Enamines in the Synthesis of 2-(Substituted Amino)-3,3-dialkylchromanones

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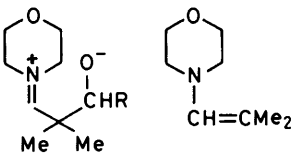
Ethanamines with two alkyl groups at position 2 react with derivatives of 2-hydroxybenzaldehyde to give 2-alkylamino-3,3-dialkylchroman-4-ols such as (4a) as mixtures in which one diasteroisomer preponderates. Oxidation supplies the corresponding chromanones of type (4b) as single racemates except for the bischromanone derived from piperazine. The enamines used were derived from morpholine, pyrrolidine, *N*-methylaniline, and piperazine as bases, and 2-methylpropanal, 2-methylbutanal, and cyclohexanecarbaldehyde as carbonyl components. 2-Hydroxybenzaldehyde itself, and its 3-methoxy-, 4-methoxy-3,5-dibromo-, 4,6-dimethyl-, 5-nitro-, and 3-nitro-derivatives, and also 2-hydroxynaphthalene-1-carbaldehyde were employed.

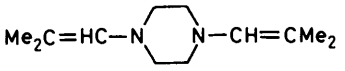
The reaction between salicyaldehyde derivatives and enamines is presumed always to give chromanols of type (4a); where the enamine substituents are alkyl the chromanols have proved to be oily and difficult to characterise [1] and where the substituents are aromatic they have suffered spontaneous dehydration to give chromens.[2-3] We have now added salicylaldehyde to the dialkylated enamine (2) and found that a rapid reaction occurs to give the chromanol (4a) ($\nu_{max.}$ 3 340 cm^{-1}) in high yield (>90%). This alcohol cannot easily suffer dehydration, and it crystallises well although the spectral results show it to consist of one diastereoisomer mixed with *ca.* 5—10% of the other. Oxidised by Sarett's reagent, the mixture readily gave the 3,3-dimethylchromanone (4b) ($\nu_{max.}$ 1 676 cm^{-1}), now a single racemate. A similar reaction with 2-hydroxy-3-methoxybenzaldehyde supplied the related alcohols (5a) and the chromanone (5b).

We could find in the literature no other simple method of preparing 3,3-dialkylchromanones except the cyanoethylation of 3-unsubstituted chromanone [4] and so we sought to generalise the reaction. It proceeded smoothly in solvent (benzene) with salicyladehydes carrying methyl, bromo-, or nitro-substituents, but a 4-methoxy-group able to liberate electrons into the aldehyde group retarded the reaction. Enamines derived from pyrrolidine and *N*-methylaniline were successful although they reacted more slowly than the morpholine enamine. The more bulky enamines from either 2-methylbutanal or cyclohexanecarbaldehyde were also slow to react even when the amine was morpholine. The speed of all these reactions could be conveniently increased by using tetrahydrofuran as the solvent, presumably because zwitterionic intermediates like (1) could be formed more readily and subsequent proton shifts facilitated. By such means the alcohols (10a), (12), (16), and (18) were prepared and then oxidised to the chromanones (10b), (13), (17), (19)—(21) except that the pyrrolidine ring was also oxidised in the case of the adduct from 2-methyl-1-pyrrolidinylpropene and salicylaldehyde so that the product was the lactam (14) along with a little of an alcohol, possibly (15). In addition, the enamine (3) from piperazine was converted into the bischromanol (18) and thence into the bischromananone (19), no separation of diastereoisomers being undertaken.

During an attempt to catalyse the reaction between 2-hydroxy-4-methoxybenzaldehyde and the morpholine enamine (2) the effect of adding toluene-*p*-sulphonic acid was investigated. A new product appeared that possessed two morpholine residues but no hydroxy-group; it was formulated as in diagram (11) on the assumption that the acid would convert the expected benzylic alcohol into a carbenium ion



(1) (2)



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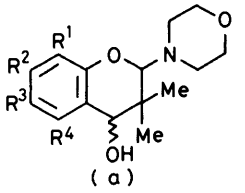
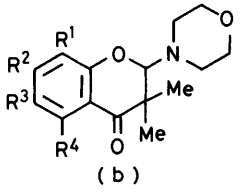
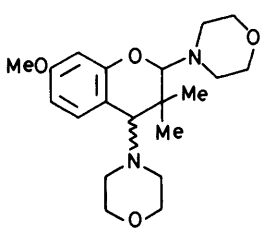


(a)

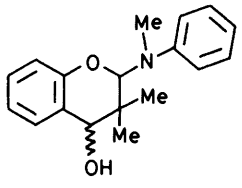


(b)

