The Stereochemistry of Isoflavan-4-ols

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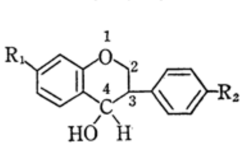
One of the present authors, Inoue, obtained isoflavan-4-ol (I), 7-methoxyisoflavan-4α-ol (II), 7-methoxyisoflavan-4β-ol (III) and 7, 4′-dimethoxyisoflavan-4-ol (IV) by the reduction of the corresponding isoflavanones; he tentatively assigned a trans configuration to II and cis configurations to I, III and IV, mainly on the basis of the mechanism of the reduction and on that of the reactions of those compounds.[1]



(I): $R_1=R_2=H$
(II), (III): $R_1=OMe$, $R_2=H$
(IV): $R_1=R_2=OMe$

The NMR spectra of hydroxyflavans have been measured by Clark-Lewis and Jackman[2] and by other authors[3], who have reported that spin-spin

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[1] N. Inoue, This Bulletin, **37**, 601 (1964).

[2] J. W. Clark-Lewis and L. M. Jackman, *Proc. Chem. Soc.*, **1961**, 165; J. W. Clark-Lewis, T. M. Spotswood and L. R. Williams, ibid., **1963**, 20; J. W. Clark-Lewis, L. M. Jackman and L. R. Williams, *J. Chem. Soc.*, **1962**, 3858.

[3] C. P. Lillya, D. Kehoe, E. M. Philbin, M. A. Vickars and T. S. Wheeler, *Chem. & Ind.*, **1963**, 84; C. P. Lillya, ibid., **1963**,

TABLE I. NMR SPECTRA OF 4-HYDROXYISOFLAVANES AND THEIR DERIVATIVES

	Position of peaks in c. p. s.	No. of protons	Assignment	Remark	Configuration
Isoflavan-4-ol (I)[*4]	181—201	1	H_3	Sextet	
	240—283	2	H_2	Multiplet	
	274.5, 277.4[*1]	1	H_4	Doublet $J_{3,4}=2.9$ c. p. s.	3(ax), 4(eq) cis
Acetate of I	368.2, 371.0	1	H_4	Doublet $J_{3,4}=3.0$ c. p. s.	3(ax), 4(eq) cis
7-Methoxy-isoflavan-4α-ol (II)	175.5—195.5	1	H_3	Sextet	
	242—266	2	H_2	Multiplet	
	288.6, 296.0	1	H_4	Doublet $J_{3,4}=7.4$ c. p. s.	3(ax), 4(ax) trans
Acetate of II	364.3, 369.3	1	H_4	Doublet $J_{3,4}=5.0$ c. p. s.	3(ax), 4(ax) trans
7-Methoxy-isoflavan-4β-ol (III)	186.5—205	1	H_3	Sextet[*3]	
	249.3—286.8	2	H_2	Multiplet[*3]	
	282.1, 285.1[*2]	1	H_4	Doublet $J_{3,4}=3.0$ c. p. s.	3(ax), 4(eq) cis
Acetate of III	364.9, 368.1[*2]	1	H_4	Doublet $J_{3,4}=3.2$	3(ax), 4(eq) cis
4-Isopropoxy-7-methoxy-isoflavan6)	264.0, 271.0	1	H_4	Doublet $J_{3,4}=7.0$	3(ax), 4(ax) trans
7,4′-Dimethoxy-isoflavan-4-ol (IV)[*4]	278.0, 280.9	1	H_4	Doublet $J_{3,4}=2.9$	3(ax), 4(eq) cis

[*1] Long range coupling ($J_{2,4}=1.0$ c. p. s.) was observed.
[*2] Long range coupling ($J_{2,4}=1.2$ c. p. s.) was observed.
[*3] The following values were calculated from the ABX pattern7):
$J_{AB}=10.4$ c. p. s., $J_{AX}=11.9$ c. p. s., $J_{BX}=3.0$ c. p. s., $\delta_{AB}=16.7$ c. p. s.
[*4] These compounds1) were also prepared from the corresponding isoflavones by reduction with sodium borohydride at room temperature.8)

coupling constants between the 2- and 3-, and the 3- and 4- protons define the stereochemistry and conformation of the heterocyclic ring.

On the other hand, the NMR spectrum of only one 4-hydroxyisoflavan, 2-methyl-4-hydroxy-7, 4′-diacetoxyisoflavan, has been reported4); the spectra of pterocarpin and similar compounds have also been discussed,5) but the simple 4-hydroxyisoflavans have not been investigated.

With this in mind, the NMR spectra of I, II, III, IV and their derivatives were measured out in order to determine their configurations and to decide whether relationships similar to those found in the case of the hydroxyflavans exist between the coupling constants and the configurations of the isoflavan-4-ols.

The experimental results are summarized in Table I.

