Synthesis of Tropolone Derivatives

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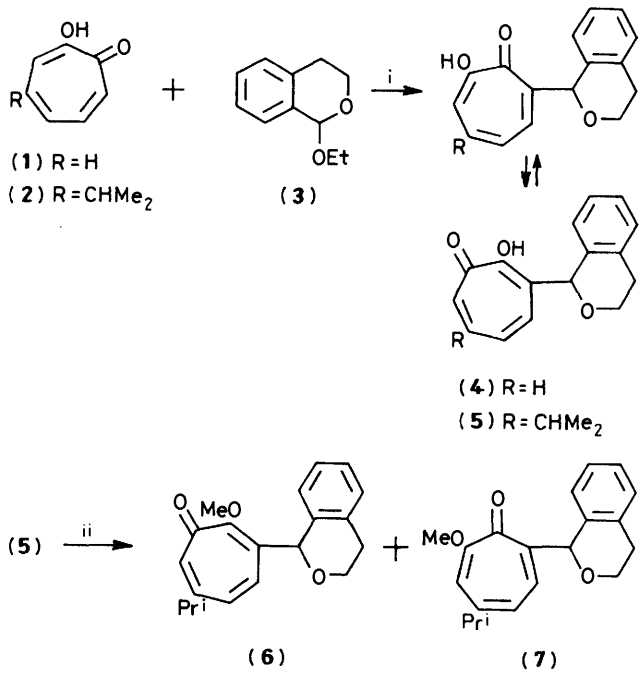
The reaction of tropolones with the benzaldehyde diethyl acetals (**10**) afforded the 3-(α-ethoxybenzyl)tropolones (**11**) and α,α-bis(2-hydroxy-1-oxocyclohepta-2,4,6-trien-3-yl)toluenes (**12**).

Although tropolones (2-hydroxycyclohepta-2,4,6-trien-1-ones) are known to be reactive towards electrophilic reagents, they do not undergo Friedel–Crafts alkylation. Therefore, only certain alkyltropolones can be prepared from tropolones; for example, 3-allyl- and 3-benzyl-tropolones were prepared by the thermal rearrangement of 2-allyloxy- and 2-benzyloxy-tropones.[1] In the course of a search for a new antitumour agent, we have developed a new convenient method for the direct alkylation of tropolones using acetals. Our previous finding, that the reaction of 1-ethoxyisochroman (**3**) with electron-rich compounds such as phenols or heterocyclic compounds gives the corresponding isochroman-1-yl derivatives,[2] suggested that it might also react with tropolones. Treatment of compound (**3**) with 4-isopropyltropolone (**2**)[3] (hinokitiol, β-thujaplicin), which occurs naturally in plants of the *Chamaecyparis* species, at 150—160 °C gave 3-isochroman-1-yl-6-isopropyltropolone (**5**). The structure of (**5**) was established on the basis of chemical and spectroscopic evidence, as follows.

Treatment of the tropolone (**5**) with diazomethane followed by chromatographic separation gave two structural isomers (**6**) and (**7**) having the same molecular formula, $C_{20}H_{22}O_3$. The n.m.r. spectra of compounds (**6**) and (**7**) each show a methoxy signal, at δ 4.04 and 4.02 respectively. In order to elucidate which position of the tropolone ring of (**5**), (**6**), or (**7**) binds to the isochroman-1-yl group, the n.m.r. data of these compounds were compared with those of the known tropolone derivatives, 3-isopropyl-7-methoxytropone (**8**)[4] and 4-isopropyl-2-methoxytropone (**9**),[4] which were prepared by treatment of hinokitiol (**2**) with diazomethane (Table 1). The isochromanyl group was shown to be attached to the 7-position in the tropolone in compounds (**5**) and (**7**) by the characteristic low-field signal [δ 7.50 (*J* 9 Hz) for (**5**) and δ 7.47 (*J* 9 Hz) for (**7**)]; this was assigned to 8-H of the isochromanyl group which would be deshielded by the neighbouring carbonyl group of the tropone ring in such an arrangement. An *X*-ray crystallographic analysis of compound (**6**) confirmed this assignment and indicated the structure to be 3-isochroman-1-yl-6-isopropyl-2-methoxytropone. Consequently, the structures of (**5**) and (**7**) were established to be 3-isochroman-1-yl-6-isopropyltropolone and 7-isochroman-1-yl-4-isopropyl-2-methoxytropone, respectively.