(4) $R^1 = R^2 = R^3 = R^4 = H$
(5) $R^1 = OMe$; $R^2 = R^3 = R^4 = H$
(6) $R^1 = R^3 = Br$; $R^2 = R^4 = H$
(7) $R^1 = R^3 = H$; $R^2 = R^4 = Me$
(8) $R^1 = R^2 = R^4 = H$; $R^3 = NO_2$
(9) $R^1 = NO_2$; $R^2 = R^3 = R^4 = H$
(10) $R^1 = R^3 = R^4 = H$; $R^2 = OMe$



(11)



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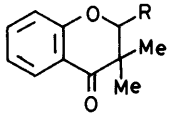
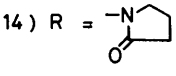


(13) R = N(Me)Ph



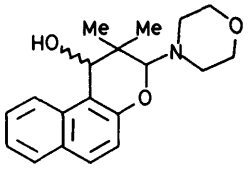
(14) R =

(15) R = OH

^{1}H N.m.r. spectra (δ values; splittings in Hz) for chroman-4-ol [a] and chroman-4-one derivatives at 220 MHz

Compd.	Aromatic nucleus 5-H	6-H	7-H	8-H	2-H (s)	4-H (s)	CH_2OCH_2 (m)	NCH_2 (m)	gem-Me (s)	OH/OMe/Me (bs, s)
(4a)	7.22	6.83 (4 H, m)			4.58	4.05	3.68	3.04, 2.78	1.14, 0.89	2.12 [b]
(4b)	7.83 (dd, 1.7, 8)	6.96 (dt, 1.7, 8)	7.47 (dt, 2, 8)	6.94 (dd, 1.5, 8)	4.76		3.57	2.8, 2.52	1.34, 1.28	
(5a)	6.96	6.79 (3 H, m)			4.61	4.07	3.70	3.09, 2.85	1.15 0.95	3.84, 2.32 [b]
(5b)	7.44 (dd, 1.7, 8)	6.91 (t, 8)	7.05 (dd, 1.7, 8)		4.93		3.35	2.84, 2.55	1.37, 1.29	3.91
(6a)	7.59 (d, 2.5)		7.29 (d, 2.5)		4.69	4.05	3.72	3.08, 2.86	1.17, 0.89	2.22 [b]
(6b)	7.91 (d, 2.5)		7.84 (d, 2.5)		4.95		3.58	2.77, 2.49	1.34, 1.28	
(7a)		6.52 (2 H, 6,8-H)			4.48	4.09	3.69	3.06, 2.80	1.17, 0.85	2.32, 2.23, 1.90 [b]
(7b)	6.61 (1 H), 6.56 (1 H) (6,8-H)				4.66		3.58	2.81, 2.52	1.30, 1.23	2.56, 2.27
(8a)	8.23 (d, 3)		8.07 (dd, 3, 9)	6.90 (d, 9)	4.79	4.10	3.70	3.07, 2.81	1.17, 0.92	5.29 [b]
(8b)	8.72 (d, 3)		8.33 (dd, 3, 9)	7.07 (d, 9)	4.95		3.60	2.78, 2.53	1.34, 1.31	
(9b)	8.13—8.07 (2 H, m, 5-,7-H), 7.07 (t, 8, 6-H)				5.03		3.58	2.88, 2.58	1.39, 1.32	
(10b)	7.77 (d, 9)	6.53 (dd, 2.5, 9)		6.39 (d, 2.5)	4.75		3.57	2.82, 2.53	1.33, 1.26	3.85

[a] Signals due to the minor isomer are given in the Experimental section. [b] Exchangeable with D_2O.



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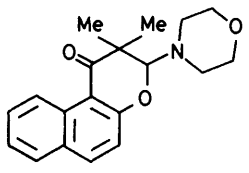

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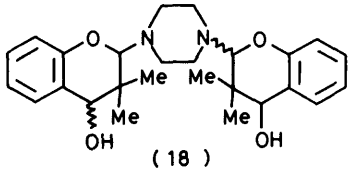

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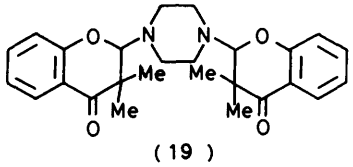

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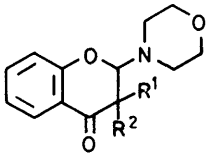

(20) R^1 = Me; R^2 = Et

(21) R^1,R^2 = $-[CH_2]_5-$

that would react with another mole of base. The same idea suggested the possibility of epimerising the benzylic alcohols with this acid, but in practice they collapsed too easily and the salicylaldehydes were regenerated. Borohydride reduction of the chromanone (4b) also generated a mixture of alcohols, like that from the initial condensation, and no further attempt was made to obtain single diastereoisomers.

