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The Conformation of *trans*-4-Acetoxyisoflavans and Related Compounds*[1]

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As a part of the investigation of the stereochemistry of isoflavan-4-ols,[1] our interest in conformational preference effects in the chroman ring led us to investigate *trans*-4-acetoxyisoflavans and related compounds.

In the NMR spectra (Table 1) of *trans*-4-acetoxy- (I), *trans*-4-acetoxy-7-methoxy- (II), and *trans*-4-acetoxy-4′,7-dimethoxyisoflavan (III), the signals of the C-2 and C-3 protons show a simple pattern; the AB portion (the C-2 proton) appears as a 1 : 1 doublet, the X region (the C-3 proton) shows a 1 : 2 : 1 triplet ($J_{2,3}=J_{3,4}=5.0$ Hz), and none of the diaxial couplings expected for the conformations (Ie), (IIe), and (IIIe) appear in them. Upon irradiation at the C-4 proton of II, the quartet due to the C-3 proton changes to a triplet ($J_{2,3}=5.0$ Hz). These results strongly suggest that I, II, and III exist largely as conformations (Ia), (IIa), and (IIIa), in which the acetoxyl group at C-4 is in a *quasi*-axial environment. The present results can be explained by the pseudo-allylic effect,[2] which has been termed the $A^{(1,3)}$ strain, inherent in the conformations (Ie), (IIe), and (IIIe).

On the other hand, 2-methyl-4,7-diacetoxyisoflavan (2/3 *trans*, 3/4 *trans*) (IV)[3] seems to exist mainly as the conformation (IVe) ($J_{2,3}=J_{3,4}=10.2$ Hz), for there is a severe 1,3-diaxial repulsion in IVa (methyl-acetoxyl, around 1.9—2.4 kcal/mol)[4] which is considerably larger than the $A^{(1,3)}$ strain in IVe.

In the *trans*-4-hydroxyisoflavans, (I′), (II′), and (III′), the preferred conformations seem to be I′e, II′e, and III′e ($J_{3,4}=7.4-8.5$ Hz).*[2] In I′, II′, and III′, the unfavourable $A^{(1,3)}$ strain is considered to be partly overcome by the intramolecular hydrogen bonding[5] between the C-3 phenyl and C-4 hydroxyl groups.

The ABX protons (decoupled at the methyl signal at 100 MHz) of *trans*-3-methyl-4-benzoyloxychroman (V) show no diaxial coupling*[2] ($J_{2,3}=$ 2.4, 4.3: $J_{3,4}=4.1$ Hz); thus, the conformation Va is favoured. This result is substantiated by the existence of the long-range coupling ($J_{2,4}=$

TABLE 1. COUPLING CONSTANTS IN ISOFLAVANS AND CHROMANS

Compounds		$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	Preferred conformation
I	*trans*-4-AcO-IF	5.0	5.0	Ia
II	*trans*-4-AcO-7-MeO-IF	5.0	5.0	IIa
III	*trans*-4-AcO-4′,7-$(MeO)_2$-IF	5.0	5.0	IIIa
IV	*trans*-2-Me-4,7-$(AcO)_2$-IF	10.2	10.2	IVe
I′	*trans*-4-OH-IF	8.5, 5.6	8.5	I′e
II′	*trans*-4-OH-7-MeO-IF	7.4, 5.3	7.4	II′e
III′	*trans*-4-OH-4′,7-$(MeO)_2$-IF	7.9, 5.3	7.4	III′e
V	*trans*-3-Me-4-BzO-CR	2.4, 4.3	4.1	Va
V′	*trans*-3-Me-4-OH-CR	3.1, 6.1	5.5	V′a
IX	4-AcO-CR		3.8	IXa
X	1-AcO-Tetralin		4.0	Xa

IF: Isoflavan, CR: Chroman

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*[1] A part of this study was presented at the 22th Annual Meeting of the Chemical Society of Japan. Tokyo, April, 1969, Proceedings III, p. 1382.

[1] S. Yamaguchi, S. Ito, A. Nakamura and N. Inoue, This Bulletin, **38**, 2187 (1965). A. S. R. Anjaneyulu, M. G. Rao, L. R. Row and C. S. Krishna, *Tetrahedron Lett.*, **1966**, 3199.

