Conformational Studies on 2-Methyl- and 2,*NN*-Trimethyl-chroman-3-amine and Derivatives

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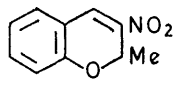
The synthesis of *cis*- and *trans*-2-methyl- and 2.*NN*-trimethylchroman-3-amines is described. Configurations and preferred conformations are assigned to the free bases. and to derivatives (hydrochlorides, *N*-acetyl, *N*-phthaloyl) by interpretation of proton magnetic resonance spectra recorded at 220 MHz.

BACHMAN and Levine [1] prepared 2-methylchroman-3-amine hydrochloride (2) in low yield as prisms, m.p. 216—217·5°, by catalytic hydrogenation of 2-methyl-3-nitro-2*H*-1-benzopyran (1). In view of our interest in chroman-3-amine hydrochlorides as potential therapeutic agents, other methods of reduction of the nitro-compound (1) were examined.



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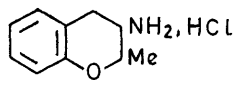

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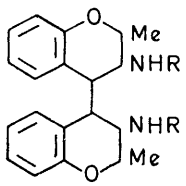

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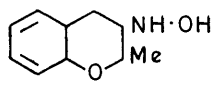

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Reduction of the nitro-compound (1) with lithium aluminium hydride afforded an isomeric 2-methylchroman-3-amine hydrochloride,[2] as needles, m.p. 260—261°, in *ca.* 70% yield.

By-products have been isolated from both methods of reduction; catalytic hydrogenation also afforded a substantial proportion of the dimer (3; R = H), which was isolated as its Schiff's base with acetone, while some 3-hydroxyamino-2-methylchroman (4) was obtained from the lithium aluminium hydride reduction.

The 2-methylchroman-3-amine hydrochlorides were originally designated α (m.p. 260—261°) and β (m.p. 216—217·5°) but the studies described below have established the configurations as *cis*- and *trans*- respectively. Interestingly, although two isomers of 3-amino-2-methylchroman-4-one are also isolable, *N*-acetylation converts both keto-amines into a single acetyl derivative.[3] Hydrogenation of this derivative yielded the corresponding alcohol, apparently as a single compound, and further hydrogenation of the latter in acidic solution over palladised charcoal gave only the β-isomer of *N*-acetyl-2-methylchroman-3-amine.

The conformations of the reduced ring in chromans and substituted chromans, in solution, have been difficult to establish. Many interpretations of the ^{1}H n.m.r. spectra of flavans [4-7] have been reported, and some of 3,4-disubstituted chromans [8] have also been published. The half-chair conformation (5) or sofa conformation (7) (C-2 out of plane) are generally favoured. However, the

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[2] B.P. 1,168,228/1969.
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[4] J. W. Clark-Lewis, *Rev. Pure Appl. Chem.* (*Australia*), 1962, **12**, 96.
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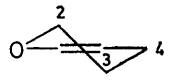
[8] W. D. Cotteril, J. Cottam, and R. Livingstone, *J. Chem. Soc.* (*C*), 1970, 1006.

sofa conformation (6) (C-3 out of plane) and the half-boat conformation (8) have also to be considered. Conformations (5) to (8) may all undergo ring-inversion processes. Although little appears to be known about the energy barriers to ring inversion in chromans, analogy with cyclohexene [9] would suggest that these barriers are relatively small.

In the present instance, where we are concerned with 2,3-disubstituted chromans, the sofa conformation (7) is expected to be less stable than the sofa conformation (6), since the eclipsing effects in (6) are between substituents and oxygen lone pairs, whereas those in (7) are between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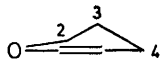
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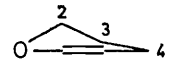
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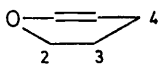
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substituents and hydrogen. Likewise, *cis*-2,3-disubstituted chromans are unlikely to assume the half-boat conformation (8), owing to marked steric interactions between the substituents. As far as the half-chair (5) and sofa conformations (7) are concerned, groups at position 2 should have a preference for the equatorial orientation which is *less* marked than in cyclohexanes, as only one axial : axial interaction is involved in the axial orientation. For 3-substituted chromans, it is quite possible than an axial orientation is preferred to an equatorial orientation, owing to the expectation of a small repulsive interaction between the axial substituent and an oxygen lone-pair (*cf.* 1,3-dioxans [10]). The following criteria are expected to be of some use in attempts to determine the conformation and configuration of 2,3-disubstituted chromans.

