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CIS-3-METHYLFLAVANONES[1]

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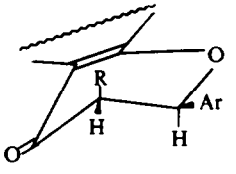
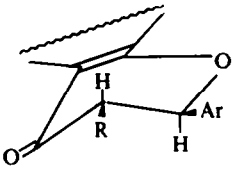
Abstract—A simple high yield preparation of *cis*-3-methylflavanones is described and the stereochemistry of the intermediate 4-oximinoflavans is discussed.

THE PREPARATION of *cis*-3-substituted flavanones (I, R = OMe, Me) is hindered by the relative ease of their epimerization in acid medium to give a mixture of *trans*-(II) and *cis*-(I) isomers.[2] *cis*-3-Hydroxyflavanones[3] are unknown but some *cis*-3-methoxy-[4, 2] and *cis*-3-bromo-[5] flavanones have been synthesized.



I



II

We report here details of a useful method for the preparation of some 2,3-*cis*-3-methylflavanones (IIIa, b, d).

Cyclization of 2′-hydroxy-α-methylchalcones with base gave the corresponding 2,3-*trans*-3-methylflavanones (IVa–d) ($J_{2,3}$ 12 Hz). Oximation of the latter compounds afforded 2,3-*cis*-3-methyl-4-oximinoflavans (Va–d) ($J_{2,3}$ 2·6 Hz), which on subsequent treatment with sodium bisulphite followed by dilute HCl at 0°[6] gave the 2,3-*cis*-3-methylflavanones (IIIa–b, d).

The change in spatial relationship of the C-2 and C-3 protons on oximation of the *trans*-flavanones (IVa–d) arises during the reaction as a result of epimerization at C-3. Experimental evidence in support of epimerization occurring during the oximation reaction is shown by the conversion of 2,3-*trans*-3′,4′-methylenedioxy-3-methylflavanone (IVb) into the 3-deutero oxime, on treatment with hydroxylamine in pyridine/D_2O. The deuterium is retained during the hydrolysis (Method 1) to give 3-deutero-3′,4′-methylenedioxy-3-methylflavanone.

When hydrolysis of the oximes was carried out under more vigorous conditions (Method 2) a mixture of 2,3-*cis*- and 2,3-*trans*-flavanones resulted.

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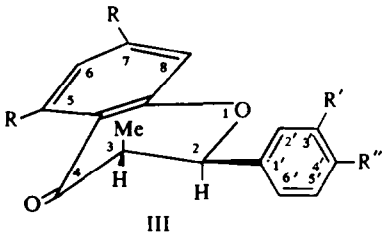
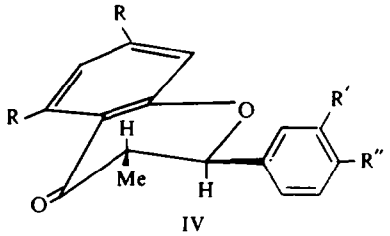
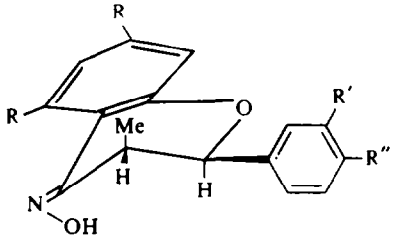


III



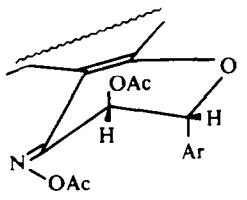
IV



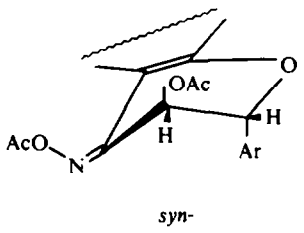
V

a R = R′ = R″ = H
b R = H: R′, R″ = O.CH_2.O
c R = R″ = OMe; R′ = H
d R = Me, R′ = H, R″ = OMe.

