Synthesis of Some Tetrahydronaphthyl- and Flavanyl-coumarins

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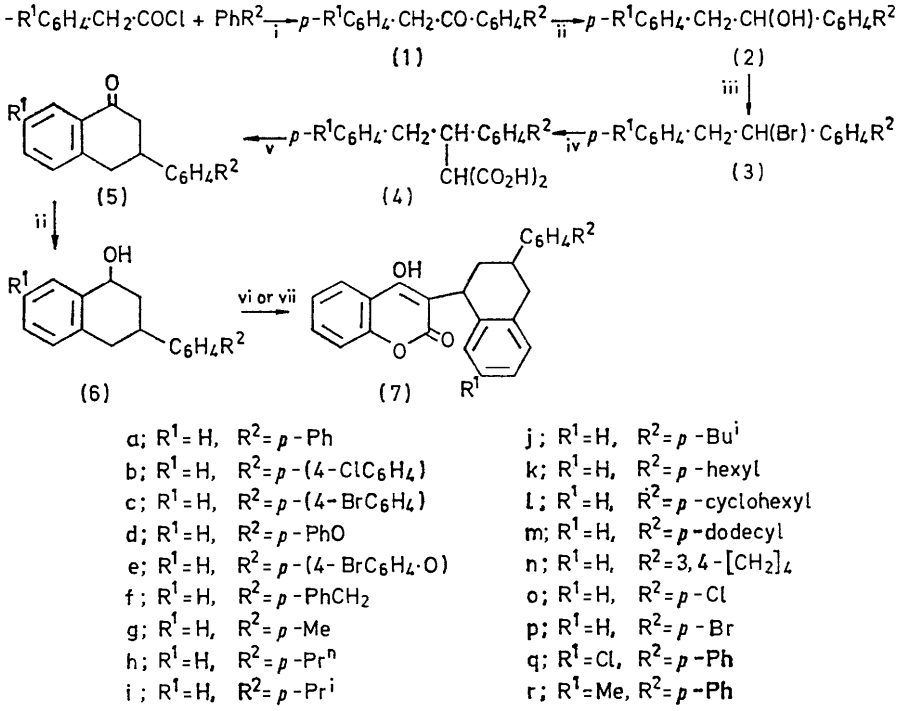
The synthesis is described of a number of 3-[3-(*p*-substituted phenyl)-1.2.3.4-tetrahydro-1-naphthyl]-4-hydroxycoumarins (7) and 3-(4'-substituted flavan-4-yl)-4-hydroxycoumarins (17), many of which show outstanding activity as anticoagulants against both Warfarin-sensitive and Warfarin-resistant rats. The final stage in the syntheses involves the reaction of either 3-(*p*-substituted phenyl)-1.2.3.4-tetrahydro-1-naphthols (6) or 4'-substituted flavan-4-ols (16) with 4-hydroxycoumarin to give the products (7) or (17). respectively. as mixtures of stereoisomers.

A NUMBER of 3-[3-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarins have been reported recently,[1-4] many of which show outstanding activity against both Warfarin-sensitive and Warfarin-resistant rats. The syntheses of these and related compounds are described below.



a; R^1 = H, R^2 = *p*-Ph
b; R^1 = H, R^2 = *p*-(4-ClC$_6$H$_4$)
c; R^1 = H, R^2 = *p*-(4-BrC$_6$H$_4$)
d; R^1 = H, R^2 = *p*-PhO
e; R^1 = H, R^2 = *p*-(4-BrC$_6$H$_4$·O)
f; R^1 = H, R^2 = *p*-PhCH$_2$
g; R^1 = H, R^2 = *p*-Me
h; R^1 = H, R^2 = *p*-Pr^n
i; R^1 = H, R^2 = *p*-Pr^i
j; R^1 = H, R^2 = *p*-Bu^i
k; R^1 = H, R^2 = *p*-hexyl
l; R^1 = H, R^2 = *p*-cyclohexyl
m; R^1 = H, R^2 = *p*-dodecyl
n; R^1 = H, R^2 = 3,4-[CH$_2$]$_4$
o; R^1 = H, R^2 = *p*-Cl
p; R^1 = H, R^2 = *p*-Br
q; R^1 = Cl, R^2 = *p*-Ph
r; R^1 = Me, R^2 = *p*-Ph

SCHEME 1 Reagents: i, $AlCl_3$; ii, $NaBH_4$; iii, PBr_3; iv, $NaCH(CO_2Et)_2$, -OH; v, polyphosphoric acid; vi, 4-hydroxycoumarin; vii, PBr_3,4-hydroxycoumarin

The ketones (1) (Scheme 1) were readily prepared by treatment of a suitable aromatic compound with the appropriate phenylacetyl chloride under Friedel–Crafts conditions, and were reduced to the corresponding alcohols (2) with sodium borohydride. The alcohols (2) on treatment with phosphorus tribromide gave the bromoethanes (3) which, although unstable, on heating with diethyl sodiomalonate followed by hydrolysis, afforded the malonic acids (4) in moderate yields, together with alkali-insoluble products. In the cases where the alkali-insoluble products were investigated, they were identified as substituted stilbenes (8)—(10).