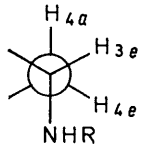
(i) *Chemical Shifts.*—An *e* proton at position 4 is expected to occur at lower field than an *a* proton at the same position. However, since the shifts of H_{4e} and H_{4a} will be sensitive to the nature and orientation of the 3-substituent, chemical-shift correlations for the protons at position 4 are not expected to be particularly helpful in making assignments. Also, comparisons of proton shifts at C-2 and C-3 of one compound, with the shifts of corresponding protons at C-2 and C-3 in the stereoisomer, are not likely to lead to reliable conclusions, in the absence of evidence on the chemical shifts in simple 2- and 3-substituted chromans, and on the effect of substituents on the shifts of neighbouring protons.

(ii) *Vicinal Coupling Constants.*—Vicinal proton–proton coupling constants are expected to provide valuable information relating to the conformation of chromans. Thus, values of 1·5 to 5 Hz imply an *ea*, *ae*, or *ee* relationship of protons in (5)—(7), whilst values of 8 to 12 Hz imply an *aa* relationship in (5)—(7) and either an *aa* or *ee* relationship in (8). However, the sensitivity of vicinal coupling constants to the nature [11] and orientation of substituents [12-14] is a major complication with 2,3-disubstituted chromans. Thus, in the half-chair conformation of chromans, $J_{2a,3a}$ is expected to be *less* than $J_{3a,4a}$, whilst in chroman-3-amines, $J_{2a,3e}$ should be *less* than $J_{2e,3a}$.

(iii) *Long-range Coupling Constants* $J_{2,4}$.—Four-bond coupling $J_{2,4}$ may occur between protons at positions 2 and 4. The easily measurable four-bond couplings of 1 Hz or more are only expected to occur through the coplanar zig-zag pathway,[15] which is only possible for 2*e*,4*e* protons in the half-chair conformation (5) or the sofa conformation (6).

(iv) *Geminal Coupling Constant* $J_{4,4}$.—The factors influencing the values of geminal coupling constants are well known.[16-20] The values of $J_{4,4}$ in chromans will depend on the orientation of the C(4)–H bonds with respect to the aromatic ring, as this will affect the π-contribution.[18,19] Therefore values of $J_{4,4}$ may be algebraically *higher* (numerically *lower*) for the half-boat conformation. However, values of $J_{4,4}$ should differ little in half-chair and sofa conformations. A major influence on $J_{4,4}$ in chroman-3-amines is likely to be the orientation of the electronegative 3-substituent.[20] Thus, *axial* orientation of the 3-substituent in the half-chair or sofa conformations [*cf.* projection (9)] should result in a numerically *higher* value of $J_{4e,4a}$; *equatorial* orientation of the 3-substituent [*cf.* projection (10)] should result in a numerically *lower* value of $J_{4e,4a}$.

Proton chemical-shifts for *cis* (α)- and *trans* (β)-2-methylchroman-3-amines and derivatives are reported in Tables 1 and 3 respectively; coupling constants are given in Table 2 (*cis*-) and Table 4 (*trans*-). Initially, it was hoped to make definite assignments of configuration to



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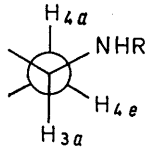

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the α- and β-isomers by analysis of the spectra of the chromanamines, the *NN*-dimethylchromanamines, and hydrochloride derivatives. However, difficulties were

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[18] M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, 1963 **85**, 1899.
[19] D. H. Williams and N. S. Bhacca, *Chem. and Ind.*, 1965, 506.
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encountered because the derived coupling constants for a given pair of ring protons showed large variations for different derivatives possessing the *same* configuration. The α- and β-2-methylchroman-3-amines were therefore converted into their phthaloyl derivatives.[21] The spectrum of β-2-methyl-*N*-phthaloylchroman-3-amine (see below) could only be interpreted on the assumption of a *trans*-configuration of the substituents at positions 2 and 3. Consequently, compounds of the β-series have the *trans*-configuration; compounds of the α-series have the *cis*-configuration.

