Conversion of (±)-3-Ethyl-3-methyl phthalides to 3,3-Dimethyl-3,4-dihydroisocoumarins. Synthesis of 3-Methylmellein.

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o-Lithio *N*-methyl benzamides (**1a-f**) upon alkylation with ethyl methyl ketone gave (±)-3-ethyl-3-methyl phthalides (**2a-f**),which upon treatment with concentrated H_2SO_4 or anhydrous $AlCl_3$ furnished corresponding 3,3-dimethyl-3,4-dihydroisocoumarins (**3a-f**) and 3-methyl mellein (**3g**).

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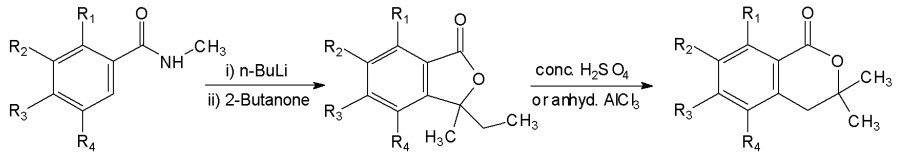
A number of phthalides and dihydroisocoumarins have interesting biological activities *e.g.* Cladosporin and its monoacetyl derivatives act as antifungal agents, Sclerotinin-A promotes growth of rice seedlings, 3-butylphthalide and 3-butyl-4,5-dihydrophthalide both are effective anticonvulsants, 7-hydroxy-3-butylidenephthalide possess cardiokinetic, antistenocardiacs, antiarrhythmics and coronary artery dilators activity [1-5].

Recently, several workers [6-8] have studied the synthesis of 3-substituted phthalides and their transformation to 3-alkyl isocoumarins. The purpose of undertaking this work to explore the synthesis of 3,4-dimethyl dihydroisocoumarins as the natural product Oospalactone has this type of substitution pattern. However the phthalides (**2a-f**), surprisingly, were converted to 3,3-dimethyl-3,4-dihydroisocoumarins. Earlier 3,3-dimethyl-3,4-dihydroisocoumarins were prepared from β,β-dimethyl-2-carbostyrenes [9].

EXPERIMENTAL

All melting and boiling points are uncorrected. Solid compounds were crystallised using ethyl acetate/*n*-hexane. ^{1}H-nmr spectra were recorded on Hitachi R-1500 (60 MHz) instrument using $CDCl_3$ as solvent. Chemical shifts are quoted in parts per million (δ) downfield from the internal tetramethylsilane reference and coupling constants (J) are given in Hz. The presence of exhangeable protons was confirmed by the use of deuterium oxide. ^{13}C-nmr spectra were recorded on Bruker DPX-200 (200 MHz) instrument with TMS as an internal standard. ir spectra were recorded in KBr on a Nicolett D-400 spectrophotometer. The progress of the reaction was monitered by thin layer chromatography. Iodine vapour was used for detection. Chromatographic separations were performed on silica gel column (60-120 mesh) (open bed chromatography) using gravity flow. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedure.

Scheme - I



	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	Cl	H
c	H	H	CH_3	H
d	H	CH_3	H	CH_3
e	H	CH_3	CH_3	H
f	OCH_3	H	H	H
g	OH	H	H	H

In the present work (±)-3-ethyl-3-methyl phthalides (**2a-f**) were synthesized in a single step by alkylating *o*-litho *N*-methyl benzamides (**1a-f**) with 2-butanone in (40-50%) yield. These phthalides underwent smooth rearrangement with concenrrated H_2SO_4 or anhydrous $AlCl_3$ to give dihydroisocoumarins (**3a-g**) in about (35-50%) yield (Scheme-I).

The above conversion was successfully used to synthesize 3-methyl mellein. The structures of phthalides and dihydroisocoumarins are supported by analytical and spectral evidences.

General Procedure for the Synthesis of (±)-3-Ethyl-3-methylisobenzofuran-1-ones (**2a-f**).

