The Stereochemistry of 2-Hydroxyisoflavanones

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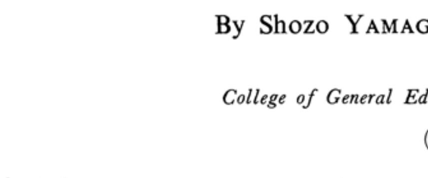
2-Hydroxyisoflavanones are often isolated as unstable intermediates in the course of the syntheses of isoflavones by means of the reactions of 2-hydroxyphenyl benzyl ketones with ethyl formate in the presence of sodium.[1,2,4]



(I): $R_1=R_2=R_3=R_4=H$
(II): $R_1=OMe$; $R_2=R_3=R_4=H$
(III): $R_1=R_2=OMe$; $\left.\begin{matrix}R_3\\R_4\end{matrix}\right\}=\begin{matrix}O\\O\end{matrix}\!\!>CH_2$

The stereochemistry of 2-hydroxyisoflavanones has been discussed previously by Whalley,[3] who reported that 2-hydroxyisoflavanones have a trans configuration with equatorial C_2 hydroxyl and equatorial C_3 phenyl groups.

In order to confirm his assignment, the NMR spectra of 2-hydroxyisoflavanones were investigated; the results will be reported in this paper.

2-Hydroxyisoflavanone (I) and 2-hydroxy-7-methoxyisoflavanone (II) were synthesized, and the NMR spectra of I, II and 2-hydroxy-5, 7-dimethoxy - 3′, 4′ - methylenedioxy - isoflavanone (III)[4] were measured in $CDCl_3$, $CHCl_3$ (containing a trace of water or hydrochloric acid) or pyridine, depending on their solubilities. The spectra were determined with a Varian A-60 spectrometer at 60 mc., using tetramethylsilane as an internal reference, the results obtained are summerized in Table I.

In the NMR spectra of I in $CDCl_3$, the broadenings of the doublet with its center at 248.4 c. p. s. and of the triplet with its center at 348.3 c. p. s. seem to be due to the slow exchange of the C_2-hydroxyl proton. In order to confirm this consideration, the NMR spectrum of I was measured in $CHCl_3$ containing a trace of water. The broad doublet at 248.4 c. p. s. became extremely broad and almost unrecognizable; however, the integration curve showed the presence of one proton between 248 and 287 c. p. s. The triplet at 348.3 c. p. s. became a sharp doublet with its center at the same position. Furthermore, in the NMR spectrum of I in $CHCl_3$ containing a trace of hydrochloric acid, the triplet at 348.3 c. p. s. observed in $CDCl_3$ became a sharper doublet than that in the spectra measured in $CHCl_3$ containing a trace of water.

From these observations, it may be concluded that the signals of I at 233.1, 248.4 and 348.3 c. p. s. are to be attributed to the C_3-proton, hydroxyl proton and C_2-proton respectively; the coupling constant between the C_2-proton and the C_3-proton has been determined to be 4.2 c. p. s.

The NMR spectrum of III was measured in a pyridine solution because of its low solubility in $CDCl_3$. As a result of the solvent effect caused by pyridine, the signals of III were shifted to a considerably low field as compared with the corresponding signals of I in $CDCl_3$; however, the complete assignments for the signals of III could be made with reference only to those of I measured in pyridine.

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[1] W. B. Whalley, *J. Am. Chem. Soc.*, **75**, 1059 (1953); W. B. Whalley, *J. Chem. Soc.*, **1953**, 3366; A. Robertson and Whalley, ibid., **1954** 1440.

[2] N. Narasimhachari, D. Rajanparan and T. R. Seshadri, *J. Sci. Ind. Research* (*India*), **12**, 287 (1954).

[3] W. B. Whalley, "The Chemistry of Flavonoid Compounds," Ed. by T. A. Geisman, Pergamon Press, Oxford (1962), p. 462.

