Interaction of Grignard Reagents with Coumarins. Part I. Novel 1,4-Addition

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Ethyl-, isopropyl-, and cyclohexyl-magnesium bromide underwent 1,4-addition to 4-substituted coumarins, best in tetrahydrofuran, to yield 4,4-disubstituted 3,4-dihydrocoumarins. This novel mode of addition was encouraged by −/ substituents in the 4-position, discouraged by a 4-methyl group, unaffected by a 5-hydroxy-group, and not apparently subject to steric effects from the 4-substituent or the Grignard reagent. Methyl- and phenyl-magnesium bromide underwent normal 1,2-addition to the 4-substituted coumarins, except that exclusive 1,4-addition occurred with a 4-(2-pyridyl)coumarin.

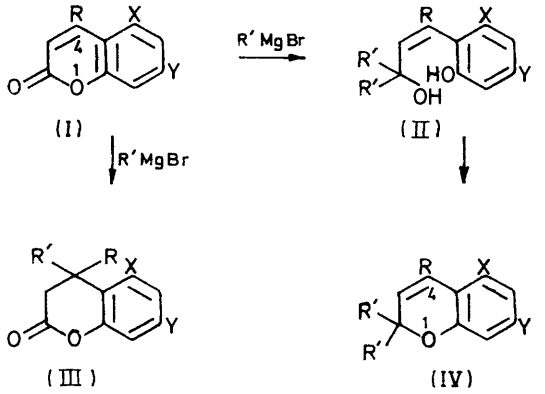
2*H*-CHROMENS were to be prepared by treating coumarins with Grignard reagents.[1,2] Thus 7-heptyl-5-hydroxy-4-(4-pyridyl)coumarin (Ia; R = 4-pyridyl) with ethylmagnesium bromide gave the diethyl carbinol (IIa; R = 4-pyridyl, R′ = Et), which readily cyclised in acetic acid to the required chromen (IVa; R = 4-pyridyl, R′ = Et). However, the yield of the carbinol was low, even though the coumarin had been consumed as evidenced by the disappearance of the characteristic i.r. absorption near 1700 cm^{-1}. A search for the reason led to the present study.

Strong absorption at 1760 cm^{-1} indicated a second product, evidently an αβ-saturated carbonyl compound, which was identified as the 4-ethyl-3,4-dihydro-4-(4-pyridyl)coumarin (IIIa; R = 4-pyridyl, R′ = Et) through its isolation as a methiodide, $C_{23}H_{29}NO_3$,MeI, and from the ^1H n.m.r. spectra of product and derivative. These last revealed an isolated ethyl group, a methylene (with non-equivalent hydrogen atoms) next to carbonyl, and the pyridyl and tetrasubstituted benzene features. With the methyl Grignard reagent, the original coumarin similarly gave a mixture, in which the presence of the 4-methyldihydrocoumarin (IIIa; R = 4-pyridyl, R′ = Me) was indicated by the i.r. absorption at 1760 cm^{-1}. Propylmagnesium bromide yielded solely the 3,4-dihydro-4-propylcoumarin (IIIa; R = 4-pyridyl, R′ = Pr), which was characterised as the methiodide.

This reaction of Grignard reagents with a 4-substituted coumarin to give 3,4-dihydrocoumarins appears to be novel. In particular, Heilbron and Hill[1] concluded that when the 4-position of the coumarin was occupied, the product was a 2*H*-chromen. Indeed in nearly all previously studied interactions with coumarins,[3] the first process encountered was 1,2-addition of Grignard reagent to the carbonyl group, this providing (after acid treatment) a good route to benzopyrylium salts.[4] Further interaction with an excess of Grignard reagent led either (as already mentioned) by 1,2-addition to 2,2-disubstituted chromens[1,2] (IV) (*via* ring-opening, and reclosure on work-up), or by 1,4-addition in the case of 3-substituted coumarins to 2,3,4-trisubstituted chroman-2-ols[3] (V). Only with 3-ethoxycarbonylcoumarins was direct 1,4-addition observed,[5] but here the

[1] I. M. Heilbron and D. W. L. Hill, *J. Chem. Soc.*, 1927, 2005.
[2] W. Bridge, A. J. Crocker, T. Cubin, and A. Robertson, *J. Chem. Soc.*, 1937, 1530; F. Bergel, A. Jacob, A. R. Todd, and T. S. Work, *ibid.*, 1938, 1375; A. R. S. Kartha and K. N. Menon, *Proc. Indian Acad. Sci.*, 1943, **18A**, 28.
[3] S. Wawzonek, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1951, vol. 2, pp. 204—208.
[4] R. Willstätter, L. Zechmeister, and W. Kindler, *Ber.*, 1924, **57**, 1938; R. Willstätter and O. T. Schmidt, *ibid.*, p. 1945.
[5] G. A. Holmberg, *Acta Chem. Scand.*, 1961, **15**, 1255; I. Renvall, *Acta Acad. Aboensis, Math. Phys.*, 1969. **29**, 1.

