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Synthesis of 3-Aryl-7-Hydroxy Isochromenes

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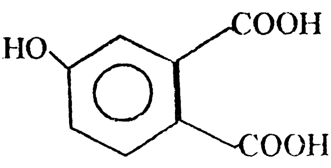
Phenol, anisole and resorcinol have been condensed with 4-hydroxyl homophthalic acid in the presence of polyphosphoric acid to give 3-(4′-hydroxy phenyl)-; 3-(4′-methoxyphenyl) and 3-(2′,4′-dihydroxyphenyl)-7-hydroxy isocoumarins. On treatment with aqueous sodium hydroxide, 3-aryl isocoumarin yield the respective ω-(2′-carboxyl-4′-hydroxyphenyl)-acetophenones. Sodium boro-hydride reduction of acetophenones gives the corresponding dihydroisocoumarins. The isocoumarins have been condensed with methyl magnesium iodide, ethyl magnesium iodide and phenyl magnesium iodide to yield 3-(4′-hydroxy phenyl), 3-(4′-methoxy phenyl)-, 3-(2′,4′-dihydroxy phenyl)-7-hydroxy-1,1-dimethyl; 3-(4′-hydroxy phenyl)-, 3-(4′-methoxy phenyl)-3-(2′,4′-dihydroxy phenyl)-7-hydroxy-1,1-diethyl and 3-(4′-hydroxy phenyl)-, 3-(4′-methoxy phenyl) and 3-(2′,4′-dihydroxy phenyl)-7-hydroxy-1,1-diphenyl ischromenes. The isocoumarins have been converted into isoquinolones with ammonia, ethyl amine and aniline.

INTRODUCTION

In general 3-phenyl isocoumarins are obtained by condensing homophthalic anhydride with aromatic hydrocarbons, phenols and phenolic ethers using anhydrous aluminium chloride or stannic chloride[1, 2]. Condensation of homophthalic anhydride with phenols using polyphosphoric acid also gives 3-phenyl isocoumarins in good yield[3–5]. These isocoumarins are known to possess coronary dilating and antispasmodic activities and also to act as a strong purgative.



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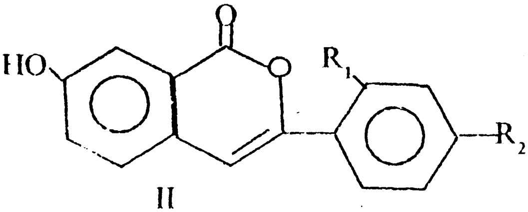

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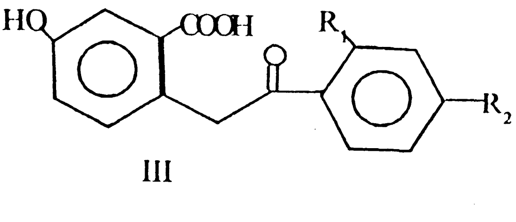

III

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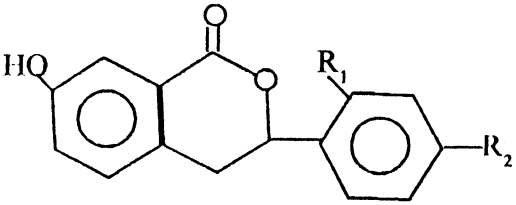
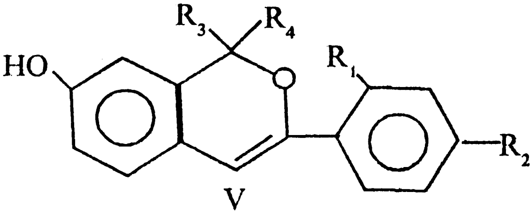


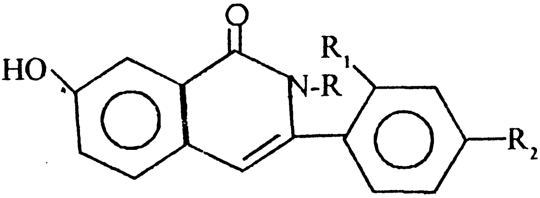
IV

(a) $R_1 = H, R_2 = OH$ (b) $R_1 = H, R_2 = OMe$ (c) $R_1 = R_2 = OH$



V

(a) $R_1 = H, R_2 = OH, R_3 = R_4 = Me$ (b) $R_1 = H, R_2 = OMe, R_3 = R_4 = Me$
(c) $R_1 = R_2 = OH; R_3 = R_4 = Me$ (d) $R_1 = H, R_2 = OH, R_3 = R_4 = Et$
(e) $R_1 = H, R_2 = OMe, R_3 = R_4 = Et$ (f) $R_1 = R_2 = OH; R_3 = R_4 = Et$
(g) $R_1 = H, R_2 = OH, R_3 = R_4 = Ph$ (h) $R_1 = H, R_2 = OH, R_3 = R_4 = Ph$
(i) $R_1 = R_2 = OH; R_3 = R_4 = Ph$



