

CHIROPTICAL PROPERTIES OF 4-SUBSTITUTED FLAVANS^a

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(Received in the UK 25 October 1972; Accepted for publication 8 November 1972)

Abstract—The negative $n \rightarrow \pi^*$ -band CD of (+)-flavanone (1) proves its absolute configuration to be (2*R*). The CD of 4-substituted flavans (*cis*- and *trans*-) is best explained by assuming a sofa conformation for the dihydropyran ring (C-2 out of plane). For these compounds second-sphere contributions are smaller than third-sphere contributions of the 4-substituent.

Recently we³ described the reduction of flavanon oxime to *cis*-4-aminoflavan and its resolution into the two enantiomers, as well as the preparation of the respective N-acetyl and N-benzoyl derivatives. In another publication⁴ we mentioned the preparation of optically active *trans*-4-hydroxyflavan by HNO₂ deamination of *cis*-4-aminoflavan; e.g. the (+)-amine (3) gave (–)-*trans*-4-hydroxyflavan (6). Oxidation of the latter with bichromate lead to (+)-flavanone (1), acetylation gave (–)-*trans*-4-acetoxyflavan (7). All compounds but the *cis*-4-hydroxyflavan (2) have been prepared in both enantiomeric series.^{3,4} Experimental details of these preparations will appear in a later communication.

Chiroptical properties. In order to simplify the discussions, only the (2*R*)-compounds 1–7 are considered in the following, the CD spectra of their enantiomers E-1–E-7 are, of course, enantiomorph to those of 1–7 (Table 1).

Flavanone 1. Dextrorotatory (+)-flavanone (1) was assigned the (2*R*)-configuration by comparison with other flavanones of known absolute configuration.⁶ This could be proven now by comparing the CD spectrum of 1 with that of other flavanones^{7–11} and referring to the phenylketone $n \rightarrow \pi^*$ -chromophore. Its CD is strongly negative (–4.93) and is thus indicating independently, that the absolute configuration of 1 is (2*R*). Contrary to the Cotton-effect of the benzene chromophore the sign of this $n \rightarrow \pi^*$ -band CD is independent on the substitution pattern of the aromatic ring system,^{7–11} and 1

can thus serve as the reference compound of known absolute configuration for all the other flavans described.

***cis*-4-Substituted flavans.** The NMR spectrum of *cis*-4-aminoflavan hydrochloride (3) and *cis*-4-acetamidoflavan (4) has been analysed in detail;³ from the respective coupling constants the relative configurations were established to be *cis* and a halfchair conformation of the dihydropyran ring was derived, though a sofa conformation could not be excluded. Similar results were obtained¹² for the benzoate of 2. Korver and Wilkins¹³ discussion of the CD spectra of some natural flavanols (8, 9) is based on such a sofa conformation, and the relative great difference of the *ele* and *eψ-e* coupling constants³ prompt us to consider the sofa conformation with O, C-3, and C-4 being coplanar with the benzene ring to be the preferred one. This is the same conformation which Korver and Wilkins¹³ use.

As the CD of 3 and E-3 in both acetonitrile and methanol solution is of similar shape and does not vary much with the solvent we can assume the same sofa conformation for all our discussions independent on the solvent.

It is known for 1-substituted tetralins and tetrahydroisoquinolines that the helicity of the cyclohexene (piperidine) ring is such that the substituent (OR, CH₃, C₆H₅, benzyl, etc) can adopt the ψ -axial conformation in order to avoid steric interaction with the *peri*-standing hydrogen (similar to 1:3-diaxial interaction).^{9–11,14} With a halfchair conformation of the dihydropyran ring the 4-substituent of 2–5 would be forced into the unfavourable ψ -equatorial position, in the other possible halfchair the phenyl group has to adopt the axial position, which is also very improbable (and excluded by the NMR spectra³); similarly the boat

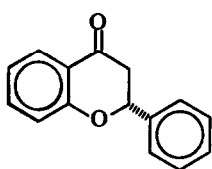
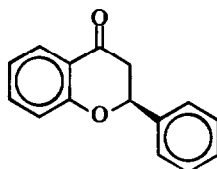
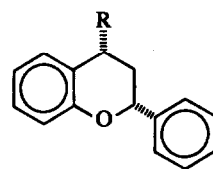
^aPart XXVIII of the Debrecen authors on Flavonoids; Part XXVII: Lit.¹—Part LXI of the Bonn authors on Circular Dichroism; Part LX: Lit.²

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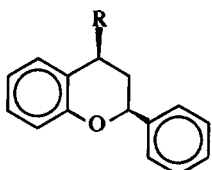
Table 1. CD-spectra of 4-substituted flavans