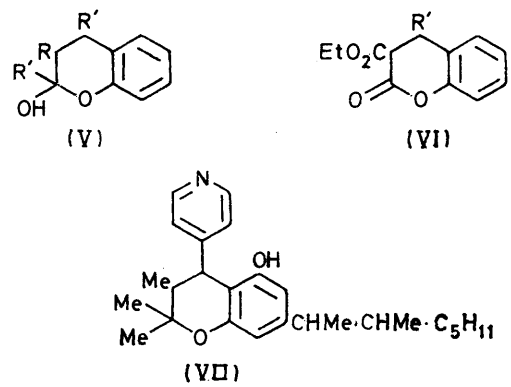
products (VI) were presumably formed through a cyclic transition state as in normal 1,4-addition to a



(I) (II) (III) (IV)

a; X = OH, Y = heptyl
b; X = OH, Y = Me
c; X = H, Y = Me
d; X = Y = H
e; X = OH, Y = CHMe·CHMe·C_5H_{11}, R = 4-pyridyl

simple αβ-unsaturated ester.[6] A 4-pyridylcoumarin (Ie) has been reported to undergo initial, double 1,2-addition



(V) (VI) (VII)

with the methyl Grignard reagent, and then when the reaction was continued at 100° for 48 h in anisole to yield, uniquely by 3-substitution, a 2,2,3-trimethyl-4-pyridylchroman [7] (VII).

Our new 1,4-additions to the 5-hydroxy-4-(4-pyridyl)-coumarin (Ia; R = 4-pyridyl), achieved under mild conditions, were at once reproducible. Using this coumarin and ethylmagnesium bromide in refluxing solvents, we found that the solvent influenced the course of reaction (Table 1), benzene–ether (3 : 1) and tetrahydrofuran favouring the 1,4-addition to the exclusion of double-1,2-addition, in spite of the use of an excess of the Grignard reagent. Because the 7-heptylcoumarins were slow to react, and the products were reluctant to crystallise and therefore difficult to isolate, or were inconveniently high-boiling for g.l.c. characterisation, further experiments were performed with 7-methylcoumarins (Ib). This change in turn necessitated using the better solvent, tetrahydrofuran. The Grignard reagent (as bromide) and the 4-substituent on the coumarin were varied, as indicated in Table 2,

TABLE 1

Reaction of the coumarin (Ia) [a] with ethyl Grignard reagent

Solvent	1,4-Addition to give (IIIa) [a] (%)	1,2-Addition to give (IIa) [a] (%)
Ether	8	22
3 : 1 Benzene–Ether	41	0
Tetrahydrofuran	38 [b]	0

[a] R = 4-pyridyl, R′ = Et. [b] Allowing for recovered coumarin.

TABLE 2

Modes of reaction of Grignard reagents with coumarins in tetrahydrofuran at ambient temperature (except where noted)

	Coumarin R	Grignard (R′MgBr) R′	1,4-Addition to give (III) (%)	1,2-Addition to give (II) (%)	(IV) (%)
(Ia)	4-pyridyl [a]	Me	Present		32
		Et	8	22	51 [b]
		Pr	38		
(Ib)	4-pyridyl	Me	0	75 (1) [c]	90 [b] (2)
		Et	77 (3)	9 (4)	
		Pr^i	60 (5)	13 (6)	
		Ph	0	76 (7)	80 [b] (8)
	2-pyridyl	Me	55 (9)	0	
		Et	64 (10)	0	
		Pr^i	70 (11)	0	
		Ph	73 (12)	0	
	3-pyridyl	Me	0	51 (13)	76 [b] (14)
		Et	60 (15)		9 (16)
		Pr^i	87 (17)	0	
		Cyclohexyl	73 (18)	0	
		Ph	7 (19)	71 (20)	90 [b] (21)
	Ph	Me	0		67 [b] (22)
		Et	80 (23)	0	
		Pr^i	72 (24)	0	
		Cyclohexyl	83 (25)	0	
		Ph	0	71 (26)	77 [b] (27)
	p-MeO·C_6H_4	Me	0		77 (28)
		Et	63 (29)	0	
		Pr^i	69 (30)	0	
		Cyclohexyl	79 (31)	0	
		Ph	0	79 (32)	83 [b] (33)
	Me	Me	0		66 (34)
		Et	No reaction [d]		
		Pr^i	No reaction [d]		
		Cyclohexyl	No reaction [d]		
		Ph	0		65 [e] (35)
(Ic)	4-pyridyl	Me	0		73 (36)
		Et	79 (37)	0	
		Pr^i	64 (38)	0	
		Cyclohexyl	74 (39)	0	
		Ph	0	51 (40)	
	Me	Me	0	87 (41)	85 [a] (42)
		Et	0	68 (43)	90 [a] (44)
		Pr^i	79 (45)	0	
		Cyclohexyl	0	72 (46)	85 [a] (47)
		Ph	0	72 (48)	81 [a] (49)