The malonic acids (4) could be decarboxylated by heating to 200 °C to give the corresponding butyric acids (11)—(13). Heating the malonic acids (4) or the derived butyric acids with polyphosphoric acid gave the dihydronaphthalenones (5). Although this cyclisation

p-RC$_6$H$_4$·CH : CHPh	RC$_6$H$_4$·CH(CH$_2$·CO$_2$H)·CH$_2$Ph
(8) R = Ph	(11) R = *p*-PhO
(9) R = *p*-ClC$_6$H$_4$	(12) R = *p*-(4-BrC$_6$H$_4$·O)
(10) R = Cl	(13) R = 3.4-[CH$_2$]$_4$

could give rise to either 3-(*p*-substituted phenyl)-3,4-dihydronaphthalen-1(2*H*)-ones or 3-(*p*-substituted benz-

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[3] M. R. Hadler, R. Redfern, and F. P. Rowe, *J. Hygiene*, 1975, **4**. 441.
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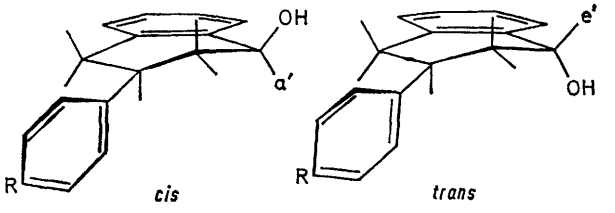
yl)indan-1-ones, it has been shown [5] that in reactions of this type six-membered rings are formed in preference to five-membered rings. Also, the carbonyl stretching bands in the i.r. spectra of the products occurred at *ca.* 1 680 cm^{-1}, characteristic of 3,4-dihydronaphthalen-1(2*H*)-ones [6] (the corresponding absorption for substituted indanones occurs at *ca.* 1 720 cm^{-1}).

Reduction of the dihydronaphthalenones (5) with sodium borohydride afforded the tetrahydronaphthols (6), which may exist as *cis*- or *trans*-isomers. It has been suggested [7,8] that reduction of 3,4-dihydro-3-phenylnaphthalen-1(2*H*)-one (5; $R^1 = R^2 = H$) by metal hydride gives *cis*-1,2,3,4-tetrahydro-3-phenyl-1-naphthol (6; $R^1 = R^2 = H$). In 1,2,3,4-tetrahydro-3-phenyl-1-naphthols, the alicyclic ring is assumed to be held in a half-chair conformation with the 3-substituent occupying an equatorial position (Figure).



FIGURE

In the ^1H n.m.r. spectrum of 3-(*p*-bromophenyl)-1,2,3,4-tetrahydro-1-naphthol (6p) ($CDCl_3$; after D_2O exchange) the 1-H signal occurs as an apparent quartet centred at τ 5.1 with a width of 17 Hz. If the 1-H is pseudo-axial, the width of the quartet [8,9] will be the sum of an axial–axial and an axial–equatorial coupling, that is *ca.* 16 Hz, whereas if the 1-H is pseudo-equatorial the width will be the sum of an equatorial–axial and an equatorial–equatorial coupling, that is *ca.* 7 Hz. This suggests that the 1-H is pseudo-axial and that the configuration in the compound is 1,3-*cis*.

The ^1H n.m.r. spectrum [$(CD_3)_2SO$] of 3-(biphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthol (6a) obtained by reduction of 3-(biphenyl-4-yl)-3,4-dihydronaphthalen-1(2*H*)-one (5a) with sodium borohydride shows the 1-H signal as a singlet with $W_{\frac{1}{2}}$ *ca.* 20 Hz (τ 5.2), whereas the 1-H band in the spectrum of the tetrahydro-1-naphthol (6a) obtained by reduction with aluminium isopropoxide appears as a singlet with $W_{\frac{1}{2}}$ *ca.* 12 Hz (τ 5.25). The $W_{\frac{1}{2}}$ values [9,10] of the 1-H absorptions suggests the former product to be the 1,3-*cis*-isomer, and, although the value for the latter is slightly high, since the two products are isomers the latter must be the 1,3-*trans*-isomer.

