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STRUCTURAL STUDIES OF FLAVAN DERIVATIVES: EFFECT OF OVERCROWDING ON CONFORMATION AND HYDROGEN BONDING OF *cis*- AND *trans*-DIPHENYL FLAVAN-3 YL CARBINOLS

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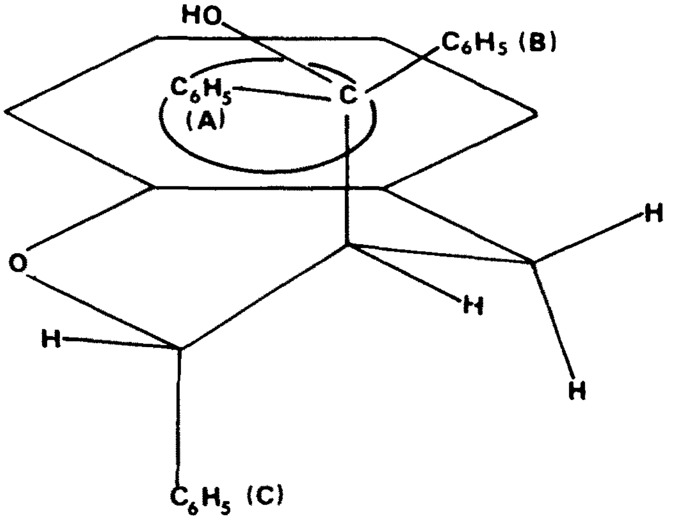
Abstract – IR, ^{1}H NMR and X-ray crystallographic studies of the title compounds show that the *trans*-isomer exhibit a diaxially substituted half-chair conformation of the dihydropyran ring owing to destabilization of the alternative overcrowded diequatorial conformation. Steric hindrance prevents a closer approach of the hydroxyl group to the ring oxygen limiting the strength of the OH...O intramolecular hydrogen bonding and allowing thermal vibration of large amplitude. The *cis* isomer adopts a C(3) sofa conformation for the dihydropyran ring, tightly bonded by a strong OH ... π intramolecular hydrogen bonding which contributes to a higher rigidity of the whole molecule.

The conformational preference of a substituent for an equatorial position of a slightly flattened chair[1] is a well-known feature of the stereochemistry of monosubstituted cyclohexanes[2] except only in particular cases (as for instance, for cyclohexylmercuric derivatives which have been reported[3] to exhibit negative A values, i.e. ΔG°'s in kcal/mol for the equatorial-to-axial conformational change).[4] If one considers heterocyclic analogues of cyclohexane, exceptions to the above preference can arise as a result of dipole–dipole interaction between the ring heteroatom and a polar substituent; this phenomenon is responsible for the anomeric effect[5] shown by 2-halo-, alkoxy- or acyloxy- tetrahydropyrans[6,7] where the polar substituent is predominantly axially orientated, and which have been described in terms of orbital interaction.[8] In other cases electrostatic interactions can favour such preferential orientation.[9] When the substituent is of non-polar nature, the preference for equatorial position on a chair conformation is still observed[10] and one can expect that this preference will be more pronounced as the bulkiness of the substituent is increased. For a vicinally trans-disubstituted six-membered ring, in absence of polar effects, the diequatorially substituted chair is still more preferred as compared to the diaxial isomer; trans-1,2-dimethylcyclohexane exists 99% in the diequatorial conformation.[11] Nevertheless one can expect some repulsion between the trans groups in equatorial position causing some flattening of the chair. This repulsion is not general, particularly in the case of some electronegative substituents, where a residual attraction (called the gauche effect) would remain between the substituents.[12] This steric repulsion has been postulated to account for the enhanced anomeric effect observed in 2-methoxy-trans-5,6-dimethyltetrahydropyran.[13]

Whether steric repulsion become sufficient to reverse the general trend for greater stability of the diequatorial conformer, causing the diaxial conformer to be the preferred one, is a point of interest discussed in this paper.

Recently[14] the conclusion was reached by calculation that *trans*-1,2,-di-*tert*-butyl cyclohexane exists as a conformational mixture, a twist conformation and a diaxial chair conformation, the latter being the major component. The existence has been reported in the solid state, of a vicinally *trans*-diaxially substituted ring in absence of polar effects. X-Ray structure determination of *trans*-1,2-di-(2-carboxy-methyl-2-propyl) cyclohexane has shown[17] that this derivative presents a chair conformation bearing the substituents in axial positions. But in this case the chair is distorted by a flattening which lowers the torsion angle in the substituted part of the ring to 37°4 (instead of 58°), so that the substituents are in fact lying in altered axial positions, their dihedral angle amounting only to 134.5°. When dipolar or anomeric effects operate *trans* diaxially substituted ring can be observed as for instance in the case of *trans*-1,2-dibromocyclohexane[15] and *trans*-2,3-dibromo-1,4-dioxan.[16]

We have undertaken a structural study of dihydropyran derivatives for which we were expecting a more perfectly diaxial disposition for bulky vicinal substituents. We report our results in the field of 2,3-disubstituted chromans which show how overcrowding between vicinal non-polar substituents can bring the diaxial conformation to become the only one observable, as well in solution as in the solid state. We also present a discussion about the half-chair and the sofa forms of the dihydropyran ring together with an analysis of the influence of overcrowding on hydrogen bonding shown by the compounds we have studied,