In the light of the results obtained in the 3-methylflavanone series, a re-examination of dihydroflavonol oxime formation was undertaken.



anti-



syn-

VI

Previously,[7] it was concluded that ring inversion accounted for unexpected decrease of the coupling constants of 3-acetoxyflavanone oxime acetates (VI), on acetylation of the *syn-* and *anti-*isomers of 2,3-*trans*-3-hydroxy-4-oximinoflavan. It was considered that ring inversion would minimize interaction between C_3—OAc and C_2—ϕ groups and that the >C=N linkage was less effective than the >C=O linkage in fixing the diequatorial conformation of the C-2 and C-3 substituents.

The dihydroflavanol oximes {$J_{2,3}$ 9·4 Hz (*syn*); 7·9 Hz (*anti*)}, when prepared using hydroxylamine, pyridine/D_2O showed no deuterium uptake. Epimerization apparently does not occur. Acetylation of the oximes afforded a mixture of 3-acetoxyflavanone oxime acetates (VI) {$J_{2,3}$ 3·6 Hz (*syn*); 3·2 Hz (*anti*)} which under controlled hydrolysis (Method 1) gave 2,3-*trans*-dihydroflavanol (II, R = OH) as the sole product. These experimental results lend support to the previous conclusion[7] that ring inversion occurred during the acetylation reaction.

The assignment of *syn*- and *anti*-configurations to 3-hydroxyflavanone oximes was based on their NMR analyses (Table 2). The NMR technique has been used in the study of isomeric oximes[8] as the anisotropy of the hydroxyimino group results in chemical shift differences. Studies on benzene induced shifts,[9] and more recently *tris*(DPM)europium[10] induced shifts on oximes have been recorded.

The 2,3-*trans*-3-methylflavanone (IVa, b) yielded only one oxime (Va, b) in each case to which an *anti*-configuration was assigned on the basis of the downfield shift of the 5-proton (Table 1). An *anti*-configuration was tentatively assigned to the oxime (Vc).

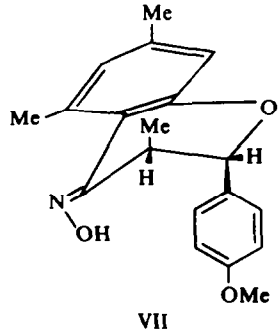
TABLE 1. NMR SPECTRA OF SOME *anti*-OXIMES

Compound	$J_{2,3}$ Hz	C_3—Me ($J_{3H,Me}$)	H-2	H-3*	H-5
2,3-*cis*-3-Methyl-4-oximinoflavan (Va)	2·9	9·09 (7·0 Hz)	4·77	6·25	2·1
2,3-*cis*-3',4'-Methylenedioxy-3-methyl-4-oximinoflavan (Vb)	2·8	9·1 (7·1 Hz)	4·76	6·27	2·15
2,3-*cis*-4',5,7-Trimethoxy-3-methyl-4-oximinoflavan (Vc)	2·6	9·07 (7.4 Hz)	4·83	6·19	—
2,3-*cis*-4'-Methoxy-3,5,7-trimethyl-4-oximinoflavan (Vd)	2·6	9·15 (7·8 Hz)	4·56	5·9	—
2,3-*trans*-4'-Methoxy-3,5,7-trimethyl-4-oximinoflavan (VIId)	3·2	8·7 (7·8 Hz)	4·98	5·85	

* Multiplet centred at the τ value given.

Table 1 NMR data, spectra run in $CDCl_3$ at 60 MHz with TMS as internal standard, all values on τ scale, J in Hz.

The introduction of a C-5 methyl substituent in the *trans*-flavanone (IVd) resulted in the formation of two oximes. The major product *anti*-2,3-*cis*-4'-methoxy-3,5,7-trimethyl-4-oximinoflavan (Vd), on bisulphite hydrolysis (Method 1) yielded the corresponding 2,3-*cis*-3-methylflavanone (IIId), the minor product (VII) ($J_{2,3}$ 3·2 Hz) on bisulphite hydrolysis gave only 2,3-*trans*-flavanone (IVd). The major product (Vd) involved epimerization at C-3 whilst the formation of the minor product (VII) was accompanied by ring inversion.



VII

The coupling constant $J_{2,3}$ 3·2 Hz for compound (VII) closely resembles that of the 3-acetoxyflavanone oxime acetates (VI) ($J_{2,3}$ 3·2–3·6 Hz).

Oximation of two 3,3-disubstituted flavanones gave *syn*- and *anti*-isomers. The minor products assigned the *anti* configurations were heat labile and readily converted to the more stable *syn*-isomers. Relevant NMR data is given in Table 2.