In these ^1H n.m.r. spectra, the OH absorption occurs as a doublet centred at τ 6.62 (J 6.5 Hz) for the *cis*-isomer and as a doublet at τ 6.84 (J 5 Hz) for the *trans*-isomer. Since it has been shown [11] that in substituted cyclohexanols an axial OH signal occurs at higher field (τ 0.21—0.27) than that of an equatorial OH, and that the coupling constant between the 1-OH and 1-H is greater for the isomer where the OH is equatorial, this substantiates the proposed assignments.

By analogy, the remaining 3-substituted 1,2,3,4-tetrahydro-1-naphthols (6), prepared by reduction with sodium borohydride, are probably *cis*-isomers.

3-Benzyl-4-hydroxycoumarins may be prepared [12,13] by heating substituted benzyl alcohols or halides with 4-hydroxycoumarin. The tetrahydronaphthylcoumarins (7) were prepared by heating the tetrahydronaphthols (6) with 4-hydroxycoumarin at 160—170°, or by conversion of the tetrahydronaphthol (6) into the corresponding 1-bromotetrahydronaphthalene with phosphorus tribromide, followed by treatment with 4-hydroxycoumarin at 130—140 °C. The former reaction results in the formation of larger amounts of by-products, and in both cases the purified products (7) are mixtures (t.l.c.) of two components believed to be *cis*- and *trans*-isomers. In the cases of 3-[3-(biphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin (7a) and 3-[3-(4'-chlorobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin (7b), the respective isomers were isolated by chromatography and gave satisfactory elemental analyses and almost identical u.v. spectra.

The product (7a), obtained by heating *cis*- or *trans*-3-(biphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthol (6a) with 4-hydroxycoumarin, contained approximately equal quantities of the two isomers (R_F 0.55 and 0.65 on silica in chloroform), whereas conversion of either the *cis*- or the *trans*-tetrahydronaphthol (6a) into the bromo-compound and subsequent treatment with 4-hydroxycoumarin gave a product consisting predominantly of one isomer (R_F 0.55).

The ^1H n.m.r. spectrum of one isomer (R_F 0.55) in $CDCl_3$ shows the 1-H signal as a double doublet centred at τ 4.89. The couplings are 6 and 11 Hz, hence the 1-H is axial. This isomer is therefore assigned the *cis*-configuration (*cf.* Figure). The spectrum of the other isomer (R_F 0.65) in $CDCl_3$ shows the 1-H signal as a triplet centred at τ 4.78 with J *ca.* 4 Hz. This indicates that the 1-H is equatorial and hence the isomer has the *trans*-configuration (*cf.* Figure).

The major by-product from the reaction of 3-(biphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthol (6a) with 4-hydroxycoumarin was isolated and identified as 2-(biphenyl-4-yl)-1,2-dihydronaphthalene, resulting from dehydration. The major by-products from the syntheses of the other tetrahydronaphthylcoumarins (7) and flavanylcoumarins (17) are probably the analogous 2-substituted 1,2-dihydronaphthalenes or flav-3-enes.

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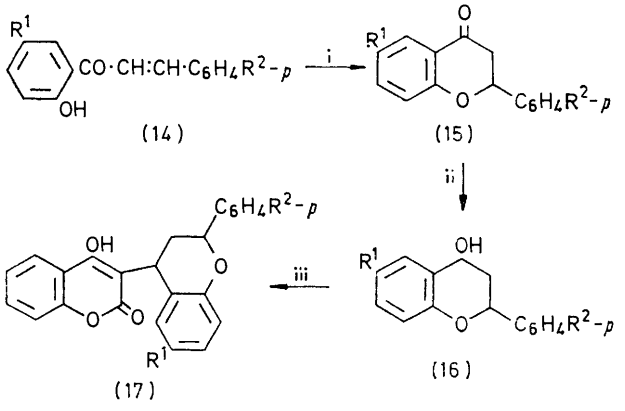
[13] H. R. Hudson, *Synthesis*, 1969, 112.