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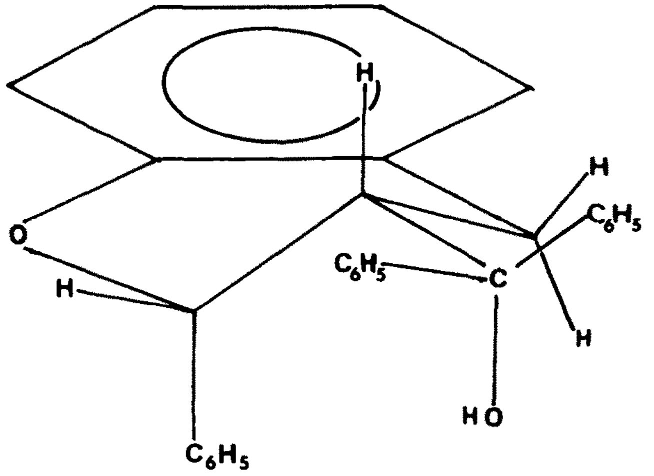

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the *trans*- and *cis*-diphenyl flavan-3-yl carbinols **1** and **2**.

These chroman derivatives have been chosen because axial positions for 2 or 3 substituents on the dihydropyran ring would be less disfavoured than in cyclohexane, since syn-axial interactions of the substituents with the aromatic sextet of the benzo group and with either one lone pair on oxygen, or the pseudo axial H(4), would be less severe than interactions involving axial C–H bonds of the corresponding cyclohexane.[18] Furthermore the presence of an OH group carried by the 3-substituent could provide further information on the conformation of the molecule through IR or NMR study: an intramolecular bond with the heterocyclic oxygen was expected to occur only if the carbinol group assumed an axial position, while OH... π bonds involving the 2-phenyl group were possible in all cases except in the diaxial conformation of the *trans* isomer. Preliminary study[19a] in solution by IR and ^{1}H NMR had led to the conclusion that indeed the *trans* isomer **1** should exist exclusively as a diaxially substituted chroman possessing a half-chair or a sofa conformation of its dihydropyran ring. In order to ascertain this conclusion, to specify the part taken by hydrogen bonding and to choose between the half-chair or the sofa conformations, an X-ray structure determination was carried out on the two isomeric diphenyl flavan-3-yl carbinols **1** and **2**. The results of this crystallographic study will be extensively published elsewhere,[20] in the present publication only the significant features needed for the conformational and hydrogen bonding studies are reported.

RESULTS AND DISCUSSION

Synthesis of the *cis* compound has been achieved by addition of the Grignard reagent of bromobenzene to *cis*-ethylflavan-3-yl carboxylate according the same

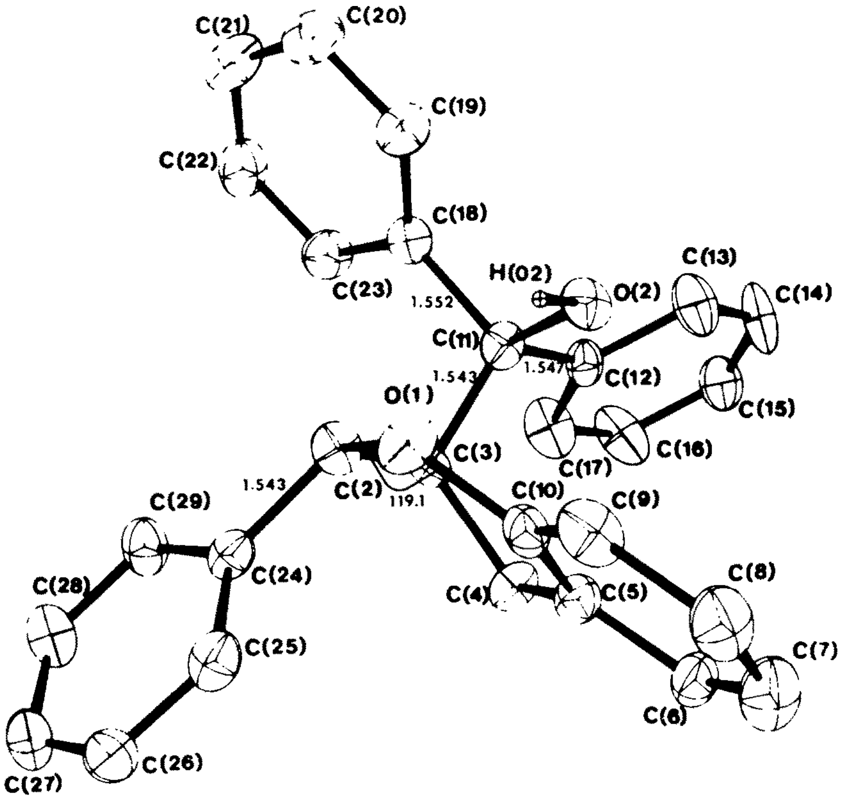

Fig. 1. A perspective view of the molecule of the *trans* isomer 1 with thermal ellipsoids scaled to 30% probability.