To a well stirred solution of *N*-methyl benzamides (**1a-f**) (25.6 mmol) in 50 mL dry THF (freshly distilled over $LiAlH_4$), *n*-BuLi [(105 mmoles, prepared from lithium 2.57 g (370 mmoles) and *n*-butyl bromide 13.73 mL (128 mmoles) in dry ether (125 mL)] was added at room temperature under nitrogen atmosphere. The resulting red metallation mixture was then refluxed for 30 minutes. The metallation mixture was condensed with 2-butanone 7.2 mL (128 mmoles) in dry ether at -10 °C and the reaction mixture was stirred for 3 hours at room temperature. The excess THF was distilled off under reduce pressure, the residue obtained was decomposed with

hydrochloric acid (6 *N*, 100 mL) and extracted with ether (2 × 50 mL). The organic layer was washed with cold water (100 mL) and saturated $NaHCO_3$ solution (50 mL). The solution was then dried over anhydrous .Na_2SO_4, and the solvent was evaporated to give phthalides (**2a-f**). The phthalides (**2a-f**) were purified by column chromatography over silica gel using 50% petroleum ether-benzene as an eluent. The liquid products were further purified by distillation.

(±)-3-Ethyl-3-methylisobenzofuran-1-one (**2a**).

This compound was obtained as colorless liquid, 2g (44.4%), bp 125 °C 15mm/Hg; ir (neat):1763cm^{-1}(γ-lactone); ^{1}H nmr : δ 0.76(t, 3H, CH_2CH_3 at C_3, J = 6.6Hz), 1.65 (s, 3H, CH_3 at C_3), 1.9 (q, 2H, CH_2CH_3 at C_3, J = 6.6Hz), 7.3-7.9 (m, 3H, C_4,C_5,C_6-H), 7.9(d, 1H, C_7-H, J = 7.8 Hz).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.75; H, 6.98.

(±)-5-Chloro-3-ethyl-3-methyl-isobenzofuran-1-one (**2b**).

This compound was obtained as white needles, 2.4g (45%), mp 85°; ir (KBr): 1760 cm^{-1} (γ-lactone); ^{1}H nmr : δ 0.77 (t, 3H, CH_2CH_3 at C_3, J = 6.5Hz), 1.63 (s, 3H, CH_3 at C_3), 1.9 (q, 2H, CH_2CH_3 at C_3, J = 6.5Hz), 7.3-7.5 (m, 2H, C_4, C_6-H), 7.9 (d, 1H, C_7-H, J = 7.8Hz).

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.56; H, 5.53.

(±)-3-Ethyl-3,5-dimethyl-isobenzofuran-1-one (**2c**).

This compound was obtained as white needles, 2.2g (44.6%), mp 62°; ir (KBr):1743 cm^{-1} (γ-lactone); ^{1}H-nmr : δ 0.76 (t, 3H, CH_2CH_3 at C_3, J = 6.6Hz), 1.63 (s, 3H,CH_3 at CH_3), 1.9 (q, 2H, CH_2CH_3 at CH_3, J = 6.6 Hz), 2.4 (s, 3H, CH_3 at C_5), 7.1-7.3 (m, 2H, C4,C6-H), 7.8 (d, 1H, C7-H, J = 7.8Hz).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.58; H, 7.56.

(±)-3-Ethyl-3,4,6-trimethyl-isobenzofuran-1-one (**2d**).

This compound was obtained as colorless liquid, 2.6g (50%), bp 118° 15mm/Hg; ir (neat): 1763 cm^{-1} (γ-lactone); ^{1}H nmr : δ 0.80 (t, 3H, CH_2CH_3 at C3, J = 6.6Hz), 1.59 (s, 3H, CH_3 at C3), 2.0 (q, 2H, CH_2CH_3 at C3, J = 6.6 Hz), 2.3 & 2.4 (2s, 6H, CH_3 at C4 & C6), 7.2 (s, 1H, C_5-H), 7.8 (s, 1H, C_7- H).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.32; H, 7.65.

(±)-3-Ethyl-3,5,6-trimethyl-isobenzofuran-1-one (**2e**).

