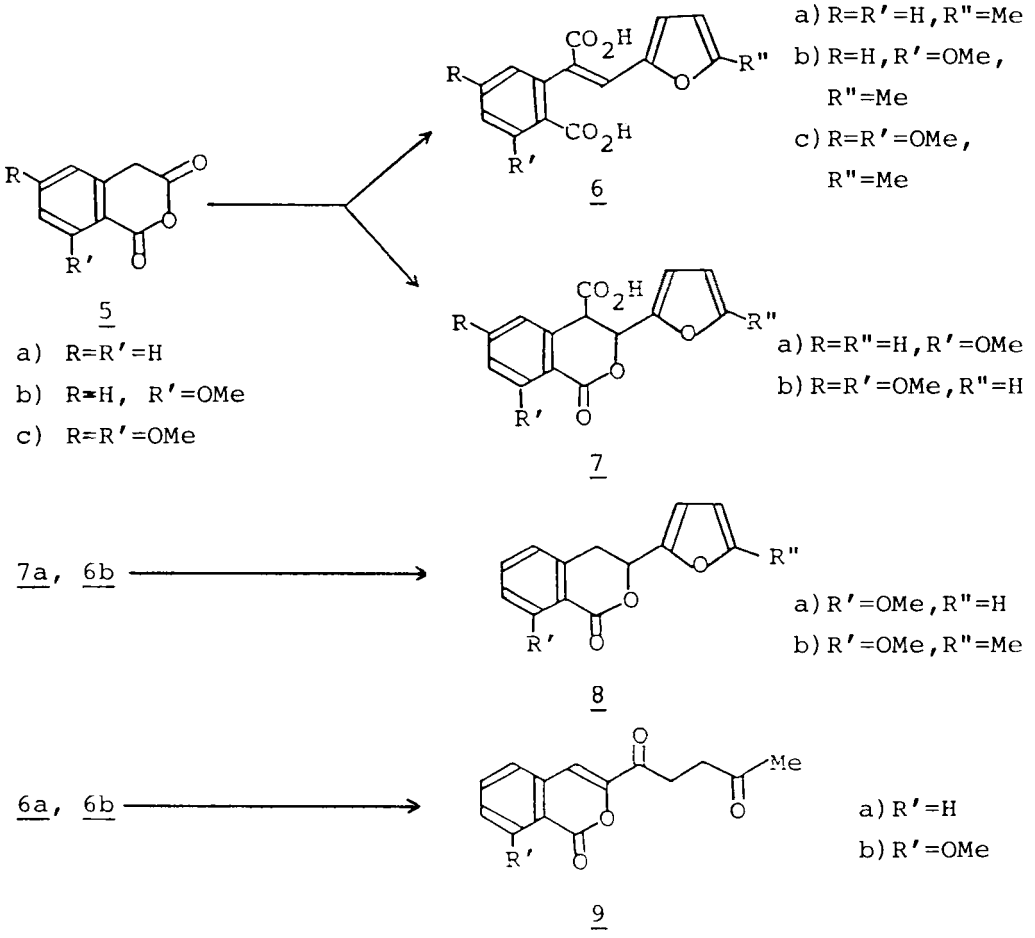
coumarins (2c-2e) and 3-alkyl-6,8-dimethoxyisocoumarins (2f-2h) with boron tribromide in methylene chloride at -5°, gave 3-alkyl-8-hydroxyisocoumarins (3a-3c) and 3-alkyl-8-hydroxy-6-methoxyisocoumarins (3d-3f); complete demethylation of both 6- and 8-methoxy groups of compounds 2f-2h occurred upon treatment with the same reagent in boiling methylene chloride.

