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NMR EFFECTS OF ACETYLATION AND LONG-RANGE COUPLING AS A TOOL FOR STRUCTURAL ELUCIDATION OF HYDROXYCHROMENES*

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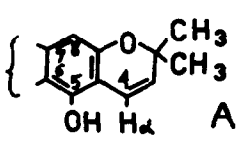
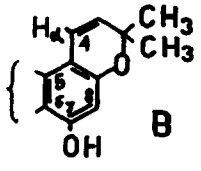
The presence of a chromene ring system in a natural substance can now be easily recognized with NMR spectroscopy (1). Because, however, most natural chromenes show at least a resorcinol or a more complicated oxygenation pattern, difficulties are still encountered in establishing the position of the ring closure, i.e. the distinction between structures A,B,C in polycyclic compounds (e.g. sericetin (2), isoallorottlerin (3)):



A



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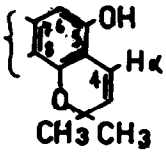

C

In some cases, the only method available is the repeatedly questioned Gibbs reaction. These difficulties can be overcome only with synthesis (e.g. jacareubin (4).) We have observed in all the compounds studied (see table) the following phenomena:

1) an interesting effect on the H_α chemical shift caused by the acetylation of the 5-OH

2) an inter-ring long-range coupling between H_α chromene proton (H_4) and H_8 ($J_{4,8}$ = 0.6–0.7).

Because these effects could be new tools for the solution of the problem of the structural isomers A,B and C, we have investigated a series of hydroxychromenes including known natural substances. The results reported here have been applied in the case of flemingins (5) and also give the final assignment of the structure of isoallorottlerin (6).

1) The acetylation of 5-OH is observed to cause a marked diamagnetic shift ($\Delta\delta_{acetyl}$ = +0.3-0.4) of the peri H (H_α) and a small paramagnetic shift ($\Delta\delta_{acetyl}$ = −0.1) of H_β. If we compare the shift of H_α in the 2,2-dimethylchromene (XIV), with its 5-hydroxy- (I) and 5-acetoxy- derivative, we see that acetylation compensates the downfield shift induced by the OH. The same holds for XX, II and its acetate. The deshielding of H_α due to the peri hydroxyl is of the same order (−0.38) as the "peri effect" found by Dudek (7) in naphtalenes (ca. −0.4δ).

* Part V of a series on Natural Chromenes. Part IV: Ricerca Sci., in press.

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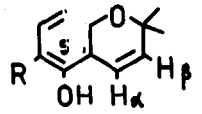
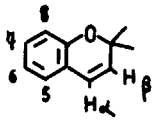
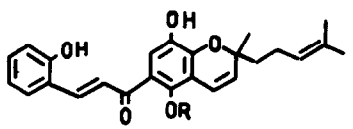