A discussion of the spectra now follows, chemical shifts being given in τ values.

cis- *and* trans-2-*Methylchroman*-3-*amine*.—The spectra of the primary amines presented difficulties because two of the three protons at positions 3 and 4 have similar chemical shifts. For the *cis*-amine (11; R = NH_2) the value of $J_{2,3}$ does not immediately distinguish (13) and

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TABLE 1

Proton chemical shifts (τ) in spectra of *cis*-2-methyl-3-R-chromans (220 MHz)

R	Solvent	Preferred conformation	H_{2e}	H_{2a}	H_{3e}	H_{3a}	H_{4e}	H_{4a}	CH_3	Misc.
NH_2	$CDCl_3$	(13)		5·86	6·9—7·0		6·9—7·0 [a]	7·36 [a]	8·66	
$\overset{+}{N}H_2$	CF_3CO_2H	(13)		5·60	5·96		6·57	6·90	8·43	
$NH_3^+Cl^-$	D_2O	(13)		5·73	6·17		6·45	7·05	8·57	
NHAc	$CDCl_3$	(21)		5·78	5·58		6·85	7·21	8·66	8·06,[b] 3·9 [c]
$N(CO)_2C_6H_4$	$CDCl_3$	(25)		5·64	5·19		6·39	6·78	8·70	
NMe_2	$CDCl_3$	(18)	5·43			7·47	7·10	7·30	8·78	7·70 [d]
$\overset{+}{N}HMe_2Cl^-$	D_2O	(17)		5·33	6·15		6·66 [a]	7·23 [a]	8·47	7·00 [d]

[a] Assignments for H_{4e} and H_{4a} may need to be reversed. [b] CH_3CO. [c] NH. [d] NMe_2.

TABLE 2

Proton–proton coupling constants (Hz) in spectra of *cis*-2-methyl-3-R-chromans (220 MHz)

R	Solvent	Preferred conformation	$J_{2e,3e}$	$J_{2a,3e}$	$J_{3e,4e}$	$J_{3e,4a}$	$J_{3a,4e}$	$J_{3a,4a}$	$J_{2e,4e}$	$J_{4e,4a}$	J_{CH_3-CH}	Misc.
NH_2	$CDCl_3$	(13)		<1	*a*	*a*				*a*	6·0	
NH_2	CF_3CO_2H	(13)		<1	4·3	<1				18·4	6·5	
$\overset{+}{N}H_3Cl^-$	D_2O	(13)		1·25	5·25	1·9				17·9	6·5	
NHAc	$CDCl_3$	(21)		1·85	5·30	1·7				17·1	6·5	9·0 [c]
$N(CO)_2C_6H_4$	$CDCl_3$	(25)		3·1	6·30	7·5				17·35	6·55	
NMe_2	$CDCl_3$	(18)	3·9				5·9	10·0	1·0	15·90	6·70	
$\overset{+}{N}HMe_2Cl^-$	D_2O	(17)		2·7	6·6 [b]	5·6 [b]				17·80	6·8	

[a] $J_{4e,4a} + J_{3e,4e}$ (or $J_{3e,4a}$) = 23·0 Hz. [b] These assignments may need to be reversed. [c] J_{3HNH}.

TABLE 3

Proton chemical shifts (τ) in spectra of *trans*-2-methyl-3-R-chromans (220 MHz)