TABLE 2. Spectral Data for 3-Alkylisocoumarins

	IR(cm^{-1})	PMR(in $CDCl_3$) δ(ppm)[a]				
	(C=O or OH)	C_4-H (1H,s)	α-CH_2 (2H,t)	Phenyl (m)	OMe (3H,s)	OH (1H,s)
2a	1720	6.25	2.52 (J=6.8Hz)	7.3-8.3(4H)		
2b	1715	6.24	2.53 (J=7.6Hz)	7.3-8.3(4H)		
2c	1720	6.15	2.48 (J=7.6Hz)	6.8-7.5(3H)	3.99	
2d	1715	6.14	2.48 (J=7.8Hz)	6.8-7.6(3H)	3.99	
2e	1720	6.14	2.32 (J=7.8Hz)	6.6-7.6(3H)	3.99	
2f	1720	6.08	2.46 (J=7.2Hz)	6.3-6.5(2H)	3.89,3.95	
2g	1725	6.08	2.46 (J=7.2Hz)	6.3-6.5(2H)	3.88,3.95	
2h	1730	6.08	2.46 (J=8.0Hz)	6.3-6.5(2H)	3.88,3.95	
3a	1670,3070	6.25	2.52 (7.9Hz)	6.8-7.5(3H)		11.00
3b	1680,3150	6.25	2.51 (J=7.6Hz)	6.8-7.6(3H)		11.00
3c	1690,3200	6.25	2.35 (J=7.6Hz)	6.8-7.6(3H)		11.00
3d	1680,3150	6.18	2.49 (J=7.3Hz)	6.3-6.5(2H)	3.89	11.10
3e	1680,3120	6.16	2.49 (7.6Hz)	6.2-6.5(2H)	3.85	11.10
3f	1685,3200	6.16	2.48 (J=7.7Hz)	6.2-6.5(2H)	3.85	11.11
4a	1680,3300	6.16	2.48 (J=7.7Hz)	6.2-6.4(2H)		7.10, 11.12
4b	1665,3200	6.15	2.49 (J=7.3Hz)	6.2-6.4(2H)		6.56, 11.10
4c	1670,3250	6.14	2.49 (J=7.2Hz)	6.2-6.4(2H)		7.35, 11.14

a) s, singlet; t,triplet; m, multiplet.

When homophthalic, 3-methoxyhomophthalic[3] or 3,5-dimethoxyhomophthalic[9] anhydrides (5a-5c) respectively were shaken with furfural or 5-methylfurfural in the presence of powdered sodium carbonate at room temperature,[1] 2,α-dicarboxy-β-(2-furyl)styrenes (6a-6c) or 3,4-dihydro-3-furylisocoumarin-4-carboxylic acids (7a, 7b) were obtained. The structures of 7a and



7b were supported by their PMR signals of the protons at C-3 and C-4 coupled with each other with respective J values of 3.5 and 4.4 Hz, indicating both compounds have the cis-configuration. The structures of the compounds (6a-6c) were clarified by their PMR spectra which showed a one proton methine of

TABLE 3. 3,4-Dihydro-3-furylisocoumarins, 2,α-Dicarboxy-β-(2-furyl)styrenes and 3,4-Dihydro-3-(1,4-dioxo)-pentylisocoumarins

	Mp (°C)	Yield (%)	Recryst. solvent	Mass(M^+)[a] (m/e)	Analysis Calcd(Found) C	H
6a	205	76	MeOH	272	66.17(65.57)	4.44(4.28)
6b	185	60	MeOH	302	63.57(63.04)	4.67(4.52)
6c	171	72	MeOH	332	61.44(61.79)	4.85(4.76)
7a	169	14	$CHCl_3$	288	62.50(62.95)	4.20(4.10)
7b	194	85	MeOH	318	60.38(60.37)	4.43(4.39)
8a	oil	21		244.0739 (244.0736)		
8b	oil	31		258.0881 (258.0891)		
9a	94	31	MeOH	246	69.42(68.28)	5.82(5.73)
9b	80	22	MeOH	276	65.40(65.21)	5.86(5.84)

a) Values in parenthesis are theoretical mass numbers.

TABLE 4. PMR Spectra for 2-α-Dicarboxy-β-(2-furyl)-styrenes

	PMR(in $CDCl_3$) δ(ppm)[a]				
	Me (3H,s)	OMe (3H,s)	β-CH (1H,s)	Phenyl (m)	Furan
6a	2.11		7.58	7.3-8.2(4H)	5.65d(1H) (J=3.4Hz) 5.82d(1H) (J=3.4Hz)
6b	2.05	3.74	8.31	7.0-7.5(3H)	5.95d(1H) (J=3.0Hz) 6.11d(1H) (J=3.0Hz)
6c	2.04	3.71 3.75	8.21	6.7-6.9(2H)	5.91d(1H) (J=3.2Hz) 6.18d(1H) (J=3.2Hz)

a) s,singlet; d,doublet; m,multiplet.