The chalcones (14) (Scheme 2), prepared by alkali-catalysed condensations of appropriately substituted acetophenones and benzaldehydes, rearranged on heating with sodium acetate in ethanol to give the flavan-4-ones (15). Reduction of the flavan-4-ones (15) with sodium borohydride gave the flavan-4-ols (16), believed to have the *cis*-configuration (i) by analogy with the tetrahydro-1-naphthols, and (ii) because reduction of flavan-4-one with sodium borohydride has been reported [14] to yield *cis*-flavan-4-ol. Treatment of the flavan-4-ols (16) with 4-hydroxycoumarin gave the flavanylcoumarins (17) as mixtures (t.l.c.) of two components which are believed to be *cis*- and *trans*-isomers.



a; R^1 = H, R^2 = H c; R^1 = H, R^2 = Cl
b; R^1 = H, R^2 = Ph d; R^1 = Cl, R^2 = Ph

SCHEME 2 Reagents: i, NaOAc; ii, $NaBH_4$; iii, 4-hydroxycoumarin

EXPERIMENTAL

T.l.c. was carried out on Merck silica gel (5 554) or on Merck alumina (5 550) and the products were detected by using a u.v. lamp. Column chromatography was carried out on Merck silica gel 60 (7 734) or on B.D.H. neutral alumina. 'Chloroform' as used for chromatography contained 1% ethanol. ^1H N.m.r. spectra were recorded with a Varian A-60 or HA-100 spectrometer with tetramethylsilane as internal standard. I.r. spectra were recorded for Nujol mulls with a Unicam SP 200 spectrophotometer (NaCl optics). U.v. spectra were recorded for solutions in methanol with a Unicam SP 800 spectrophotometer. Yields quoted are those before recrystallisation, and those for solid products obtained from oils are overall yields from the previously characterised intermediate. Products which are described as oils consisted largely of one component (t.l.c.) and were used directly in subsequent reactions. M.p.s are of analytically pure samples. Analytical data for new compounds were within accepted limits for C and H, and are available as Supplementary Publication No. SUP 21714 (4 pp.).†

Ketones (1).—The ketones (1a),[15] (1d),[16] (1f),[17] (1g),[18] (1j),[19] (1m),[20] (1n),[17] (1o),[21] (1p),[22] (1r),[23] were prepared by literature methods.

General Procedure.—Aluminium chloride (0.52 mol) was added in portions to a stirred mixture of the phenylacetyl chloride (0.5 mol), the aromatic compound (0.5 mol), and dichloromethane (300 ml) below 10 °C. The mixture was stirred for 16 h, then added to ice–hydrochloric acid, and extracted with chloroform; the extract was washed (H_2O), dried, and evaporated to give the *product* (Table 1).

TABLE 1

Ketones (1)

Product	Yield (%)	Recryst. solvent [a]	M.p. (°C)
(1b)	65	A	172—173
(1c)	51	A	180—183
(1e)	57	B	118—121
(1h)	86	C	56—59
(1i)	73	D	36—38
(1k)	73	C	54—57
(1l)	81	E	107—109
(1q)	70	F	191—194

[a] A, EtOAc; B, EtOH; C, hexane; D, light petroleum (b.p. 40—60°); E, light petroleum (b.p. 80—100°); F, HOAc.

Alcohols (2).—Sodium borohydride (0.5 mol) was added in portions with stirring to a suspension of the ketone (1) (0.5 mol) in ethanol (500 ml). The clear solution (if necessary the solution was heated to 60 °C until clear) was stirred for 1 h, diluted with water, and extracted with chloroform. The extract was washed (H_2O), dried, and evaporated, and the solid was collected with light petroleum and/or recrystallised to give the 1-(p-*substituted phenyl*)-2-*phenylethanol* (Table 2).

Bromoethanes (3).—Phosphorus tribromide (0.25 mol) was added dropwise over 1 h to a solution of the alcohol (2) (0.5 mol) in dichloromethane (500 ml) below 10 °C. The solution was stirred for 2 h at 20 °C, then washed with ice–water, dried, and evaporated. In most cases the residue was used directly in the subsequent reaction owing to the unstable nature of the product. The 1-*bromo*-1-(p-*substituted phenyl*)-2-*phenylethanes* which were characterised were collected and recrystallised (Table 2). Two examples illustrate the instability of the bromoethanes. (i) In the synthesis of the malonic acids (4) a solid was obtained which was insoluble in dichloromethane–water. This solid was combined with that remaining at the end of the alkaline hydrolysis and was identified as the substituted stilbene resulting from dehydrobromination. The following were characterised: 4-phenylstilbene (8), m.p. 211—213° (lit.,[24] 209°); 4-(p-*chlorophenyl*)*stilbene* (9), m.p. 237—239° (Found: C, 82.45; H, 5.3. $C_{20}H_{15}Cl$ requires C, 82.55; H, 5.2%); 4-chlorostilbene (10), m.p. 125—127° (lit.,[25] 129°) (ii) an attempt to recrystallise 1-bromo-1-(4'-chlorobiphenyl-4-yl)-

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

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2-phenylethane (3b) from ethanol gave 1-(*4'-chlorobiphenyl-4-yl*)-1-*ethoxy*-2-*phenylethane*, m.p. 88—90° [from light petroleum (b.p. 80—100°)] (Found: C, 78.3; H, 6.1; Cl, 10.3. $C_{22}H_{21}ClO$ requires C, 78.5; H, 6.3; Cl, 10.5%).