R	Solvent	Preferred conformation	H_{2e}	H_{2a}	H_{3e}	H_{3a}	H_{4e}	H_{4a}	CH_3	Misc.
NH_2	$CDCl_3$	(15)		6·20		7·05—7·12	7·05—7·12	7·47	8·65	
NH_2	CF_3CO_2H	(16)	5·28		6·02		7·00 [a]	6·65 [a]	8·62	
$\overset{+}{N}H_3Cl^-$	D_2O	(16)	5·55		6·30		7·40	6·80	8·64	
NHAc	$CDCl_3$	(24)	5·7—5·75		5·7—5·75		6·91 [a]	7 30 [a]	8·68	8·04,[b] 3·83 [c]
$N(CO)_2C_6H_4$	$CDCl_3$	(27)		5·20		5·57	7·14	6·33	8·70	
NMe_2	$CDCl_3$	(19)		5·95		←——7·2 to 7·35——→			8·60	7·72 [d]
$NHMe_2Cl^-$	D_2O	(20)	5·13		6·22		6·77	6·60	8·58	7·02 [d]

[a] Assignments for H_{4e} and H_{4a} may need to be reversed. [b] CH_3CO. [c] NH. [d] NMe_2.

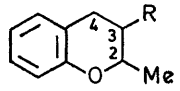
TABLE 4

Proton–proton coupling constants (Hz) in spectra of *trans*-2-methyl-3-R-chromans (220 MHz)

R	Solvent	Preferred conformation	$J_{2e,3e}$	$J_{2a,3a}$	$J_{3e,4e}$	$J_{3e,4a}$	$J_{3a,4e}$	$J_{3a,4a}$	$J_{2e,4e}$	$J_{4e,4a}$	J_{CH_3CH}	Misc.
NH_2	$CDCl_3$	(15)		7·7			*a*	*b*		*b*	6·1	
NH_2	CF_3CO_2H	(16)	<1·0		<0·5 [c]	4·8 [c]				18·35	*d*	
$\overset{+}{N}H_3Cl^-$	D_2O	(16)	4·25		4·25	5·45			1·0	17·90	6·5	
NHAc	$CDCl_3$	(24)	*a*		5·10 [c]	4·25 [c]				17·05	6·4	
$N(CO)_2C_6H_4$	$CDCl_3$	(27)		9·95			5·70	12·10		15·62	6·2	
$N(CH_3)_2$	$CDCl_3$	(19)		8·10			*a*	*a*		*a*	6·3	
$\overset{+}{N}HMe_2Cl^-$	D_2O	(20)	2·8		2·9	5·75			1·5	18·5	6·65	

[a] Not measurable. [b] $J_{4e,4a} + J_{3a,4a}$ = 28·0 Hz. [c] These assignments may need to be reversed. [d] Not measured.

(14). In the symmetrical quartet (X of ABX) at 7·36, the separations of the more intense, *inner* pair of lines and of the outer pair, are 14·0 and 20·0 Hz respectively. For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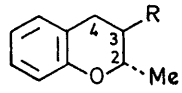
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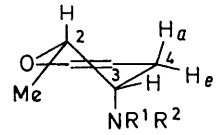
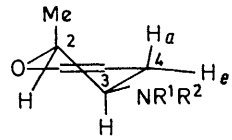
benzene as solvent, the corresponding separations are 14·0 and 18·5 Hz. The pattern of two strong and two weak lines, for the X part of an ABX system, is typical of cases in which J_{AX} and J_{BX} are opposite in sign. Therefore, we assign the 7·36 quartet to either H_{4e} or H_{4a}, with H_A as its geminal partner, and H_B being H_3. Since $|J_{AX} + J_{BX}| = 14{\cdot}0$ Hz, and since J_{AX} is expected to be in the range −16 to −18 Hz, J_{BX} must be +2 to +4 Hz, but again this value is compatible with either (13) or (14). However, two facts indicate a preponderance of (13): (*a*) the absence of observable long-range coupling $J_{2.4}$ and (*b*) the very low value of $J_{2.3}$ which is more compatible with $J_{2a.3e}$ than with $J_{2e.3a}$.[13] The spectrum of the *trans*-amine (12; R = NH_2) yields $J_{2.3}$ as 7·7 Hz, suggesting (15), rather than (16), as the dominant conformation. The arguments used in the analysis of the spectrum of the *cis*-amine can be applied to the quartet (X of ABX) at 7·47, which is therefore assigned to H_{4e} or H_{4a}, with H_A as its geminal partner. The separation of the more intense, inner pair of lines gives $|J_{AX} + J_{BX}|$ as 7·0 Hz (6·5 Hz in benzene). Therefore J_{BX} is in the range +9 to +11 Hz, confirming the strong preference for conformation (15).