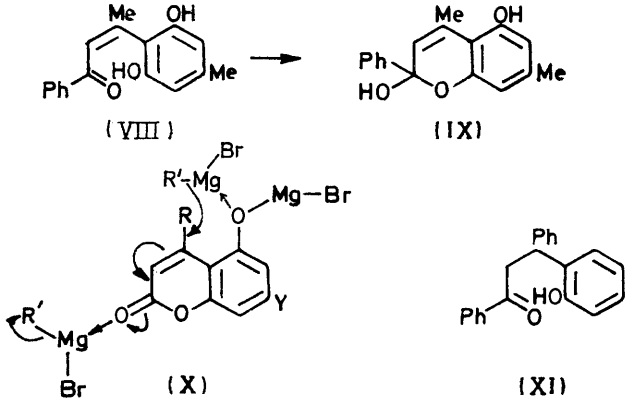
[a] In boiling diethyl ether or ether–benzene (see Experimental section). [b] Conversion yield from the carbinol (II). [c] No. of compound in Table 5. [d] Also under reflux. [e] Product isolated was the propenone (VIII) which on recrystallisation gave the chromen-2-ol (IX).

and all experiments were conducted at ambient temperature.

[6] J. Munch-Petersen, *Bull. Soc. chim. France*, 1966, 471; R. E. Lutz and W. G. Reveley, *J. Amer. Chem. Soc.*, 1941, **63**, 3178.

[7] R. K. Razdan, W. R. Thompson, H. G. Pars, and F. E. Granchelli, *Tetrahedron Letters*, 1967, 3405.

The results (Table 2) show that the course of interaction is affected also by the nature of the Grignard reagent, the 4-substituent on the coumarin ring, and to some extent the 7-substituent. Thus the change from 7-heptyl (Ia; R = 4-pyridyl) to -methyl (Ib; R = 4-pyridyl) gave much improved yields (at lower temperature) of 1,4-addition product from ethyl- and isopropyl-magnesium bromide but accompanied by some product from double 1,2-addition. The methyl and phenyl Grignard reagents usually differed from the others and did not undergo 1,4-addition. The main exceptions were their reactions with that coumarin with the most strongly electron-withdrawing, 2-pyridyl substituent at the 4-position. With this coumarin (Ib; R = 2-pyridyl), *only* 1,4-addition was encountered even with the phenyl reagent, for which steric hindrance to this mode of addition might have been expected. Results with the 4-(3-pyridyl)-, 4-phenyl-, and 4-*p*-methoxyphenyl-coumarins (Ib) resembled those for the 4-(4-pyridyl) cases, emphasising that all of these substituents exert no more than a moderate $-I$ effect at the coumarin 4-position: none can exert electromeric effects there. With the 4-methylcoumarin (Ib; R = Me), where a $+I$ effect is exerted at the 4-position, those alkyl Grignard reagents which had previously undergone 1,4-addition failed to react even under reflux, whilst the methyl reagent still afforded a good yield of the double 1,2-addition product (IVb; R = R′ = Me). The phenyl reagent, unexpectedly gave the mono-1,2-addition product (VIII), this phenolic propenone structure being indicated by i.r. absorptions at 3300 and 1691 cm^{-1}. Crystallisation at once effected cyclisation to the 2-phenylchromen-2-ol (IX).



To obtain further information, some reactions were performed with coumarins (Ic) which lacked the 5-hydroxy-group. Co-ordination of the reagent to the latter might have been responsible for promoting the novel 1,4-additions, as indicated in (X). This mechanism was evidently not operating, however, because the results with 7-methyl-4-(4-pyridyl)coumarin (Ic; R = 4-pyridyl) (see Table 2) were similar to those given by the 5-hydroxy-analogue (Ib; R = 4-pyridyl). Changing the 4-substituent to methyl, *i.e.* using 4,7-dimethylcoumarin (Ic; R = Me), promoted double 1,2-addition as expected, the ethyl and cyclohexyl Grignard reagents giving products (IIc) and (IVc) from that mode of addition, to the exclusion of 1,4-addition. However, isopropylmagnesium bromide still gave an excellent yield of the 1,4-addition product (IIIc; R = Me, R′ = Pr^i). The last two coumarins (Ic; R = 4-pyridyl) and (Ic; R = Me) were noticeably more soluble and faster to react than their 5-hydroxy-analogues (Ib). With coumarin itself (Id; R = H) under our conditions (see Table 3) the isopropyl and cyclohexyl Grignard reagents

TABLE 3

Modes of reaction of Grignard reagents with coumarin (Id; R = H) in tetrahydrofuran at ambient temperature

Grignard (R′MgBr) R′	1,4-Addition to give (IIId) (%)	1,2-Addition to give (%)	1,2- + 1,4-Addition to give (XI) (%)
Et	53 (50) [a]	(IVd) 13 (51)	0
Pr^i	94 (52)	0	0
Cyclohexyl	85 (53)	0	0
Ph	0	(IId) 48 (54)	13 (55)

[a] No. of compound in Table 5.

