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Isocoumarins : Part 7. New synthesis of 3-phenyl-3, 4-dihydroisocoumarins and their antifungal activity

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Abstract. *o*-Lithio-N-methylbenzamides upon condensation with styrene oxide give corresponding 3-phenyl-3, 4-dihydroisocoumarins. The antifungal activity of the compounds has been tested.

Keywords. *o*-Lithio-N-methylbenzamides ; 3-phenyldihydroisocoumarins ; antifungal activity.

1. Introduction

The dihydroisocoumarins having C_3-phenyl group are quite common in nature, *e.g.*, Phyllodulcin (Henri and Gilbert 1977), Homalicin (Govindachari *et al* 1975) and Hydrangenol (Ibrahim and Towers 1962) etc. There are a few methods for the synthesis of 3-phenyl-3, 4-dihydroisocoumarins (Brown *et al* 1975 ; Nizamuddin and Ghosal 1974 ; Usgaonkar 1971 ; Naoi *et al* 1976 ; Tobinga and Akiteru 1971). However these methods comprise several steps and have no general applicability. Hence it seemed desirable to explore a simple and general method for synthesising 3-phenyl-3, 4-dihydroisocoumarins.

The N-methylbenzamides are known to undergo lithiation at ortho positions and these *o*-lithio-N-methyl benzamide upon alkylation with epoxides give dihydroisocoumarins (Bhide and Shah 1980 ; Bhide and Brahmbhatt 1980). In the present work *o*-lithio-N-methylbenzamides have been condensed with styrene oxide to give 3-phenyl-3, 4-dihydroisocoumarins.

2. Results and discussion

The condensation of *o*-lithio-N-methylbenzamide, 2- and 4-methoxy-N-methylbenzamide, 3, 4-dimethoxy-N-methylbenzamide, 3, 4, 5-trimethoxy-N-methylbenzamide and 4-methyl-N-methylbenzamide with styrene oxide gave after hydrolysis

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corresponding 3-phenyl-3, 4-dihydroisocoumarins (I–VI) respectively. Besides dihydroisocoumarins, the alkylation reaction also gave a side product having m.p. 95° C. It was identified as α,β-diphenyl-γ-butyrolactone (VII) on the basis of spectral and analytical evidences. It has been reported (Shinsuke *et al* 1970) that styrene oxide isomerizes to (VII) when treated with a catalyst like lithium benzoylnickel carbonate, lithium-*p*-toluoylnickel carbonate etc. This suggested that the *o*-lithio-N-methylbenzamides probably bring about the isomerization of styrene oxide to (VII). This side reaction could be a possible reason for the poor yields of the dihydroisocoumarins in the present work.

2.1. *Antifungal activity of* 3-phenyl-3, 4-dihydroisocoumarins

The 3-phenyl dihydroisocoumarins possess antifungal activity (Nakajima *et al* 1979; Maeakwa and Yoshikawa 1978). Hence the present compounds were screened for antifungal activity by modified paper disc assay (Sharvelle 1960) using different fungi. The testing was carried out in the DMF solution at different concentrations as it was innocuous. The petri dishes were incubated in the UV chamber at room temperature for 4–7 days and examined for the fungal growth on filter-paper.

Compounds I, II and V showed good fungicidal activity against *A. niger*, *Curvularia fusarium* and *Rhicopus* while compounds III, IV and VI showed slight fungicidal activity against *Fusarium*, *Rhizopus*, *Rhizoctonia helminthosporium* and *alternaria cotton*.

3. Experimental

3.1. *Preparation of all N-methylbenzamides*

This was described in the earlier papers in this series.