Experimental

M.p.s were determined with a Reichert hot-stage apparatus and are uncorrected. The ^{1}H n.m.r. spectra were recorded for solutions in deuteriochloroform on Perkin-Elmer R34 spectrometer operating at 220 MHz with tetramethylsilane as internal standard. I.r. spectra were measured on Perkin-Elmer 125 spectrometer and mass spectra on AE1 MS12 spectrometer by direct inlet technique. Light petroleum refers to the fraction of boiling range 40—60 °C. Benzene and tetrahydrofuran (THF) used were redistilled after drying over sodium and potassium respectively and solutions in organic solvents were dried with anhydrous magnesium sulphate. Enamines were prepared by published procedure [5,6] and their reactions were carried out under nitrogen. All oxidations were carried out using Sarett's reagent.[7]

General Procedure for the Reaction of Aldehydes with Enamines.—To a solution of aldehyde (0.01 mol) in benzene or tetrahydrofuran (5 ml) was added a solution of an equimolar quantity of the enamine in the same volume of the identical solvent at room temperature under nitrogen. After 24 h crystalline compounds had formed in most cases and these were filtered off and recrystallised. If no crystals had formed the solvent was removed under reduced pressure and the viscous oil was either used as such without purification or crystallised from an appropriate solvent.

Chromium(VI) *Oxide–Pyridine Oxidations.*—A solution of the alcohol in pyridine was added dropwise to a stirred suspension of the ice-cold chromium(VI) oxide–pyridine complex in pyridine. The reaction mixture was then stirred

with cooling (ice–water) for 2—5 h before being set aside overnight at room temperature. The mixture was poured into ice–water and the dark brown slurry was repeatedly extracted with ether. The combined extracts were washed with water, dried, filtered, and concentrated. Any pyridine present was removed either on a water-bath under reduced pressure or by passing a solution of the product in ether–hexane (1 : 1) through a small column of alumina. The crystalline product was then recrystallised to constant melting point.

3,3-*Dimethyl*-2-*morpholinochroman*-4-*one* (4b).—From 2-methyl-1-morpholinopropene (2.82 g) and salicylaldehyde (2.44 g) in benzene (10 ml) were obtained thick cubes (4.7 g, 90%) of 3,3-dimethyl-2-morpholinochroman-4-ol (4a), m.p. 90—100 °C (ether); $\nu_{max.}$ (Nujol) 3 340, 1 612, and 1 585 cm^{-1}; δ (minor isomer) singlets at 4.38, 4.24, 1.09, and 1.03 (Found: M^+, 263.151 77. Calc. for $C_{15}H_{21}NO_3$ M, 263.152 13); m/z 263 (M^+), 246, 177, 141 (100%), 126, 122, and 121.

Oxidation of this alcohol (4a) with chromium(VI) oxide (10 g) in pyridine (90 ml) gave the *chromanone* (4b) (90%) as thick rectangular prisms, m.p. 85—86 °C (hexane–ether); $\nu_{max.}$ (Nujol) 1 676, 1 608, 1 582, 1 310, 1 186, 1 151, 1 119, 992, 890, 810, 766, and 745 cm^{-1} (Found: M^+, 261.134 83. $C_{15}H_{19}NO_3$ requires M, 261.136 485); m/z 261 (M^+), 175, 141 (100%), and 126.

8-*Methoxy*-3,3-*dimethyl*-2-*morpholinochroman*-4-*one* (5b).—A mixture of 2-methyl-1-morpholinopropene (2.82 g) and 3-methoxysalicylaldehyde (3.04 g) in benzene (7 ml) overnight afforded 8-methoxy-3,3-dimethyl-2-morpholinochroman-4-ol (5a) (4.5 g, 77%), m.p. 115—117 °C (hexane–ether); $\nu_{max.}$ (Nujol) 3 430, 1 590, 1 258, 1 240, 1 183, 1 112, 1 081, 1 036, 980, 944, 916, 882, 795, and 750 cm^{-1}; δ (minor isomer) singlets at 4.32, 4.30, 1.13, and 1.09 (Found: M^+, 293.161 12. Calc. for $C_{16}H_{23}NO_4$: M, 293.162 69); m/z 293 (M^+), 207, and 144.