TABLE 2. NMR SPECTRA OF SOME *syn*- AND *anti*-OXIMES†

Compound	*anti*-	*syn*-	
3-Hydroxy-3-methyl-4-oximinoflavan	4·9	4·9	H-2
	8·7	8·8	C_3—Me
	2·0	1·25	H-5
	(*J* 9·4 Hz)	(*J* 9·5 Hz)	
3-Hydroxy-3',4'-methylenedioxy-3-methyl-4-oximinoflavan	4·98	4·95	H-2
	8·67	8·86	C_3—Me
	2·0	1·28	H-5
	(*J* 8·2 Hz)	(*J* 8·3 Hz)	
3-Hydroxy-4-oximinoflavan[7]	4·92	4·98	H-2
	4·73	5·41	H-3
	2·38	1·42	H-5
	7·9 ± 0·1	9·4 ± 0·2	$J_{2,3}$ (Hz)

† The NMR spectra were run in $(CD_3)_2CO$ at 60 MHz with TMS as internal standard, all values on τ scale, *J* in Hz.

The production of 2,3-*cis*-3-methylflavanones (III), on hydrolysis (Method 1) of the corresponding 2,3-*cis*-oximes (V), provides a useful route to their preparation, and to the elucidation of the stereochemistry of the oximes. An analogous situation has been observed for the 3-phenylflavanones. For example, 2,3-*trans*-3-phenylflavanone when treated with hydrazine hydrochloride yielded 2,3-*cis*-3-phenylflavan hydrazone.

EXPERIMENTAL

Unless otherwise stated, IR spectra were measured as KBr discs and 60 MHz. NMR spectra in $CDCl_3$ (TMS as internal reference). Only significant bands from IR spectra are quoted.

Merck Kieselgel $HF_{254+366}$ was used for thick and thin layer chromatography.

General preparation of chalcones. Equimolar quantities of the respective acetophenone and the aldehyde in EtOH were treated dropwise, under stirring, with NaOH aq. (50%). After 24 hr at 20° (or reflux for 1 hr), the product was poured into excess of ice–HCl (3:1) to precipitate the chalcone. The chalcones were purified in the usual manner. Details for individual chalcones, their m.p. (solvent), % yield and analyses are given below:

2'-Hydroxy-α-methylchalcone[11] b.p. 140°/1·8 mm, 50%.

2'-Hydroxy-3',4'-methylenedioxy-α-methylchalcone,[12] m.p. 110–111° (EtOH), 89%.

2'-Hydroxy-4,4',6'-trimethoxy-α-methylchalcone m.p. 99–100° (EtOH): 50% (Found: C, 69·7; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

2'-Hydroxy-4-methoxy-α,4',6'-trimethylchalcone, m.p. 150–151° (MeOH), 52%, (Found: C, 76·8; H, 6·8. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

2'-Hydroxy-α-phenylchalcone, m.p. 132° (MeOH): 50% (Found: C, 83·6; H, 5·5. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4%).

2,3-trans-3-*Methylflavanone formation.* The appropriate α-methylchalcone (1 g) was cyclized with NaOH aq. (10 ml: 1·5%) in EtOH (25 ml). The mixture was stirred for 24 hr at room temp and diluted with water. The dried ethereal extract gave the *trans*-flavanone. Elemental analyses and details of physical properties of the series are in Table 3.