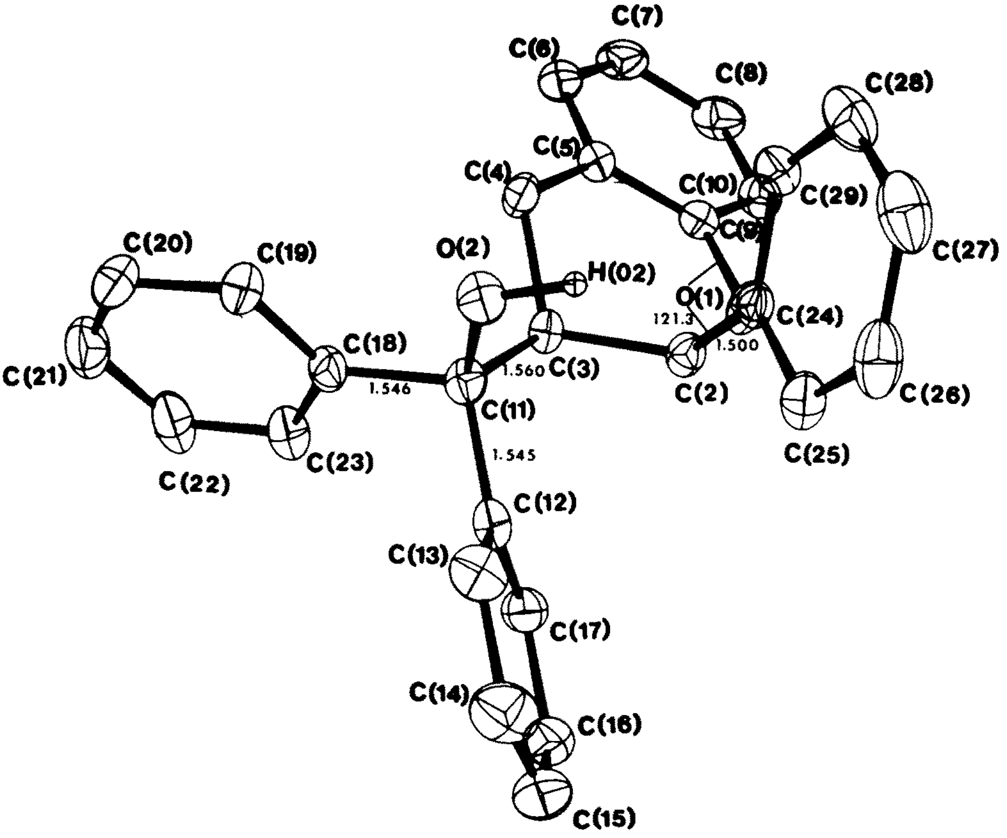

Fig. 2. A perspective view of the molecule of the *cis* isomer 2 with thermal ellipsoids scaled to 30% probability.

procedure we have previously described for the preparation of the *trans* isomer.[19] The results of IR and ^{1}H NMR spectroscopic measurements are reported in Tables 1 and 2. The X-ray crystallographic data are summarized, in Figs. 1 and 2 giving a stereoscopic view of the molecular structure of each isomer, of the most important bond lengths and bond angles which are needed for the further discussion. From the results of the X-ray study it was noticed that all the intramolecular distances of the phenyl rings A, B and C, which are far from the centre of the molecule were shorter than the standard values, for the *trans* isomer. It was expected that these discrepancies were caused by thermal agitation, so a least-squares analysis of rigid body motion of the molecule was carried out, according the method of Shoemaker and Trueblood,[21] and the bond lengths corrected for the effect of molecular vibration[22] have been calculated. For comparison the rigid body parameters of the *cis* isomer have also been determined: the results[20] show that while the molecule of the *cis* isomer can be considered as rigid, the molecule of the *trans* isomer does not behave like a rigid body.

In addition to these data Fig. 3 represents Newman projections along the C(2) C(3) bond. In Fig. 4 the observed ring torsional angles of the dihydropyran ring of each isomer are compared to those calculated for the half-chair and the sofa conformation in cyclohexene[1] and Table 3 give atomic displacements from the relevant least-squares plane of the dihydropyran ring.

The fact that two distinct isomers are produced by addition of the Grignard reagent of bromobenzene to *trans*- and *cis*-ethyl flavan-3 carboxylate shows that no epimerization takes place during this reaction, so that the stereochemistry of the starting diastereoisomeric esters is preserved.

Infrared study in dilute solution shows that neither of the two alcohols exhibits the absorption of a free hydroxyl group which would be expected in the range 3605–3617 cm^{-1} for a tertiary alcohol.[23] Furthermore, since no change in IR spectra is observed when concentration is raised, intermolecular hydrogen bonding does not occur at higher concentrations. These facts mean that the hydroxyl group is entirely involved in an intramolecular hydrogen bonding which is not affected by varying the concentration.

This conclusion is consistent with the results of the NMR study: the chemical shift of the hydroxyl proton is independent of concentration. The different values observed for the chemical shifts as well as the differences in IR absorption suggest that these intramolecular hydrogen bondings are of different nature. From the NMR data one can postulate that the lower shift for the *cis* isomer is to be related to an OH...π bond involving the 2-phenyl substituent

Table 1. IR absorption in the O–H region

Compound	ν_{OH} in dilute solution			ν_{OH} in concentrated solution	
1 (*trans*)	3583 cm^{-1}	c = 0.009	$W_{1/2}$ = 56 cm^{-1}	3583 cm^{-1}	c = 0.16
2 (*cis*)	3567 cm^{-1}	c = 0.005	$W_{1/2}$ = 33 cm^{-1}	3567 cm^{-1}	c = 0.08

Table 2. ^{1}H NMR parameters of alcohols **1** and **2**

Compound	Aromatic H	H(2)	H(3)	H(4a)	H(4e)	OH
1 (*trans*)	δ = 6.8–7.8	δ = 5.51	δ = 3.51	δ = 2.76		3.07
		J_{2-3} = 1.6	J_{3-4} = 4.8			
2 (*cis*)	δ = 6.7–7.9	δ = 5.75	δ = 3.76	δ = 3.21	δ = 2.51	1.55
		J_{2-3} = 4.2	J_{3-4a} = 12.4	J_{3-4e} = 4.2	J_{4a-4e} = 16.2	