Oxidation of this adduct (5a) with chromium(VI) oxide (10 g) in pyridine (100 ml) gave the *chromanone* (5b) (100%) as thick needles, m.p. 122—123 °C (hexane–ether); $\nu_{max.}$ (Nujol) 1 682, 1 605, 1 585, 1 300, 1 258, 1 224, 1 151, 1 119, 1 005, 882, 870, and 760 cm^{-1} (Found: M^+, 291.147 52. $C_{16}H_{21}NO_4$ requires 291.147 05); m/z 291 (M^+), 205, 176, and 141 (100%).

6,8-*Dibromo*-3,3-*dimethyl*-2-*morpholinochroman*-4-*one* (6b).—A mixture of 2-methyl-1-morpholinopropene (0.71 g) and 3,5-dibromosalicylaldehyde (1.4 g) in THF (7 ml) overnight gave a syrupy residue which upon trituration with ether gave the chromanol derivative (6a) (1.1 g, 50%), m.p. 140—141 °C (ether); $\nu_{max.}$ (KBr) 3 370, 1 554, 1 450, 1 108, 1 026, 857, 798, and 730 cm^{-1}; δ (minor isomer) singlets at 4.38, 1.12, and 0.99.

Oxidation of this chromanol (6a) with chromium(VI) oxide (4 g) in pyridine (60 ml) gave the *chromanone* (6b) as thick rectangular rods (>95%), m.p. 159—160 °C (MeOH–CH_2Cl_2); $\nu_{max.}$ (Nujol) 1 681, 1 586, 1 280, 1 255, 1 195, 1 151, 1 118, 865, and 822 cm^{-1} (Found: C, 42.9; H, 4.0; N, 3.4. $C_{15}H_{17}NO_3Br_2$ requires C, 42.95; H, 4.05; N, 3.34%); m/z 419 (M^+), 333 (M^+ − 86), 277, 141, 140 (100%), and 125.

3,3,5,6-*Tetramethyl*-2-*morpholinochroman*-4-*one* (7b).—2,4-Dimethylsalicylaldehyde (0.008 mol) was heated with 2-methyl-1-morpholinopropene (0.008 mol) in refluxing THF (10 ml) for 72 h and was then set aside at 25 °C overnight. THF was removed under reduced pressure and the residue crystallised from methanol–chloroform to give 3,3,5,7-tetramethyl-2-morpholinochroman-4-ol (7a), as rhombic prisms (86%), m.p. 150—151 °C; $\nu_{max.}$ (KBr) 3 390, 1 616, 1 577, 1 452, 1 300, 1 287, 1 262, 1 157, 1 106, 1 046, 1 034, 980, 872, and 837 cm^{-1}; δ (minor isomer) singlets at 4.08 and 1.89 due to minor isomer (Found: M^+, 291.1840. Calc. for $C_{17}H_{25}NO_3$: M, 291.1834), m/z 291 (M^+), 150, 149, 142, 141 (100%), 126, 96, 83, and 82.

Oxidation of the chromanol (7a) (1 g) with chromium(VI) oxide (5 g) in pyridine (60 ml) gave a product (>90%) which on column chromatography over silica gel with hexane–ether (9 : 1) as eluant afforded the *chromanone* (7b) as a gum; $\nu_{max.}$ (film) 1 672, 1 610, 1 565, 1 450, 1 314, 1 282, 1 259, 1 116, 992, and 883 cm^{-1} (Found: M^+, 289.1677. $C_{17}H_{23}NO_3$ requires M, 289.1678), m/z 289 (M^+), 203 (M − 86), 174, 159, 141 (100%), 126, 83, and 82.

3,3-*Dimethyl*-2-*morpholino*-6-*nitrochroman*-4-*one* (8b).—A mildly exothermic reaction of 5-nitrosalicylaldehyde (1.67 g) with 2-methyl-1-morpholinopropene (1.41 g) in THF (8 ml) overnight gave an orange-red syrup. THF was removed under reduced pressure and 3,3-dimethyl-6-nitro-2-morpholinochroman-4-ol (8a) could be precipitated with ether as a pale yellow solid (>90%), m.p. 117—118 °C; $\nu_{max.}$ (Nujol) 3 385, 1 615, 1 585, 1 340, 1 250, 1 115, 905, 832, and 725 cm^{-1}; δ (minor isomer); singlets at 4.46, 1.18, and 0.93 due to the minor isomer; m/z M^+ (not observed), 167, 141, 126, 83 (100%), and 82 (Found: C, 58.15; H, 6.6; N, 8.95. Calc. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09%).