Compound	Solvent ^a	λ_{\max} ($\Delta\epsilon$)
1	A	355 (-2.35), 339 (-4.93), 310 (+6.16), 249 (+3.58), 225 (-7.69)
E-1	A	355 sh (+1.48), 338 (+4.51), 310 (-5.55), 248 (-3.75)
2	A	283 (+1.22), 276 (+1.28), 266 sh (+0.72) 227 (+2.23), 214 (+3.94)
	C	282 (+0.92), 272 (+0.92), 231 (+3.05)
3	M	281 (+1.47), 276 (+1.73), 245 sh (+0.05), 228 (-4.42)
E-3	A	283 (-2.30), 277 (-2.48), 227 (+3.29), 206 (-6.0)
4	A	283 (+2.00), 276 (+2.15), 233 (+1.26), 218 (-1.12), 208 (+17.4), 194 (-48)
E-4	A	282 (-1.83), 276 (-1.86), 233 (-1.67), negative at shorter wavelengths
5	A	283 (+2.25), 276 (+2.44), 232 (+2.89), 222 (-1.92)
E-5	A	283 (-2.55), 276 (-2.93), 232 (-3.75), 215 (+0.97)
6	A	282 (-1.17), 276 (-1.17), 226 (-7.62)
E-6	A	282 (+1.44), 276 (+1.41), 265 sh (+0.80), 226 (+8.92), negative at shorter wavelengths
7	A	284 (-1.81), 277 (-1.92), 225 (-11.40)
E-7	A	284 (+1.94), 276 (+1.94), 264 sh (+0.85), 225 (+8.95)

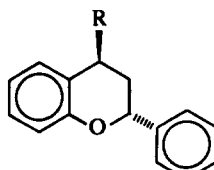
^aA: acetonitril, C: chloroform, M: methanol.

**1 (R)****E-1 (S)**

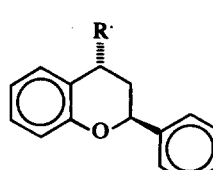
2: R=OH
3: R= NH_3^+Cl^-
4: R=NHAc
5: R=NHBz



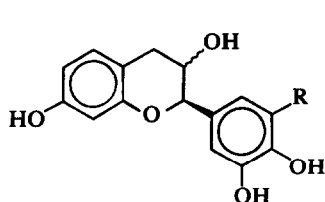
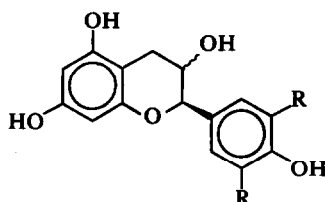
E-3: R= NH_3^+Cl^-
E-4: R=NHAc
E-5: R=NHBz



6: R=OH
7: R=OAc



E-6: R=OH
E-7: R=OAc

**8****9**

conformation can be discarded by conformational analysis. In the sofa conformation (Fig 1) this 4-substituent is, however, already so oriented that the aforementioned *peri*-interaction is avoided, so also from this point of view the sofa conformation seems more probable than the halfchair conformation.

In explaining the Cotton-effect of tetralins and tetrahydroisoquinolines we^{9-11, 14-17} differentiated between second-sphere contributions and third-sphere contributions, the former in general being stronger than the latter. In all these many cases discussed the chiral part of the molecule was connected to the benzene chromophore by C-atoms whose spectroscopic moments^{18, 19} are approximately identical. For compounds not further substituted in the benzene ring *P*-helicity of the chiral ring leads to a positive Cotton-effect within both the ${}^1B_{2u}$ - and ${}^1B_{1u}$ -absorption bands, for substituted compounds it depends on the substitution pattern, whether this same rule holds, or the inverse one.^{14, 15, 17} For example in their discussion of the CD of differently substituted natural flavanols Korver and Wilkins¹³ mention that for the two types of compounds investigated (general formula 8 and 9) on the basis of experimental data the original rule⁹ connecting the helicity of the chiral second-sphere with the sign of the Cotton-effect has to be inverted. As we have shown, however, recently,^{14, 15} the substitution pattern of 8 and 9 indeed requires such an inversion of the original rule.

Though thus the experimental data obtained with some naturally occurring flavanols¹³ can be explained, the difficulty remains that the chiral part of the molecule is connected to the chromophore by unlike atoms, *viz.* C and O. Hitherto in our first approximation^{14, 15, 17} we have neglected such differences. Furthermore, with a sofa conformation present the chirality of the second sphere is no longer as strong as in cases of tetralins or tetrahydroisoquinolines with their half-chair conformation. We can thus expect that second-sphere contributions to the Cotton-effect will be smaller, and especially in case of 4-substituted molecules with the chiral center next to the chromophore third-sphere contributions may become even stronger.

With the conformation assumed (Fig 1) a negative second-sphere contribution is expected for the chroman chromophore, if the "usual" rule^{9, 14, 16, 17} holds, as is supposed by the data recorded by Korver and Wilkins.¹³ The contribution of the second phenyl chromophore to the CD is expected to be one or two orders of magnitude smaller, because no atom with free electron pairs is directly connected to it,²⁰ this phenyl can, however, also contribute as any other substituent to the third-sphere effects for the chroman chromophore. Its contribution depends strongly on its preferred conformation, but in any case will be very small because of partial internal compensation.