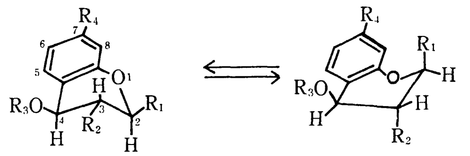
[2] S. K. Malhotra and F. Johnson, *J. Amer. Chem. Soc.*, **87**, 5493 (1965). F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

[3] N. Inoue and S. Ito, *Chem. Ind.* (London), **84**, 1382 (1965).

[4] E. L. Eliel, N. J. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, (1965), pp. 44, 114, 356.

*[2] The ABX portion of these spectra were analysed by the method of Pople. J. A. Pople, W. G. Schneider and H. J. Bernstein, *Can. J. Chem.*, **35**, 63 (1957).

[5] K. Hanaya, private communication.



(Ie)	$R_1=R_4=H$, $R_2=Ph$, $R_3=Ac$	(Ia)
(I'e)	$R_1=R_3=R_4=H$, $R_2=Ph$	(I'a)
(IIe)	$R_1=H$, $R_2=Ph$, $R_3=Ac$, $R_4=OMe$	(IIa)
(II'e)	$R_1=R_3=H$, $R_2=Ph$, $R_4=OMe$	(II'a)
(IIIe)	$R_1=H$, $R_2=p\text{-MeO-}C_6H_4$, $R_3=Ac$, $R_4=OMe$	(IIIa)
(III'e)	$R_1=R_3=H$, $R_2=p\text{-MeO-}C_6H_4$, $R_4=OMe$	(III'a)
(IVe)	$R_1=Me$, $R_2=Ph$, $R_3=Ac$, $R_4=OAc$	(IVa)
(Ve)	$R_1=R_4=H$, $R_2=Me$, $R_3=Bz$	(Va)
(V'e)	$R_1=R_3=R_4=H$, $R_2=Me$	(V'a)
(IXe)	$R_1=R_2=R_4=H$, $R_3=Ac$	(IXa)

Fig. 1

1.0 Hz) expected from the W letter rule. Unlike as in the spectra of I′, II′, and III′, the $J_{3,4}$ values of *trans*-3-methyl-4-hydroxychroman (V′), in which the stabilization by the intramolecular hydrogen bonding can not be expected, is similar (5.5 Hz) to that of I—III; the preferred conformation is probably V′a, as in the case of V.

For the estimation6) of the conformational equilibrium of II, standard $J_{3,4}$ valuse are selected as follows; $J_{3a,4a'}$: $J_{3a,4a'}$ (10.2 Hz) in IV3); $J_{3e,4e'}$: $J_{3e,4e'}$ (3.2 Hz) in *cis*-4-acetoxy-7-methoxyisoflavan (VI).1) This assumption seems to be correct on the basis of the following points: (1) as has been described above, the conformation of IV is considered to be almost fixed to IVe; this is also supported by the equal value of $J_{3a,4a'}$ (10.2 Hz) in *cis*-4-benzoyloxyflavan (VII),7) in which the conformation should be homogeneous. (2) Since the value of $J_{2a,3a}$ (11.9 Hz) in VI1) is as large as that of *trans*-4-benzoyloxyflavan (VIII),7) the conformation of VI is almost fixed; the assumption ($J_{3a,4e'} \approx J_{3e,4e'}$) is supported by the experimental data ($J_{3e,4e'}=J_{3e,4e'}=3.0$ Hz in VIII7) and 3.2 Hz in *trans*-2-alkyl-4-acetoxychromans).*3 The calculation using the above standard $J_{3,4}$ values shows that IIa exists mainly ($\sim$75%) in the conformational equilibrium. A consideration of the 1,3-diaxial interaction (acetoxyl-hydrogen, $\sim$0.35 kcal/mol)4) associated with IIa and the free energy difference of 0.65 kcal/mol between the conformers in favor of IIa implies that the $A^{(1,3)}$ interaction (acetoxyl-hydrogen) in IIe is $\sim$1.0 kcal/mol.*4