Table 3. Equations of least-squares planes and deviations (Å) of relevant atoms from the plane of the dihydropyran ring

trans 1				*cis* 2			
Plane C(4)-C(5)-C(10)-O(1)							
0.7714 X - 0.5977 Y - 0.2180 Z =- 9.7888				0.4757 X + 0.4234 Y + 0.7709 Z = 8.016			
C(5)	0.010	O(1)	0.004	C(5)	-0.012	O(1)	-0.006
C(4)	-0.004	C(3)	0.501	C(4)	0.006	C(3)	0.674
C(10)	-0.10	C(2)	-0.187	C(10)	0.012	C(2)	0.017

which would shield the alcoholic proton, while the higher shift for the *trans* isomer would be correlated to an OH... O bond occurring between the heterocyclic ring oxygen and the hydroxyl group which is consequently deshielded.[24,25] This assumption leads to assign the lower $\Delta\nu$ in infrared (estimated lesser than 34 cm^{-1} in **1**) to the OH... O bond, and the larger one (upper limit: 50 cm^{-1}) to the OH... π bond, that is rather unusual. As far as the $\Delta\nu$ value is correlated to the strength of hydrogen bonding,[23b] OH... π bonds are generally considered to be weaker than OH... O bonds.[26] As ν_{OH} is unknown free an upper limit to $\Delta\nu$ (ν_{OH} free-ν_{OH} bonded) can be assigned using the highest value of the standard frequencies that have been calculated for a tertiary alcohol[23] *ca.* 3605–3617 cm^{-1}. More especially an OH...O intramolecular bond which occurs between an oxygen and a γ-hydroxyl group (i.e. which involves a six membered chelating cycle), displays a $\Delta\nu$ value included in the range 75–110 cm^{-1}.[27] So the observed 34 cm^{-1} value appears to be too weak and this fact will need some comment (*vide infra*). On the other hand a $\Delta\nu$ value of 50 cm^{-1} for the *cis* isomer is in good agreement with the general values observed for OH... π bonded 3-aryl propanols.[28,29] But whereas this bonding seems to be generally rather limited as shown by a very low intensity of the absorption band correlated with the bonded form of the studied alcohols[28] our case is probably unique owing to the fact that the OH... π bonded form is the only one observable.

Concerning the geometries that have been generally assigned to flavan derivatives and more particularly to 3-substituted flavans, the literature mentions that the half-chair[30] conformation and the sofa[31] conformation are the more stable and that they are of nearly equal stability.[32] Suprisingly the sofa conformation that has been considered is the C(2) sofa, i.e. the conformation in which all but the C(2) atoms lie in the same plane (Fig. 5); but there is apparently no reason to neglect the C(3) sofa which can be considered to possess approximatively the same energy. So the half-chair conformation can be described as a compromise between the two above sofa conformations.

The available data on cyclohexene stereochemistry show that sofa forms (which are in this case of identical energy since they are symmetrical) lie 1.2 kcal per mole higher than the half-chair form, and this difference can be lowered to 0.8 by taking into account a twisting of the double bond.[1] In the case of the dihydropyran ring, the introduction of the oxygen atom in the ring shortens the bonds involved in its linkage, so that the half-chair is no longer symmetrical. The different conformations can be characterized by the coordinate of the atom (or atoms) standing above (or below) the plane of the benzene ring which also contains, in absence of twisting, the oxygen and the C(4) atoms. These coordinates show the following relationships:

$$|h_2| < |h_3| < |s_3|$$
$$|h_2| < |s_2| < |s_3|$$

that can be deduced from the fact that C–O bonds are shorter than C–C ones and assuming that the COC angle is not significantly modified as compared with a CCC angle.

It is not necessary to take into account a half-boat conformation since its energy is too high (6.1 or 6.9 kcal/mole above the half-chair according to whether twisting is introduced or not).[1] Furthermore a half-boat does not seem appropriate to relieve the steric strain, as well in the *trans* compound where the substituents will not be spread further apart comparatively to the half-chair, as in the *cis* isomer, where the bulky groups will be forced to eclipse one with each other.

Returning to the conformations of lowest energy, one can notice that the relative orientations of the substituents in -2 or -3 positions will be nearly the same as that of axial (a) and equatorial (e) substituents standing on a chair conformation, whereas hydrogens in -4 position will have a pseudo axial (ψa) or a pseudo equatorial (ψe) orientation. Of course, differences in dihedral angles exist, but they are not significant enough to allow distinction between sofa and half-chair to be made by applying the Karplus equation to flavan compounds.[32] So we will examine how the observed NMR data can fit a half-chair conformation keeping in mind that the results could also apply to sofa conformations as well.