Malonic Acids (4).—The bromoethane (3) (0.1 mol) was added to a solution prepared from sodium hydride (60%; 0.1 mol), dimethylformamide (80 ml), and diethyl malonate (0.1 mol), and the mixture was stirred at 90 °C for 16 h. Water and dichloromethane were added and the mixture was filtered. The dichloromethane layer was separated, washed (H_2O), dried, and evaporated. Sodium hydroxide (0.4 mol), water (200 ml), and ethanol (200 ml) were added to the residue and the mixture was heated on a steam bath for 6 h, while the ethanol distilled off. The mixture was filtered, acidified, and extracted with ethyl acetate, and the extract was washed (H_2O) and evaporated. The residue was collected with light petroleum (b.p. 60—80°) or recrystallised to give the [1-(p-*substituted phenyl*)-2-*phenylethyl*]*malonic acid* (Table 2).

3-(p-*Substituted phenyl*)-4-*phenylbutyric Acids*.—The (1-*p*-substituted phenyl-2-phenylethyl)malonic acid (4) was heated at 200 °C until evolution of carbon dioxide ceased.

3-p-*Phenoxyphenyl*-4-*phenylbutyric acid* (11) was obtained in 70% yield by chromatography on silica in chloroform (R_F 0.2); m.p. 105—106° [from light petroleum (b.p. 60—80°)] (Found: C, 79.1; H, 6.1. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.0%).

TABLE 2

Alcohols (2)				Bromoethanes (3)				Malonic acids (4)			
Product	Yield (%)	Recryst. solvent [a]	M.p. (°C)	Product	Yield (%)	Recryst. solvent [a]	M.p. (°C)	Product	Yield (%)	Recryst. solvent [a]	M.p. (°C) [f]
(2a)	98	A	107—108	(3a)	92	A	100—101	(4a)	75	B	199—201
(2b)	98	B	134.5—135.5	(3b)	80	D	105—107	(4b)	30		176—178
(2c)	80	A	141—143	(3c)	80	A	113—115	(4c)	39	B–E	187
(2d)	76	A	66—69	(3d)			(Oil)	(4d)	27	A–B	154—157
(2e)	99		82—83	(3e)	85	C	58—63	(4e)	70	A–B	176—178
(2f)			(Oil)	(3f)			(Oil)	(4f)	43	A–B	163—164
(2g)			(Oil) [b]	(3g)			(Oil)	(4g)	70	B	180
(2h)			(Oil)	(3h)			(Oil)	(4h)	68	A–B	173—174
(2i)	87	A	39	(3i)			(Oil)	(4i)	38	A–B	180
(2j)	89	A	66—70	(3j)			(Oil)	(4j)	51	A–B	170
(2k)			(Oil)	(3k)			(Oil)	(4k)	41		157—159
(2l)	95	C	80—83	(3l)	80	A	52—56	(4l)	50	A–B	189—190
(2m)	90	D	49—53	(3m)			(Oil)	(4m)	65	A–B	156—157
(2n)	72	E	47—48	(3n)			(Oil)	(4n)	35	A–B	180—181
(2o)	70	A	50—52.5 [c]	(3o)			(Oil)	(4o)	53		168—170
(2p)			(Oil) [b]	(3p)			(Oil)	(4p)	70	A–B	172—173
(2q)	97		129—130.5	(3q)	90	A	115	(4q)	58	F	172—174
(2r)			(Oil)	(3r)	80		127—128	(4r)	60	A–B	162

[a] A, light petroleum (b.p. 80—100°); B, EtOAc; C, hexane; D, light petroleum (b.p. 60—80°); E, light petroleum (b.p. 40—60°); F, C_6H_6. [b] Lit. m.p. 69—70° (D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, 1968, **90**, 3794). [c] Lit. m.p. 52.5—53.6° (A. Feldstein and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1954, **76**, 1626). [d] Decomposed with CO_2 evolution.