Oxidation of the chromanol (8a) (1 g) with chromium(VI) oxide (6 g) in pyridine (80 ml) gave in near quantitative yield the *chromanone* (8b), m.p. 193—194 °C (MeOH–CH_2Cl_2); $\nu_{max.}$ (KBr) 1 690, 1 612, 1 580, 1 513, 1 470, 1 332, 1 286, 1 188, 1 108, 1 079, 838, 776, and 750 cm^{-1}; m/z 306 (M^+), 220 (M^+ − 86), 191, 166, 141 (100%), 126, 86, 84, 83, and 82 (Found: C, 58.4; H, 5.9; N, 8.95. $C_{15}H_{18}N_2O_5$ requires C, 58.81; H, 5.92; N, 9.15%).

3,3-*Dimethyl*-2-*morpholino*-8-*nitrochroman*-4-*one* (9b).—A mildly exothermic reaction of 3-nitrosalicylaldehyde (1.6 mmol) with 1-morpholinoisobut-1-ene (1.6 mmol) in THF (5 ml) overnight gave an orange–red syrup. THF was removed under reduced pressure and the residue was oxidised with chromium(VI) oxide (4 g) in pyridine (46 ml) to give the *chromanone* (9b) (>90%), m.p. 155—156 °C (MeOH–CH_2Cl_2); $\nu_{max.}$ (KBr) 1 687, 1 608, 1 576, 1 520, 1 465, 1 359, 1 308, 1 295, 1 114, 1 009, 865, 792, and 742 cm^{-1}; m/z 306 (M^+) 220 (M^+ − 86), 166, 141 (100%), 126, 83, and 82 (Found: C, 58.7; H, 6.1; N, 8.85. $C_{15}H_{18}N_2O_5$ requires C, 58.81; H, 5.92; N, 9.15%).

7-*Methoxy*-3,3-*dimethyl*-2-*morpholinochroman*-4-*one* (10b).—4-Methoxysalicylaldehyde (1.52 g) was heated with 2-methyl-1-morpholinopropene (1.41 g) in refluxing THF (10 ml) for 24 h and was then set aside at 22 °C for 5 days. THF was removed under reduced pressure and the residue oxidised with chromium(VI) oxide (7 g) in pyridine (65 ml). The product was chromatographed on a column of silica gel with hexane–ether (7 : 3) as eluant to afford the *chromanone* (10b) (46%) as a gum; $\nu_{max.}$ (film) 1 673, 1 605, 1 578, 1 255, 1 148, 1 115, 1 028, and 910 cm^{-1} (Found: M^+, 291.1467. $C_{16}H_{21}NO_4$ requires M, 291.1470), m/z 291 (M^+), 205 (M − 86), 176, 161, 141 (100%), and 126.

7-*Methoxy*-3,3-*dimethyl*-2,4-*dimorpholinochroman* (11).—4-Methoxysalicylaldehyde (1.52 g) was heated with 2-methyl-1-morpholinopropene (2.82 g) and toluene-*p*-sulphonic acid (50 mg) in refluxing THF (15 ml) for 24 h. THF was removed under reduced pressure and the residue gave the *chroman* (11) (48%), m.p. 155—156 °C (ether–hexane); $\nu_{max.}$ (KBr) 1 614, 1 572, 1 500, 1 462, 1 324, 1 261, 1 107, 1 028, 995, 976, and 843 cm^{-1}; δ ($CDCl_3$) 6.85 (1 H, d, J 8 Hz, 5-H), 6.42 (1 H, dd,

J 2.5, 8 Hz, 6-H), 6.35 (1 H, d, *J* 2.5 Hz, 8-H), 4.47 (1 H, s, 2-H), 3.76 (3 H, s, OMe), 3.73—2.41 (16 H, m, 4 × NCH_2 and 2 × CH_2OCH_2), 2.90 (1 H, s, 4-H) and 1.16 and 0.84 (3 H, s, gem-Me); *m/z* 362 (M^+), 276, 275, 222 (100%), 221, 141, and 126 (Found: C, 66.15; H, 8.25; N, 7.75. $C_{20}H_{30}N_2O_4$ requires C, 66.27; H, 8.34; N, 7.73%).

The chroman derivative (11) was also obtained (52%) by heating 4-methoxysalicylaldehyde (0.01 mol) with 2-methyl-1-morpholinopropene (0.02 mol) in the presence of morpholinotoluene-*p*-sulphonic acid (0.01 mol) in refluxing THF (15 ml) for 30 h.