The striking differences which appear in the NMR spectra of the two isomers are a very low value for J_{2-3} and an AB_2 pattern for H(3) and the two H(4) of the *trans* compound as compared with the ABX figure shown by the *cis* isomer. Arguing for a fixed half-chair conformation, these features are well explained if a diaxially substituted conformation is assigned to the *trans* alcohol. Since then the small coupling constant is relative to an equatorial–equatorial coupling which is lowered by the anti orientation of the C(2)–O(1) bond with respect to the C(3)–H bond;[33] and in addition the C(3)–H(3) bond roughly bisects the two H(4) dihedral angle so that the corresponding coupling constants are equal (the observed value of 4.8 Hz is in good agreement with e–e or e–a coupling[34]). Concerning the *cis* isomer the NMR data lead to assign an equatorial position for the bulkier diphenyl carbinyl group and an axial position for the phenyl substituent. The coupling constant $J_{2,3}$ ($=4.2$ Hz) exhibit a normal value for an axial-equatorial coupling;[34] the axial position of H(3) explains that two different coupling constants with the two H(4) are observed, the highest one (12.4 Hz) being in agreement with an axial-pseudo-axial relationship.[34]

With regard to hydrogen bonding, the axial position of the carbinyl group in the *trans* isomer allows either an OH... O bond with ring oxygen or an OH... π bond with the benzo group of the chroman nucleus. But in this latter case a shielding effect by the benzo group would be expected.[35] As in fact a deshielding is observed, the correct assignment is an OH... O bond with the ring oxygen. The requisite geometry put the exocyclic C–O bond antiparallel to the C(3)–H bond, which provides additional lowering effect on the J_{2-3} coupling constant. In the *cis* isomer the equatorial position of the carbinyl substituent does not allow the formation of an OH... O bond; instead, the 2-phenyl group is well located for the fixing of an OH... π bond, which is indeed corroborated by the upfield shift observed for the hydroxyl proton.

The conformations that have been thus assigned are fixed conformations which are not affected by ring inversion: the consequence of any equilibrating process between two half-chair conformations would be to raise the J_{2-3} coupling constant of the *trans*

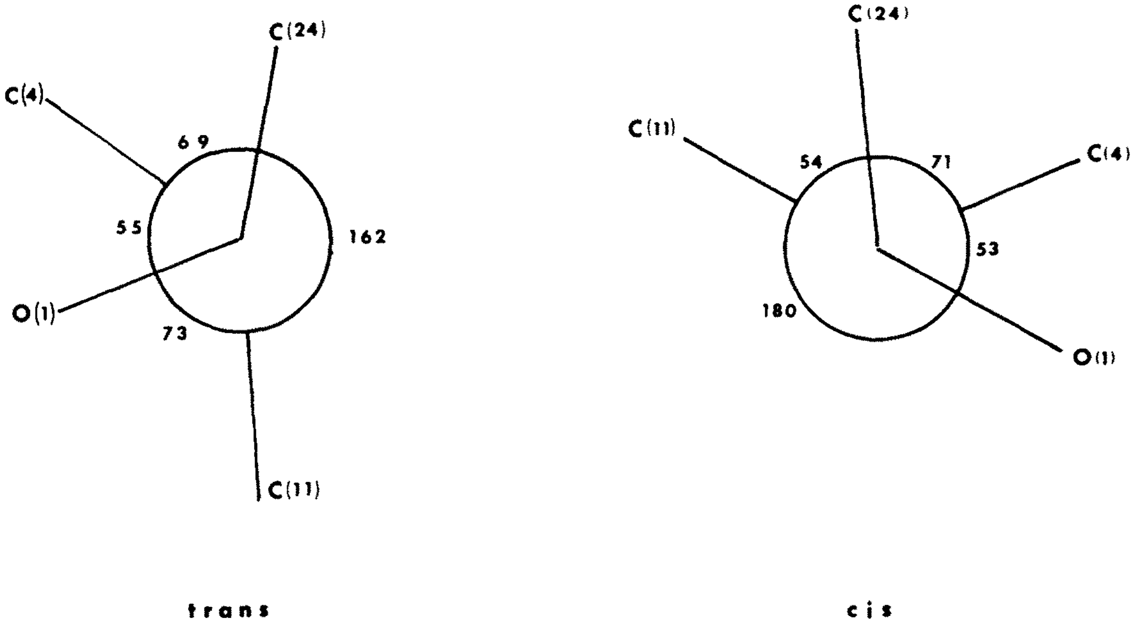

Fig. 3. Newman projections along the C(2)–C(3) bond. (a) in the *trans* isomer **1**, (b) in the *cis* isomer **2**.

compound, since it would be averaged with an a–a coupling, and to destroy the OH…O bond, so that an OH free or π bonded absorption would be observable. In the same manner ring inversion of the *cis* isomer would lower the H(3a)–H(4a) coupling by averaging it with an e–e one.

The crystallographic studies confirm in the solid state the geometry observed in solution.

Concerning the conformation of the chroman ring, the data collected in Table 3, which indicate the out-of-plane distances of C(2) and C(3) from the unit weighted least squares mean plane definite by O(1), C(10), C(5) and C(4) allows us to eliminate any participation of the C(2) sofa. One can notice that, while the *trans* compound assumes a conformation between the half-chair and the C(3) sofa ($z_2 = -0.187$ Å, $z_3 = 0.501$ Å) the *cis* isomer adopts essentially a C(3) sofa conformation ($z_2 = +0.017$ Å, $z_3 = 0.674$ Å).

The relation of the actual shape of this two molecules with the half-chair and the C(3) sofa can also be deduced from the comparison of the observed torsion angles with that calculated for an ideal half-chair and a sofa in the case of cyclohexene.[1]

This comparison (Fig. 4) shows that the *cis* isomer is really a C(3) sofa and presents maximum deviation of its torsion angles from that of the cyclohexene sofa being only 3°, while the *trans* compound has an