3.2. *Lithiation and condensation of o-lithio derivatives with styrene oxide* :

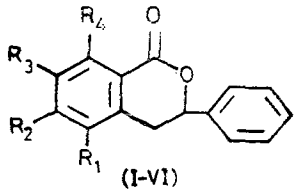
The following general procedure was used. To a well-stirred solution of N-methylbenzamides (0·037 mol) in dry THF (75 ml) was added at room temperature *n*-BuLi (0·30 mole) in dry ether under nitrogen atmosphere for 10 min. The

I. $R_1 = R_2 = R_3 = R_4 = H$. II. $R_1 = {}_3 = R_4 = H$, $R_2 = OMe$.

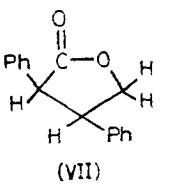
III. $R_1 = R_2 = R_3 = H$, $R_4 = OMe$.

IV. $R_1 = R_2 = OMe$, $R_3 = R_4 = H$. V. $R_1 = R_2 = R_3 = OMe$, $R_4 = H$.

VI. $R_1 = R_3 = R_4 = H$, $R_2 = Me$.



(I-VI)



(VII)

resulting red metalation mixture was then refluxed for 30 min. It was then cooled at 0° C. The metalation mixture upon condensation with styrene oxide (12·8 ml) under nitrogen atmosphere at reflux temperature for 45 min and alkaline hydrolysis work up as before (Narasimhan and Bhide 1971) gave the following 3-phenyl 3,4-dihydroisocoumarins (I-VI) and VIII.

3.2a. 3-*Phenyl*-3, 4-*dihydroisocoumarin* (I) : White needles, crystallised from ethylacetate-hexane, yield 8%, m.p. 89–90° (found : C, 80·24 ; H, 5·13 : $C_{15}H_{12}O_2$ requires C, 80·37 ; H, 5·35% ; IR (KBr) : 1720 cm^{-1}, (δ lactone) ; UV (95% ethanol) : 240, 257 nm (log ε 4·0, 3·65) ; NMR ($CDCl_3$) : δ 3·15 (2H, complex, benzylic $-\underline{CH_2}-$), 5·55 (4 lines, H_3 proton J_{Ax} = 4Hz, J_{Bx} = 12 Hz), 7·60 (8H, complex, aromatic protons), 8·1 (1H, complex, H_8 proton).

3.2b. 6-*Methoxy*-3-*phenyl*-3,4-*dihydroisocoumarin* (*II*) : White needles, crystallised from ether-hexane, yield 5% ; m.p. 115–16° : (found : C,75·16 ; H, 5·86 ; $C_{16}H_{14}O_3$ requires C, 75·60 ; H, 5·50%) ; IR (KBr) : 1710 cm^{-1} (δ lactone) ; UV (95% ethanol) : 251, 293 nm (log ε 4·2, 3·77) ; NMR ($CDCl_3$) ; δ 3·0 (2H complex, benzylic $-CH_2-$), 3·6 (3H, singlet $-OCH_3$ group), 5·2 (4 lines, H_3 proton, J_{Ax} = 4Hz, J_{Bx} = 12Hz), 6·1–7·0 (7H, complex, aromatic protons), 7·55 (1H, doublet, J_0 = 8Hz, H_8 proton).

3·2c. 8-*Methoxy*-3-*phenyl*-3, 4-*dihydroisocoumarin* (*III*) : White needles, crystallised from ether-hexane, yield 30% ; m.p. 151° (found C, 75·49 ; H, 5·76 ; $C_{16}H_{14}O_3$ requires C, 75·60 ; H, 5·76 ; IR (KBr) : 1745 cm^{-1} (δ lactone) ; UV (95% ethanol) : 305, 350 nm (log ε 4·0, 3·90) ; NMR ($CDCl_3$) δ 3·1 (2H, complex, benzylic $-CH_2-$), 3·85 (3H, singlet $-OCH_3$ group), 5·30 (4 lines, H_3 proton, J_{Ax} = 4Hz, J_{Bx} = 12Hz). 6·7–7·5 (8H, complex, aromatic protons).