TABLE 3

Dihydronaphthalenones (5)						Tetrahydronaphthols (6)			
Product	Yield (%)	R_F [a]	Recryst. solvent [a]	M.p. (°C)	ν_{CO}/cm^{-1}	Product	Yield (%)	Recryst. solvent [a]	M.p. (°C)
(5a)	80	(A,B) 0.9	F	92—94	1 675	(6a)	60	K	159
(5b)	55	(A,C) 0.5		155—157	1 675	(6b)	95		150—152
(5c)	46		D–G	156—158		(6c)	71	K	149—152
(5d)	*b*	(S,D) 0.6		(Oil)		(6d)	49	F	80—82
(5e)	21 [b]	(S,D) 0.4	F–H	136—138	1 675	(6e)	77		79—82
(5f)		(S,D) 0.4		(Oil)		(6f)			(Oil)
(5g)	36	(S,D) 0.5	J	92		(6g)	26	J	92
(5h)		(S,D) 0.5		(Oil)		(6h)	30	F	114—115
(5i)		(S,D) 0.5		(Oil)	1 680	(6i)	14	G	99—101
(5j)		(S,D) 0.5		(Oil)	1 685	(6j)	21	G	103—106
(5k)		(A,D) 0.8		(Oil)		(6k)	37	J	65—66
(5l)	25	(S,D) 0.5	I	111—113	1 675	(6l)	94	F	108—112
(5m)	79			37—40	1 690	(6m)	89	M	66—70
(5n)	*b*	(S,D) 0.8		(Oil)		(6n)			(Oil)
(5o)		(A,E) 0.2		99—105	1 675	(6o)	44	F	101—102.5
(5p)	60	(A,E) 0.3	E	127—130	1 675	(6p)	82	F	104—108
(5q)		(S,D) 0.5		(Oil)		(6q)	10	F–L	161—162
(5r)	12	(A,D) 0.7	D–G	138—140	1 670	(6r)	65	K	165—166

[a] S, silica; A, alumina; B, CH_2Cl_2; C, CCl_2:CHCl; D, C_6H_6; E, CCl_4; F, light petroleum (b.p. 80—100°); G, light petroleum (b.p. 60—80°); H, EtOAc; I, hexane; J, light petroleum (b.p. 40—60°); K, EtOH; L, $CHCl_3$; M, MeOH. [b] Prepared by cyclisation of the 3-(*p*-substituted phenyl)-4-phenylbutyric acid.

3-[4-(*p*-Bromophenoxy)phenyl]-4-phenylbutyric acid (12) was obtained as a gum and used without purification.

4-*Phenyl*-3-(5,6,7,8-*tetrahydro*-2-*naphthyl*)*butyric acid* (13) was obtained (73%) by chromatography on silica in ethyl acetate (R_F 0.89); m.p. 91.5° [from light petroleum (b.p. 80—100°)] (Found: C, 81.2; H, 7.9. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%).

Dihydronaphthalenones (5).—The malonic acid (4) or the derived butyric acid [(11)—(13)] and polyphosphoric acid (5 parts by weight) were stirred at 160—170 °C for 1 h. The mixture was cooled to 100 °C and toluene was added,

followed cautiously by water. The toluene layer was separated, washed (H_2O), dried, and evaporated. The residue was purified by chromatography to give the 3-(p-*substituted phenyl*)-3,4-*dihydronaphthalen*-1(2H)-*one* (Table 3).

Tetrahydronaphthols (6).—The dihydronaphthalenones (5) were reduced with sodium borohydride in the same way as the ketones (1). The 3-(p-*substituted phenyl*)-1,2,3,4-*tetrahydro*-1-*naphthols* (Table 3) are believed to have the *cis*-configuration.

Tetrahydronaphthylcoumarins (7).—*Method A*. The tetrahydronaphthol (6) (20 mmol) and 4-hydroxycoumarin (20 mmol) were heated together at 160—170 °C for 1 h. The cooled residue was purified by chromatography on silica (eluant benzene and then chloroform). The initial fractions contained a by-product which, in the one case examined [in the preparation of the tetrahydronaphthylcoumarin (7a)], was identified as 2-(*biphenyl*-4-*yl*)-1,2-*dihydronaphthalene* (39%), m.p. 96—99° [from light petroleum (b.p. 80—100°)], R_F 0.93 (silica; benzene) (Found: C, 93.5; H, 6.6. $C_{22}H_{18}$ requires C, 93.6; H, 6.4%); τ [$CDCl_3$; 100 MHz] 2.34—3.20 (13 H, m, aromatic), 3.47 (1 H, q, $J_{3,4}$ 10, $J_{2,4}$ or $J_{4,5}$ 3 Hz, H-4), 4.00 (1 H, q, $J_{3,4}$ 10, $J_{2,3}$ 3.5 Hz, H-3), 6.10—6.42 (1 H, m, H-2), and 6.82—7.14 (2 H, m, H-1). Fractions containing two components having R_F 0.4—0.7 (silica; chloroform), and believed to be the *cis*- and *trans*-isomers, were evaporated to give the 3-[3-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin (Table 4).