a double bond. Compound 7a upon heating at 165° in a sealed tube for 4 hrs, gave the decarboxylated product 3,4-dihydro-3-(2-furyl)-8-methoxyisocoumarin (8a), while compound (6a) gave 3,4-dihydro-3-(1,4-dioxo)pentylisocoumarin (9a) apparently re-

TABLE 5. NMR Spectra for 3,4-Dihydro-3-furylisocoumarins and 3,4-dihydro-3-(1,4-dioxo)pentylisocoumarins

	PMR(in $CDCl_3$) δ(ppm)[a]					
	Me (3H,s)	OMe (3H,s)	C_3-H (1H)	C_4-H (1H,d) or (2H,m)	Phenyl (m)	Furan or CH_2CH_2(4H,m)
7a		3.97	5.67d (J=3.5Hz)	4.19d (J=3.5Hz)	7.3-7.6(3H)	6.26d(1H) (J=1.7Hz) 6.54m(1H) 6.76m(1H)
7b		3.71 3.75	6.50d (J=4.4Hz)	4.80d (J=4.4Hz)	6.5-7.0(2H)	6.28m(1H) 6.50m(1H) 7.50d(1H) (J=2.0Hz)
8a		3.97	5.63t (J=6.5Hz)	3.15m	6.7-7.6(3H)	6.12dd(1H) (J=0.7 & 3.1Hz) 6.29dd(1H) (J=1.7 & 3.1Hz) 7.30dd(1H) (J=0.7 & 1.7Hz)
8b	2.25	3.98	5.61t (J=6.3Hz)	3.14m	6.7-7.6(3H)	5.87d(1H) (J=2.9Hz) 6.01d(1H) (J=2.9Hz)
9a	2.22		5.95t (J=6.1Hz)	3.07m	7.5-7.9(4H)	2.75
9b	2.21	3.99	5.85t (J=6.6Hz)	3.02m	6.1-7.7(3H)	2.77

a) s,singlet; d,doublet; t,triplet; dd,double doublet; m, multiplet.

sulting from cyclization, decarboxylation and the simultaneous furan ring cleavage; similarly compound 6b afforded both 3,4-dihydro-3-[2-(5-methyl)furyl]isocoumarin (8b) and 3,4-dihydro-3-(1,4-dioxo)pentyl-8-methoxyisocoumarin (9b). The PMR spectra of the compounds 8a and 8b showed a triplet one-proton signal for the proton at C-3 and two-protons multiplet for the protons at C-4. In the PMR spectra of the compounds 9a and 9b, all furan protons disappeared, and in CMR spectra, three carbonyl, two for ketones and one for a lactone, appeared.

Investigation into the antifungal activity for all the isocoumarins synthesized disclosed that the compounds (2c, 3d,

4a, 8a and 8b) were active at the minimum inhibition concentration against plant-pathogenic molds, i.e., Alternaria maritima, Cochliobolus miyabeanus, Fusarium splendens, Giberella zeae, and Penicillium expansum, in the range of 25 to 400 μg per ml.

EXPERIMENTAL SECTION

All mps are uncorrected. The IR spectra were taken as KBr pellets in the case of solid samples, and by the film method in the case of liquid samples, on a Hitachi model 215 spectrophotometer. PMR and CMR spectra were measured with a JEOL JNM-FX 100 spectrometer operating at 99.60 MHz for proton and 25.05 MHz for carbon-13, using tetramethylsilane as an internal standard. Low resolution and high resolution mass spectra were obtained on a JEOL JMS-D 300 spectrometer.

Reaction of Homophthalic Acid (1a, 1b or 1c) with Hexanoyl, Octanoyl, or Hexadecanoyl Chloride.- A mixture of the homophthalic acid (1a, 1b or 1c) (4.8 mmol) and the acyl chloride (hexanoyl, octanoyl or hexadecanoyl chloride) (20 mmol) was heated in an oil bath at 200° for 3 hrs, and then refluxed for 1 hr with MeOH (15 ml) to convert excess acyl chloride into esters. The residue after concentration was chromatographed on a silica gel column either in benzene-hexane (1:1) (for 2a-2b) or benzene-acetone (50:1) (for 2c-2h, 3b, and 3e) affording isocoumarins clearly separated from fatty acid esters. The eluted products were purified by recrystallization. The melting points, yields, solvents for recrystallization, and data for mass and elemental analyses are listed in Table 1; spectral data are shown in Table 2.