gave high yields of 1,4-addition products (IIId; R = H), whereas the ethyl reagent gave, as well, some product (IVd; R = H, R′ = Et) from double 1,2-addition. Although not so surprising in the present context, these 1,4-additions to coumarin nevertheless represent new findings. Shriner and Sharp [8] obtained from coumarin and the ethyl reagent in ether only the double 1,2-addition product (IVd; R = H, R′ = Et). Reinvestigation indicated that their finding was incomplete: a slight modification of the work-up led to isolation of both 1,4- (IIId) and double 1,2-addition products (IVd). The change from ether to tetrahydrofuran solvent in this case had then been without appreciable effect. From the phenyl Grignard reagent and coumarin in ether, Barnes *et al.*[9] obtained the double 1,2-addition product (IVd; R = H, R′ = Ph) together with a product from 1,2- plus 1,4-addition, namely 3-(2-hydroxyphenyl)-1,3-diphenylpropan-1-one (XI). These results we confirmed. When tetrahydrofuran was used, less of the second product resulted.

To summarise, the novel 1,4-addition of ethyl and higher alkyl Grignard reagents to coumarins is assisted somewhat by tetrahydrofuran solvent; 4-substituents on the coumarin appear to be without steric effect; and there is no directing effect from a 5-hydroxy-group. 4-Substituents which are $-I$ in type assist the 1,4-addition: a 4-methyl substituent ($+I$) distinctly discourages this mode of addition. The methyl Grignard reagent stands apart from its higher homologues, resembling the phenyl reagent in undergoing 1,2-addition. Only when the coumarin 4-substituent is 2-pyridyl do these two reagents undergo 1,4-addition, and then to the exclusion of the 1,2-mode. No steric effect of the Grignard reagent on the course of reaction

[8] R. L. Shriner and A. G. Sharp, *J. Org. Chem.*, 1939, **4**, 575.
[9] C. S. Barnes, M. I. Strong, and J. L. Occalowitz, *Tetrahedron*, 1963, **19**, 839.

was discerned. Reasons for the novel 1,4-additions are now being sought.

EXPERIMENTAL

Reactions were monitored by t.l.c. on Eastman silica gel plates (No. 6060), developed with ethyl acetate, chloroform, or benzene. For preparative chromatography, columns of silica gel MFC (100—200 mesh, Hopkin and Williams) (40 g per g of compound) were used. I.r. spectra (Nujol mulls or liquid films) were recorded with a Unicam SP 200 or Perkin-Elmer 137 instrument; only strong absorptions are noted. ^{1}H N.m.r. spectra ($CDCl_3$ solutions, or as specified, containing $SiMe_4$) were measured at 60 MHz using a Varian A60 or Perkin-Elmer R12 spectrometer.

Preparation of Coumarins.[10]—Concentrated sulphuric acid (50 ml) was added during 0·5 h to a stirred mixture of the resorcinol (or phenol) (0·1 mol) and the β-keto-ester [11] (0·1 mol) cooled in ice. Phosphoryl chloride (25 ml) was added in one portion and stirring continued at ambient temperature for 17 h. The liquid was poured slowly into saturated sodium hydrogen carbonate solution (70 ml) and ice (50 g), and the coumarin isolated by extraction into chloroform and evaporation. Known coumarins [12] had correct m.p.s and analyses, the new 4-pyridylcoumarins (Table 4) had $\nu_{max.}$ 1720 cm^{-1} (CO), and all had the expected ^{1}H n.m.r. characteristics.

TABLE 4

Coumarin (1b) R	Yield (%)	M.p. (°C)	Found (%) C	H	N
4-pyridyl	36	320—321	70·9	4·3	5·3 [a]
2-pyridyl	50	179—180	70·75	4·4	5·4 [a]
3-pyridyl	45	310—312	70·8	4·55	5·4 [a]
(1c) 4-pyridyl	20, 60 [b]	149—150	75·7	4·75	5·65 [c]

[a] $C_{15}H_{11}NO_3$ requires C, 71·1; H, 4·3; N, 5·5%. [b] By omitting the $POCl_3$ and heating at 55° for 3 days. [c] $C_{15}H_{11}NO_2$ requires C, 75·9; H, 4·6; N, 5·9%.

Orcinol hydrate (1·7 g) and ethyl *p*-anisoylacetate [13] (2·7 g) were stirred with phosphoryl chloride (10 ml) in benzene (20 ml) for 7 days. The suspension was then poured into water (35 ml) and the precipitate extractively crystallised from ethanol to give *5-hydroxy-4-p-methoxyphenyl-7-methylcoumarin* (2·1 g, 60%), m.p. 262—263° (Found: C, 72·1; H, 5·05. $C_{17}H_{14}O_4$ requires C, 72·3; H, 4·95%), $\nu_{max.}$ 1680 (CO), 1600, 1245, 1080, and 930 cm^{-1}.