Similarly, 3-isochroman-1-yltropolone (**4**) was prepared by the reaction of tropolone (**1**) with ethoxyisochroman (**3**). Compound (**3**), which can be considered to be the intramolecular diethyl acetal of benzaldehyde, seemed to have a similar reactivity to benzaldehyde diethyl acetal. Indeed, hinokitiol (**2**) on treatment with benzaldehyde diethyl acetal (**10a**) at 150—160 °C gave 3-(α-ethoxybenzyl)-6-isopropyltropolone (**11a**) and α,α-bis(2-hydroxy-6-isopropyl-1-oxocyclohepta-2,4,6-trien-3-yl)toluene (**12a**) in 22 and 16% yields, respectively. When the reaction temperature was raised to 180 °C, only (**12a**) was obtained in 34% yield. Similarly, some analogues, (**11b—e**) and (**12b—e**), with a substituent on the benzene ring, were prepared. The yields and physical data are collected in Tables 2—4.



Scheme 1. *Reagents:* i, heat; ii, CH_2N_2

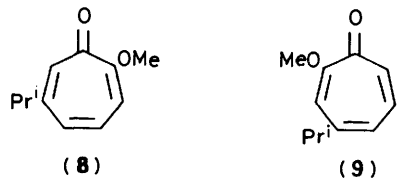
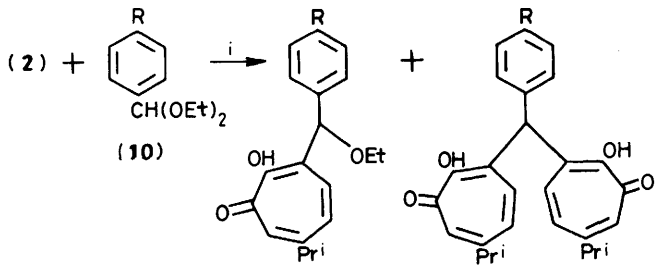


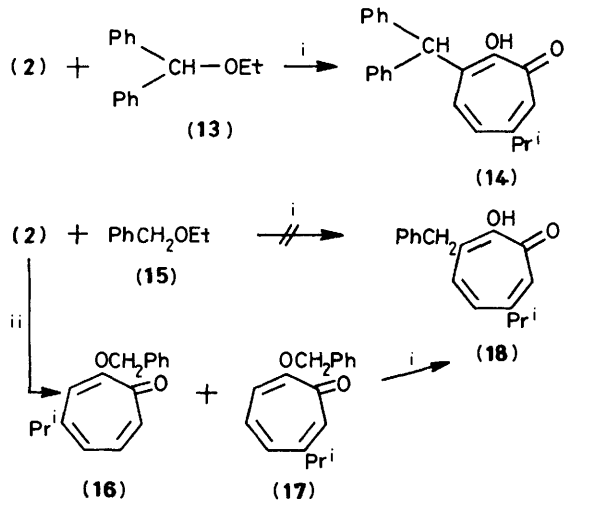
Table 1. N.m.r. chemical shifts of the aromatic protons of the tropolones (**4**)—(**9**)

Compound	δ($CDCl_3$)
(**4**)	6.73—7.71 (8 H, m)
(**5**)	6.79—7.40 (6 H, m), 7.50 (1 H, d, *J* 9 Hz)
(**6**)	6.70—7.30 (7 H, m)
(**7**)	6.65—7.30 (6 H, m), 7.47 (1 H, d, *J* 9 Hz)
(**8**)	6.60—7.10 (3 H, m), 7.24 (1 H, s)
(**9**)	6.70—7.12 (2 H, m), 7.15—7.37 (2 H, m)

The limitations of this direct alkylation of tropolones using acetals were examined and it was found that aliphatic acetals such as phenylacetaldehyde diethyl acetal, heterocyclic acetals such as α-ethoxytetrahydropyran, and ketone acetals such as benzophenone diethyl acetal do not react with tropolones. The