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TABLE I. NMR SPECTRA OF 2-HYDROXYISOFLAVANONES

Isoflavanones	Position of peaks in c.p.s.	No. of protons	Assignment	Remarks	Configuration
2-OH*(I)	233.1	1	3-H	Doublet, $J_{2,3}=4.2$ c.p.s.	
	248.4	1	Hydroxyl proton	Broad doublet	
	348.3	1	2-H	Broad triplet	
2-OH**(I)	233.1	1	3-H	Doublet $\}$ $J_{2,3}=4.2$ c.p.s.	2(eq), 3(ax) cis
	348.3	1	2-H	Doublet	
2-OH, 7-MeO*(II)	236.5	1	3-H	Partly screened by methyl signal	
	351.0	1	2-H	Doublet, $J_{2,3}=4.0$ c.p.s.	2(eq), 3(ax) cis
2-OH***(I)	265.9	1	3-H	Doublet $\}$ $J_{2,3}=3.7$ c.p.s.	
	280.3	1	2-H	Doublet	
2-OH, 5,7-di-MeO-3′,4′-methylenedioxy*** (III)	255.2	1	3-H	Doublet $\}$ $J_{2,3}=3.5$ c.p.s.	2(eq), 3(ax) cis
	269.9	1	2-H	Doublet	

* $CDCl_3$ was used as solvent.
** $CHCl_3$ + trace H_2O or trace HCl was used as solvent.
*** Pyridine was used as solvent.

Since 2-hydroxyisoflavanones have the hemi-acetal structure, the coupling constant of glucopyranose can be used for determining the configurations of the compounds I, II and III.

Considering Karplus' calculated results,[5] the coupling constant of glucopyranose[6] and the observed $J_{2,3}$, of I, II and III (4.2 c.p.s., 4.0 c.p.s. and 3.5 c. p. s., respectively), it may be concluded that the 2-hydroxyisoflavanones obtained as the intermediates in the syntheses of isoflavones have cis configurations.

2-Hydroxyisoflavanones are generally converted to the corresponding isoflavones through dehydration by heating or treatment with acid.[3] However, I and II were found to give the corresponding isoflavones in a quantitative yield even when treated with ethanol or benzene under the mild conditions described in Table II.

TABLE II. TRANSFORMATIONS OF 2-HYDROXYISOFLAVANONES TO ISOFLAVONES

(a)*—Ethanol (10 ml.), reflux 30 min.
(b)*—Pyridine (0.5 ml.) in benzene (5 ml.), 50°C, 20 min.
(c)*—Ethanolic potassium hydroxide (5% 10 ml.), room temperature, 20 hr.

* In each case 50 mg. of the sample (I or II) was employed.

Experimental

2-Hydroxyisoflavanone (I).—Into 3 g. of sodium dust there was stirred, drop by drop, over a period of 40 min. under cooling with ice, a mixture of 60 ml. of ethyl formate and 6 g. of 2-hydroxyphenyl benzyl ketone. After had been stirred the mixture three more hours, it was allowed to stand overnight under cooling with ice. To the reaction mixture there was then added ice water. The separated crystals were filtered, dried, and washed with hot petroleum ether and then with a small amount of ethanol. Recrystallization from benzene - petroleum ether (1:1) gave 2-hydroxyisoflavanone (ν_{OH} 3600 cm^{-1}, 3400 cm^{-1}; $\nu_{C=O}$ 1695 cm^{-1}; $CHCl_3$ solution), m. p. 110—111°C (decomp.), 2.2 g. (32%).

Found: C, 74.95; H, 5.26. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%.

One gram of isoflavone, m. p. 132—133°C, was obtained from the mother liquor of I.

2-Hydroxy-7-methoxyisoflavanone (II).—2-Hydroxy-4-methoxyphenyl benzyl ketone was treated with ethyl formate and sodium in a manner similar to that used for the formation of I. The crude crystals were recrystallized from benzene yielding II (ν_{OH} 3350 cm^{-1}, 3460 cm^{-1}; $\nu_{C=O}$ 1688 cm^{-1}; $CHCl_3$ solution) m. p. 145—146°C (decomp.)[2] in a 43% yield. By refluxing II in acetic acid for 20 min., it was quantitatively converted to 7-methoxyisoflavone, m. p. 154—155°C.

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[6] R. V. Lemieux, R. K. Kulling, H. J. Bernstein and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).