Reactions of 7-Heptyl-5-hydroxy-4-(4-pyridyl)coumarin.—(a) *With ethylmagnesium bromide.* (i) The coumarin [14] (6·74 g, 0·02 mol), suspended in ether (50 ml), was added in portions during 0·5 h to ethylmagnesium bromide (0·06 mol) in ether (120 ml), and the mixture heated under reflux for 2 h. Addition of an excess of saturated aqueous ammonium chloride, extraction into ether, and evaporation, afforded *1,1-diethyl-3-(4-heptyl-2,6-dihydroxyphenyl)-3-(4-pyridyl)-prop-2-en-1-ol hydrate* (1·7 g, 22%), m.p. 161—162° (from carbon tetrachloride; the filtrate *A* was retained) (Found: C, 72·5; H, 8·6; N, 3·3. $C_{25}H_{35}NO_3,H_2O$ requires C, 72·3; H, 8·4; N, 3·3%), $\nu_{max.}$ 3300 (OH), 1602, 1280, 1050, 1020, and 830 cm^{-1}, τ 9·3—8·1 (complex, 2 × Et + C_6H_{13}), 7·54 (t, *J* 6·5 Hz, 4-CH_2 on C_6 ring), 6·0br (2 × OH), 3·64 (s, 3-, 5-H on C_6 ring), 3·48 (s, 2-H), 2·83 (dd, *J* 4·0 and 1·4 Hz, pyridyl 3-, 5-H), and 1·68 (dd, pyridyl 2-, 6-H).

(ii) By heating this diethylpropenol (0·3 g) in acetic acid (5 ml) under reflux for 1 h and pouring the solution into water (10 ml), *2,2-diethyl-7-heptyl-4-(4-pyridyl)-2H-chromen-5-ol hemihydrate* was obtained (0·15 g, 51%), m.p. 121—122° (from acetonitrile) (Found: C, 76·9; H, 8·6; N, 3·6. $C_{25}H_{33}NO_2,0·5H_2O$ requires C, 77·3; H, 8·7; N, 3·6%), τ 9·03br (3 × Me), 8·7br ($[CH_2]_5$), 8·20 [q, *J* 7 Hz, 2,2-$(CH_2)_2$], 7·5 (m, 7-CH_2), 5·42 (s, OH and H_2O), 4·45 (s, 3-H), 3·72 and 3·60 [s,s, 6-, 8-(8-,6-)H], 2·68 (dd, *J* 4·5 and 1·5 Hz, pyridyl 3-, 5-H), and 0·60 (dd, pyridyl 2-, 6-H).

(iii) The filtrate *A* [see (i)] was evaporated: t.l.c. showed a compound with $\nu_{max.}$ 1760 cm^{-1} and τ ($CDCl_3$) 9·13 and 9·08 (*ca.* t,t, 2 × Me at C-4, C-7), 8·8—8·1 (complex, C_5H_{10} at C-7), 8·5 (m, 4-CH_2 + 7-CH_2), 7·08br (s, 3-H_2), 3·47 (s, 6-, 8-H), 2·71 (m, pyridyl 3-, 5-H), and 1·67 (m, pyridyl 2-, 6-H). Treatment in acetone (10 ml) with an excess of methyl iodide gave *4-ethyl-7-heptyl-3,4-dihydro-5-hydroxy-4-(4-pyridyl)coumarin methiodide* (0·77 g, 8%), m.p. 247—249° (from ethanol) (Found: C, 56·3; H, 6·2; I, 25·2; N, 2·7. $C_{24}H_{32}INO_3$ requires C, 56·4; H, 6·3; I, 25·0; N, 2·8%), $\nu_{max.}$ 1745 (CO), 1650, 1622, 1580, and 1220 cm^{-1}, τ [$(CD_3)_2SO$] 9·13 (t, 2 × Me), 8·9—8·4 (complex, C_5H_{10} at C-7), *ca.* 7·45 (m, 4-, 7-CH_2), 6·89 (*ca.* ABq, 3-H_2), 5·66 (s, MeN^+), 3·47 (s, 6-, 8-H), 2·04 (*ca.* d, *J* 6·5 Hz, pyridyl 3-, 5-H), 1·15 (*ca.* d, pyridyl 2-, 6-H), and 0·6br (OH).

(iv) The coumarin (0·01 mol) in benzene (150 ml) was treated with the Grignard (0·1 mol) in ether (50 ml) as in (i) but with refluxing for 1 h. Heating the product with methyl iodide gave the 4-ethyl-4-pyridyldihydrocoumarin methiodide (2·1 g, 41%), m.p. and mixed m.p. 249—251°.

(v) Repetition of the preceding reaction, but with only tetrahydrofuran as solvent, afforded a gum that with ether yielded the starting coumarin (1·0 g, 30%). Evaporation of the filtrate and heating with methyl iodide then gave the dihydrocoumarin methiodide (1·85 g, 27%).