Scheme 2. *Reagents:* i, heat



Scheme 3. *Reagents:* i, heat; ii, $PhCH_2OH$–DCC

reaction of hinokitiol (**2**) with benzhydryl ethyl ether gave 3-benzhydryl-6-isopropyltropolone (**14**) in 12.5% yield, while the analogous reaction with benzyl ethyl ether (**15**) did not take place. The preparation of 3-benzyl-6-isopropyltropolone (**18**) was achieved by the thermal rearrangement of benzyloxytropone according to the method of Takeshita *et al.* The reaction of hinokitiol (**2**) with *O*-benzyl-*N*,*N*-dicyclohexylisourea at 100 °C afforded a mixture of 2-benzyloxy-4-isopropyltropone (**16**) and 7-benzyloxy-3-isopropyltropone (**17**) in 78% yield, which was converted into (**18**) when heated at 190 °C in decalin.

The antitumour activities of the compounds prepared here will be reported elsewhere.

Experimental

M.p.s are uncorrected. N.m.r. spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as the internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 spectrometer.

3-*Isochroman*-1-*yltropolone* (**4**).—A mixture of tropolone (**1**) (1.3 g, 10 mmol) and 1-ethoxyisochroman (**3**) (2.9 g, 16 mmol) was heated at 150—160 °C for 16 h under argon. The reaction mixture was chromatographed on silica gel with light petroleum (b.p. 40—60 °C)–ethyl acetate (4:1) as eluant to give the *product* (**4**) [1.3 g, 46% based on (**1**)], m.p. 175—178 °C (from benzene) (Found: C, 75.4; H, 5.5. $C_{16}H_{14}O_3$ requires C, 75.57; H, 5.55%); $\delta_H(CDCl_3)$ 2.53—3.51 (2 H, m, 4′-H_2), 3.80—4.45 (2 H, m, 3′-H_2), 6.66 (1 H, s, 1′-H), 6.73—7.71 (7 H, m, ArH), and 9.30 (1 H, br s, OH); *m*/*z* 254 (M^+).

3-*Isochroman*-1-*yl*-6-*isopropyltropolone* (**5**).—A mixture of hinokitiol (**2**) (5 g, 30 mmol) and compound (**3**) (8 g, 45 mmol) was heated at 150—160 °C for 6 h under argon. Recrystallization of the resulting precipitate from ethyl acetate–light petroleum (1:8) afforded the *product* (**5**) (5.9 g, 66% based on hinokitiol), m.p. 135—138 °C (Found: C, 76.7; H, 6.9. $C_{19}H_{20}O_3$ requires C, 77.00; H, 6.80%); $\delta_H(CDCl_3)$ 1.23 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.50—3.50 (3 H, m, 4′-H_2 and C*H*Me$_2$), 3.80—4.45 (2 H, m, 3′-H_2), 6.62 (1 H, s, 1′-H), and 9.30 (1 H, br s, OH); *m*/*z* 296 (M^+).

3-*Isochroman*-1-*yl*-6-*isopropyl*-2-*methoxytropone* (**6**) *and* 7-*Isochroman*-1-*yl*-4-*isopropyl*-2-*methoxytropone* (**7**).— Excess of a solution of diazomethane in diethyl ether was added to a suspension of (**5**) (1.5 g, 5 mmol) in diethyl ether (200 ml). After being left overnight, the remaining diazomethane was decomposed with acetic acid. The ether layer was washed with saturated aqueous potassium hydrogen carbonate and water and evaporated to dryness. The residue was chromatographed on silica gel with light petroleum–ethyl acetate (6:1) as eluant. The first elution gave the *product* (**6**) (0.75 g, 48%), m.p. 130—132 °C (from ethyl acetate–light petroleum) (Found: C, 77.1; H, 7.1. $C_{20}H_{23}O_3$ requires C, 77.39; H, 7.14%); $\delta_H(CDCl_3)$ 1.25 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.50—3.60 (3 H, m, 4′-H_2 and C*H*Me$_2$), 3.70—4.57 (2 H, m, 3′-H_2), 4.04 (3 H, s, OMe), and 6.45 (1 H, s, 1′-H); *m*/*z* 310 (M^+). The second elution gave *compound* (**7**) (0.65 g, 42%), m.p. 96—97 °C [from cyclohexane–benzene (4:1)] (Found: C, 77.4; H, 7.2. $C_{20}H_{23}O_3$ requires C, 77.39; H, 7.14%); $\delta_H(CDCl_3)$ 1.25 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.50—3.60 (3 H, m, 4′-H_2 and C*H*Me$_2$), 3.70—4.57 (2 H, m, 3′-H_2), 4.02 (3 H, s, OMe), and 6.57 (1 H, s, 1′-H); *m*/*z* 310 (M^+).

