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STEREOCHEMISTRY OF 3-HYDROXY- AND 3-ACETOXYFLAVANONE OXIMES

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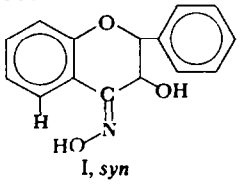
Abstract—3-Hydroxyflavanone oxime has been separated into *syn* and *anti* isomers and the structures of the products are proved by IR and NMR spectroscopy. NMR investigation of the acetylated oximes has shown that these compounds probably exist in a new conformation produced by the joint action of the C_3–O acetyl substituent and the presence of the C=N linkage. Results obtained with 3-hydroxy-5,7,3',4'-tetramethoxyflavanone oxime and acetylated 3-hydroxyflavanone hydrazones support these conclusions.

OUR investigations on the reactions of the CO function of 3-hydroxyflavanones[1] have recently been extended to a study of the oximes and acetylated oximes of these compounds.

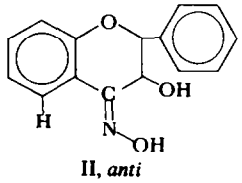
A few years ago, Bognár *et al.*[2] reported the synthesis of 3-hydroxyflavanone oxime and 3-hydroxy-5,7,3',4'-tetramethoxyflavanone oxime. Considering the stereochemical relationships in 3-hydroxyflavanones, it appears reasonable to suppose that the well-known *syn-anti* isomerism of oximes may also apply to these compounds.

Reproduction of the synthesis of 3-hydroxyflavanone oxime gave a product identical in all respects with the reported[2] compound (m.p. 154°) which, however, has been shown by TLC to consist of a two-component mixture. Separation can be achieved by preparative column chromatography to obtain pure oxime I (m.p. 173°) and oxime II (m.p. 146°). Both compounds are quantitatively converted into 3-hydroxyflavanone on acid hydrolysis, thus excluding the possibility that the flavanone skeleton has suffered rearrangement in either of them.

IR spectroscopy gave C=N stretching 1642 cm^{-1} and 1627 cm^{-1} in I and II, respectively. The higher C=N frequency in oxime I may be readily explained by the steric repulsion, also shown by the Stuart model of the compound, between the oxime OH group and the hydrogen atom at C_5. Accordingly, the structures of oximes I and II should be:



I, *syn*
M.p. 173°



II, *anti*
M.p. 146°

[1] G. Janzsó, F. Kállay and I. Koczor, *Tetrahedron* **22**, 2909 (1966).

[2] R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **19**, 391 (1963).

It follows that when the substituent at C_5 is a group bulkier than hydrogen, formation of a *syn* isomer is not probable at all. This expectation has been fully justified in the case of 3-hydroxy-5,7,3',4'-tetramethoxyflavanone oxime[2] that consists, according to our TLC tests, of a single isomer (m.p. 194°).

In order to confirm the correctness of the above structures, measurements by NMR spectroscopy have been made. Chemical shifts of the protons that may give information in this respect and the 2,3-coupling constants are shown in Table 1.

TABLE 1.

Compound	Chemical shifts δ (ppm in $CDCl_3$)			Coupling constants $J_{2,3}$ (c/s)
	H-2	H-3	H-5	
3-Hydroxyflavanone	5·14	4·64	7·94	12·5 ± 0·1
3-Hydroxyflavanone oxime I	5·02	4·59	8·58	9·4 ± 0·2
3-Hydroxyflavanone oxime II	5·08	5·27	7·72	7·9 ± 0·1
3-Hydroxy-5,7,3',4'-tetramethoxy-flavanone oxime	4·92	5·27	—	8·5 ± 0·1

The problem of *syn–anti* isomerism is conclusively decided by the chemical shifts of H-3 and H-5. Interaction of the oxime OH-group with the former is expected in II, and with the latter in I, as shown by the formulas. It is seen from Table 1 that the downfield shift resulting from such interactions may actually be observed for H-3 in the *anti*, and for H-5 in the *syn* oxime. The magnitude of this shift is in both cases about 0·6 ppm, compared with the starting 3-hydroxyflavanone.

As expected, the chemical shift of H-3 in 3-hydroxy-5,7,3',4'-tetramethoxyflavanone oxime is the same as in 3-hydroxyflavanone oxime II, proving the *anti* configurations of both compounds.

