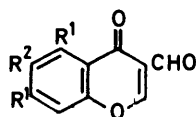


## Reactions of Formylchromone Derivatives. Part 2.<sup>1</sup> Addition Reactions of 3-(Aryliminomethyl)chromones

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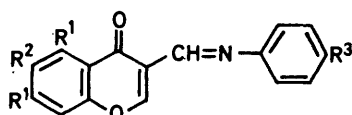
Whereas chromones are usually cleaved by amines, 3-(aryliminomethyl)chromones undergo nucleophilic addition with aromatic primary amines to give 2-amino-3-(aryliminomethylene)chroman-4-one derivatives. The 3-(aryliminomethyl) group also facilitates addition to the system of a variety of alcohols and thiols, and certain thiol adducts can be cyclised to thiazepine derivatives. The action of manganese dioxide on 3-(aryliminomethyl)chromones leads to 3-(aryliminomethylene)chroman-2,4-diones.

CHROMONES are usually readily ring-opened *via* nucleophilic attack at the 2-position.<sup>2</sup> We have recently shown,<sup>3</sup> however, that the presence of a 3-(aryliminomethyl) group alters the reactivity of the system towards



(1)

- a; R<sup>1</sup> = R<sup>2</sup> = H  
b; R<sup>1</sup> = H, R<sup>2</sup> = Me  
c; R<sup>1</sup> = Me, R<sup>2</sup> = H



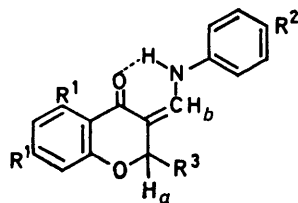
(2)

- a; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = Cl  
b; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = OMe  
c; R<sup>1</sup> = H, R<sup>2</sup> = Me, R<sup>3</sup> = OMe  
d; R<sup>1</sup> = Me, R<sup>2</sup> = H, R<sup>3</sup> = Cl

nucleophiles, and in certain cases facilitates nucleophilic ring addition rather than ring fission. Thus, interaction of 3-formylchromone (1a) and *p*-chloroaniline gave a

traces of moisture, for example, during chromatographic separations is sufficient to cause hydrolysis of the anil, and the resulting amine fragment adds to unchanged anil to re-form the adduct. A much improved yield of anil, virtually uncontaminated with adduct can, however, be obtained from condensation of the 3-formylchromone with the amine in the presence of toluene-*p*-sulphonic acid.

With aromatic primary amines, the anils gave stable crystalline adducts (see Table 1) possessing a characteristic u.v. absorption at *ca.* 385 nm. Non-aromatic secondary amines, *e.g.* dimethylamine and piperidine, also formed adducts (u.v. evidence) which were stable only in solution and which reverted to starting materials when the solutions were evaporated. No evidence was obtained for the occurrence of any reaction between the anils and aliphatic primary amines (*e.g.* *n*-propylamine) or aromatic secondary amines (*e.g.* *N*-methylaniline).

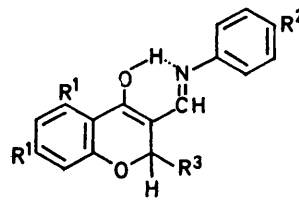


(3)

- a; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = *p*-NHC<sub>6</sub>H<sub>4</sub>Cl  
b; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = NHPh  
c; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = *p*-NHC<sub>6</sub>H<sub>4</sub>Me  
d; R<sup>1</sup> = H, R<sup>2</sup> = Me, R<sup>3</sup> = *p*-NHC<sub>6</sub>H<sub>4</sub>Me  
e; R<sup>1</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = *p*-NHC<sub>6</sub>H<sub>4</sub>OMe  
f; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = OPr<sup>1</sup>  
g; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = OMe  
h; R<sup>1</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = OMe  
i; R<sup>1</sup> = Me, R<sup>2</sup> = Cl, R<sup>3</sup> = OEt  
j; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = OCH<sub>2</sub>Ph

mixture of the anil (2a) and the 2-anilino-3-(anilino-methylene)chroman-4-one (3a), formed by addition of *p*-chloroaniline to the anil. We suggested<sup>3</sup> that the reason for this rather unusual ring-addition was the formation of the stable hydrogen-bonded ketoamine system<sup>4</sup> (3  $\rightleftharpoons$  4),† and this also explained the readiness with which the anils gave adducts with other amines, alcohols, and thiophenols.