TABLE 1

	R		C_6H_{12} OH	C_6H_{12} OAc	CCl_4 OH	CCl_4 OAc	$CDCl_3$ OH	$CDCl_3$ OAc	acetone OH	acetone OAc	DMSO OH	DMSO OAc	C_6H_{12}	CCl_4	$CDCl_3$	acet.	DMSO
														$\Delta\delta$ acetyl			
I	H	α	6.59	6.29	6.56	6.25	6.61	6.33	6.66	6.39	6.57	6.38	+0.30	+0.31	+0.28	+0.27	+0.19
		β	5.42	5.49	5.47	5.55	5.57	5.64	5.58	5.75	5.62	5.81	−0.07	−0.08	−0.07	−0.17	−0.19
II	$COCH_3$	α	6.72	6.36	6.66	6.36	6.71	6.38	6.67	6.48	6.60	6.45	+0.36	+0.30	+0.33	+0.19	+0.15
		β	5.42	5.54	5.47	5.64	5.57	5.71	5.73	5.88	5.75	5.90	−0.12	−0.17	−0.14	−0.15	−0.15
III	$COOCH_3$	α	6.71	6.37	6.68	6.36	6.71	6.39	6.70	6.52	6.61	6.48	+0.34	+0.32	+0.32	+0.18	+0.13
		β	5.39	5.51	5.48	5.60	5.57	5.68	5.74	5.87	5.74	5.91	−0.12	−0.12	−0.11	−0.15	−0.17
IV	COOH	α					6.71	6.39	6.67	6.51	6.60	6.46			+0.32	+0.16	+0.14
		β					5.58	5.69	5.72	5.84	5.74	5.88			−0.11	−0.12	−0.14
V	CO−CH=CH−Ph	α	6.77	6.36	6.73	6.34	6.76	6.38	6.72	6.50	6.66	6.49	+0.41	+0.39	+0.38	+0.22	+0.17
		β	5.42	5.55	5.48	5.64	5.60	5.72	5.75	5.90	5.77	5.93	−0.13	−0.16	−0.12	−0.15	−0.16
					R=H	R=Ac	R=H	R=Ac	R=H	R=Ac	R=H	R=Ac					
VI	Allorottlerin	α					6.68	6.15							+0.53		
	tetraac. vs. pentaac.	β					5.52	5.61							−0.09		
VII	Rottlerin	α					6.66	6.16			6.63	6.37			+0.50		+0.26
	rottl. vs. pentaac.	β					5.46	5.67			5.61	5.89			−0.21		−0.28
VIII	Flemingin A (5)	α					6.78	6.41	6.76	6.57					+0.37	+0.19	
	diac. vs. triac.	β					5.56	5.69	5.74	5.90					−0.13	−0.16	
IX	Maclurauxanthone (11)	α			6.71	6.44	6.75	6.49			6.61	6.56		+0.27	+0.26		+0.05
	diac. vs. triac.	β			5.49	5.65	5.58	5.73			5.76	5.98		−0.16	−0.15		−0.22
X	Jacareubin (12)	α					6.73	6.48							+0.25		
	diac. vs. triac.	β					5.63	5.77							−0.14		
XI	Desoxymorellin (13)	α					6.63	6.35							+0.28		
	desoxymor. vs. monoac.	β					5.50	5.58							−0.08		
XII	Isoallorottlerin	α					6.60	6.35	6.55	6.43	6.47	6.39			+0.25	+0.12	+0.08
	triac. vs. tetraac.	β					5.48	5.61	5.58	5.74	5.59	5.76			−0.13	−0.16	−0.17
XIII	Gambogic acid (14)	α					6.55	6.32							+0.23		
	gamb. acid vs. monoac.	β					5.33	5.52							−0.19		

			C_6H_{12}		CCl_4		$CDCl_3$		acetone		DMSO		C_6H_{12}	CCl_4	$CDCl_3$	acet.	DMSO
			OH	OAc	OH	OAc	OH	OAc	OH	OAc	OH	OAc	$\Delta\delta_{acetyl}$				
XIV		α	6.21		6.23		6.31		6.38		6.40						
		β	5.45		5.51		5.59		5.72		5.73						
XV	7-OH	α	6.15	6.18	6.15	6.22	6.22	6.27	6.27	6.38	6.26	6.41	-0.03	-0.07	-0.05	-0.11	-0.15
		β	5.32	5.42	5.34	5.48	5.44	5.55	5.49	5.69	5.47	5.72	-0.10	-0.14	-0.11	-0.20	-0.25
XVI	6-OH	α			6.16	6.21	6.25	6.25	6.30	6.36				-0.05	-0.02	-0.06	
		β			5.53	5.55	5.63	5.63	5.69	5.76				-0.02	0.00	-0.07	
XVII	8-OH	α	6.22	6.21	6.26	6.27	6.32	6.32	6.35	6.42	6.32	6.44	+0.01	-0.01	0.00	-0.07	-0.12
		β	5.45	5.48	5.51	5.55	5.60	5.62	5.69	5.75	5.69	5.79	-0.03	-0.04	-0.02	-0.06	-0.10
XVIII	7-OH, 6-$COCH_3$	α	6.16	6.22	6.19	6.27	6.28	6.32	6.42	6.48			-0.06	-0.08	-0.04	-0.06	
		β	5.43	5.49	5.48	5.55	5.58	5.64	5.71	5.80			-0.06	-0.07	-0.06	-0.09	
XIX	6-OH, 5-$COOCH_3$	α	7.05	6.60	7.00	6.52	7.07	6.56	7.05	6.54	6.37	6.46	+0.45	+0.48	+0.51	+0.51	-0.09
		β	5.54	5.54	5.58	5.63	5.71	5.72	5.82	5.85	5.83	5.91	0.00	-0.05	-0.01	-0.03	-0.08
XX	6-$COCH_3$	α	6.27		6.31		6.36		6.50		6.50						
		β	5.53		5.58		5.66		5.82		5.83						
XXI	6-$COOC_2H_5$	α	6.26		6.30		6.35		6.47		6.51						
		β	5.51		5.56		5.64		5.80		5.83						
XXII	5-$COOCH_3$	α	7.44		7.29		7.25		7.25		7.11						
		β	5.59		5.66		5.74		5.87		5.91						
XXIII	<u>Toxicarol isoflavone</u> (15) methylether vs. acetate	α					6.70	6.78							-0.08		
		β					5.53	5.68							-0.15		