3,3-*Dimethyl*-2-N-*methylanilinochroman*-4-*one* (13).—Salicylaldehyde (0.01 mol) was mixed with *N*-2-methylpropyl-*N*-methylaniline (0.01 mol) in benzene (10 ml) and kept for 2 months; prisms of 3,3-dimethyl-2-*N*-methylanilinochroman-4-ol (12) (41%), m.p. 135—136 °C (benzene), separated; $\nu_{max.}$ (KBr) 3 310, 1 599, 1 580, 1 495, 1 457, 1 228, 1 117, 1 030, 918, and 757 cm^{-1}; δ (major isomer) 7.30—6.80 (9 H, m, ArH), 5.75 (1 H, s, 2-H), 4.16 (1 H, s, 4-H), 3.07 (3 H, s, NMe), 1.91 (1 H, s, CH-O*H*, exch. with D_2O), 1.15, (3 H, s, gem-Me), and 0.99 (3 H, s, gem-Me); additional peaks due to minor isomer at 4.15 and 1.89 (Found: M^+, 283.1571. Calc. for $C_{18}H_{21}NO_2$: *M*, 283.1572), *m/z* 283 (M^+), 266, 162, 161 (100%), 160, 146, 122, 121, 105, and 77.

Oxidation of this product with chromium(VI) oxide (5 g) in pyridine (55 ml), gave the *chromanone* (13) (>95%) as gum, $\nu_{max.}$ (film) 1 685, 1 605, 1 468, 1 458, 1 298, 1 140, 991, 896, and 760 cm^{-1}; δ ($CDCl_3$) 7.90 (1 H, dd, *J* 2.0, 7.5 Hz, 5-H), 7.46 (1 H, dt, *J* 1.5, 7.5 Hz, 6-H), 7.32—6.90 (7 H, m, ArH), 5.59 (1 H, s, 2-H), 2.82 (3 H, s, N-Me), 1.38 (3 H, s, gem-Me), and 1.32 (3 H, s, gem-Me) (Found: M^+, 281.1415. $C_{18}H_{19}NO_2$ requires *M*, 281.1415), *m/z* 281 (M^+), 175, 161 (100%), 146, 131, 91, and 77.

3,3-*Dimethyl*-2-(2-*oxopyrrolidinyl*)*chroman*-4-*one* (14) *and* 2-*Hydroxy*-3,3-*dimethylchroman*-4-*one* (15).—To salicylaldehyde (0.01 mol) in THF (8 ml) was added 2-methyl-1-pyrrolidinyl propene (0.01 mol) to give a mildly exothermic reaction. After 24 h, THF was removed under reduced pressure and the orange-red residue was oxidised with chromium(VI) oxide (5 g) in pyridine (55 ml). The residue obtained (0.9 g) upon work-up was chromatographed on silica gel to give the *chromanone* (15) (14%) as a gum with ether–hexane (3 : 17) as eluant; $\nu_{max.}$ (film) 3 410, 1 670, 1 610, 1 468, 1 320, 1 149, 1 090, 1 002, 955, and 760 cm^{-1}; δ ($CDCl_3$) 7.86 (1 H, dd, *J* 1.5, 7.5 Hz, 5-H), 7.46 (1 H, dt, *J* 1.5, 7.5 Hz, 7-H), 7.01 (1 H, dt, *J* 1.5, 7.5 Hz, 6-H), 6.92 (1 H, dd, *J* 1.3, 7.5 Hz, 8-H), 5.37 (1 H, s, 2-H), 4.48 (1 H, bs, CH-O*H*, exch. with D_2O), and 1.24 (6 H, bs, 2 × gem-Me) (Found: M^+, 192.079 25. ($C_{11}H_{12}O_3$ requires *M*, 192.078 64), *m/z* 192 (M^+), 164 (*M* − 18), and 121 (100%). The *chromanone* (14) (22%), eluted with ether–hexane (3 : 2), had m.p. 66—67 °C (hexane–ether); $\nu_{max.}$ (Nujol) 1 690, 1 610, 1 290, 1 203, 1 145, 1 000, 928, and 753 cm^{-1}; δ ($CDCl_3$) 7.88 (1 H, dd, *J* 1.5, 7.5 Hz, 5-H), 7.50 (1 H, dt, *J* 1.5, 7.5 Hz, 7-H), 7.05 (1 H, dt, *J* 1.5, 7.5 Hz, 6-H), 6.97 (1 H, dd, *J* 1.3, 7.5 Hz, 8-H), 6.05 (1 H, s, 2-H), 3.23 (2 H, t, $COCH_2$), 2.40 (2 H, t, NCH_2), 1.97 (2 H, m, CCH_2), 1.36 (3 H, s, gem-Me), and 1.18 (3 H, s, gem-Me) (Found: M^+, 259.121 97. $C_{15}H_{17}NO_3$ requires *M*, 259.120 83), *m/z* 259 (M^+), 233, 174, 139 (100%), and 84.