TABLE 3

Compound	m.p. (Solvent)	Yield %	Found % C	Found % H	Requires % C	Requires % H	IR (cm^{-1})	NMR (τ) (*J* Hz) 2-H	3-H	3-Me
2,3-*trans*-3-Methylflavanones										
					Calc. for $C_{16}H_{14}O_2$					
3-Methylflavanone[11]	95–96° (MeOH)	59	80·3	5·9	80·6	5·9	1692	4·95 d (12·5)	6·98 m	8·99 (6·6)
					$C_{17}H_{14}O_4$					
3′,4′-Methylenedioxy-3-methylflavanone	106° (EtOH)	63	72·3	5·2	72·3	5·0		5·0 d (12·2)	6·9 m	9·0 (7·7)
					$C_{19}H_{20}O_5$					
4′,5,7-Trimethoxy-3-methylflavanone	143–144° (EtOH)	65	69·9	6·2	69·5	6·1		5·04 (12·1)	7·1 m	8·97 (7·8)
					$C_{19}H_{20}O_3$					
4′-Methoxy-3,5,7-trimethylflavanone	91–92°	47	76·8	6·8	77·0	6·8		4·97 (12·0)	6·95 m	9·0 (7·7)
					$C_{21}H_{16}O_2$					
2,3-*trans*-3-Phenylflavanone	162–163° (MeOH)	70	83·8	5·4	84·0	5·4	1698	4·38 d (11·5)	5·68 d 11·5 Hz	
2,3-*cis*-3-Methylflavanones										
					$C_{16}H_{14}O_2$		liq. film			
3-Methylflavanone	oil	64	81·1	6·2	80·7	5·9	1658	4·49 d (2·65)	7·2 m	9·03 d (7·4)
					$C_{17}H_{14}O_4$		liq. film			
3-Methyl-3′,4′-methylenedioxylflavanone	oil	63	72·8	5·1	72·3	5·0	1680	4·49 d (2·52)	7·22 m	9·0 d (7·1)
					$C_{19}H_{20}O_3$		liq. film			
4′-Methoxy-3,5,7-trimethylflavanone	oil	68	77·3	7·0	77·0	6·8	1675	4·49 d (2·6)	7·15 m	9·01 d (7·4)

General procedure for oxime formation. A solution of the *trans*-flavanone (1 g), hydroxylamine hydrochloride (0·022 m) and piperidine (1·2 ml) in aqueous pyridine (20 ml; 66%) was refluxed for 6 hr. Dilution with ice/HCl gave the *cis*-3-methyl-4-oximinoflavan in 90–95% yield.

2,3-cis-3-*Methyl*-4-*oximinoflavan* (Va) m.p. 179–180°, needles from MeOH (Found: C, 75·71; H, 6·2; N, 5·6. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%).

2,3-cis-3',4'-*Methylenedioxy*-3-*methyl*-4-*oximinoflavan* (Vb), m.p. 151–152°, needles from MeOH (Found: C, 69·0; H, 5·2; N, 4·9. $C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·1; N, 4·7%). By replacement of water by D_2O in the reaction mixture 2,3-cis-3-deutero-3',4'-*methylenedioxy*-3-*methyl*-4-*oximinoflavan* was prepared.

2,3-cis-4',5,7-*Trimethoxy*-3-*methyl*-4-*oximinoflavan* (Vc), m.p. 230° (dec.), plates from benzene (Found: C, 66·8; H, 6·4; N, 4·2. $C_{19}H_{21}NO_5$ requires C, 66·5; H, 6·2; N, 4·1%).

2,3-cis-4'-*Methoxy*-3,5,7-*trimethyl*-4-*oximinoflavan* (Vd), and 2,3-trans-4'-*methoxy*-3,5,7-*trimethyl*-4-*oximinoflavan* (VII). The mixture was refluxed for 20 hr. The dried ethereal solution gave an oil which was separated (TLC) into three fractions. Fraction (i) (8%) yielded a mixture of *cis*- and *trans*-4'-methoxy-3,5,7-trimethylflavanones. Fraction (ii) (40%) gave 2,3-*cis*-4'-methoxy-3,5,6-trimethyl-4-oximinoflavan m.p. 177°, amorphous powder from benzene–light petroleum (b.p. 60–80°). (Found: C, 73·6; H, 6·6; N, 4·6. $C_{19}H_{21}NO_3$ requires C, 73·3; H, 6·8; N, 4·5%); ν_{max} 3280 1615 cm^{-1}. Fraction (iii) (10%) gave 2,3-*trans*-4'-methoxy-3,5,7-trimethyl-4-oximinoflavan, m.p. 161–162°, needles from benzene–light petroleum (b.p. 60–80°). (Found: C, 73·7; H, 7·1; N, 4·5. $C_{19}H_{21}NO_3$ requires C, 73·3; H, 6·8; N, 4·5); ν_{max} 3290, 1615 cm^{-1}.