VI

(a) $R_1 = H, R_2 = OH, R = H$ (b) $R_1 = H, R_2 = OMe, R = H$
(c) $R_1 = R_2 = OH; R = H$ (d) $R_1 = H, R_2 = OH, R = Et$
(e) $R_1 = H, R_2 = OMe, R = Et$ (f) $R_1 = R_2 = OH; R = Et$
(g) $R_1 = H, R_2 = OH, R = Ph$ (h) $R_1 = H, R_2 = OMe, R = Ph$
(i) $R_1 = R_2 = OH; R = Ph$

In the present investigation we are going to present the synthesis of 3-(4′-hydroxy phenyl)-(IIa), 3-(4′-methoxy phenyl)-(IIb), and 3-(2′,4′-dihydroxy phenyl)-(IIc)-7-hydroxy isocoumarins by condensing 4-hydroxy homophthalic acid with phenol, anisole and resorcinol. The structural assignments of IIa–c (Table-1) were based on analogy to the earlier work[1]. Treatment of IIa–c with aqueous NaOH (10%) brought about opening of the lactone ring resulting in the formation of the corresponding 2-carboxy benzyl-phenyl ketones (IIIa–c) which could be cyclised back to IIa–c (Table-2).

TABLE-1
3-ARYL-7-HYDROXY ISOCOUMARINS (IIa–c)

Isocoumarin	m.p. (°C)	IR (cm^{-1})	UV (nm)	Mol. formula
IIa	226–27	3580, 1710, 1620	315, 270	$C_{15}H_{10}O_4$
IIb	201–02	3480, 1715, 1620	320, 275	$C_{16}H_{12}O_4$
IIc	235–36	3600, 3420, 1710, 1615	315, 280, 240	$C_{15}H_{10}O_5$

These isocoumarins gave satisfactory C and H analysis.

TABLE-2
ω-(2-CARBOXY-4-HYDROXY PHENYL)-ACETOPHENONES (IIIa–c)

Compound	m.p. (°C)	IR (cm^{-1})	Mol. formula
IIIa	170–71	3410, 1680, 1600, 1450	$C_{15}H_{12}O_5$
IIIb	159–60	1675, 1610, 1460	$C_{16}H_{14}O_5$
IIIc	189–90	1680, 1605, 1490	$C_{15}H_{12}O_6$

All the compounds gave satisfactory C and H analysis.

Reduction to IIIa–c with sodium borohydride in ethanol yielded the corresponding dihydro-isocoumarins (IVa–c) (Table-3). The isocoumarins (IIa–c) were then subjected to grignard reaction with methyl magnesium iodide, ethyl magnesium iodide and phenyl magnesium iodide to yield 1,1-dimethyl-, 1,1-diethyl and 1,1-diphenyl isochromenes (Va–i) (Table-4). The isocoumarins (IIa–c) were converted to the corresponding 1-(2-H)-isoquinolones, 1-(2-Et)-isoquinolones and 1-(2-Ph)-isoquinolones (VIa–i) (Table-5) with liquor ammonia, ethyl amine and aniline respectively.

TABLE-3
3-ARYL-3,4-DIHYDRO ISOCOUMARINS (IVa–c)

Compound	m.p. (°C)	IR (cm^{-1})	Mol. formula
IVa	109–10	1735, 1580	$C_{15}H_{12}O_4$
IVb	90–91	1710, 1460	$C_{16}H_{14}O_4$
IVc	119–20	1720, 1460, 1400	$C_{15}H_{12}O_5$

All the compounds gave satisfactory C and H analysis.

TABLE-4
3-ARYL-1,1-DIALKYL- AND 3-ARYL-1,1-DIARYL CHROMENES (Va–i)

Compound	m.p. (°C)	IR (cm^{-1})	Mol. formula
Va	190–91	1610, 1575, 1130	$C_{17}H_{16}O_3$
Vb	175–76	1620, 1570, 1120	$C_{18}H_{18}O_3$
Vc	220–21	1615, 1570, 1120	$C_{17}H_{16}O_4$
Vd	211–12	1605, 1560, 1100	$C_{19}H_{20}O_3$
Ve	205–06	1610, 1570, 1105	$C_{20}H_{22}O_3$
Vf	215–16	1620, 1570, 1120	$C_{19}H_{20}O_4$
Vg	229–30	1620, 1580, 1120	$C_{27}H_{20}O_3$
Vh	220–21	1610, 1570, 1110	$C_{28}H_{22}O_3$
Vi	219–20	1620, 1560, 1120	$C_{27}H_{20}O_4$

All the compounds gave satisfactory C and H analysis.