Salts of cis- *and* trans-2-*Methylchroman*-3-*amine*.—Spectra of the primary amine salts were obtained from the hydrochlorides in D_2O, and the bases in CF_3CO_2H. The J values were obtained directly from line separations in the 220 MHz spectra, which were nearly first-order. For the *cis*-amine, the rather low value of $J_{2.3}$, the values of $J_{3.4}$, the relatively high value of $J_{4e,4a}$ (numerically), and the absence of long-range coupling $J_{2.4}$ all point to a conformation of type (13) in both D_2O and CF_3CO_2H. Conformation (14) is disfavoured by the 1,3-(repulsive)-interaction CH_3···H; the corresponding interaction in (13) is between $\overset{+}{N}H_3$ and oxygen lone pair and may be attractive in character. Salts of the *trans*-amine, in both D_2O and CF_3CO_2H, show a clear preference for the diaxial conformation of type (16), probably as a result of an attractive force similar to that favouring (13) for the protonated *cis*-amine. This is evident from the vicinal coupling constants, together with the observation of a long-range coupling $J_{2.4}$ for the hydrochloride in D_2O. However, the changes in $J_{2e,3e}$ and $J_{3e,4e}$ which accompany the change of solvent from D_2O to CF_3CO_2H (Table 4) are more difficult to explain.

cis- *and* trans-2,NN-*Trimethylchroman*-3-*amine*.—The conclusion that the *cis*-base prefers (18), rather than (17), relies on the values of the vicinal coupling constants, the observation of long-range coupling $J_{2.4}$, and the rather low value (numerically) for $J_{4e.4a}$. The spectrum of the *trans*-base is difficult to analyse because H_3, H_{4e}, and H_{4a} have similar chemical shifts. The suggestion that (19) is preferred over (20) rests on the relatively high value of $J_{2.3}$ and the absence of observable long-range coupling $J_{2.4}$.

Hydrochlorides of cis- *and* trans-2,NN-*Trimethylchroman*-3-*amine*.—The spectra of both hydrochlorides are practically first-order at 220 MHz. For the *cis*-hydrochloride, the values of $J_{3,4}$ do not enable a distinction to be made between a conformation of type (17) and


(13) $R^1 = R^2 = H$
(17) $R^1 = R^2 = Me$
(21) $R^1 = H, R^2 = Ac$
(25) $R^1, R^2 = -COC_6H_4CO-$


(14) $R^1 = R^2 = H$
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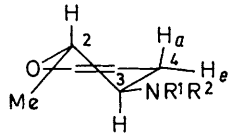
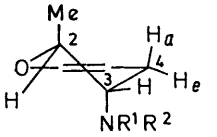
(26) $R^1, R^2 = -COC_6H_4CO-$


(15) $R^1 = R^2 = H$
(19) $R^1 = R^2 = Me$
(23) $R^1 = H, R^2 = Ac$
(27) $R^1, R^2 = -COC_6H_4CO-$


(16) $R^1 = R^2 = H$
(20) $R^1 = R^2 = Me$
(24) $R^1 = H, R^2 = Ac$
(28) $R^1, R^2 = -COC_6H_4CO-$

one of type (18). However, the relatively high (numerically) value of $J_{4e.4a}$ and the absence of observable long-range coupling $J_{2.4}$ point to a conformation of type (17). Moreover, the relatively small value of $J_{2.3}$ also suggests type (17), in which the orientation of C(2)–O and C(3)–N gives a maximum attenuation of $J_{2.3}$. The values of the vicinal and long-range coupling constants provide convincing evidence that the *trans*-hydrochloride assumes the diaxial conformation of type (20), like the corresponding primary amine, and probably for similar reasons.