Hydrolysis of the oximes. Method 1. A mixture of the 4-oximinoflavan (1·2 mm), sodium metabisulphite (2·6 mm) and EtOH aq. (10 ml, 50%) was refluxed for 6 hr. The bisulphite salt formed was purified by prep. TLC and subsequently decomposed rapidly with dilute HCl at 0°. The aqueous mixture was extracted with $CHCl_3$. Evaporation of $CHCl_3$ extract yielded the 2,3-*cis*-3-methylflavanone. Elemental analysis and details of the physical properties of the *cis*-series are in Table 3.

Method 2. Hydrolysis of the 2,3-*cis*-3-methyl-4-oximinoflavan (50 mg) in ethanolic HCl (7 ml; 50%) gave 2,3-*trans*-3-methylflavanone (60%) and 2,3-*cis*-3-methylflavanone (28%).

2,3-cis-3-deutero-3-*Methyl*-3',4'-*methylenedioxyflavanone* (63%) was prepared by hydrolysis (Method 1) of the corresponding *deutero* oximinoflavan.

Hydrolysis of 2,3-*trans*-4'-methoxy-3,5,7-trimethyl-4-oximinoflavan with sodium metabisulphite gave the corresponding *trans*-flavanone m.p. and m.m.p. 91–92°.

syn- and anti-3-*Hydroxy*-3-*methyl*-4-*oximinoflavans.* 3-Hydroxy-3-methylflavanone[11] (0·01 m) was refluxed with hydroxylamine hydrochloride (0·05 m) and piperidine (3 ml) in aqueous pyrydine (50 ml); 66%) for 6 hr. The products were poured on ice–HCl and extracted with ether. Removal of the solvent yielded a pale yellow oil which was separated by TLC into two fractions. The first m.p. 163–170° proved to be anti-3-*hydroxy*-3-*methyl*-4-*oximinoflavan* (27%). (Found: C, 71·7; H, 5·9; N, 5·0. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6; N, 5·2%). ν_{max} 3450, 3200, 1610 cm^{-1}: NMR {$(CD_3)_2CO$}: τ −0·5 (broad s, =N—OH), 2·0 (*J* 9·4 Hz, 5-H), 4·26 (s, 3-OH), 4·9 (s, 2-H), 8·7 (s, Me). The second fraction crystallized from MeOH in needles of syn-3-*hydroxy*-3-*methyl*-4-*oximinoflavan* (34%), m.p. 173–175°. (Found: C, 71·7; H, 5·9; N, 5·3. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6; N, 5·2%); ν_{max} 3330, 1610 cm^{-1}.

syn- *and* anti-3-*Hydroxy*-3',4'-*methylenedioxy*-3-*methyl*-4-*oximinoflavan.* Oximation of 3-hydroxy-3',4'-methylenedioxy-3-methylflavanone was carried out as for 3-hydroxy-3-methylflavanone. TLC analysis indicated the presence of two compounds. Compound (i) m.p. 148–150° proved to be *anti*-3-hydroxy-3',4'-methylenedioxy-3-methyl-4-oximinoflavan (35%). (Found: C, 65·2; H, 4·7; N, 4·3. $C_{17}H_{15}NO_5$ requires C, 65·2; H, 4·8; N, 4·5%); ν_{max} 3450, 3250, 1610 cm^{-1}. Compound (ii) crystallized from MeOH as needles of *syn*-3-hydroxy-3',4'-methylenedioxy-3-methyl-4-oximinoflavan (41%) m.p. 163°. (Found: C, 65·0; H, 5·1; N, 4·2. $C_{17}H_{15}NO_5$ requires C, 65·2; H, 4·8; N, 4·5%); ν_{max} 3220, 1610 cm^{-1}.

3-*Phenylflavan hydrazone.* 2,3-*trans*-3-Phenylflavanone (500 mg) was dissolved in pyridine (10 ml) and treated with a solution of hydrazine monohydrochloride (1 g) in aqueous pyridine (10 ml, 50%). After 5 days at room temp, the mixture was poured onto ice-water. The crude product was collected and crystallized from EtOH in pale yellow needles of 3-phenylflavan hydrazone, m.p. 177–179°. (Found: C, 80·6; H, 5·5; N, 8·9; O, (direct) 5·4. $C_{21}H_{18}N_2O$ requires C, 80·4; H, 5·7; N, 8·9; O, 5·08%). NMR spectrum $J_{2,3}$ 3·2 Hz.

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