In 4-acetoxychroman (IX) and 1-acetoxytetralin (X), the preferred conformations are IXa and Xa, since the signals of the C-4 proton show a pattern [4-H(*t*), $J_{3,4}=3.8$ and 4.0 Hz respectively] similar to that of VIII [4-H(*t*), $J_{3,4}=3.0$ Hz]7) and since the conformational equilibrium of IX can be calculated8) from the distance (4-acetoxychroman; 8.0 Hz) between the two outside peaks of the C-4 proton resonance based on the distances of *cis*- and *trans*-2-methyl-4-acetoxychromans*3 ($J_A=$ 16.5 Hz and $J_B=6.0$ Hz), selected as model compounds.*5 This calculation affords the results that IXa ($\sim$81%) is predominant and that the allylic strain is 1.1—1.2 kcal/mol, as large as that of II.

Experimental

Measurement. The NMR spectra were determined in $CDCl_3$ at 37°C (60 MHz) and 30°C (100 MHz), using a Varian A-60 and H-100 spectrometer with TMS as the internal standard.

Materials. The *trans*-4-acetoxyisoflavan (I),9) *trans*-4-acetoxy-7-methoxyisoflavan (II)9), *trans*-4-acetoxy-4′,7-dimethoxyisoflavan (III),9) *trans*-2-methyl-4,7-diacetoxyisoflavan (IV),3) *trans*-4-hydroxyisoflavan (I′),9) *trans*-4-hydroxy-7-methoxyisoflavan (II′),9) and *trans*-4-hydroxy-4′,7-dimethoxyisoflavan (III′)9) were prepared by methods previously reported. The 4-acetoxychroman (IX) and 1-acetoxytetralin (X) were obtained by the acetylation of chroman-4-ol and tetralin-1-ol respectively with acetyl chloride in pyridine.

trans-3-Methyl-4-hydroxychroman (V′). To a solution of 11.0 g of sodium borohydride in 220 m*l* of ethanol, 11.3 g of 3-methylchromone10) was added. The mixture was refluxed for 4 hrs and then left to stand overnight at room temperature. After the ethanol had been removed under reduced pressure, 200 m*l* of water and 100 m*l* of 50% acetic acid were added to the residue. The solution was then extracted with ether. The extract was washed with 5% sodium hydroxide and with water, and was dried on anhydrous sodium sulfate. The mixture of *cis*- and *trans*-3-methyl-4-hydroxychromans remaining after the removal of the ether was partly crystallized. One of the isomers was obtained by repeated recrystallization from *n*-hexane - benzene; 2.2 g; mp 97.5—98.0°C.

Found: C, 73.31; H. 7.52%. Calcd for $C_{10}H_{12}O_3$: C, 73.14; H, 7.37%.

This isomer was identical with the *trans*-3-methyl-4-hydroxychroman (V′) prepared by the hydroboration of the 3-methylchromene obtained by the dehydration

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6) N. C. Franklin and H. Feltkamp, *Angew. Chem. In. Ed.*, Engl. **4**, 774 (1956).

7) B. J. Bolger, A. Hirwe, K. G. Marathe, E. M. Philibin and M. A. Vickars, *Tetrahedron*, **22**, 621 (1966).

*3 Unpublished results. Synthesis and stereochemistry of these compounds will be reported elsewhere.

*4 Johnson and Malhotra have shown that the magnitude of $A^{(1,3)}$ strain (methyl-hydrogen) is approximately 1.4 kcal/mol. S. K. Malhotra and F. Johnson, *Chem. Commun.*, **1968**, 1149.

8) G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **33**, 2572 (1968).

*5 The coupling constants observed for other 2-alkyl-4-acetoxychromans are consistent with the values chosen for J_A and J_B.

9) S. Yamaguchi, S. Ito, I. Suzuki and N. Inoue, This Bulletin, **41**, 2073 (1968).

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of a mixture of 3-methyl-4-hydroxychromans with acetic acid - hydrochloric acid (4 : 1).

trans-3-Methyl-4-benzoyloxychroman (V). By the usual method, the benzoate (V) was prepared by reaction with acetyl chloride - pyridine; mp 84.5—85.0°C.

Found: C, 76.26; H, 6.17%. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%.