TABLE 4

Tetrahydronaphthylcoumarins (7)

Product	Method	Yield (%)	R_F [a]	Recryst.[c] solvent	M.p. (°C)
(7a)	A	20	0.55, 0.65	A	215—217
(7b)	A	32	0.80, 0.70	A	233—237
(7c)	A	38	0.56, 0.65	A	228—230
(7d)	A	14	0.56, 0.61	B	200—201
(7e)	A	20	0.58, 0.67	A	199—201
(7f)	A	13	0.60, 0.67	C	75—85
(7g)	B	29	0.54, 0.61	A	169—170
(7h)	A	18	0.61, 0.67	D	102—106
(7i)	B	49	0.52, 0.58	D	100—104
(7j)	B	50	0.58, 0.62	D	164—167
(7k)	A	48	0.62, 0.67	D	109—111
(7l)	A	25	0.62, 0.67	A	170—174
(7m)	B	47	0.52, 0.58	D	110—111
(7n)	A	12	0.65	B	206—207
(7o)	B	36	0.1, 0.22 [b]	E	197—201
(7p)	B	37	0.51, 0.61	A	210—213
(7q)	A	23	0.42, 0.58	A	255—256
(7r)	A	11		A	230—232

[a] Silica; chloroform. [b] Silica; 1,1,2-trichloroethylene. [c] A, EtOAc; B, Me_2CO; C, light petroleum (b.p. 100—120°); D, light petroleum (b.p. 80—100°); E, Et_2O.

Method B. Phosphorus tribromide (7.4 mmol) was added dropwise to a stirred solution of the tetrahydronaphthol (6) (20 mmol) in dichloromethane (50 ml) below 10 °C. After 2 h the solution was washed (ice–water), dried, and evaporated. [In another experiment, the residue was recrystallised to give 3-(*biphenyl*-4-*yl*)-1-*bromo*-1,2,3,4-*tetrahydronaphthalene* (70%), m.p. 133—135° (decomp.) (from ethyl acetate) (Found: C, 72.55; H, 5.4. $C_{22}H_{19}Br$ requires C, 72.8; H, 5.3%).] 4-Hydroxycoumarin (20 mmol) was added to the residue and the mixture was heated at 140 °C for 0.3 h. The cooled residue was chromatographed on silica (chloroform) to give the *product* (Table 4).

Separation of the Isomers of Tetrahydronaphthylcoumarins (7).—(i) 3-[3-(*Biphenyl*-4-*yl*)-1,2,3,4-*tetrahydro*-1-*naphthyl*]-4-*hydroxycoumarin* (7a). The isomers were separated by preparative t.l.c. on silica (multiple development with benzene). The bands were extracted with ethyl acetate to give two isomers: (a) R_F 0.18 (silica; benzene), m.p. 228—229° (from ethyl acetate), $\lambda_{max.}$ 257 (ε 27 000) and 309 nm (12 300) (Found: C, 83.6; H, 5.4. $C_{31}H_{24}O_3$ requires C, 83.8; H, 5.4%); and (b) R_F 0.24 (silica; benzene), m.p. 200—202° (from ethyl acetate), $\lambda_{max.}$ 257 (ε 26 500) and 309 nm (12 300) (Found: C, 83.7; H, 5.5%).

(ii) 3-[3-(4′-*Chlorobiphenyl*-4-*yl*)-1,2,3,4-*tetrahydro*-1-*naphthyl*]-4-*hydroxycoumarin* (7b). The isomers were separated by column chromatography on silica [chloroform–1,1,2-trichloroethylene (1 : 1)] to give two isomers: (a) R_F 0.80 (silica; chloroform), m.p. 222—225° (from ethyl acetate), $\lambda_{max.}$ 265.5 (ε 41 800) and 308 nm (15 100) (Found: C, 77.5; H, 5.0. $C_{31}H_{23}ClO_3$ requires C, 77.8; H, 4.8%); and (b) R_F 0.70 (silica; chloroform), m.p. 233—234° (from ethyl acetate), $\lambda_{max.}$ 265.5 (ε 36 900) and 309 nm (14 100) (Found: C, 77.5; H, 5.1%).

2-*Hydroxy*-4′-*phenylchalcone* (14b).—*o*-Hydroxyacetophenone (8.8 g, 65 mmol), biphenyl-4-carbaldehyde (11.8 g, 65 mmol), ethanol (250 ml), and aqueous sodium hydroxide (50%; 40 ml) were stirred for 4 h, and the solution was acidified to give the *chalcone* (95%), m.p. 148—150° [from benzene–light petroleum (b.p. 80—100°)] (Found: C, 83.9; H, 5.2. $C_{21}H_{16}O_2$ requires C, 84.0; H, 5.3%).