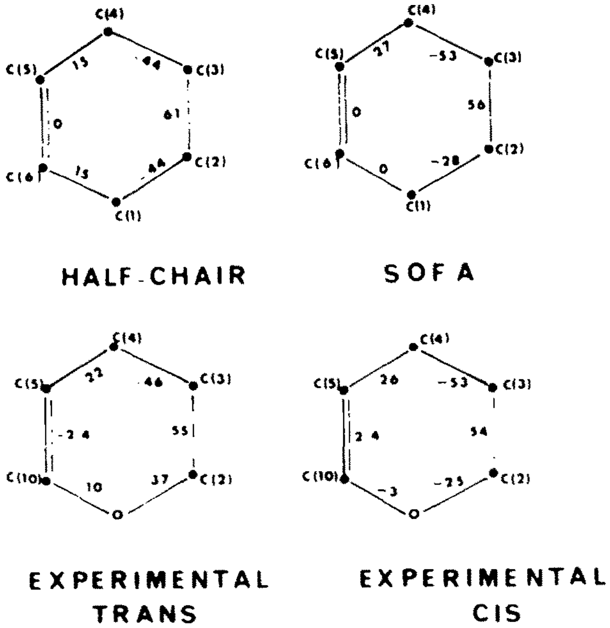

Fig. 4. Comparison of the observed torsion angles in the two isomers with those calculated for cyclohexene.

intermediate conformation which deviates more from the sofa (maximum deviation 10°) than from the half-chair (maximum deviation 7°).

The disposition of the substituents on the ring are in accordance with the results emerging from the studies in solution. In the *trans* alcohol, indeed, the substituents stand in axial position. The Newman projection along the C(2)–C(3) bond (Fig. 3) shows nevertheless that the substituents are bent away from the heterocyclic ring, the 2-phenyl group by 4° and the bulkier diphenyl carbinyl group by 8°. This bending-out together with a flattening of the half-chair (dihedral angle O(1)–C(2)–C(3)–C(4) = 55°) prevents the substituents to be exactly antiperiplanar, their angle amounting to 162° only. This angle must be compared, not with the 180° value for a perfect chair, but with the 173° value which is actually the angle between vicinal axial bonds in the flattened chair of cyclohexane.[1]

In the *cis*-isomer the diphenyl carbinyl group lies, as expected, in equatorial position, while the 2-phenyl substituent stands in an axial one, slightly bent outwards by about 4 . The flattening of the sofa in this part amounts to 2° only.

The different nature of the intramolecular hydrogen bonding shown by these compounds is clearly ascertained by the crystallographic studies. The *trans* isomer presents an OH...O bond involving the heterocyclic oxygen with a distance O(1)...H of 2.09 Å, while van der Waals contact distance would be 2.6 Å.[36] Comparison with the usual length of hydrogen bonds of the OH...O type, *ca* 1.7 Å[36] shows that indeed this is a "weak" hydrogen bonding as it was expected from the low $\Delta\nu$ value exhibited in the IR spectrum. The reason for this weakening lies in the bulkiness of the 3-axial substituent which is bent away from the ring preventing closer approach of hydroxyl to the ring oxygen. In the *cis* isomer intramolecular hydrogen bonding is observed between the hydroxyl and the -2 phenyl substituent. The hydroxyl proton is located in proximity of this phenyl group from the barycenter of which it is separated by 2.6 Å. But actually the distance from C(24) is the shortest, 2.36 Å, what is significantly less than the van der Waals contact distance evaluated to 3.0 Å.

In each case, the chelating cycle corresponding to the fixing of hydrogen bonding, either with the oxygen atom or with the 2-phenyl group, is chair-like shaped in order to minimize the steric interaction between the atoms involved. It is interesting to correlate the X-ray data with the observed shape of IR bands associated with these two kinds of hydrogen bonding. While IR spectra of the *cis*-compound exhibit a narrow peak, that of the *trans* isomer displays a larger band (width at half-height, $W_{1/2} = 56\,\mathrm{cm}^{-1}$). This difference can be interpreted assuming that in the *cis* compound the hydrogen atom is well located in a fixed position relative to the 2-phenyl group, while in the *trans*-isomer the localization is less well defined respectively to the heterocyclic oxygen atom. This difference is to be related to a stronger hydrogen bonding and a higher rigidity of the whole molecule in the case of the *cis* isomer as it is corroborated by thermal vibration analysis, while in the *trans* compound, thermal vibration of large amplitude does not allow a fixed position of the hydroxylic group with respect to the oxygen atom; furthermore as the steric crowding prevents a closer approach of the two groups, the OH...O bond is not so strong as is the OH...π one in the *cis* isomer. This is reflected by the values of the dihedral angles involved in hydrogen bonding: the torsion angle between O(1)–C(2) and C(3)–C(11) bonds amounts up to 73° in the *trans* compound, while the torsion angle between C(2)–C(24) and C(3)–C(11) bonds is lowered to 54° in the *cis* isomer. So the unusual weakness of the OH...O bond (as compared to intramolecular hydrogen bonding involving a six membered chelating cycle[27]) is a consequence of the bulkiness of the substituent at position −3 which is bent outwards the dihydropyran ring. On the opposite steric crowding in the *cis* compound is responsible of a tighter OH...π bonding in the sense that the 2-phenyl group in axial position is bent outwards the dihydropyran ring, i.e. towards the 3-substituent, allowing a better bonding. Another fact to take into consideration is hybridation of the oxygen atom of the dihydropyran ring. The angles C(10)–O(1)–C(2) are in the two isomers close to 120° and are typical of an sp^2 hybridation, which allows a better conjugation with the annelated benzene ring, and provides a more remote position from the benzo group for the C(2) carbon atom. Sp^2 hybridation and conjugation with benzene ring of the heterocyclic oxygen contribute to the weakening of the OH...O bonding of the *trans* isomer since they lower its ability as proton acceptor.[37]