The reaction between equimolar quantities of a chromone and an aromatic primary amine invariably leads to a mixture of the anil and the 1,4-adduct (3) and isolation of the pure anil is difficult. The presence of



(4)

- k; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SPh  
l; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = *p*-SC<sub>6</sub>H<sub>4</sub>Me  
m; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SPr<sup>n</sup>  
n; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SEt  
o; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SCH<sub>2</sub>Ph  
p; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SCH<sub>2</sub>CO<sub>2</sub>H  
q; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R<sup>3</sup> = SCH<sub>2</sub>CO<sub>2</sub>Et  
r; R<sup>1</sup> = Me, R<sup>2</sup> = Cl, R<sup>3</sup> = *p*-SC<sub>6</sub>H<sub>4</sub>Me  
s; R<sup>1</sup> = Me, R<sup>2</sup> = Cl, R<sup>3</sup> = *p*-SC<sub>6</sub>H<sub>4</sub>Cl

The reactions between the amines and the anils are clearly reversible and the differences in amine behaviour can be explained in terms of amine nucleophilicity, which affects the addition step, and amine basicity, which governs the elimination step. Thus, if the base is sufficiently strong to remove the hydrogen-bonded proton in the adduct (3  $\rightleftharpoons$  4), its main stabilising feature is lost and the amine is eliminated (or the ring is cleaved). Aromatic primary amines are sufficiently

† N.m.r. spectra of the adducts are consistent with the chroman-4-one structure (3) although, in some cases, minor contributions from other tautomers are evident.

TABLE 1  
Amine, alcohol, and thiol adducts of 3-(arylimino-methyl)chromones (3)

Compound (3)	M.p. (°C)	Yield (%)	Found (%)			Formula	Required (%)			$\tau^*$ (J/Hz)			$\lambda_{\max.}$ (CHCl <sub>3</sub> )/ nm
			C	H	N		C	H	N	H <sub>a</sub>	H <sub>b</sub> (d)	H <sub>c</sub> (d)	
a	170—172	61	Could not be obtained analytically pure							3.8d (7)	2.15 (12)	—1.8 (12)	256, 385
b	142—144	56	76.8	5.4	7.95	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	77.2	5.3	8.2	3.66d (7.5)	2.36 (12)	—2.3 (12)	247, 383
c	151—153	73	71.1	5.0	7.5	C <sub>23</sub> H <sub>19</sub> N <sub>2</sub> O <sub>2</sub> Cl	70.7	4.9	7.2	3.71d (7)	2.13 (12)	—2.05 (12)	247, 387
d	161—163	84	77.8	6.35	7.3	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	77.8	6.0	7.6	3.6d (7)	1.87 (12)	—2.17 (12)	252, 391
e	152—154	85	71.4	5.7	6.8	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	71.6	5.5	7.0	3.71d (8)	2.00 (12)	—2.08 (12)	250, 391
f	133—135	88	66.4	5.6	4.4	C <sub>19</sub> H <sub>18</sub> NO <sub>3</sub> Cl	66.4	5.3	4.1	4.08s (12)	2.55 (12)	—2.24 (12)	258, 388
g	112	66	64.7	4.5	4.5	C <sub>17</sub> H <sub>14</sub> NO <sub>3</sub> Cl	64.7	4.5	4.4	4.30s (12)	2.50 (12)	—2.23 (12)	257, 388
h	120	75	69.2	5.4	4.4	C <sub>18</sub> H <sub>17</sub> NO <sub>4</sub>	69.4	5.5	4.5	4.30s (12)	2.50 (12)	—2.30 (12)	262, 396
i	154—155	73	87.1	5.3	3.5	C <sub>20</sub> H <sub>20</sub> NO <sub>3</sub> Cl	67.1	5.6	3.9	4.32s (13)	2.62 (13)	—2.11 (13)	257, 382
j	133	54	71.0	4.45	3.65	C <sub>23</sub> H <sub>18</sub> NO <sub>3</sub> Cl	70.5	4.6	3.6	4.13s (13)	2.64 (13)	—2.23 (13)	257, 388
k	148—152	86	67.1	4.1	3.6	C <sub>22</sub> H <sub>16</sub> NO <sub>2</sub> SCl	67.1	4.1	3.6	3.40s (12)	2.55 (12)	—2.20 (12)	248, 273, 406
l	157—158	70	68.1	4.6	3.5	C <sub>23</sub> H <sub>18</sub> NO <sub>2</sub> SCl	67.7	4.5	3.4	3.15s (12)	2.91 (12)	—1.82 (12)	250, 385
m	129—131	68	63.6	5.1	3.8	C <sub>19</sub> H <sub>18</sub> NO <sub>3</sub> SCl	63.4	5.0	3.9	3.42s (12)	3.05 (12)	—1.87 (12)	258, 387
n	135—136	69	62.4	4.75	4.1	C <sub>18</sub> H <sub>16</sub> NO <sub>2</sub> SCl	62.5	4.65	4.05	3.31s (13)	1.95 (13)	—1.88 (13)	247, 267, 397
o	129—130	82	67.3	4.6	3.4	C <sub>23</sub> H <sub>18</sub> NO <sub>2</sub> SCl	67.7	4.45	3.4	3.69s (12)	2.82 (12)	—1.90 (12)	249, 264, 396
p	167—169	81	57.5	3.9	3.6	C <sub>18</sub> H <sub>14</sub> NO <sub>4</sub> SCl	57.5	3.75	3.7	3.30s (12)	2.12 (12)	—1.85 (12)	258, 387
q	145—147	89	59.6	4.4	3.35	C <sub>20</sub> H <sub>18</sub> NO <sub>4</sub> SCl	59.5	4.5	3.5	3.30s (13)	2.00 (13)	—1.85 (13)	245, 366, 393
r	159	53	69.9	5.1	2.9	C <sub>25</sub> H <sub>22</sub> NO <sub>2</sub> SCl	69.8	5.1	3.2	3.49s (12)	3.36 (12)	—1.93 (12)	248, 380
s	159—160	76	63.3	4.1	2.9	C <sub>24</sub> H <sub>19</sub> NO <sub>2</sub> SCl <sub>2</sub>	63.15	4.2	3.0	3.40s (12)	2.65 (12)	—1.87 (12)	253, 388