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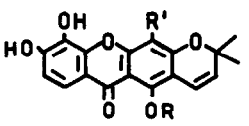
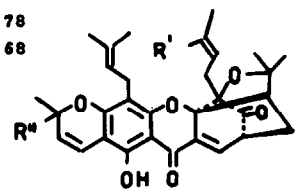


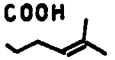
IX R' = 

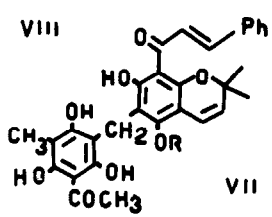
X R' = H



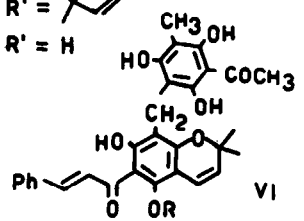
XI R' = R'' = CH_3

XIII R' = COOH

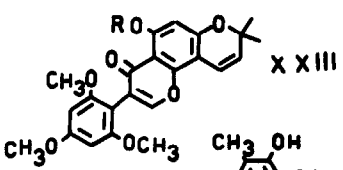
R'' = 



VII



VI



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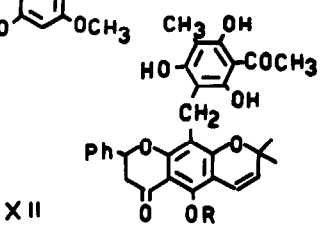
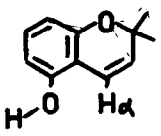


XII

This effect can be explained, as in α-naphtol, by an interaction of H_a with the electron pair of the oxygen in the preferred trans configuration (electron pair cis to H_a):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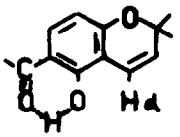
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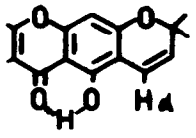
F

A similar shift of H_a is found in I (6.59)(D) and II (6.72)(E), where the intramolecular hydrogen bond locks the OH in the trans configuration*. With acetylation:

i) either a planar trans configuration is still preferred, and the electron pair is delocalized on the ester group, and consequently the deshielding of the hydroxyl is destroyed,

ii) or the acetyl group is slightly twisted out of the plane, because of steric hindrance, and H_a becomes near to the positive conical area of the C=O; thus, the deshielding effect of the oxygen is compensated by the shielding of the carbonyl.