This compound was obtained as white needles, 2.45g (48%), mp 83°; ir (KBr): 1756 cm^{-1} (γ-lactone); ^{1}H-nmr : δ 0.79 (t, 3H, CH_2CH_3 at C_3, J = 6.8Hz), 1.5 (s, 3H,CH_3 at C_3), 2.1 (q, 2H, CH_2CH_3 at C_3, J = 6.8Hz), 2.3 (s, 6H,CH_3 at C_5 & C_6), 7.2 (s, 1H,C_4-H), 7.7 (s, 1H, C_7-H); ^{13}C-nmr : δ 8.2 (-CH_2-CH_3), 20.24 & 21.13 (CH_3 at C_5 & C_6), 26.17 (CH_3 at C_3), 33.26 (-CH_2-), 87.96 (C_3), 122.19 (=C<), 124.45 (=C<), 126.17 (=C<), 138.32 (=C<), 144.59 (=C<), 152.26 (=C<), 170.76 (C_1 Carbonyl).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.35; H, 7.71.

(±)-3-Ethyl-3-methyl-7-methoxy-isobenzofuran-1-one (**2f**).

This compound was obtained as white needles, 2.1g (41%), mp 58°; ir (KBr): 1770 cm^{-1} (γ-lactone); ^{1}H-nmr : δ 0.75 (t, 3H, CH_2CH_3 at C_3, J = 6.8Hz), 1.6 (s,3H,CH_3 at C_3), 1.99 (q, 2H, CH_2CH_3 at C_3, J = 6.8Hz), 3.9 (s, 3H,OCH_3 at C_7), 6.8-7.5 (m, 3H, C_4,C_5, C_6-H).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.98; H, 6.73.

General Procedure for the Conversion of Isobenzofuran-1-ones (**2a-f**) to1*H*,4*H*-3,3-Dimethyl-2-benzopyran-1-ones (**3a**-f) and (**3g**).

Method A.

Phthalides (**2a-f**) (1.7 mmoles) were mixed with cold conc. H_2SO_4 (2mL) and after shaking well the mixture was warmed on a boiling water bath for 1 hr and kept at room temperature for 24 hrs. The reaction mixture was decomposed by adding cold water (50mL) and extracted with ether (2 × 25mL). The organic layer was washed with saturated sodium bicarbonate solution(50mL) and cold water (50mL), dried over anhydrous sodium sulfate and evaporated to give a product (**3a-f**) in 35-40% yield.

Method B.

Phthalides (**2a-e**) (1.7 mmoles) were treated with anhydrous $AlCl_3$ (300mg) in dry methylene chloride (25mL) at reflux temperature for 1-2 hrs (monitored by TLC). Methylene chloride was evaporated and the residue decomposed with HCl (6N) and extracted with ether (2 × 25mL). The organic layer was washed with saturated sodium bicarbonate solution(50mL) and cold water (50mL), dried over anhydrous sodium sulfate and evaporated to give crude (**3a-e**). Reaction of **2f** with $AlCl_3$ gave 3f and demethylated product 3-methyl mellein (**3g**). They were purified by column chromatography over silica gel using 50% pet.ether-benzene as an eluent to give **3a-f** and **3g** in (45-50%) yield, identical with those obtained from method A.

1*H*,4*H*-3,3-Dimethyl-2-benzopyran-1-one (**3a**).

This compound was obtained as colorless liquid, 0.14g (48%), bp 145° 15mm/Hg; lit[9].,bp 153-154° 11mm/Hg; ir(KBr): 1710 cm^{-1} (δ-lactone); ^{1}H nmr : δ 1.45(s, 6H, 2 CH_3 at C_3), 3.02 (s, 2H, benzylic -CH_2), 7.1-7.5(m, 3H, C_5,C_6,C_7-H), 7.8 (d, 1H, C_8-H, J= 8 Hz).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.20; H, 6.92.

1*H*,4*H*-6-Chloro-3,3-dimethyl-2-benzopyran-1-one (**3b**).