\* For solutions in CDCl<sub>3</sub>—(CD<sub>3</sub>)<sub>2</sub>SO [compounds (3a—e, h—s)] or CDCl<sub>3</sub> [compounds (3f—j)].

Mass spectra of (3a—s) gave molecular ions corresponding to the parent 3-(aryliminomethyl)chromones, formed by thermal decomposition of the adducts in the spectrometer.

TABLE 2  
3-(Aryliminomethylene)chroman-2,4-diones (6)

Compound <sup>a</sup>	Cryst. solvent	M.p. (°C)	Yield (%)	Found (%)			Formula	Required (%)			$\tau[(CD_3)_2SO]$	$M^+$
				C	H	N		C	H	N		
(6a)	CHCl <sub>3</sub> —LP <sup>b</sup>	250	76	63.8	3.5	4.5	C <sub>16</sub> H <sub>10</sub> ClNO <sub>3</sub>	64.1	3.4	4.7	2.78—2.25 (m, Ar); 1.95 (dd, 5-H); 1.1 (br s, H <sub>a</sub> )	299
(6b)	EtOH	195	38	69.8	4.85	4.7	C <sub>18</sub> H <sub>15</sub> NO <sub>4</sub>	69.9	4.9	4.5	7.6 (s, 6-Me); 6.15 (s, OMe); 3.2—2.13 (m, Ar); 1.31 (d, <i>J</i> 14 Hz, H <sub>a</sub> ); —2.7 (br s, NH <sup>c</sup> )	309
(6c)	EtOH—H <sub>2</sub> O	190	44	70.8	5.45	4.1	C <sub>19</sub> H <sub>17</sub> NO <sub>4</sub>	70.6	5.3	4.3	7.7 (s, 7-Me); 7.3 (s, 5-Me); 6.21 (s, OMe), 3.09—2.42 (m, Ar); 1.3 (d, <i>J</i> 13 Hz, H <sub>a</sub> ); —3.35 (br s, NH <sup>c</sup> )	323