cis- *and* trans-N-*Acetyl*-2-*methylchroman*-3-*amine*.—The coupling constants deduced from the spectrum of the *cis*-amide in $CDCl_3$ indicate a clear preference for conformation (21), a preference probably dictated by steric considerations alone. Interestingly, the relatively high value of J_{CHNH} suggests a preference for a conformation about the C(3)–N bond which places the nitrogen attached hydrogen *trans*- with respect to H_3, a situation in which the N–H is close to an orbital containing an unshared electron pair of the ring oxygen. There is thus the possibility that attraction between the N–H and the unshared pair provides a further stabilisation of (21) over (22). The spectrum of the *trans*-amide is complicated by

the closeness in shift of H_2 and H_3. However, a first-order analysis of the well-separated quartets for H_{4e} and H_{4a} gives values for J_{gem} and J_{vic} which lead to the tentative suggestion of a preponderance of (24) in a mixture of (23) and (24).

cis- *and* trans-2-*Methyl*-N-*phthaloylchroman*-3-*amine*.—The n.m.r. parameters for the *cis*-imide suggest a preponderance of conformation (25), with phthalimido-axial. Thus the spectrum discloses a relatively high value of $J_{4e,4a}$ and a low field position for H_3 (*cf.* ref. 22). The unusually high values for $J_{3e,4a}$ and $J_{3e,4e}$ may be reconciled with (25) by recalling: (i) the relatively high value of 5·8 Hz for $J_{1e,2a}$ in 3,5-dimethyl-1-phthalimidocyclohexane with phthalimido *axial*,[22] and (ii) the general tendency in chromans for many $J_{3,4}$ values to be unusually high.[6] That the *trans*-imide exists entirely as (27) is clear from the values of J_{gem} and J_{vic} in Table 4. The assignment of the quartet at 6·33 to H_{4a} rests on the high value of $J_{3a,4a}$ and on its low-field shift, which implies axial character when adjacent to equatorial phthalimido.[22]

Finally, the pK_a values of the bases prepared during this investigation were measured. *cis*- and *trans*-2-Methylchroman-3-amines had almost identical pK_a values of 7·61 and 7·64 respectively. However, *cis*-2,*NN*-trimethylchroman-3-amine (21) pK_a 6·51, was an appreciably weaker base than *trans*-2,*NN*-trimethylchroman-3-amine (23), pK_a 7·20. Both (21) and (23) have equatorial NMe_2 substituents whilst the most stable conformation of the protonated amines, (25) and (28) respectively, have axial $H\overset{+}{N}Me_2$ groups. We are unable at present to offer any explanation of the appreciable difference in basicity of (21) and (23).

cis-2,*NN*-Trimethylchroman-3-amine hydrochloride shows interesting pharmacological activity on the central nervous system [23] and is now undergoing clinical trial.

EXPERIMENTAL

N.m.r. spectra were measured on a Varian A-60 spectrometer, a Varian HA-100 spectrometer, and a Varian HR-220 spectrometer. Internal references were tetramethylsilane and sodium 3-trimethylsilylpropane-1-sulphonate (for D_2O solutions). pK_a Determinations were carried out in 50% ethanol.

cis-2-*Methylchroman*-3-*amine Hydrochloride* (α-*Isomer*) (2) *and* 3-*Hydroxyamino*-2-*methylchroman* (4).—2-Methyl-3-nitro-2*H*-1-benzopyran [1] (29·5 g) in ether (500 ml) was added dropwise to a suspension of lithium aluminium hydride (20 g) in ether (500 ml) during 1¼ h. The mixture was refluxed for 4½ h, and then cooled; excess of reagent was then decomposed by addition of water (80 ml). The mixture was filtered, and the residue washed thoroughly with hot ethyl acetate. The combined washings and filtrate were extracted with 2N-hydrochloric acid and the acid extracts were basified with 10N-sodium hydroxide; the bases were extracted in ether. The ether extracts were dried (Na_2SO_4) and evaporated, and the residual oil was distilled *in vacuo*. 2-Methylchroman-3-amine (rich in the *cis*-isomer) was obtained as a colourless liquid (17·6 g), b.p. 85—86° at 0·8 mmHg. 3-Hydroxylamino-2-methylchroman co-distilled with the chromanamine but crystallised from the distillate on cooling. On separation, 3-*hydroxylamino*-2-*methylchroman* was obtained as white needles (up to *ca.* 7% of the total weight of product) of m.p. 175·7° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 66·5; H, 6·9; N, 7·7. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%).