Concerning the bond lengths a significant difference is shown by comparison of the C(2)–C(24) bond in the two isomers; the *cis* compound displays the usual 1.500 Å length for a sp^2–sp^3 bond while the *trans*

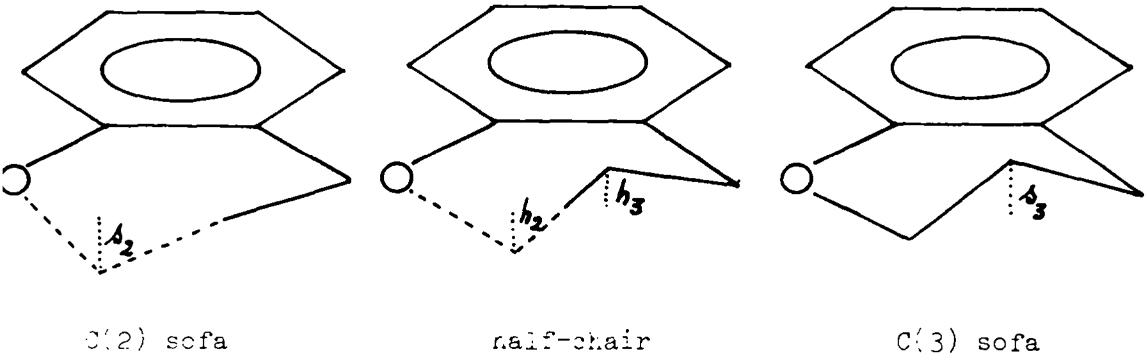

Fig. 5. The more stable conformations of chroman.

isomer presents a longer bond amounting to 1.543 Å.

Generally, lengthening of an axial C–X bond geminal with a C–O heterocyclic bond has been considered to reflect an anomeric effect, as a consequence of an overlap of the oxygen n electrons with the vacant antibonding C(2)–X orbital.[8] But in our case one can observe a similar lengthening of the C(11)–C(12) and C(11)–C(18) bonds as well in the *cis*-isomer than in the *trans* one; and obviously the two phenyl groups attached on C(11) cannot both achieve the antiperiplanar orientation with respect to the two lone pairs of the hydroxylic oxygen, required by the orbitals overlap, owing to the chair-like geometry of the chelating cycle involved in hydrogen bonding. Thus the lengthening of these bonds must be related essentially to a steric factor and reflects the mutual crowding effect that the phenyl groups experience. In the case of the *trans* isomer the lengthening of the C(2)–C(24) bond, together with the afore-mentioned outwards bending, allow a better accommodation of the phenyl substituent in axial position of the half-chair ring. But in the *cis* compound the phenyl substituent assumes the axial orientation without lengthening of the axial bond, since a C(3) sofa conformation of the dihydropyran ring provides a more remote axial position from the benzo group than in the half-chair conformation. Furthermore the OH...π bonding contributes also to discard the 2-phenyl substituent from the benzo group as it is shown by the value of the dihedral angle O(1)–O(2)–C(3)–C(24) which is slightly higher than usual, amounting to 124°.

Another interesting point concerns the length of the C(3)–C(11) bond which is shorter (1.543 Å) in the *trans* isomer where it stands in axial position than in the *cis* isomer (1.560 Å) where it lies in an equatorial one; that means that the diphenyl carbinyl group accommodates more easily the axial orientation in the *trans* compound than it does for the equatorial position of the *cis* one. In the *cis* isomer this bulky group suffer indeed a buttressing effect from the gauche 2-phenyl substituent which is closer than usual, the corresponding dihedral angle being reduced to 54°.

CONCLUSION

The preference shown by the *trans* isomer for the diaxially substituted half-chair arises, not from stabilization brought by an OH...O intramolecular hydrogen bonding (since this is rather weak compared to a stronger OH...π bond that would occur in the diequatorial conformation), but from destabilization of the alternative diequatorial conformation. Overcrowding of the latter is shown by examination of the different possible rotamers around the C(3)–C(11) bond. These show either a syn diaxial interaction between two phenyl rings (A or B with C) or a double gauche interaction of a phenyl ring (A or B) with the two benzyl groups to which can be identified each moiety of the heterocyclic ring joined to C(3).

Although unusually weak the intramolecular hydrogen bonding of the OH...O type shown by the *trans* isomer seems to act as a lock since no free hydroxyl group can be observed. In fact this is a consequence of the overcrowding attached to the diphenyl carbinyl group: the less hindered rotamer around the C(3)–C(11) bond is indeed the one giving the right orientation for hydrogen bonding, where the phenyl rings A and B are anti to the above mentioned benzyl moieties; and any other staggered orientation around the C(3)–C(11) bond would force a phenyl group to stand above the chroman ring.

The geometry of the *trans* flavan-3 yl diphenyl carbinol **1** appears to be the more diaxially depicted for a vicinally disubstituted six-membered ring, in absence of polar effects. Comparison with the molecular structure of trans-1,2-bis-(2-carboxymethyl-2propyl) cyclohexane (**3**) previously reported,[17] shows that in our compound the dihedral angle between the substituents is closer to the value of 173° found in cyclohexane for vicinal axial C–H bonds[1] (162° in **1**, instead of 134.5° in **3**) and the flattening in the substituted part of the ring, far less pronounced than in **3**, is very close to that of cyclohexane itself (torsion angle of 55° in **1**, 37.4° in **3**, and 56° in cyclohexane[1]).