This compound was obtained as white needles, 0.17g (47.6%), mp 157°; ir (KBr): 1716 cm^{-1} (δ-lactone); ^{1}H-nmr : δ 1.45(s, 6H, 2 CH_3 at C_3), 2.9 (s, 2H, benzylic -CH_2), 7.2-7.5 (m, 2H, C_5 & C_7-H), 7.8 (d, 1H, C_8-H, J = 7.9Hz).

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.85; H, 5.43.

1*H*,4*H*-3,3,6-Trimethyl-2-benzopyran-1-one (**3c**).

This compound was obtained as a white needle, 0.11g (37%), mp 55° ; ir (KBr): 1715 cm^{-1} (δ-lactone); ^{1}H-nmr : δ 1.45 (s, 6H, 2 CH_3 at C_3), 2.3 (s, 3H, CH_3 at C_3), 2.89 (s, 2H, benzylic -CH_2), 6.9-7.2 (m, 2H, C_5, C_7-H), 7.9 (d, 1H, C_8-H, J = 7.9Hz); ^{13}C-nmr : δ 12.10 & 12.25 (2 CH_3 at C_3), 22.4(CH_3 at C_6), 32.0(C_4), 82.3(C_3), 125.0 (=C<), 128.53 (=C<), 135.24(=C<), 135.37 (=C<), 136.40(=C<), 136.99 (=C<), 166.57 (C_1 Carbonyl).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.88; H, 7.51.

1*H*,4*H*-3,3,5,7-Tetramethyl-2-benzopyran -1-one (**3d**).

This compound was obtained as white needles, 0.13g (40%), mp 77°; ir (KBr): 1720 cm^{-1} (δ-lactone); ^{1}H-nmr: δ 1.44 (s, 6H,

2CH_3 at C_3), 2.3 (s, 3H, CH_3 at C_5), 2.4 (s,3H, CH_3 at C_7), 2.93 (s, 2H, benzylic -CH_2), 7.1 (s, 1H,C_6-H), 7.8 (S, 1H,C_8-H).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.65; H, 7.75.

1*H*,4*H*-3,3,6,7-Tetramethyl-2-benzopyran-1-one (**3e**).

This compound was obtained as white needles, 0.17g (50%), mp 117°; ir (KBr): 1709 cm^{-1} (δ-lactone); ^{1}H-nmr: δ 1.4 (s, 6H, 2 CH_3 at C_3); 2.3 (s, 6H, CH_3 at C_6, C_7), 2.8 (s, 2H, benzylic -CH_2), 6.9 (s, 1H,C_5-H), 7.8 (s, 1H, C_8-H);^{13}C-nmr: δ 12.14 & 12.84 (2 CH_3 at C_3), 27.37 (2 CH_3 at C_6 & C_7 merged), 38.81 (C_4), 80.46 (C_3), 122.01 (=C<), 128.95 (=C<), 130.63 (=C<), 135.45 (=C<), 135.83 (=C<), 143.36 (=C<), 165.30 (C_1 Carbonyl).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.59; H, 7.72.

1*H*,4*H*-3,3-Dimethyl-8-methoxy-2-benzopyran-1-one *i.e*., 3-Methyl Mellein Methyl Ether (**3f**).

This compound was obtained as white needles, 0.16g (47%), mp 95°; ir (KBr): 1708 cm^{-1} (δ-lactone); ^{1}H-nmr : δ 1.41 (s, 6H, 2 CH_3 at C_3), 2.9 (s, 2H, benzylic -CH_2); 3.9 (s, 3H, OCH_3 at C_8), 6.7-7.6 (m, 3H, C_5, C_6, C_7-H).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.74; H, 6.97.

1*H*,4*H*-3,3-Dimethyl-8-hydroxy-2-benzopyran-1-one *i.e*., 3-Methyl Mellein (**3g**).

This compound was obtained as white needles, 0.12 g (48%), mp 65°; ir (KBr): 1677 cm^{-1} (δ-lactone); ^{1}H-nmr : δ 1.4 (s, 6H, 2 CH_3 at C_3), 2.9 (s, 2H, benzylic -CH_2), 6.6-7.5 (m, 3H, C_5, C_6, C_7-H); 11.17 (1H, s, C_8-OH, D_2O exchangeable).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.62; H, 6.52.

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