(b) *With methylmagnesium bromide.* The coumarin (0·06 mol) in benzene (400 ml) was treated with the Grignard (0·6 mol) in ether (400 ml), as in (a) (i) and (ii), to yield *7-heptyl-2,2-dimethyl-4-(4-pyridyl)-2H-chromen-5-ol hemihydrate* (6·76 g, 32%), m.p. 154—155° (from acetonitrile) (Found: C, 76·7; H, 8·35; N, 3·9. $C_{23}H_{29}NO_2,0·5H_2O$ requires C, 76·7; H, 8·3; N, 3·9%). The acetonitrile filtrate had $\nu_{max.}$ 1760 cm^{-1}.

(c) *With propylmagnesium bromide.* The coumarin (0·01 mol) in benzene (50 ml) was treated with the Grignard (0·1 mol) in ether (110 ml), as in (b) but with refluxing for 1 h. Heating the gum with methyl iodide afforded *7-heptyl-3,4-dihydro-5-hydroxy-4-propyl-4-(4-pyridyl)coumarin methiodide hemihydrate* (2·2 g, 38%), m.p. 277—279° (from aqueous ethanol) (Found: C, 56·5; H, 6·4; I, 25·2; N, 2·6. $C_{25}H_{34}INO_3,0·5H_2O$ requires C, 56·4; H, 6·6; I, 23·9; N, 2·6%), $\nu_{max.}$ 1750 (CO), 1660, 1630, 1585, 1220, and 1070 cm^{-1}, τ [$(CD_3)_2SO$] 9·3—8·2 (complex, Et of Pr + C_6H_{13}), *ca.* 7·5 (m, 4-, 7-CH_2), 6·88br (3-H_2), 6·29 (s, OH + H_2O), 5·67 (s, MeN^+), 3·46 (s, 6-, 8-H), 2·05 (*ca.* dd, *J* 6 Hz, pyridyl 3-, 5-H), and 1·18 (*ca.* dd, pyridyl 2-, 6-H).

Reactions of Coumarins with Grignard Reagents.—Preparation of reagent. To magnesium turnings (0·1 g atom) under

[10] *Cf.* H. von Pechmann and C. Duisberg, *Ber.*, 1883, **16**, 2119; S. Sethna and R. Phadke, *Org. Reactions*, 1953, **7**, 1.
[11] R. B. Moffet, *J. Medicin. Chem.*, 1964, **7**, 446.
[12] L. L. Woods and J. Sapp, *J. Org. Chem.*, 1962, **27**, 3703; J. N. Collie and E. R. Chrystall, *J. Chem. Soc.*, 1907, **91**, 1802 K. Fries and W. Klostermann, *Ber.*, 1906, **39**, 871.
[13] Neth. P. 6,404,841/1964 (*Chem. Abs.*, 1965, **62**, 16271f).
[14] B.P. 1,162,784/1968.