5-*Chloro*-2-*hydroxy*-4′-*phenylchalcone* (14d) was obtained similarly (95%) from 5′-chloro-2′-hydroxyacetophenone; m.p. 120° [from light petroleum (b.p. 80—100°)] (Found: C, 75.1; H, 4.7. $C_{21}H_{15}ClO_2$ requires C, 75.4; H, 4.5%).

Flavan-4-ol (16a) was prepared by reduction of flavan-4-one with sodium borohydride and had m.p. 143—145° (lit.,[26] 146°).

4′-*Chloroflavan*-4-*ol* (16c).—4′-Chloroflavan-4-one [27] was reduced with sodium borohydride to give the *flavanol* (66%), m.p. 160—162° [from light petroleum (b.p. 100—120°)] (Found: C, 68.9; H, 5.2. $C_{15}H_{13}ClO_2$ requires C, 69.1; H, 5.0%).

4′-*Phenylflavan*-4-*ol* (16b).—2-Hydroxy-4′-phenylchalcone (20.6 g, 69 mmol), sodium acetate (6.4 g), and ethanol (475 ml) were heated under reflux for 16 h. The solution was evaporated and the residue partitioned between chloroform and water. The chloroform layer was separated and the solvent removed. Chromatography of the residue on alumina (benzene) gave crude 4′-phenylflavan-4-one (11.8 g, 39 mmol), which was reduced with sodium borohydride to give the *flavanol* (6.5 g, 31%), m.p. 173.5—175° (Found: C, 83.5; H, 5.8. $C_{21}H_{18}O_2$ requires C, 83.4; H, 6.0%).

Similarly 5-chloro-2-hydroxy-4′-phenylchalcone was converted into 6-*chloro*-4′-*phenylflavan*-4-*ol* (16d) (32%), m.p. 173—175° (from ethanol) (Found: C, 74.7; H, 5.1. $C_{21}H_{17}ClO_2$ requires C, 74.8; H, 5.1%).

Flavanylcoumarins (17).—The flavanol (16) and 4-hydroxycoumarin (equimolar amounts) were heated at 160—170° for 1 h, and the residue was chromatographed on silica (chloroform) to give, as mixtures of two components believed to be *cis*- and *trans*-isomers, the following: (a) 3-(4′-*chloroflavan*-4-*yl*)-4-*hydroxycoumarin* (17c) (25%),

[26] L. Bauer, A. J. Birch, and W. E. Hillis, *Chem. and Ind.*, 1954, 433.

[27] Peng Li Cheng, P. Fournari, and J. Tirouflets, *Bull. Soc. chim. France*, 1963, 2248.

m.p. 90—110° [from light petroleum (b.p. 100—120°)], R_F 0.49 and 0.61 (Found: C, 71.3; H, 4.6. $C_{24}H_{17}ClO_4$ requires C, 71.2; H, 4.3%); (b) 3-(6-*chloro*-4′-*phenylflavan*-4-*yl*)-4-*hydroxycoumarin* (17d) (25%), m.p. 230—232° (from ethyl acetate), R_F 0.41 and 0.51 (Found: C, 75.2; H, 4.6. $C_{30}H_{21}ClO_4$ requires C, 74.9; H, 4.4%).

3-(*Flavan*-4-*yl*)-4-*hydroxycoumarin* (17a).—Water (0.17 ml), sulphuric acid (0.45 ml), and flavan-4-ol (5.5 g, 23 mmol) were added to a stirred suspension of 4-hydroxycoumarin (4.0 g, 24 mmol) in acetic acid (12.5 ml) at 100 °C. After 0.5 h the mixture was diluted with water and extracted with ethyl acetate. The extract was washed (H_2O), dried, and evaporated. Chromatography of the residue on silica (chloroform) gave the *flavanylcoumarin* (0.74 g 8%), R_F 0.50, m.p. 178—180° [from light petroleum (b.p. 100—120°)] (Found: C, 77.7; H, 4.8. $C_{24}H_{18}O_4$ requires C, 77.8; H, 4.9%).

3-(4′-*Phenylflavan*-4-*yl*)-4-*hydroxycoumarin* (17b) was obtained similarly (11%), m.p. 207—210° (from ethyl acetate), R_F 0.41 and 0.51 (Found: C, 80.4; H, 5.1. $C_{30}H_{22}O_4$ requires C, 80.7; H, 5.0%).

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