This second hypothesis is more probable. If we observe compounds of type F (IX, X, XI, XII, XIII), where chelation occurs as well as in E, a planar trans configuration for the corresponding acetates is unlikely, because of the two peri interactions, and we obtain on acetylation the same $\Delta\delta$. However, it cannot be excluded that a certain delocalization of the electron pair on the ester group may contribute to this effect. When R is a bulky substituent (V-VIII) one could suggest that the acetyl is more twisted toward the chromene double bond, and, as a consequence, H_a becomes nearer to the C=O and experiences a stronger shielding (due to the anisotropic magnetic susceptibility and to the electric dipole moment of the substituent). An increased value of the shift is indeed found (V, $\Delta\delta_{acetyl}$ = +0.41 in C_6H_{12}; VIII, +0.37; VI and VII, +0.50 in $CDCl_3$), whereas the very small difference between $\Delta\delta_{acetyl}$ of I and II is somewhat surprising.

The acetylation of hydroxyls in 6,7, and 8 position does not show any appreciable effect on H_a ** (see table 2).

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* taking into account that the small difference has in part to be attributed to the substituent effect of the group in 6 position (-0.06 δ, see later).

** There is one exception, when a carbonyl is in 5 position. On acetylation of the near 6-OH, a strong upfield shift ($\Delta\delta \cong +0.5$) is observed for H_a in every solvent, except in DMSO (XIX). Nevertheless, a carbonyl in the position 5 is easily recognized by the strong deshielding of H_a, mainly due to the magnetic anisotropy and the dipolar moment of the carbonyl (H_a being on the same plane). In XIX we have H_a = 7.05 δ, in XXII H_a = 7.44 δ. In the first case, the H-bond locks the C=O in a trans configuration; in the second one, a cis configuration must be preferred for steric reasons, as the lower shift is observed (compare $\Delta\delta$ of vinyl protons in dimethylfumarate and dimethylmaleate = +0.53 (9)). As a result of the steric hindrance of 6-OAc, with the consequent twisting of the carbonyl slightly out of the plane of the ring, the H_a does not experience the whole deshielding effect of the carbonyl and is found upfield ($^{\alpha}\Delta\delta_{acetyl}$ = +0.45). The same reasons must be in-

We have examined the effect of the substituents and solvents on H_α and H_β chemical shifts. As expected the hydroxyl in 6 or 8 does not greatly influence the H_α and H_β chemical shifts, whereas the mesomeric effect of the 7-OH causes a small deshielding on H_β ($\Delta\delta$ = +0.1-0.2) with respect to 2,2-dimethylchromene (XIV), which increases slightly in the more polar solvents. On acetylation of the 7-OH, the OH mesomeric effect disappears, and we can thus explain the deshielding of H_β on acetylation ($\Delta\delta_{acetyl}$ = -0.10-0.25). As for the 6-substituent, a very small shielding is observed for H_α with 6-OH ($\Delta\delta \simeq$ +0.08), and an equally small deshielding with 6-COR ($\Delta\delta$ = -0.06-0.10), but they have no diagnostic significance. Now it follows that strong deshielding, by the peri 5-OH, of the H_α, discussed above, and the shielding by the 5-OAc, must be attributed to steric effects. Any mesomeric or inductive effect of OH on the chromene ring is only diamagnetic, even if greatly reduced in magnitude.

The effect of polar solvents on the chemical shifts of H_α and H_β is strong. We have noted in 2,2-dimethylchromene (XIV) a regular deshielding of both H_α and H_β on going from C_6H_{12} to the more polar solvents (acetone and DMSO), this effect being mainly due to the reaction field induced by polar molecules dissolved in a medium of high dielectric constant (ε). When the substituents are OH, specific solvent-solute interactions (H-bonding) may arise. When the OH are in 6,7,8 position, H_α and H_β show about the same behaviour as in XIV (deshielding), whereas the effect of intermolecular H-bonding is particularly significant in compounds with the 5-OH. The shift of H_α is observed to go in the opposite sense with respect to the polarity of the solvent. A possible explanation might be that the strong donor DMSO molecule, interacting with the 5-OH, twists it slightly out of the plane, in such a way as to decrease the steric hindrance with the 6-substituent. Consequently H_α does not experience the whole effect of the lone pair of the peri hydroxyl and it goes upfield (average $\delta_{C_6H_{12}} - \delta_{DMSO}$ = +0.1). In the less hindered 5-hydroxychromene (I) $\Delta\delta$ is smaller (+0.02).