Quantitative NMR measurements have also shown that the 3-hydroxyflavanone oximes I and II are produced in the ratio 1:3, i.e. formation of the sterically less hindered form is preferred. The IR and NMR spectra clearly indicate the absence of intramolecular hydrogen bonding between the neighbouring OH groups in II. (The two OH protons appear in both I and II as a collapsed broad line, line width ~12 c/s, at about 6 ppm in $CDCl_3$. The shift values show a variation with concentration, typical for intermolecular H-bonding).

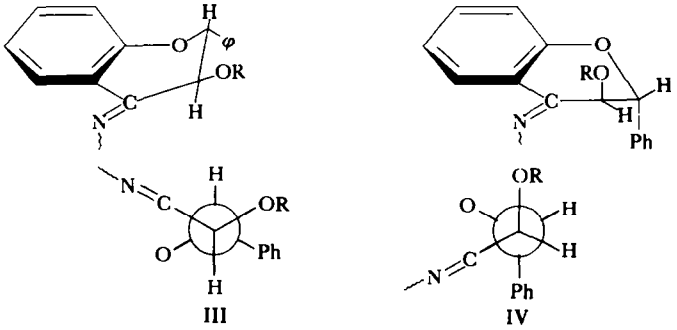
From the NMR data presented in Table 1 it can be seen that substitution by N of the CO oxygen atom is accompanied by a decrease of the 2,3-coupling constant ($J_{2,3}$) as compared with that of 3-hydroxyflavanone. Interpreting this decrease in terms of the angular dependence of the vicinal coupling constant, one obtains, according to the well-known approximate relationship,[3] a change by 20–30° of the H-2–H-3 dihedral angle. This distortion of the hetero ring is approximately of the same magnitude in both oxime isomers.

[3] See, e.g.: N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* Chap 3–4. Holden-Day, San Francisco (1964).

TABLE 2.

Compound	$J_{2,3}$	Coupling constants (c/s)			Solvent
		$J_{3,3\,gem}$	$J_{2,3\,ax}$	$J_{2,3\,eq}$	
Flavanone	—	$-17{\cdot}4 \pm 0{\cdot}2$	$12{\cdot}2 \pm 0{\cdot}2$	$3{\cdot}4 \pm 0{\cdot}2$	$CDCl_3$, C_6D_6
Flavanone oxime	—	$-17{\cdot}3 \pm 0{\cdot}2$	$12{\cdot}2 \pm 0{\cdot}2$	$3{\cdot}4 \pm 0{\cdot}2$	CD_3COCD_3
Flavanone hydrazone	—	$-17{\cdot}5 \pm 0{\cdot}2$	$12{\cdot}1 \pm 0{\cdot}2$	$3{\cdot}3 \pm 0{\cdot}2$	CD_3COCD_3–$CDCl_3$ 1:1
3-Acetoxyflavanone	$12{\cdot}5 \pm 0{\cdot}1$	—	—	—	$CDCl_3$, C_6D_6
3-Acetoxyflavanone oxime I acetate	$3{\cdot}6 \pm 0{\cdot}1$	—	—	—	$CDCl_3$, C_6D_6
3-Acetoxyflavanone oxime II acetate	$3{\cdot}2 \pm 0{\cdot}1$	—	—	—	$CDCl_3$,C_6D_6
3-Hydroxyflavanone hydrazone	$7{\cdot}0 \pm 0{\cdot}2$	—	—	—	$DMSOD_6$–$CDCl_3$ 1:1
3-Hydroxyflavanone N-acetylhydrazone	$9{\cdot}5 \pm 0{\cdot}5$	—	—	—	C_5D_5N–C_6D_6 1:3
3-Acetoxyflavanone N-acetylhydrazone	$3{\cdot}0 \pm 0{\cdot}2$	—	—	—	$CDCl_3$
3-Acetoxy-5,7,3',4'-tetramethoxyflavanone oxime acetate	$3{\cdot}5 \pm 0{\cdot}2$	—	—	—	$CDCl_3$

An unexpected decrease of the coupling constants is observed in both cases when oxime I and II are acetylated at room temperature to give the corresponding 3-acetoxyflavanone oxime acetates (Table 2). The values of the coupling constants of the diacetates can only be interpreted by assuming that the conformation of the hetero ring has suffered a profound change. This may be illustrated as follows:



III

R = H
$J_{2,3}$ = 8–9 c/s
φ ~ 170°

IV

R = Ac
$J_{2,3}$ = 3 c/s
φ ~ 70°

Since the decrease of $J_{2,3}$ is observed with the *syn* as well as with the *anti* diacetate, it must be assumed that the conformational change has been brought about by an interaction of the C_3–OAc and C_2–Ph groups, instead of the oxime OAc and C_3–OAc groups. Measurement on Dreiding models[4] of the dihedral angle made by the H-2 and H-3 atoms gave $\varphi_{III} = 169°$ for the '*gauche*', and $\varphi_{IV} = 69°$ for the '*trans*' conformation. (The names '*gauche*' and '*trans*', denote here the relative positions of the Ph and C_3–O–Ac groups).

Since the coupling constant of 3-acetoxyflavanone is the same as that of 3-hydroxyflavanone (Table 2), it appears, at first sight, rather surprising that introduction of the Ac group has produced such a change of the ring conformation in the flavanone oximes. However, there are several facts that may help explaining the experimental evidence. Clark-Lewis[5] showed that the hetero ring of *trans*-3-bromoflavanones is to a certain extent distorted in comparison with *trans*-dihydroflavanols. Similarly, the conformation of (±)-*trans*-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan is also distorted considerably from a half-chair towards a boat conformation.[6] Finally, it has been shown that our results with 3-hydroxyflavanone oximes indicate that the hetero ring is again distorted as compared with the ketone.

These experimental facts may be simply explained with the assumption that distortion of the hetero ring depends on two factors: it is induced by the C_3 substituent whose action becomes displayed to an extent determined by the hybridization of the C_4 atom.

In the above examples, the flavan skeleton, as shown by the Dreiding model, may exist without strain in the boat form, thus a considerable change is produced by C_3–OAc substitution. When C_4 is present in a CO group, a bulky bromine atom is required to produce some change in this direction. If the C_4 atom is bonded to N, even the action of a C_3–OH substituent is distinctly felt. In other words, the C=N linkage is less effective in fixing the original (III) conformation than a C=O group. Therefore, a complete change of the conformation of the hetero ring produced by the interaction of C_3–OAc with the Ph group in flavanone oximes should not be regarded as unexpected, especially since a boat conformation would be highly strained in this case.

The chemical shifts of the CH_3 protons of the C_3OAc group further support the interpretation of the coupling constants of the diacetyloximes by a new *trans* conformation. The chemical shift in 3-acetoxyflavanone is $\delta = 1{\cdot}98$ ppm, while in both diacetyloxime isomers it is 2·08 ppm. This difference may well correspond to a change in the relative positions of the C_3OAc and Ph groups.[5]

In order to find additional evidence, the action of the two factors believed to produce together *trans* (IV) conformation was also investigated with flavanone oxime, flavanone hydrazone[7] and 3-hydroxyflavanone hydrazone.[8] An inspection of Table 2 shows that mere introduction of C=N instead of C=O produces no change of the coupling constants when C_3 is unsubstituted. However, the presence of C=N linkage allows a distortion in case of C_3–OH substitution which is increased to give a new conformation when the C_3 substituent is still bulkier, such as OAc. The N-monoacetyl

[4] J. W. Clark-Lewis and E. J. Wigley, *Chem. & Ind.* 1419 (1962).
[5] J. W. Clark-Lewis, L. M. Jackman and T. M. Spotswood, *Austral. J. Chem.* **17**, 632 (1964).
[6] J. W. Clark-Lewis, I. Dainis and G. C. Ramsay, *Austral. J. Chem.* **18**, 1035 (1965).
[7] F. Kállay, G. Janzsó and I. Koczor, *Tetrahedron* **21**, 19 (1965).
[8] G. Janzsó, F. Kállay and I. Koczor, to be published.

derivative[8] of 3-hydroxyflavanone hydrazone as well as the parent compound have still *gauche* conformation, while the N,O-diacetyl compound[8] has changed into *trans*. The coupling constants of acetylated 3-acetoxy-5,7,3',4'-tetramethoxyflavanone oxime are also in agreement with the above conclusion.

In this work we have not considered the possibility that another interpretation of the measured coupling constants may be given by assuming conformational equilibria, i.e. changes in the relative population of the conformers. These results are, therefore considered a qualitative picture about the stereochemistry of the compounds discussed. An unequivocal decision between these two alternative interpretations may be arrived at by measuring the temperature dependence of the vicinal coupling constants ($J_{2,3}$). Such measurements, as well as studies on new model compounds containing bulkier substituents at positions 2 and 3 are in progress.