2,2-*Dimethyl*-3-*morpholino*-2,3-*dihydro*-1H-*naphtho*[2,1-b]-*pyran*-1-*one* (17).—2-Hydroxynaphthalene-1-carbaldehyde (1.72 g) was heated with 2-methyl-1-morpholinopropene (1.41 g) in refluxing THF (15 ml) overnight. THF was removed under reduced pressure and the residue gave the naphthopyran-1-ol (16) (85%), m.p. 143—144 °C (ether); $\nu_{max.}$ (KBr) 3 385, 1 624, 1 603, 1 515, 1 469, 1 240, 1 156, 1 115, 940, 910, and 820 cm^{-1}; δ ($CDCl_3$) 8.01 (1 H, dd, *J* 1.5, 8 Hz, 10-H), 7.75 (1 H, dd, *J* 1.4, 8 Hz, 7-H), 7.71 (1 H, d, *J* 8 Hz, 6-H), 7.50 (1 H, dt, *J* 1.5, 8 Hz, 9-H), 7.73 (1 H, dt, *J* 1.5, 8 Hz, 8-H), 4.70 (1 H, s, 3-H), 4.64 (1 H, s, 1-H), 3.74 (4 H, m, CH_2OCH_2), 3.13 (2 H, m, NCH_2), 2.86 (2 H, m, NCH_2), 2.08 (1 H, bs, CH*OH*, exch. with D_2O), 1.28 (3 H, s, gem-Me), and 0.95 (3 H, s, gem-Me). Additional peaks due to minor isomer at 4.62, 2.06, 1.56, and 1.45; *m/z* 313 (M^+), 227, 172, 171, 144, 142, 141 (100%), and 126 (Found: C, 72.45; H, 7.45; N, 4.5. Calc. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47%). Oxidation of the alcohol (16) (0.5 g) with chromium(VI) oxide (4 g) in pyridine (50 ml) gave the *naphthopyran* (17) (>95%), m.p. 92—93 °C (hexane); $\nu_{max.}$ (Nujol) 1 663, 1 615, 1 594, 1 343, 1 149, 1 116, 887, and 830 cm^{-1}; δ ($CDCl_3$) 9.43 (1 H, dd, *J* 1.3, 8 Hz, 10-H), 7.91 (1 H, d, *J* 9 Hz, 6-H), 7.72 (1 H, dd, *J* 1.7, 7.5 Hz, 7-H), 7.60 (1 H, dt, *J* 1.7, 7.5 Hz, 9-H), 7.39 (1 H, dt, *J* 1.5, 7.5 Hz, 8-H), 7.08 (1 H, d, *J* 9 Hz, 5-H), 4.82 (1 H, s, 3-H), 3.60 (4 H, m, CH_2OCH_2), 2.89 (2 H, m, NCH_2), 2.55 (2 H, m, NCH_2), 1.39 (3 H, s, gem-Me) and 1.32 (3 H, s, gem-Me); *m/z* 311 (M^+), 225, 171, 141 (100%), and 126 (Found: C, 73.0; H, 6.9; N, 4.5. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.90; N, 4.50%).

1,4-*Bis*-(3,3-*dimethyl*-4-*oxochroman*-2-*yl*)*piperazine* (19).—1,4-Bis-(2-methylprop-2-enyl)piperazine (3) (0.01 mol) was added to salicylaldehyde (0.01 mol) in THF (10 ml) to give after 5 days colourless flakes of 1,4-bis-(4-hydroxy-3,3-dimethylchroman-2-yl)piperazine (18) (30%), m.p. 166—167 °C (sintered at 110 °C); $\nu_{max.}$ (Nujol) 3 400, 1 610, 1 585, 1 194, 1 030, 905, and 755 cm^{-1}; δ [$CDCl_3$–$(CD_3)_2SO$] 7.17 (4 H, m, ArH), 6.79 (4 H, m, ArH), 5.30 (2 H, bs, CH*OH*, exch. with D_2O), 4.63, 4.38, 3.93, and 2.51 (1 H, bs, 2-H and 4-H), 3.05 (4 H, m, N-CH_2), 2.75 (4 H, m, NCH_2), 1.08 (6 H, s, gem-Me) and 0.87 (6 H, s, gem-Me).