Although less anomalous the *cis* isomer present the particularities to possess a C(3) sofa conformation of its dihydropyran ring and to be wholly bonded by an intramolecular OH...π bonding. Description of such an X-ray determined structure appears to have a significant importance in the field of conformational analysis of dihydropyran derivatives as well in the chroman or flavan field as in the ethylenic sugars series, and would further shed some light, giving experimental support on previously discussed[28] possible geometries of the OH...π bond involving a phenyl ring.

EXPERIMENTAL

The synthesis of the *trans* isomer **1** has already been described.[19] The *cis* isomer **2** has been prepared following a similar procedure, by condensation of phenyl magnesium bromide with *cis*-ethyl flavan-3yl carboxylate.[19]

Cis-3-(1′-hydroxy-1′-phényl)benzylflavan

To a cooled solution of the Grignard reagent prepared from 4.3 g of phenyl bromide and 0.70 g of magnesium in 50 cm^3 of ether, was added dropwise with stirring a solution of 3.5 g of *cis*-ethyl-flavan-3-yl carboxylate in 50 cm^3 of ether. The mixture was stirred for 2 hr at ambient temperature and then was hydrolyzed by addition of 20 cm^3 of a saturated solution of ammonium chloride. After filtration and decantation the aqueous phase was extracted with ether; the combined organic solutions were dried over Na_2SO_4. Evaporation of the solvent afforded 2.2 g of crude alcohol **2** (45%) as a solid which was recristallized in a mixture of ether and chloroform, m.p. 220°.

Spectroscopic measurements

IR spectra were recorded on a Beckmann 4200 spectrophotometer in carbon tetrachloride at various concentrations and were calibrated with polystyrene film. Absorptions in the OH region are reported in Table 1 where concentrations are given in mole per liter.

Nuclear magnetic resonance spectra (CW^{1}H) were obtained with a Varian A-60-A instrument in $CDCl_3$ solution using tetramethylsilane as internal standard. First order analysis led to the results shown in Table 2.

Crystallographic Studies

Crystal data. Prismatic crystals were obtained from a mixture (1/1) of ether and chloroform. Those selected for X-ray intensity measurements were 0.6 × 0.4 × 0.2 mm (*trans*) and 0.3 × 0.15 × 0.4 mm (*cis*). The crystallographic data[20] show that the *trans* isomer is orthorhombic (Pbca) while the *cis* one is monoclinic ($P2_{1/c}$).

Collection of X-ray diffraction data. Intensities for respectively 3545 (*trans*) and 3826 (*cis*) reflexions were measured by the $\omega - 2\theta$ scan technique on a four-circle diffractometer Philips PW 1100. The width of the scan was $1.5 + 0.30 \operatorname{tg} \theta$ for **1** and 1.40° for **2**. The data were corrected for the Lorentz and polarization factors but not for absorption or extinction. Respectively 1834 (*trans*) and 1489 (*cis*) reflexions having $I \geq 3\sigma$ (I) were considered in the determination of the structure.

Structure determination and refinement. The two structures were solved by direct methods; 450 reflexions with normalized structure factors $|E| \geq 1.42$ for the *trans* compound and 300 reflexions with normalized structure factors $|E| \geq 1.75$ for the *cis* isomer were used in the MULTAN program.[38] A Fourier synthesis based on the solution with respectively the highest Σ_2 consistency (*trans*) or with the highest ABSFOM test (*cis*) revealed the complete molecule. The structure was refined by full-matrix least squares. The H atoms were located from a difference synthesis. The non $-$H and H atoms were refined anisotropically and isotropically respectively, the refinement converged for all the reflexions with $I \geq 3\sigma$ (I) to an R of 6% ($R\omega = 0.053$) in the case of the *trans* compound and of 4.8% ($R\omega = 0.047$) in the case of the cis isomer ($R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$). From the final atomic parameters bond lengths and bond angles have been calculated. The scattering factors for the heavy atoms were those of Hanson, Herman, Lea and Skillman[39] and for H those of Stewart, Davidson and Simpson.[40] Unit weights were used throughout. The absolute values of peaks and troughs in the final difference synthesis did not exceed $0.2\,e/Å^3$ for the *trans* compound and $0.17\,e/Å^3$ for the *cis* isomer. Figures 1 and 2 give a stereoview of the molecules with the numbering of the atoms.

Thermal vibration analysis

A least squares analysis of rigid body motion of the molecule was carried out according to the method of Shoemaker and Trueblood.[21] Two rigid body models were used, comprising different group of atoms: the first consisting of all non hydrogen atoms, and the second in which the molecule was divided into four fragments consisting of 3 phenyl rings and the chroman group. The results show that the whole molecule cannot be considered as rigid. The root mean square difference between the observed Uij terms and those calculated from the derived T, L and S for the 3 phenyl A, B, C with the adjacent atom taken as origin are respectively 0.0043, 0.0049, 0.0044. The bond lengths corrected for the effects of molecular vibrations[22] are in better agreement with the standard values, and shows that the phenyl ring A which is the farthest fragment from the chroman group, is more agitated than the other two.

For comparison, the rigid body parameters of the cis isomer have also been calculated: the eigenvalues of T represent a more anisotropic translation of the whole molecule in the trans compound than in the cis one. The rotational motion in the two cases are quite negligible and the fit of the calculated Uij terms to those observed is better for the cis isomer, the bond lengths of which are in good agreement with the standard values. By contrast, the trans isomer does not behave like a rigid body: the independent librations of the different fragments A, B and C recoil on the agitation of the whole molecule and explain the important values of T and the misfit of the calculated and observed Uij terms. Those results are also in agreement with the partial correction of bond lengths according to the formula of Busing and Levy.[22]

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