TABLE 5

Details of products listed in Tables 2 and 3

No.	M.p. (°C)	Solvent	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	ν(CO)/cm⁻¹ Nujol or film (f)	τ (3-H$_2$)	J_{gem}/Hz
				3,4-Dihydrocoumarins (IIIb)								
3	157—158	EtOAc	$C_{17}H_{17}NO_3$,-0·25H_2O	70·8 71·0	6·1 6·1	4·8 4·8	70·9	6·1	4·9		7·11br(s) [a]	
5	313—314	EtOAc–EtOH	$C_{18}H_{19}NO_3$	72·9	6·5	4·7	72·7	6·4	4·7		7·08, 6·79 [b] (ABq)	16
9	161—162	EtOAc	$C_{16}H_{15}NO_3$	71·0	5·7	5·1	71·4	5·6	5·2	1765	7·12, 6·72 [a] (ABq)	16
10	127—129	EtOAc	$C_{17}H_{17}NO_3$	71·9	6·1	4·9	72·1	6·0	4·9	1760	7·02, 6·80 [a] (ABq)	16
11	200—202	EtOAc	$C_{18}H_{19}NO_3$	72·5	6·6	4·7	72·7	6·4	4·7	1750	7·12, 6·82 [a] (ABq)	16
12	198—199	EtOAc	$C_{21}H_{17}NO_3$	76·5	5·2	4·2	76·15	5·2	4·2	1760	6·97, 6·57 [a] (ABq)	16·5
15	223—224	MeCN–H_2O	$C_{17}H_{17}NO_3$,-0·5H_2O	70·3	6·1	4·8	69·9	6·2	4·8	1775	6·92br(s) [b]	
17	300—301	Me_2SO–H_2O	$C_{18}H_{19}NO_3$	72·4	6·4	4·6	72·7	6·4	4·7	1770	7·03, 6·75 [b] (ABq)	17
18	306—307	EtOH	$C_{21}H_{23}NO_3$	74·3	6·9	4·0	74·7	6·8	4·1		7·04, 6·72 [b] (ABq)	16
19	272—273	EtOAc	$C_{21}H_{17}NO_3$,-0·25H_2O	74·9	5·3	4·1	75·1	5·2	4·2	1760	6·49br (s) [b]	
23	183—184	EtOAc	$C_{18}H_{18}O_3$	76·2	6·4		76·6	6·4		1740	7·20, 7·04 [a] (ABq)	16
24	154—155	C_6H_6	$C_{19}H_{20}O_3$	77·25	6·7		77·0	6·75		1720	7·10, 6·83 [b] (ABq)	16
25	204—205	C_6H_6	$C_{22}H_{24}O_3$	78·7	7·3		78·6	7·1		1760	7·19, 6·84 [a] (ABq)	16
29	153—154	Pet [c]–Et_2O	$C_{19}H_{20}O_4$	72·95	6·4		73·0	6·4		1760	7·20, 7·08 [a] (ABq)	16
30	158—159	EtOH–H_2O	$C_{20}H_{22}O_4$	73·5	7·0		73·6	6·8			7·22, 6·91 [a] (ABq)	16
31	148—149	EtOH–H_2O	$C_{23}H_{26}O_4$,-0·5H_2O	73·7	7·7		73·6	7·2		1735	7·22, 6·90 [a] (ABq)	17
				3,4-Dihydrocoumarins (IIIc)								
37	174—175	$CHCl_3$ [d]	$C_{17}H_{17}NO_2$	76·7	6·6	5·6	76·4	6·8	5·2	1760	7·70br (s) [a]	
38	165—166	MeCN	$C_{18}H_{19}NO_2$	76·55	6·5	4·75	76·8	6·8	5·0		7·19, 6·72 [a] (ABq)	16
39	70—71	$CHCl_3$ [d]	$C_{21}H_{23}NO_2$	78·1	7·4	4·1	78·5	7·2	4·3	1760	7·19, 6·70 [a] (ABq)	16
45	Oil	1 : 1-Pet [c]–C_6H_6 [d]	$C_{14}H_{18}O_2$	77·45	8·6		77·1	8·2		1770 (f)	7·72, 7·27 [e] (ABq)	16
				3,4-Dihydrocoumarins (IIId)								
50	Oil		$C_{11}H_{12}O_2$	75·0	7·1		75·0	6·8		1775 (f)	7·33br (s) [e]	
52	Oil	*f*	$C_{12}H_{14}O_2$	75·9	7·4		75·8	7·4		1765	7·28br (s) [e] (superimposed on 4-H)	
53	Oil	$CHCl_3$ [d]	$C_{15}H_{18}O_2$	78·3	8·1		78·3	7·8		1775 (f)	7·28br (s) [e] (superimposed on 4-H)	
				Prop-2-en-1-ols (IIb)						τ (2-H)		
1	199—200	MeCN–EtOH	$C_{17}H_{19}NO_3$	71·8	6·8	5·0	71·6	6·7	4·9	3·41 (s) [b]		
4	238—239	EtOAc	$C_{19}H_{23}NO_3$	73·1	7·4	4·5	72·8	7·3	4·5	3·60 (s) [b]		
6	223—225	EtOAc	$C_{21}H_{27}NO_3$	73·9	8·1	4·2	73·9	7·9	4·1	3·66 (s) [a]		
7	240—241	EtOH	$C_{27}H_{23}NO_3$,0·25H_2O	78·4	5·8	3·3	78·3	5·7	3·4	3·03 (s) [b]		
13	205—206	MeCN–H_2O	$C_{17}H_{19}NO_3$	71·5	6·7	4·8	71·6	6·7	4·9	3·67 (s) [b]		
20	316—318	Me_2CO–Pet [c]	$C_{27}H_{33}NO_3$,0·5H_2O	77·4	6·1	3·3	77·5	5·8	3·3	3·17 (s) [b]		
26	158—159	C_6H_6	$C_{28}H_{24}O_3$	82·2	6·0		82·3	6·0		2·70 (m) [a]	(superimposed on 15 × ArH)	
32	131—134	EtOH–H_2O										
				Propenols (IIc)								
40	156—158	MeCN–Et_2O	$C_{27}H_{23}NO_2$,-H_2O	78·7	6·3	3·15	79·0	6·1	3·4	3·45 (s) [a]		
41	105—106	Et_2O	$C_{13}H_{18}O_2$	75·9	8·65		75·8	8·7		4·20 (q, *J* 1·5 Hz) [a]		
43	89—90	Pet [c]	$C_{15}H_{22}O_2$	77·15	9·55		76·9	9·8		4·38 (q, *J* 1·5 Hz) [a]		
46	157—158	C_6H_6–Pet [c]	$C_{23}H_{34}O_2$	80·6	10·1		80·7	9·9		4·58 (m) [c]	(superimposed on 2 × OH)	
48	134—135	Me_2CO	$C_{23}H_{22}O_2$	83·3	6·8		83·6	6·7		3·54 (q, *J* 1·5 Hz) [a]		

TABLE 5 (*Continued*)