Crystal Data for the Tropone (**6**).—The crystal was monoclinic, space group $2_1/n$, $Z = 4$, $a = 14.601$ (1), $b = 13.427$ (1), $c = 9.139$ (1) Å, $\beta = 108.40$ (1)°, $U_o = 1\,700.28$ (35) Å^3, $D_c = 1.212$ g/cm^3. The reflection data were collected on a Rigaku four-circle diffractometer using graphite monochromated Cu-K_α radiation.

Intensities of reflections with 2θ values to 135° were collected by the ω–2θ scan method with a 2θ scan rate of 2° min^{-1}. The background was measured at each end of the scan range for 10 s.

2 349 Reflections were used as data [$F_O \geq 3.0\sigma(F_O)$], and corrected for Lorentz and polarization factor but not for absorption and extinction factors.

The atomic scattering factors used in the calculations were taken from the International Tables for *X*-Ray Crystallography.[5]

Determination of the Structure of Compound (**6**).—The structure was solved by the direct phase determination using the symbolic addition procedure.[6]

Reaction of Hinokitiol (**2**) *with Benzaldehyde Diethyl Acetal* (**10a**) *at* 150—160 °C. *Typical Procedure*—A mixture of benzaldehyde diethyl acetal (**10a**) (4.7 g, 24 mmol) and hinokitiol (**2**) (3.2 g, 20 mmol) was heated at 150—160 °C for 5 h under argon. The reaction mixture was chromatographed on silica gel with light petroleum–ethyl acetate (20:1) to give 3-(α-ethoxybenzyl)-6-isopropyltropolone (**11a**) (1.3 g, 22% based on hinokitiol) as a viscous oil. A second elution with light petroleum–ethyl acetate (5:1) gave α,α-bis(2-hydroxy-6-isopropyl-1-oxocyclohepta-2,4,6-trien-3-yl)toluene (**12a**) (0.7 g, 16% based on hinokitiol), m.p. 199—200 °C (from methanol).

Table 2. Reaction of hinokitiol (**2**) with benzaldehyde diethyl acetals (**10**)

Acetal	Amount of (**2**) [moles relative to (**10**)]	Temp. (°C)	Time (h)	Yield (%) (**11**)	(**12**)
(**10a**)	1:1.2	150—160	6	12	7
(**10a**)	1:1.2	180	6	0	34
(**10b**)	1:1.2	150—160	6	18	19
(**10b**)	1:1.2	180	6	1	37
(**10c**)	1:1.2	150—160	6	31	15
(**10c**)	2:1	180	2	0	34
(**10d**)	1:1.2	150—160	6	8	0
(**10d**)	1:1.2	180	6	11	25
(**10e**)	1:1.2	150—160	6	11	0
(**10e**)	2:1	180	2	0	31

Table 3. 3-(α-Ethoxybenzyl)-6-isopropyltropolones (**11**)