<sup>a</sup>  $\nu_{\max.}$  1630—1655 cm<sup>-1</sup> (C=O). <sup>b</sup> Light petroleum (b.p. 60—80°). <sup>c</sup> Exchangeable proton.

nucleophilic to add to the anil, but not sufficiently basic to deprotonate the adduct and initiate the elimination. The failure of aromatic secondary amines to add to the anil is attributable to their reduced nucleophilicity for the usual steric reasons. On the other hand, aliphatic amines are sufficiently nucleophilic to form adducts but too basic to accommodate a protonated adduct, and the

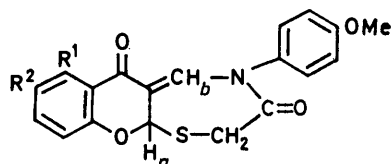
equilibrium favours amine and anil rather than adduct. The fact that *n*-propylamine caused instant decomposition of the 'stable' aromatic amine adducts supports this argument.

Alcohols are also sufficiently nucleophilic to add to 3-(aryliminomethyl)chromones. Primary and secondary alcohols gave crystalline adducts (see Table 1) although

t-butyl alcohol gave an unstable compound providing further evidence that the course of addition is subject to steric influences. As with the stable amine adducts, the alcohol adducts were rapidly decomposed by aliphatic amines. Merely heating the alcohol adducts above their melting-points under vacuum also causes elimination of the alcohol providing an additional route to the pure anil.

The anils gave increased yields of adducts when thiols were used in place of alcohols, reflecting the higher nucleophilicity of the sulphur compounds. Similarly, thiophenols reacted to give stable crystalline adducts, whereas *p*-methoxyphenol formed adducts which were stable only in solution (u.v. evidence).

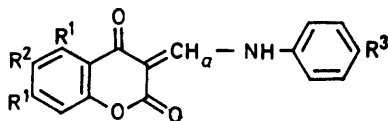
The adducts derived from certain anils and appropriately substituted thiols are capable of cyclisation. Thus, the reaction between 3-(*p*-methoxyphenyliminomethyl)chromone (2b) and thioglycolic acid (or its ethyl ester) gave either a mixture of the adduct and the fused thiazepinone (5a), or only the latter when the



(5)

- a;  $R^1 = R^2 = H$   
b;  $R^1 = H, R^2 = Me$

reaction time was increased from 15 min to 20 h. A corresponding result was obtained when 3-(*p*-methoxyphenyliminomethyl)-6-methylchromone (2c) was used in place of anil (2b). However, the reaction between 3-(*p*-chlorophenyliminomethyl)chromone (2a) and thioglycolic acid (or its ester) gave only the adducts (3p and 3q, respectively) even after prolonged heating, and the ability of the adduct to cyclise apparently depends on the presence of an electron-donating substituent in the amine moiety of the anil.



(6)

- a;  $R^1 = R^2 = H, R^3 = Cl$   
b;  $R^1 = H, R^2 = Me, R^3 = OMe$   
c;  $R^1 = Me, R^2 = H, R^3 = OMe$

The action of activated manganese dioxide<sup>5</sup> on the anils gave 3-(arylamino-methylene)chroman-2,4-dione derivatives (6), presumably *via* oxidation of 2-hydroxy-3-(arylamino-methylene)chroman-4-one intermediates. The chroman-2,4-diones are formed in reasonable yield and this method represents a considerable improvement on the previous route<sup>6</sup> to this system.

## EXPERIMENTAL

N.m.r. spectra were determined at 90 MHz on a Perkin-Elmer R32 instrument with tetramethylsilane as internal reference. Mass spectra were recorded with an A.E.I. MS12 spectrometer. U.v. spectra were recorded on a Pye-Unicam SP 800 instrument for solutions in chloroform, and i.r. spectra were determined for nujol mulls. Silica gel for column chromatography was Hopkin and Williams M.F.C. grade.

**2-Arylamino-3-(arylamino-methylene)chroman-4-ones (3a—e).**—(a) A solution of the 3-formylchromone (0.005 mol) [or the 3-(aryliminomethyl)chromone<sup>1</sup> (0.01 mol)] and the aromatic amine (0.01 mol) in dry benzene (100 ml) was heated under reflux for 30 min using a Dean-Stark water-trap. The solvent was evaporated off and on crystallisation from benzene–light petroleum (b.p. 80–100°) the residue gave the *chroman-4-one adduct* (see Table 1).