The piperazine derivative (18) (0.5 g) was oxidised with chromium(VI) oxide (4 g) in pyridine (50 ml), to give 1,4-*bis*-(3,3-*dimethyl*-4-*oxochroman*-2-*yl*)*piperazine* (19) (0.46 g, 93%), m.p. 229—230 °C (methanol); $\nu_{max.}$ (KBr) 1 678, 1 605, 1 310, 1 182, 986, 890, and 765 cm^{-1}; δ ($CDCl_3$) [7.81 (2 H,) 7.46 (2 H), 6.93 (4 H), m, Ar-H], 4.71 and 4.69 (2 × 1 H, s, 2 × 2-H), 2.67 (4 H, m, NCH_2), 2.39 (4 H, m, NCH_2), 1.28 and 1.27 (2 × 3 H, s, 2 × gem-Me), 1.21 (3 H, s, gem-Me), and 1.08 (3 H, s, gem-Me) (Found: M^+, 434.215 11. $C_{26}H_{30}N_2O_4$ requires *M*, 434.220 54), *m/z* 434 (M^+), 314 (100%), 120, and 92.

3-*Ethyl*-3-*methyl*-2-*morpholinochroman*-4-*one* (20).—To salicylaldehyde (0.01 mol) in THF (10 ml) was added 2-methyl-1-morpholinobut-1-ene and the reaction mixture was heated under reflux for 48 h. THF was removed under reduced pressure and the residue was oxidised using chromium(VI) oxide (6 g) in pyridine (60 ml) to afford a product which on column chromatography on silica gel with ether–hexane (1 : 9) as eluant gave the *chromanone* (20) (22%) as gum, $\nu_{max.}$ (film) 1 675, 1 605, 1 460, 1 305, 1 149, 1 115, 925, and 885 cm^{-1}; δ ($CDCl_3$) 7.82 (1 H, dd, *J* 2, 8 Hz, 5-H), 7.46 (1 H, dt, *J* 2, 8 Hz, 7-H), 6.95 (2 H, m, 6-H and 8-H), 4.82 (1 H, s, 2-H), 3.57 (4 H, m, CH_2OCH_2), 2.80 (2 H, m, NCH_2), 2.50 (2 H, m, NCH_2), 1.68 (2 H, q, *J* 7.5 Hz, CH_2), 1.23 (3 H, s, Me) and 0.85 (3 H, t, *J* 7.5 Hz, CH_2CH_3); additional peaks due to the minor isomer at 4.74, 1.84 (m), 1.31, and 0.97 (t) (Found: M^+, 275.1526. $C_{16}H_{21}NO_3$ requires *M*, 275.1521), *m/z* 275 (M^+), 260, 155 (100%), 154, 145, and 140.

[2-*Morpholinochroman*-3-*spirocyclohexan*]-4-*one* (21).—Morpholinomethylenecyclohexane (0.01 mol) was added to salicylaldehyde (0.01 mol) in THF (10 ml) and the reaction

mixture was refluxed for 48 h. THF was removed under reduced pressure and the residue was oxidised with chromium(VI) oxide (5 g) in pyridine (55 ml) to give the product which on column chromatography over silica gel with ether–hexane (1 : 5) as eluant afforded the *spirone* (21) (10%) as a gum, $\nu_{max.}$ (film) 1 703, 1 605, 1 460, 1 450, 1 398, 1 257, 1 180, and 1 116 cm^{-1}; δ ($CDCl_3$) 7.79 (1 H, dd, *J* 1.5, 7.5 Hz, 5-H), 7.43 (1 H, dt, *J* 1.5, 7.5 Hz, 7-H), 6.91 (2 H, m, 6-H and 8-H), 5.06 (1 H, s, 2-H), 3.57 (4 H, m, CH_2OCH_2), 2.80 (2 H, m, NCH_2), 2.50 (2 H, m, NCH_2), and 2.37—1.20 (*ca.* 10 H, m, cyclohexyl-H) (Found: M^+, 301.1680. $C_{18}H_{23}NO_3$ requires *M*, 301.1678), *m/z* 301 (M^+), 215, 181 (100%), 180, 157, 121, and 81.

Sodium Borohydride Reduction of Chroman-4-one (4b).—To a stirred suspension of sodium borohydride (22 mg) in methanol (15 ml) was added the chromanone derivative (4b). The mixture was stirred at ambient temperature for 3 h. Methanol was removed under reduced pressure and water (20 ml) was added to the residue. The organic products were extracted with methylene chloride (3 × 50 ml), washed with water, dried, and concentrated. The product, m.p. 95—100 °C was identical (t.l.c., n.m.r.) with the mixture of isomeric chromanol obtained by direct condensation of salicylaldehyde and 2-methyl-1-morpholinopropene.

Attempted Epimerisation of the Chromanol (4a) *with Toluene-p-sulphonic Acid.*—The chromanol derivative (4a) (200 mg) in THF (7 ml) and was heated under reflux in the presence of toluene-*p*-sulphonic acid (20 mg) for 2 h. Examination (t.l.c.) of the product indicated the absence of starting material, only salicylaldehyde being detected.

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