Addition of ethereal hydrogen chloride to an ether solution rich in *cis*-2-methylchroman-3-amine afforded the *cis*-2-*methylchroman*-3-*amine hydrochloride* after recrystallisation from isopropyl alcohol as white needles, m.p. 260—261° (Found: C, 60·4; H, 6·9; N, 6·6. $C_{10}H_{14}ClNO$ requires C, 60·1; H, 7·1; N, 7·0%). An n.m.r. spectrum of a further crop of crystals from the mother liquors indicated a mixture of *cis*- and *trans*-isomers.

trans-2-*Methylchroman*-3-*amine Hydrochloride* (β-*Isomer*) (2) *and* NN′-*Di-isopropyl*-2,2′-*dimethyl*-(4,4′-*bichroman*)-3,3′-*diamine* (3; R = Pr^i).—2-Methylchroman-3-amine was prepared as described by Bachman and Levine.[1] Like those authors we only obtained poor yields after distillation of the basic product *in vacuo* but there was a large proportion of high-boiling basic residue. Addition of acetone to the residue afforded some white needles which were isolated and characterised as NN′-*di-isopropylidene*-2,2′-*dimethyl*-(4,4′-*bichroman*)-3,3′-*diamine*, m.p. 240–241° (from acetone) (Found: C, 77·2; H, 8·1; N, 7·2. $C_{26}H_{32}N_2O_2$ requires C, 77·2; H, 8·0; N, 6·9%). Hydrogenation of the di-isopropylidene compound in ethanol in the presence of 10% Pd-C and PtO_2 at atmospheric temperature and pressure, followed by conventional isolation procedures and conversion of the crude base into the hydrochloride, afforded NN′-*di-isopropyl*-2,2′-*dimethyl*-(4,4′-*bichroman*)-3,3′-*diamine hydrochloride* (3; R = Pr^i) as white prisms decomposing above 270° (Found: C, 60·3; H, 8·2; N, 5·4. $C_{26}H_{38}Cl_2N_2O_2,2H_2O$ requires C, 60·8; H, 7·7; N, 5·85%).

On conversion of the 2-methylchroman-3-amine into the hydrochloride [1] the *trans*-isomer was obtained as white prisms (from ethanol), m.p. 217—218°.

cis-2,NN-*Trimethylchroman*-3-*amine Hydrochloride*.—*cis*-2-Methylchroman-3-amine hydrochloride (92·3 g) was dissolved in 5N-sodium hydroxide and extracted with ether. Evaporation of the dried ether extracts afforded the free base (74·0 g) which was refluxed with 40% (w/w) aqueous formaldehyde (100 ml) and 90% formic acid (180 ml) for 6 h. The mixture was evaporated and water was added to the residue; it was then basified with 10N-sodium hydroxide and extracted with ether. Evaporation of the dried ether extracts, followed by distillation of the residue *in vacuo*, afforded cis-2,NN-*trimethylchroman*-3-*amine* as a colourless liquid (67·8 g), b.p. 90—96° at 0·9 mmHg (Found: C, 75·6; H, 9·0; N, 7·4. $C_{12}H_{17}NO$ requires C, 75·35; H, 9·0; N, 7·3%). Addition of ethereal hydrogen chloride to an ethereal solution of the base afforded the *hydrochloride* as needles (79·6 g), m.p. 217—218° (from ethanol) (Found: C, 63·3; H, 8·1; N, 6·2. $C_{12}H_{18}ClNO$ requires C, 63·3; H, 8·0; N, 6·15%).

trans-2,NN-*Trimethylchroman*-3-*amine Hydrochloride*.—*trans*-2-Methylchroman-3-amine hydrochloride (9·1 g), sodium formate (3·3 g), 98% formic acid (30·1 ml), and formaldehyde (30·1 ml; 40% aq. w/v) were refluxed and stirred for 6 h. The cooled solution was basified with 10N-sodium hydroxide and extracted with ether. The base was extracted into 2N-hydrochloric acid and the aqueous extract was basified and extracted with ether. The ether extracts

[22] H. Booth and P. R. Thornburrow, *J. Chem. Soc.* (*B*), 1971, 1051.