Compound	M.p. (°C)	Formula	Found (%) (Required) C	H	N	δ(CDCl$_3$–SiMe$_4$)
(**11a**)	Oil	$C_{19}H_{22}O_3$	76.5 (76.48)	7.5 (7.43)		1.24 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.25 (3 H, t, *J* 7 Hz, CH$_2$*Me*), 2.8—3.2 (1 H, m, C*H*Me$_2$), 3.58 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 6.12 (1 H, s, CH), 6.9—7.7 (7 H, m, ArH), 7.95 (1 H, d, *J* 11 Hz, ArH), 9.26 (1 H, br, OH)
(**11b**)	Oil	$C_{20}H_{24}O_3$	76.9 (76.89)	7.8 (7.74)		1.20 (3 H, t, *J* 7 Hz, CH$_2$*Me*), 1.38 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.29 (3 H, s, Me), 2.6—3.2 (1 H, m, C*H*Me$_2$), 3.51 (2 H, q, *J* 7 Hz, *CH*$_2$Me), 5.97 (1 H, s, CH), 6.7—7.6 (6 H, m, ArH), 7.84 (1 H, d, *J* 11 Hz, ArH), 8.7—9.3 (1 H, br, OH)
(**11c**)	Oil	$C_{20}H_{24}O_4$	73.3 (73.14)	7.5 (7.37)		1.30 (3 H, t, *J* 7 Hz, CH$_2$*Me*), 1.30 (6 H, d, *J* Hz, CH*Me*$_2$), 2.5—3.2 (1 H, m, C*H*Me$_2$), 3.58 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 3.80 (3 H, s, OMe), 6.08 (1 H, s, CH), 6.7—7.6 (6 H, m, ArH), 8.05 (1 H, d, *J* 11 Hz, ArH), 9.35 (1 H, br, OH)
(**11d**)	Oil	$C_{19}H_{21}ClO_3$	68.4 (68.57)	6.4 (6.32)		1.22 (3 H, t, *J* 7 Hz, CH$_2$*Me*), 1.30 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.52 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 6.00 (1 H, s, CH), 6.6—7.6 (6 H, m, ArH), 7.84 (1 H, d, *J* 11 Hz, ArH), 9.3 (1 H, br, OH)
(**11e**)	72—73	$C_{21}H_{27}NO_3$	74.1 (73.83)	7.95 (7.97)	4.0 (4.10)	1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.30 (3 H, t, *J* 7 Hz, CH$_2$*Me*), 2.5—3.1 (1 H, m, C*H*Me$_2$), 2.81 (6 H, s, NMe$_2$), 3.55 (2 H, q, *J* 7 Hz, *CH*$_2$Me), 6.01 (1 H, s, CH), 6.5—7.7 (6 H, m, ArH), 8.05 (1 H, d, *J* 11 Hz, ArH), 9.22 (1 H, br, OH)

Table 4. α,α-Bis(2-hydroxy-6-isopropyl-1-oxocyclohepta-2,4,6-trien-3-yl)toluenes (**12**)

Compound	M.p. (°C)	Formula	Found (%) (Required) C	H	N	δ(CDCl$_3$–SiMe$_4$)
(**12a**)	199—200	$C_{27}H_{28}O_4$	77.8 (77.86)	6.8 (6.78)		1.27 (12 H, d, *J* 7 Hz, 2 CH*Me*$_2$), 2.5—3.2 (2 H, m, 2 C*H*Me$_2$), 6.76 (1 H, s, CH), 6.8—7.4 (11 H, m, ArH), 9.53 (2 H, br, OH)
(**12b**)	231—233	$C_{28}H_{30}O_4$	78.2 (78.10)	7.1 (7.04)		1.28 (12 H, d, *J* 7 Hz, 2 CH*Me*$_2$), 2.37 (3 H, s, Me), 2.5—3.2 (2 H, s, 2 C*H*Me$_2$), 6.65 (1 H, s, CH), 6.7—7.5 (10 H, m, ArH), 9.3 (2 H, br, OH)
(**12c**)	204—205	$C_{28}H_{30}O_5$	75.4 (75.31)	6.75 (6.77)		1.30 (12 H, d, *J* 7 Hz, 2 CH*Me*$_2$), 2.5—3.2 (2 H, m, 2 C*H*Me$_2$), 3.58 (3 H, s, OMe), 6.56 (1 H, s, CH), 6.6—7.5 (10 H, m, ArH), 9.02 (2 H, br, 2 OH)
(**12d**)	227—228	$C_{27}H_{27}ClO_4$	71.7 (71.90)	6.0 (6.05)		1.14 (12 H, d, *J* 7 Hz, 2 CH*Me*$_2$), 2.4—3.2 (2 H, m, 2 C*H*Me$_2$), 6.62 (1 H, s, CH), 6.7—7.6 (10 H, m, ArH), 9.35 (2 H, br, 2 OH)
(**12e**)	224—226	$C_{29}H_{33}NO_4$	75.4 (75.79)	7.25 (7.24)	2.9 (3.05)	1.32 (12 H, d, *J* 7 Hz, 2 CH*Me*$_2$), 2.98 (6 H, s, NMe$_2$), 2.5—3.2 (2 H, m, 2 C*H*Me$_2$), 6.62 (1 H, s, CH), 6.7—7.6 (10 H, m, ArH), 8.0—9.2 (2 H, br, 2 OH)