A consideration of the dependence of the proton vicinal coupling constants on the dihedral angle, as in the Karplus equation,9) leads unambiguoulsy to the assignment of the same configuration as was proposed in the preceding paper. The relationship between the 3, 4-coupling constants and the configurations which was observed with hydroxyisoflavans is the same as that seen in the case of the hydroxyflavans.2,3) Therefore, it may be concluded that the configuration of a 4-hydroxyisoflavan can be determined from the coupling constant of the 3- and 4-protons.

Furthermore, the *S*-methylxanthates of II and III were submitted to thermal elimination in order to confirm the stereochemical relations obtained by NMR measurements. The *S*-methylxanthates

TABLE II

Heating time min.	Yield of isoflavene, %	
	Xanthate of II	Xanthate of III
10	20	4
20	30	7
40	37	22
60	43	31

783; E. J. Corey, *Tetrahedron Letters*, **1961**, 429.

4) R. A. Micheli, A. N. Booth, A. L. Livingston and E. M. Bickoff, *J. Med. & Pharm. Chem.*, **5**, 321 (1962).

5) J. B. Bredenberg and J. N. Shoolery, *Tetrahedron Letters*, **1961**, 285; D. R. Perrin, ibid., **1964**, 29; D. D. Perrin and D. R. Perrin, *J. Am. Chem. Soc.*, **84**, 1922 (1962).

6) N. Inoue, S. Yamaguchi and S. Fujiwara, This Bulletin, **37**, 588 (1964).

7) H. J. Bernstein, J. A. Pople and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

8) After this work had been completed, a report appeared by L. R. Row, A. S. R. Anjaneyulu and C. S. Krishna (*Curr. Sci.*, **32**, 67 (1963)) in which 7-methoxy and 7, 4′-dimethoxyisoflavanones were reduced to isoflavan-4-ols by the same procedure.

9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

of II and III were prepared by Corey's method[10] and were subjected to elimination reactions at 180°C. The rate of the formation of the corresponding isoflavene was determined by measuring the extinction of the product at 332.5 mμ (Table II).

From the results summarized in Table II, it is apparent that the xanthate of II decomposes faster than that of III, consequently, II has the cis, and III has the trans, configuration.

Experimental

The NMR spectra were determined with a Varian A-60 spectrometer, at 60 Mc., using deuterochloroform as the solvent and tetramethylsilane as the internal reference.

Isoflavan-4-ol (I) and 7, 4'-Dimethoxyisoflavan-4-ol (IV). — A solution of isoflavone (0.7 g.) and sodium borohydride (0.3 g.) in methanol (130 ml.) was stirred for 2 days at room temperature. The methanol was then distilled off under reduced pressure, and the residue was decomposed with 70% acetic acid. The resulting solution was diluted with water and extracted with ether. The ether layer was washed once with a sodium bicarbonate solution and twice with water, then dried over anhydrous sodium sulfate and evaporated. The residue crystallized from petroleum ether as prisms (0.4 g.); m. p. 75°C.

7, 4'-Dimethoxyisoflavan-4-ol (37%) m.p. 143—144°C was similarly prepared from the corresponding isoflavone.

***S*-Methylxanthates of II (V) and III (VI).**—A dimethyl sulfoxide solution (10 ml.) of sodium methylsulfinylcarbanion (prepared from 0.3 g. of sodium hydride and 20 ml. of dimethyl sulfoxide) was added to a stirred solution of II (0.25 g.) in dimethyl sulfoxide (5 ml.); the mixture was then stirred for 30 min. Then carbon disulfide (0.16 g.) was added and, after 30 min., 0.29 g. of methyl iodide, after which stirring was continued for 2.5 hr. All of these operations were carried out at room temperature under an atmosphere of nitrogen. Finally, the resulting solution was diluted with water and extracted with ether. The evaporation of the ether gave pale yellow crystals, which were treated with 5 ml. of methanol. The insoluble solid was collected and recrystallized from ethanol - ethyl acetate to give the *S*-methylxanthate of II (0.15 g.), m. p. 136—137.5°C.

Found: C, 62.17; H, 5.14. Calcd. for $C_{18}H_{18}O_3S_2$: C, 62.42; H, 5.24%.

S-Methylxanthate of III, m. p. 93—95°C (after recrystallization from ethanol - ethyl acetate), was similarly prepared from the corresponding isoflavan-4-ol.

Found: C, 62.31; H, 5.08. Calcd. for $C_{18}H_{18}O_3S_2$: C, 62.42; H, 5.24%.

The Decomposition of the Xanthates.—The weighed xanthates (ca. 0.1 mg.) described above were placed in separate glass tubes (4 × 150 mm.) under a nitrogen atmosphere; the tubes were then clamped vertically in an oil bath at 180°C. At the end of a given time, the tubes were removed from the bath, the reaction product was dissolved in methanol, and the extinction at 332.5 mμ for each solution was measured in order to determine the yield of isoflavene by reference to a previously-prepared calibration curve.

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[10] E. J. Corey and H. Uda, *J. Am. Chem. Soc.*, **85**, 1790 (1963).