3.2d. 5, 6-*Dimethoxy*-3-*phenyl*-3, 4-*dihydroisocoumarin* (*IV*) : White needles, crystallised from ether-hexane, yield 10% ; m.p. 127°, (found : C, 71·46 ; H, 6·00 ; $C_{17}H_{16}O_4$ requires C, 71·82 ; H, 5·63%) : IR (KBr): 1715 cm^{-1} (δ lactone) ; UV (95% ethanol) 221, 266 nm (log ε 4·83, 4·33), NMR ($CDCl_3$) : δ 3·2 (2H, 8 lines, the AB part of an ABx system, J_{AB} = 16Hz, J_{Ax} = 4Hz, J_{Bx}=11 Hz, $-Ar-\underline{CH_2}-\overset{\overset{-O}{|}}{C}-Ph$) 3·75 and 3·9 (6H, two singlets, two $-OCH_3$ groups) 5·4 (4 lines, $\underline{H_3}$ proton, J_{Ax} = 4Hz, J_{Bx} = 12Hz), 6·9 (1H, doublet, J = 8Hz, H_7 proton, 7·0–7·5(7H, complex, aromatic protons), 7·85 δ (1H, doublet, J = 8Hz, H_8 proton).

3.2e. 5, 6, 7-*Trimethoxy*-3-*phenyl*-3, 4-*dihydroisocoumarin* (*V*) : White needles, crystallised from ether-hexane, yield 9% ; m.p. 111° (found C, 68·56 ; H, 5·43 ; $C_{18}H_{18}O_5$ requires C, 68·80 ; H, 5·73%) ; IR (KBr) : 1730 cm^{-1} (δ lactone) ; UV (95% ethanol) : 224, 259 nm (log ε 3·90, 3·40) ; NMR ($CDCl_3$) : δ 3·0 (2H, 8 lines, the AB part of an ABx system, J_{AB} = 17Hz, J_{Ax} = 5Hz, J_{Bx} = 12Hz, $Ar-\underline{CH_2}-\overset{\overset{-O}{|}}{C}-Ph$), 3·6, 3·7 and 3·8 (9H, three singlets, three $-OCH_3$ groups), 5·3 (4 lines, H_3 proton, J_{Ax} = 4Hz, J_{Bx} = 12Hz, 6·1–6·8 (5H, complex, aromatic protons), 7·2 (1H, singlet, H_8 proton).

3.2f. 6-*Methyl*-3-*phenyl*-3, 4-*dihydroisocoumarin* (VI) : White needles, crystallised from ether-hexane, yield 7%, m.p. 96° (found : C, 80·56, H, 5·54 ; $C_{16}H_{14}O_2$ requires C, 80·67 ; H, 5·88) ; IR (KBr) : 1725 cm^{-1} (δ lactone), UV (95% ethanol) ; 240, 257 nm (log ε 4·0, 3·65), NMR ($CDCl_3$) δ 2·4 (3H, singlet, $-CH_3$ protons), 3·15 (2H, complex, benzylic $-CH_2-$), 5·55 (4 lines, H_3 protons, J_{AB} = 4Hz, J_{BX} = 12Hz) 7·40 (7H, complex, aromatic protons) 8·0δ (1H, doublet J_0 = 8Hz, H_8 proton).

3.2g. α,β-*Diphenyl*-γ-*butyrolactone* (*VII*) : White needles, crystallised from ether-hexane, yield 10% ; m.p. 95° (found : C, 80·48 ; H, 5·68 ; $C_{16}H_{14}O_2$ requires C, 80·64 ; H, 5·92%), IR (KBr) : 1780 cm^{-1} (ν lactone) ; UV (95% ethanol) 250, 310 nm (log ε 4·50, 3·45), NMR ($CDCl_3$) : δ 3·95 (2H, $-CH_2-$ group), 4·2–4·8 (2H, complex), 7·3 (10H, complex, aromatic protons).

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