Reaction of Hinokitiol (**2**) *with Benzaldehyde Diethyl Acetal* (**10a**) *at* 180 °C. *Typical Procedure.*—A mixture of hinokitiol (3.2 g, 16 mmol) and benzaldehyde diethyl acetal (**10a**) (3.5 g, 19 mmol) was heated at 180 °C for 6 h under argon. The reaction mixture was chromatographed on silica gel with light petroleum–ethyl acetate (10:1) as eluant to give *compound* (**12a**) (1.5 g, 34% based on hinokitiol).

3-*Benzhydryl*-6-*isopropyltropolone* (**14**).—A mixture of hinokitiol (6.2 g, 37 mmol) and benzhydryl ethyl ether (8 g, 37 mmol) was heated at 180 °C for 20 h under argon. The reaction mixture was chromatographed on silica gel with light petroleum–ethyl acetate (20:1) to give *compound* (**14**) (1.2 g, 10%), m.p. 146—147 °C (from tetrahydrofuran) (Found: C, 83.75; H, 6.8. $C_{23}H_{22}O_2$ requires C, 83.60; H, 6.71%); δ_H(CDCl$_3$) 1.24 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.85 (1 H, m, C*H*Me$_2$), 6.34 (1 H, s, CH), 7.00—7.40 (13 H, m, ArH), and 9.40 (1 H, br s, OH); *m/z* 330 (M^+).

3-*Benzyl*-6-*isopropyltropolone* (**18**).—A mixture of benzyl alcohol (4.6 g, 43 mmol) and dicyclohexylcarbodi-imide (DCC) (8.8 g, 43 mmol) was heated at 50—60 °C for 24 h in the presence of cuprous chloride (catalytic amount), and hinokitiol

(**2**) (7 g, 43 mmol) was added. The mixture was heated at 100 °C for 3 h and diluted with ethyl acetate. The resulting precipitate was filtered and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with light petroleum–ethyl acetate (20:1) as eluant to give a mixture of the isomers (8.4 g, 78%) 2-benzyloxy-4-isopropyltropone (**16**) and 7-benzyloxy-3-isopropyltropone (**17**) as a viscous oil (Found: C, 80.35; H, 7.1. $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13%); $\delta_H(CDCl_3)$ [for (**16**) or (**17**), 50% of mixture] 1.25 (6 H, d, *J* 7 Hz, $CHMe_2$), 2.40—3.10 (1 H, m, $CHMe_2$), 5.13 (2 H, s, OCH_2Ph), and 6.50—7.60 (9 H, m, ArH); $\delta_H(CDCl_3)$ [for (**16**) or (**17**), 50% of mixture] 1.11 (6 H, d, *J* 7 Hz, $CHMe$), 2.40—3.10 (1 H, m, $CHMe_2$), 5.18 (2 H, s, OCH_2Ph), and 6.50—7.60 (9 H, m, ArH).

A solution of the mixture of isomers (**16**) and (**17**) in decalin (50 ml) was heated at 190 °C for 12 h and the solvent was removed to dryness. The residual oil was chromatographed on silica gel with light petroleum–ethyl acetate as eluant to give *compound* (**18**) (0.6 g, 5% based on hinokitiol), m.p. 63—65 °C (from methanol) (Found: C, 80.05; H, 7.06. $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13%); $\delta_H(CDCl_3)$ 1.25 (6 H, d, *J* 7 Hz, $CHMe_2$), 2.55—3.40 (1 H, m, $CHMe_2$), 4.16 (2 H, s, CH_2Ph), 6.80—7.50 (4 H, m, ArH and OH), and 7.32 (5 H, s, Ph).

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