In the cases of the reactions of the compound (1b or 1c) with octanoyl chloride, the demethylation product (3b or 3e), along with compound 2d or 2g, was produced by this procedure.

Demethylation of 3-Alkyl-8-methoxyisocoumarins (2c-2e) and

Partial Demethylation of 3-Alkyl-6,8-dimethoxyisocoumarins (2f-2h).- One ml of BBr_3 in 2 ml of CH_2Cl_2 was added to a solution of 3-alkyl-8-methoxyisocoumarin (2c-2e) or 3-alkyl-6,8-dimethoxyisocoumarin (2f-2h) (100 mg) in 1.5 ml of CH_2Cl_2 under N_2. After 5 min, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The evaporated residue was dissolved in MeOH, treated with charcoal and crystallized to give pure products; 3-alkyl-8-hydroxyisocoumarins (3a-3c) and 3-alkyl-8-hydroxy-6-methoxyisocoumarins (3d-3f). The melting points, yields, solvents for recrystallization, and data for mass and elemental analyses are listed in Table 1. Spectral data are shown in Table 2.

Complete Demethylation of 3-Alkyl-6,8-dimethoxyisocoumarins (2f-2h).- Three ml of CH_2Cl_2 solution containing 1 ml of BBr_3 was added to 3-alkyl-6,8-dimethoxyisocoumarin (2f, 2g or 2h) (100 mg) in 2 ml of CH_2Cl_2 at 0° under N_2, and the mixture was refluxed for 1 hr. After cooling, the reaction mixture was treated as mentioned in the preceeding column to give pure 3-alkyl-6,8-dihydroxyisocoumarin (4a, 4b or 4c). The melting points, yields, solvents for recrystallization, and data for mass and elemental analyses are listed in Table 1. Spectral data are shown in Table 2.

Reaction of Homophthalic Anhydrides (5a-5c) with Furfural or 5-Methylfurfural.- A mixture of homophthalic anhydride (5a, 5b or 5c) (2 mmol), furfural or 5-methylfurfural (3 mmol), and finely powdered Na_2CO_3 (4 mmol) in benzene (5 ml) was vigorously shaken for 10 hrs at room temperature. Water (5 ml) and benzene (5 ml) were added and shaken. Then the aqueous layer was separated, acidified with HCl to give the precipitate of

the crude 2,α-dicarboxy-β-(2-furyl)styrene (6a, 6b or 6c), or 3,4-dihydro-3-furylisocoumarin-4-carboxylic acid (7a or 7b) which was purified by recrystallization. The melting points, yields, solvents for recrystallization, and data for mass and elemental analyses of the products are listed in Table 3. And the PMR spectral data are shown in Table 4 or 5.

Reaction of Hydrochloric Acid on 2,α-Dicarboxy-β-(2-furyl)styrenes (6a, 6b) or 3,4-Dihydro-3-furyl-8-methoxyisocoumarin-4-carboxylic Acid (7a) under Pressure.- A suspension of the compound (6a, 6b or 7a) (100 mg) in 7% HCl (2 ml) was heated in a sealed tube in an oil bath at 165° for 4 hrs. The reaction mixture was cooled, extracted with $CHCl_3$, and the extract was washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product thus obtained were purified by recrystallization. By this procedure, the compound (6a) gave 3,4-dihydro-3-(1,4-dioxo)pentylisocoumarin (9a) while the compound (7a) gave 3,4-dihydro-3-furyl-8-methoxyisocoumarin (8a). But the compound (6b) gave both 3,4-dihydro-3-(1,4-dioxo)pentyl-8-methoxyisocoumarin (9b) and 3,4-dihydro-8-methoxy-3-(3-furyl)isocoumarin (8b). In the latter case, the product components were separated by silica gel chromatography in benzene before crystallization. The melting points, yields, solvents for recrystallization, and data for mass and elemental analyses are listed in Table 3; spectral data are shown in Table 5. The 3,4-dihydro-3-(1,4-dioxo)pentylisocoumarins (9a-9b) exhibited CMR signals in deuterated pyridine at 205.6 and 205.3 ppm , and 206.5 and 206.1 ppm respectively for two ketones, and at 170.1 and 167.3 ppm respectively for a lactone.

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