TABLE-5
3-ARYL-7-HYDROXY ISOQUINOLONES (VIa–i)

Compound	m.p. (°C)	N (%) Found	N (%) Calcd.	Mol. formula
VIa	250–51	5.52	5.57	$C_{15}H_{11}O_3N$
VIb	240–41	5.14	5.24	$C_{16}H_{13}O_3N$
VIc	274–76	5.12	5.20	$C_{15}H_{11}O_4N$
VId	260–61	4.90	4.98	$C_{17}H_{15}O_3N$
VIe	249–50	4.67	4.74	$C_{18}H_{17}O_3N$
VIf	270–71	4.66	4.71	$C_{17}H_{15}O_4N$
VIg	280–81	4.30	4.25	$C_{21}H_{15}O_3N$
VIh	287–88	4.00	4.08	$C_{22}H_{17}O_3N$
VIi	270–71	4.10	4.05	$C_{21}H_{15}O_4N$

All the compounds gave satisfactory C and H analysis.

EXPERIMENTAL

3-Aryl-7-hydroxy isocoumarins (IIa–c)

4-Hydroxy homophthalic acid (1 mol) and phenolic compound (1.1) mol were heated with polyphosphoric acid (8 parts) at 130–40°C for 1.5 h in a glycerol bath. The reaction mixture was poured into crushed ice with stirring and left for few hours. The precipitated solid that separated was filtered and subjected to steam distillation to drive away the unreacted phenolic compound. The crude product was suspended in aqueous sodium carbonate, allowed to stand for few hours, filtered, washed with water, dried and recrystallised from ethyl acetate-pet ether (60–80°C) to give II.

ω-(2′-carboxy-4′-hydroxy phenyl)-acetophenones (IIIa–c)

Isocoumarin (II) (0.01 mol) was refluxed with aqueous sodium hydroxide (50 mL, 10%) for 40 min and acidified with ice-cooled HCl. The solid that separated was filtered, washed with water and crystallised from ethanol to give colourless crystals of (III).

The keto acids (IIIa–c) could be cyclodehydrated to the original isocoumarins (IIa–c) by heating under reflux with hydrochloric acid (1 : 1).

3-Aryl-7-hydroxy-3,4-dihydro isocoumarins (IVa–c)

Compound III (0.003 mol) dissolved in methanol (25 mL, 10%) was treated with sodium borohydride (0.065 g) in small portions at room temperature. After the completion of the addition, the reaction mixture was kept overnight and acidified with HCl. The precipitate was filtered, washed with water and crystallised from ethanol to give IV.

3-Aryl-7-hydroxy-1,1-dialkyl/diphenyl isocoumarins (Va–i)

A solution of 3-aryl-7-hydroxy isocoumarins (IIa–c) (0.5–0.6 g) in dry benzene (30–40 mL) was gradually added to the solution of methyl magnesium iodide, [magnesium (0.2–0.3 g) and methyl iodide (1–1.2 g) in ether-benzene (10 mL + 15 mL)]; ethyl magnesium iodide [magnesium (0.2–0.3 g) and ethyl iodide (1.2–1.5 g) in ether-benzene (10 mL + 15 mL) and phenyl magnesium iodide [magnesium (0.25–0.35 g) and iodobenzene (1.0–1.5 g) in ether-benzene (10 mL + 15 mL)] respectively at room temperature with stirring, maintaining complete anhydrous condition. After removal of the ether, the mixture was refluxed overnight on a water bath. It was cooled and poured into crushed ice and dilute hydrochloric acid. Benzene and aqueous layer was separated and aqueous benzene layer and benzene extract were mixed, washed with water and dried over anhydrous sodium sulphate. Most of the benzene was evaporated and rest was left to crystallise. It was again recrystallised from pet ether-ethyl acetate to give (Va–i).

3-Aryl-7-hydroxy isoquinolones (VIa–i)

A solution of 3-aryl-7-hydroxy isocoumarins (IIa–c) (0.5 g) in ethanol (30 mL) was refluxed with liquor ammonia (15–20 mL), ethyl amine (8–10 mL) and aniline (5–10 mL) separately for 3 to 6 h on a water bath. The reaction mixture was left overnight. The solid that separated was treated with dilute hydrochloric acid, filtered and recrystallised from ethanol to give (VIa–i).

RESULTS AND DISCUSSIONS

All the solvents were purified by the standard methods[6]. Structures were assigned on the basis of elemental analysis, mixed melting point and electronic spectral studies. IR spectra (KBr) were recorded on a Perkin-Elmer 577 spectrophotometer and UV-visual spectra were recorded on Chemito-2100. m.pts. were recorded in open capillary tube and are uncorrected.

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