No.	M.p. (°C)	Solvent	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) M	τ (3-H)
			Chromens (IVb)							
2	259—260	EtOAc	$C_{17}H_{17}NO_2$	76·3	6·3	5·0	76·4	6·4	5·2	4·33 (s) [b]
8	275—276	EtOH–Me_2CO	$C_{27}H_{21}NO_2$	83·3	5·5	3·5	82·9	5·4	3·6	3·72 (s) [b]
14	202—203	MeCN	$C_{17}H_{17}NO_2$	76·1	6·4	5·4	76·4	6·4	5·2	4·38 (s) [b]
16	168—169	MeCN	$C_{19}H_{21}NO_2$,-$0·5H_2O$	75·25	7·15	4·8	75·0	7·2	4·6	4·52 (s) [a]
21	313—315	Ppt. from HOAc with H_2O [g]	$C_{27}H_{21}NO_2$,-H_2O	79·7	5·4	3·4	79·2	5·3	3·4	3·76 (s) [b]
22	119—120	Pet [c]	$C_{18}H_{18}O_2$	81·4	7·0		81·2	6·8		4·51 (s) [a]
27	170—171	Et_2O	$C_{28}H_{22}O_2$	86·2	5·9		86·1	5·6		
28	127—128	C_6H_6–Pet [c]	$C_{19}H_{20}O_3$	77·2	7·0		77·0	6·8		4·57 (s) [a]
33	152—153	Pet [c]	$C_{29}H_{24}O_3$	82·5	5·8		82·8	5·7		4·05 (s) [a]
34	94—95	Pet [c]	$C_{13}H_{16}O_2$	76·15	8·0		76·5	7·8		4·73 (s) [a]
			Chromen-2-ol (IX)							
35	155—156	Et_2O	$C_{17}H_{16}O_3$	76·4	6·2		76·1	6·0		3·28 (q, J 1·5 Hz) [a]
			Chromens (IVc)							
36	119—120	MeCN	$C_{17}H_{17}NO$	81·3	6·9	5·6	81·3	6·8	5·8	4·39 (s) [a]
42	Oil	Pet [c,d]	$C_{13}H_{16}O$	83·2	8·6		83·0	8·5		4·78 (q, J 1·5 Hz) [e]
44	Oil	Pet [c,d]	$C_{15}H_{20}O$	83·6	9·5		83·3	9·3		4·89 (q, J 1·0 Hz) [e]
47	114—115	Pet [c]	$C_{23}H_{32}O$	85·2	10·1		85·2	9·9		5·01 (q, J 1·0 Hz) [e]
49	84—85	C_6H_6 [d]	$C_{23}H_{20}O$	88·3	6·7		88·5	6·4		4·27 (q, J 1·5 Hz) [e]
			Chromen (IVd)							
51	Oil [h]	*f*	$C_{13}H_{16}O$	82·7	8·7		83·0	8·5		3·70 (d, J 9 Hz) [e]
			Propenol (IId)							
54	99—100 [i]	CCl_4								
			Propan-3-one (XI)							
55	168—170 [i]	Et_2O								

[a] In $CDCl_3$. [b] In $(CD_3)_2SO$. [c] Pet = light petroleum (b.p. 60—80°). [d] Column chromatography in stated solvent. [e] In CCl_4. [f] Separation by g.l.c. on 3% XE60 (General Electric Co.). [g] Washed with hot Me_2CO. [h] n_D^{21} 1·5428; R. L. Shriner and A. G. Sharp (*J. Org. Chem.*, 1939, **4**, 575) give n_D^{20} 1·5428. [i] C. S. Barnes, M. I. Strong, and J. L. Occalowitz (*Tetrahedron*, 1963, **19**, 839) give m.p. 98—99° for No. 54 and m.p. 168—169° for No. 55.

tetrahydrofuran (100 ml) and dry nitrogen, iodine (1 crystal) was added, followed by the alkyl (or aryl) bromide (few drops). Reaction began on warming. With stirring the bromide (0·1 mol) in tetrahydrofuran (10 ml) was added during 20 min, and stirring was continued for 20 min: methyl bromide was added as vapour carried in nitrogen.

Interaction of reagent and a coumarin. The coumarin (0·01 mol) in tetrahydrofuran (50 ml) was added to the stirred Grignard solution during 0·5 h. After 1 h, the mixture was poured slowly into saturated ammonium chloride solution (175 ml). The upper layer was separated and shaken with ether (2 × 150 ml). The extract was evaporated to small bulk and the residue extracted with ether (150 ml); the solution was dried ($MgSO_4$) and evaporated, and the residue chromatographed and/or crystallised. If no dihydrocoumarin or solid carbinol resulted, the following procedure was used.

Cyclisation with acid. The crude material (1 g) was boiled in acetic acid (5 ml) for 1 h and the solution poured into water (25 ml). Precipitates were collected; oils were taken into ether and the extract was washed (aq. $NaHCO_3$), dried ($MgSO_4$), and evaporated. The product was then chromatographed and/or crystallised.

Products. These are listed in Tables 2 and 3 with yields, starting coumarins, and the Grignard reagents. Table 5 lists m.p.s, solvents for crystallisation, and analytical results.

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