To apply the correct sector rule for estimation of

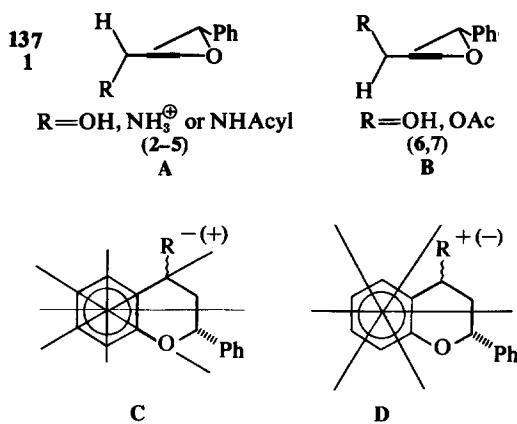


Fig 1. A,B: Projection of the sofa conformation of the dihydroxyran ring from the benzene ring towards the heterocyclic ring. — represents the benzene ring. A: *cis*-configuration; B: *trans*-configuration.

C,D: Sector Rule for third-sphere contributions to the ${}^1B_{2u}$ -band (C) and ${}^1B_{1u}$ -band CD (D). Signs without brackets refer to upper, signs in brackets to lower sectors.

the influence of the 4-substituent we will have to know, whether C_2 - or C_3 -symmetry is a better approximation for the chroman molecule, as only in the first case the plane of the benzene ring is a nodal plane.¹⁴ As experimentally it is found (see later) that epimerization at C-4 changes the sign of the ${}^1B_{2u}$ -band CD we have thus to assume the first. With this rule (Fig 1C,D) we expect a positive contribution from substituent R to the Cotton-effect within the ${}^1B_{2u}$ -band, a negative for the ${}^1B_{1u}$ -band CD. This is what is found for 3, but we have already noticed earlier¹⁴ that a ψ -axial group next to the benzene chromophore may influence the sign of the ${}^1B_{1u}$ -band CD; the influence of such a group attached to a sofa conformation of the chiral ring is as yet unknown. Indeed, for 2, 4 and 5 the ${}^1B_{1u}$ -band CD is positive and thus inverse to that in the spectrum of 3. At least for the ${}^1B_{2u}$ -band we can, however, say that with a sofa conformation of the chiral ring the influence of the second sphere is much smaller than that of the group next to the chromophore (third-sphere contribution). It is interesting to note that—again at least for the ${}^1B_{2u}$ -band CD, but perhaps not for the ${}^1B_{1u}$ -band CD—neutral groups and the positive ammonium grouping have contributions of the same sign, contrary to the experience in the ketone series.^{21, 22}

trans-4-Substituted flavans. For the benzoate of 6 the NMR spectrum analysis¹² gave not only the relative configuration but again also the preferred conformation for the chiral ring. It is either a half-chair or a sofa conformation; as in this case the 4-substituent on a halfchair is ψ -axial, conformational analysis cannot differentiate between these two forms. Whatever it is, second-sphere helicity

and third-sphere contribution of the OR group are both predicted to be negative, and **6** and its acetate **7** both show negative Cotton-effects within the ${}^1B_{2u}$ - as well as the ${}^1B_{1u}$ -band. As the absolute value of the rotational strength of the better measurable ${}^1B_{2u}$ -band CD is practically the same for the two epimers **2** and **6** we can conclude that the dihydropyran ring of the *trans*-compounds **6** and **7** also prefers the sofa conformation (C-2 out of the plane of the benzene ring). It should be mentioned that this same sofa conformation is also in agreement with the CD-data of 4-flavanones, like **1** and similar ones.¹⁰

Katekar and Moritz²³ on the basis of IR data concluded that the dihydropyran ring in *cis*- and *trans*-4-hydroxyflavin adopts different conformations. *cis*-3-Phenyl-tetral-1-ol gave an IR spectrum similar to that of *cis*-4-hydroxyflavin and without discussion the authors²³ assumed a halfchair conformation in analogy to other tetralins. On the contrary we believe that in this *cis*-compound for the same reason as discussed earlier for the *cis*-4-hydroxyflavin the sofa conformation is the preferred one. A halfchair conformation for the *trans*-4-hydroxyflavin is, however, not excluded by our CD measurement.

EXPERIMENTAL

All CD spectra were recorded on a Roussel-Jouan Dichrograph model 185 at 20° for concentrations of approx 1 mg/cm³ in cells of 0.01 to 1.00 cm length.

Acknowledgement—G. S. thanks the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for financial support, F. W.-Z. the *German Academic Exchange Service* for a grant; Debrecen authors: our thanks are due to the *Hungarian Academy of Sciences* for sponsoring the present investigations; technical assistance of Mrs. N. Elgmal is highly appreciated.

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