(b) A solution of the 3-formylchromone (0.005 mol) and the aromatic amine (0.01 mol) in chloroform (50 ml) was heated at 50 °C for 15 min. An excess of light petroleum (b.p. 40–60°) was added and the product was filtered off and purified as above.

**2-Alkoxy-3-(arylamino-methylene)chroman-4-ones (3f—i).**—A solution of the 3-(aryliminomethyl)chromone (0.005 mol) in the minimum amount of the alcohol was heated under reflux for 5 min. After cooling, the 2-alkoxy-3-(arylamino-methylene)chroman-4-one (3f—i) was filtered off, and crystallised from the appropriate alcohol.

**2-Benzoyloxy-3-(*p*-chloranilinomethylene)chroman-4-one (3j).**—A solution of 3-(*p*-chlorophenyliminomethyl)chromone (0.5 g) and benzyl alcohol (0.5 ml) in dry benzene (15 ml) was stirred at room temperature for 1 h, then evaporated. Crystallisation of the residue from benzene–light petroleum (b.p. 80–100°) gave the *adduct* (3j) (Table 1).

**2-Alkyl (or aryl)thio-3-(arylamino-methylene)chroman-4-ones (3k—s).**—Equimolar quantities (0.01 mol) of the 3-(aryliminomethyl)chromone and the alkyl (or aryl) thiol were heated under reflux in dry benzene (100 ml) for 5 min. Evaporation and crystallisation of the residue from benzene–light petroleum (b.p. 80–100°) gave the 2-alkyl (or aryl)thio-3-(arylamino-methylene)chroman-4-ones (3k—s). (Table 1).

**4,11a-Dihydro-4-(*p*-methoxyphenyl)-1-benzopyrano[2,3-b][1,4]thiazepine-3,6(2H)-dione (5a).**—A solution of 3-(*p*-methoxyphenyliminomethyl)chromone (1 g) and thioglycolic acid (0.3 g) in benzene (100 ml) was heated under reflux for 20 h, using a Dean-Stark water-trap. The volume of the resulting solution was halved and after cooling, filtration gave the *thiazepinedione* (5a) (0.4 g) as silky needles, m.p. 173–175° (from benzene) (Found: C, 64.8; H, 4.4; N, 4.05.  $C_{19}H_{15}NO_4S$  requires C, 64.6; H, 4.3; N, 4.0%;  $\tau(CDCl_3)$  6.26 (s,  $OCH_3$ ), 6.1 (m,  $CH_2$ ), 3.95 (s,  $H_a$ ), 3.85–2.21 (m, Ar), 2.12 (s,  $H_b$ ), and 1.75 (dd, 5-H);  $\lambda_{max}$ : 245 and 305 nm;  $M^+$ , 353).

Similarly, interaction of 3-(*p*-methoxyphenyliminomethyl)-6-methylchromone (2c) with thioglycolic acid gave the *thiazepinedione* (5b) (54%) as needles, m.p. 176° (from benzene) (Found: C, 65.2; H, 4.55; N, 3.6.  $C_{20}H_{17}NO_4S$  requires C, 65.4; H, 4.7; N, 3.8%;  $\tau(CDCl_3)$  7.56 (s,  $CH_3$ ), 6.30 (s,  $OCH_3$ ), 3.9 (s,  $H_a$ ), 3.23–2.10 (m, Ar), and 1.84 (s,  $H_b$ );  $\lambda_{max}$ : 252 and 310 nm;  $M^+$ , 367).

**3-(Arylamino-methylene)chroman-2,4-diones (6a—c).**—A solution of the 3-(aryliminomethyl)chromone (0.005 mol)

in benzene (75 ml) was stirred at room temperature with 'activated' <sup>5,6</sup> manganese dioxide (0.05 mol) for 24 h. The mixture was filtered and the residue was extracted with chloroform in a Soxhlet apparatus for 4 h. The combined extract and filtrate was evaporated and the residue chromatographed. Gradient elution with light petroleum (b.p. 60–80°) and chloroform gave the 3-(arylaminoethylene)chroman-2,4-diones (6a–c) which were further purified by crystallisation (see Table 2).

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