On acetylation of the 5-OH, this upfield effect disappears as expected (average $\delta_{C_6H_{12}} - \delta_{DMSO}$ = -0.1). For these reasons the H_α upfield shift observed on acetylation of 5-hydroxychromenes is stronger in C_6H_{12}, CCl_4, $CDCl_3$ and weaker in acetone and DMSO. It is even zero for macluraxanthone ($\Delta\delta_{acetyl}$ = +0.05) and isoallorottlerin (+ 0.08) in DMSO. Consequently for diagnostic purposes the spectra must be recorded in the former solvents.

2) The long-range coupling ($J_{4,8}$), first suggested by Elvidge and Foster (10), was measured on both H_4 and H_8. The signals are double doublets in compounds II, III and their acetates, XVIII acetate, XXII ($J_{4,8}$ = 0.6-0.7, $J_{\alpha,\beta}$ = 10), XIX ($J_{4,8}$ = 0.5), XIX acetate ($J_{4,8}$ = 0.3,

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voked to explain the abnormal upfield shift of H_α in DMSO ($\delta_{C_6H_{12}} - \delta_{DMSO}$ = +0.68) in XIX. DMSO, interacts with the 6-OH in competition with the 5-COOMe and induces the same distortion in coplanarity. Hence on acetylation of 6-OH we did not obtain in DMSO any effect on H_α chemical shift ($\Delta\delta_{acetyl}$ = -0.09) (see later).

deduced from width differences). In II there is evidence (from the width of the signals, 100 MHz) of interaction between H_4 and H_7 ($J_{4,7} \leq 0.2$). In 2,2-dimethylchromene (XIV) other inter-ring couplings may be present, because the two lines of H_α doublet are broad (width: H_α = 1.4, H_β = 0.9 Hz; $J_{4,8} < 0.5$). Even if small, $J_{4,8}$ is clearly visible in all 2,2-dialkylchromenes with free position 8, including lonchocarpin and jacareubin, and it can be useful in deciding the substitution of the benzene ring in unknown natural products.

Together with this inter-ring coupling, the effect of acetylation is a useful tool in structural elucidation of polycyclic compounds. This is shown in table 1, where we have presented pertinent data which are available in the literature (*).

All NMR spectra were measured at 60 MHz (Varian A-60, temp. 33°); II and XIV were also measured at 100 MHz. The shifts are in ppm (δ) from TMS as internal standard, J in Hz. Accuracy in chemical shift is within 1 Hz. The accuracy of sweep-width was checked using the separation between the singlets due to the $CHCl_3$ and TMS in CCl_4. The concentrations are 0.1 M. No appreciable variation in chemical shifts was found within the concentrations range 0.05–0.2 M.

All synthetic compounds were prepared by Nickl's method (16), hydroxychromenes by decarboxylation for 5 minutes in boiling quinoline of the corresponding ortho carboxylic acids.

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* The chemical shift values of α- and β-toxicarol and their acetates are in agreement with our results (α-toxicarol, structure type B: H_α 6.56, H_β 5.48 (17), acetate 6.59, 5.51, $\Delta\delta_{acetyl}$ = −0.03, −0.03; β-toxicarol, structure type A: H_α 6.59, H_β 5.47, acetate 6.31, 5.58, $\Delta\delta_{acetyl}$ = +0.28, −0.11 $CDCl_3$). The values for β-toxicarol do not correspond to those given by Crombie (17). Our thanks to Prof. H.S. Harper for samples of β-toxicarol and α-toxicarol acetate. We cannot explain the values found in scandenin (A. Pelter, P. Stainton, J. Chem. Soc. C 1966, 701). This seems to be the only exception.

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(10) J.A. Elvidge, R.G. Foster, J. Chem. Soc. 1964, 981.
(11) We are deeply indebted to Prof. M.L. Wolfrom for a generous gift of macluraxanthone.
(12) Spectra kindly measured for us by Prof. T.J. King.
(13) Data kindly communicated by Prof. K. Venkataraman.
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