[23] B.P. 1,151,474/1969.

were washed with water and dried ($CaSO_4$), and an excess of ethereal hydrogen chloride was added. Recrystallisation from ethanol–ether afforded the *hydrochloride* as needles (6·7 g), m.p. 195—197° (Found: C, 61·3; H, 7·9; N, 6·0. $C_{12}H_{18}ClNO,0{\cdot}5H_2O$ requires C, 60·9; H, 8·1; N, 5·9%).

Reduction of 3-*Acetamido-2-methylchroman-4-one.*—3-Acetamido-2-methylchroman-4-one [2] (2·2 g) in absolute ethanol (80 ml) was hydrogenated at atmospheric temperature and pressure. The catalyst was filtered off at the boil and washed with hot ethanol. Evaporation of the combined washings and filtrate afforded 3-*acetamido-2-methylchroman-4-ol* as needles (1·95 g), m.p. 245—246° (from ethanol) (Found: C, 65·1; H, 6·9; N, 6·1. $C_{12}H_{15}NO_2$ requires C, 65·1; H, 6·8; N, 6·3%).

3-Acetamido-2-methylchroman-4-ol (1·8 g) in glacial acetic acid (100 ml) and concentrated sulphuric acid (3 ml) was hydrogenated at atmospheric pressure and 60° in the presence of 10% Pd–C (1 g). The catalyst was filtered off and sodium acetate (4·7 g) was added to the filtrate. The acetic acid was evaporated off, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried ($CaSO_4$), and evaporated. The residual oil crystallised as needles (1·2 g), m.p. 88—90°, identical with *trans*-N-acetyl-2-methylchroman-3-amine (see below).

cis- *and* trans-N-*Acetyl-2-methylchroman-3-amines.*—The appropriate 2-methylchroman-3-amine hydrochloride (2 g), water (10 ml), ethyl acetate (40 ml), acetic anhydride (5 ml), and sodium acetate (4·1 g) were stirred at room temperature for 4 h. The ethyl acetate layer was separated and washed with water. The combined aqueous solutions were extracted with ethyl acetate and the organic phases were combined, dried ($CaSO_4$), and evaporated. The residual oil eventually crystallised.

cis-N-*Acetyl-2-methylchroman-3-amine* was obtained as prisms (1·6 g), m.p. 112—112·5° (from isopropyl alcohol) (Found: C, 70·5; H, 7·8; N, 6·6. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%). trans-N-*Acetyl-2-methylchroman-3-amine* was obtained as needles (1·65 g), m.p. 96—97° (Found: C, 70·3; H, 7·6; N, 6·7. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%).

Acid Hydrolysis of trans-N-*Acetyl-2-methylchroman-3-amine.*—*trans-N*-Acetyl-2-methylchroman-3-amine (1 g) in 6N-hydrochloric acid (25 ml) was refluxed for 17 h. Concentration of the solution afforded *trans*-2-methylchroman-3-amine hydrochloride as white prisms, identical with an authentic sample.

cis- *and* trans-2-*Methyl*-N-*phthaloylchroman-3-amines.*—*trans*-2-Methylchroman-3-amine hydrochloride (1·38 g), sodium acetate (0·6 g), phthalic anhydride (1·1 g), and glacial acetic acid (7 ml) were refluxed for 1 h. The mixture was filtered while hot and the N-*phthaloyl derivative* of the *trans*-isomer separated as white needles (0·9 g), m.p. 158—160° (Found: C, 73·2; H, 5·4; N, 4·7. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·15; N, 4·8%).

When the above experiment was repeated with the *cis*-isomer of 2-methylchroman-3-amine hydrochloride (5·5 g), no crystalline phthaloyl derivative was obtained. The reflux time was, therefore, extended to 4¼ h. After the mixture had been set aside for 2 weeks, 1·3 g of solid separated having m.p. 139—141°. The N-*phthaloyl derivative* of the *cis*-isomer was finally obtained as prisms (0·55 g), m.p. 148—149° (from glacial acetic acid) (Found: C, 71·3; H, 5·1; N, 4·8. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·15; N, 4·8%). A mixed m.p. with the phthaloyl derivative of the *trans*-isomer was 130—134°.

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