EXPERIMENTAL

The NMR measurements were made at 60 Mc/s with an AEI RS2 spectrometer, using 5–10% w/v solns at room temp. The solvent was usually $CDCl_3$. In some cases, owing to the poor solubility of the compound, or in order to eliminate the accidental coincidence of the chemical shifts of H-2 and H-3, solvents such as DMSO, C_6D_6, $(CD_3)_2CO$, C_5D_5N (or their mixture with $CDCl_3$) were used. Chemical shifts were determined relative to internal TMS with an accuracy of ±0·01 ppm by means of the usual side band technique.

All m.p.s were determined on a Kofler block and are uncorrected. TLC examinations were made a Kieselgel HF_{254} using the system benzene—AcOEt (50:10 v/v).[9]

Preparative separation of the 3-hydroxyflavanone oxime isomers. A mixture of 3-hydroxyflavanone oxime isomers (1·1 g: m.p. 154°; lit[2]. m.p. 154°) was dissolved in a mixture (80 ml) of benzene and AcOEt (20:1 v/v). A column (length 1 m, i.d. 12 mm) was prepared of silica gel (100–200 mesh; 90 g) which had been treated with Walpole buffer soln (10 ml, diluted with 10 ml water) and suspended in a solvent mixture of the above composition. The soln of the oxime mixture was introduced to the column, followed by elution at a flow-rate of 53 ml/hr with the same solvent mixture. The effluent was passed through a detector cell which continuously indicated the presence of any oxime in the soln by registering the UV absorption at 315 mμ by means of an automatic recorder.

The fractions containing oximes I and II, respectively, were evaporated under reduced press at room temp to 20 ml each. In this way oxime I (172 mg; m.p. 173°) and oxime II (568 mg; m.p. 146°) were obtained. (Found: N, 5·27 for I, and N, 5·34 for II. $C_{15}H_{13}O_3N$ requires: N, 5·51%).

Oxime I decomposed after standing several weeks with the evolution of nitrogen oxides, to give mainly—as shown by TLC—3-hydroxyflavanone. The green spots of the two oximes which appeared on spraying with 2% $CuCl_2$, had R_f = 0·44 for I and R_f = 0·58 for II.

Hydrolysis of the 3-hydroxyflavanone oxime mixture. 3-Hydroxyflavanone oxime (100 mg; mixture of both isomers, m.p. 154°) was dissolved in a warm mixture of EtOH (5 ml) and 7% HCl aq (10 ml). Refluxing the soln for 1 hr caused the separation of white needles. Storage overnight in a refrigerator gave 3-hydroxyflavanone (84·2 mg; 89·5%), m.p. and mixed m.p. with an authentic sample 192–194°.

Hydrolysis of the separated oximes I and II under similar conditions, followed by TLC, showed that both compounds were converted quantitatively into 3-hydroxyflavanone.

Acetylation of 3-hydroxyflavanone oxime I and II. A soln of oxime I or II (150 mg) was allowed to stand 2 hr in a mixture of Ac_2O (2 ml) and pyridine (2 ml), then poured into ice-water. The separated crude product was recrystallized from EtOH (2 ml) to obtain white crystals of the diacetyl derivative, m.p. 135–136° from I, and m.p. 130–131° from II. (Found: N, 4·23 from I, and N, 4·11 from II. $C_{19}H_{17}O_5N$ requires: N, 4·14%).

IR analysis: C=O frequencies of Ac groups: 1753 and 1785 cm^{-1} for the diacetate of I; 1763 cm^{-1} and shoulder at 1770 cm^{-1} for the diacetate of II.

Acetyl derivative of 3-acetoxy-5,7,3',4'-tetramethoxyflavanone oxime. 3-Hydroxy-5,7,3',4'-tetramethoxyflavanone oxime[2] was acetylated as described above. The crude product was recrystallized from EtOH to give white needles, m.p. 174°. (Found: N, 2·87. $C_{23}H_{25}O_9N$ requires: N, 3·06%).

[9] M. Hranisavljević-Jakovljević, I. Pejković-Tadić and A. Stojilković, *J. Chromatog.* **12**, 70–73 (1963).

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