

Syntheses of *trans*-Isoflavan-4-ols

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The reaction of nitrous acid and three 4-aminoisoflavan hydrochlorides (III, IV, and V) obtained by the catalytic hydrogenation of isoflavanone oximes, and the hydroboration of three isoflavenes (XII, XIII, and VIII), were investigated in the hope of finding a general method of synthesizing *trans*-isoflavan-4-ols. The reaction of III and IV with nitrous acid afforded the corresponding *trans*-4-ols, though in a poor yield, but that of V produced no expected compound, the corresponding isoflavene (VIII) being obtained instead. The hydroboration of XII, XIII, and VIII afforded the corresponding *trans* alcohols (VI, VII, and XIV) in good yields. In addition, it became clear that 4-aminoisoflavans obtained by the catalytic reduction of the oximino compounds possess the 3,4-*cis* configuration.

Inoue obtained *cis*-7-methoxyisoflavan-4-ol (X) as a main product and *trans*-7-methoxyisoflavan-4-ol (VII) as a by-product by the reduction of 7-methoxyisoflavanone with sodium borohydride. However, the hydride reduction of isoflavanone and 4',7-dimethoxyisoflavanone did not afford the *trans*-4-ols.^{1,2} Later, the present authors³ obtained VII

by the reaction of 4-amino-7-methoxyisoflavan hydrochloride (IV) with nitrous acid, but we could not apply this reaction to other aminoisoflavans, since these amines had not yet been prepared in our laboratory.

In order to find out a general method of synthesizing *trans*-isoflavan-4-ols, we undertook the

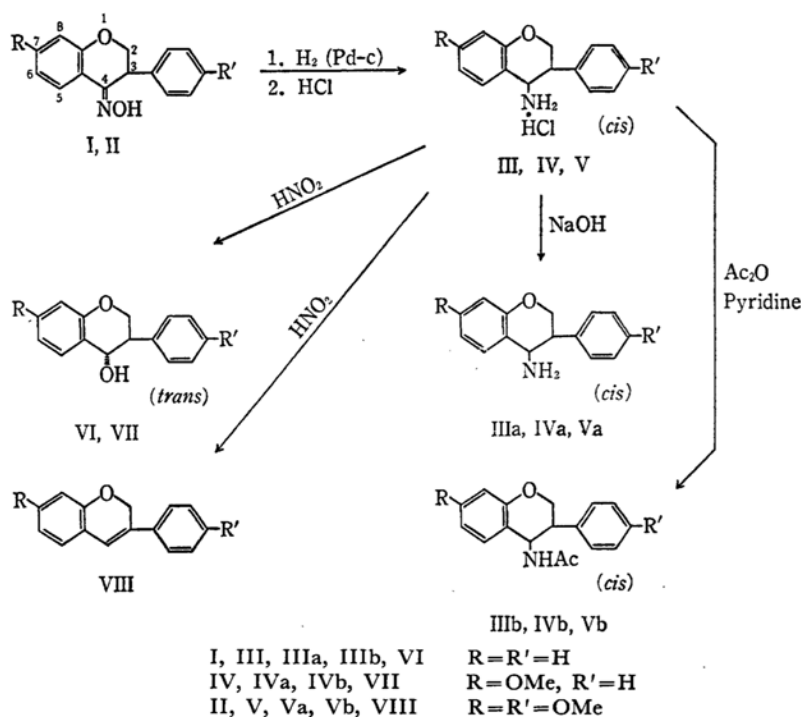


Chart 1

1) N. Inoue, This Bulletin, **37**, 601 (1964).2) S. Yamaguchi, S. Ito, A. Nakamura and N. Inoue, *ibid.*, **38**, 2187 (1965).3) N. Inoue, S. Yamaguchi and S. Fujiwara, *ibid.*, **37**, 604 (1964).

TABLE 1. CHEMICAL SHIFTS OF METHYL PROTONS OF ACETYL GROUPS OF 4-AcO-F*, 4-AcO-IF* and 4-AcNH-IF

Entry	Compound	cis (ppm)	trans (ppm)	$\Delta\delta$ (ppm)
1	4-AcO-F	2.05	2.05	0.0
2	4-AcO-7-MeO-F**	2.07	2.05	0.02
3	4-AcO-IF	1.83	2.02	0.19
4	4-AcO-7-MeO-IF	1.83	2.05	0.22
5	4-AcO-4',7-(MeO) ₂ -IF		2.04	
6	4-AcNH-IF	1.83		
7	4-AcNH-7-MeO-IF	1.83		
8	4-AcNH-4',7-(MeO) ₂ -IF	1.83		

* F: Flavan; IF: Isoflavan.

** Unpublished results. The syntheses and the stereochemistry of these compounds will be reported elsewhere.

synthesis of 4-aminoisoflavan (IIIa) and 4-amino-4',7-dimethoxyisoflavan (Va), and also the examination of their reaction with nitrous acid and of the hydroboration of isoflavones. The results obtained will be presented in this paper.

4-Aminoisoflavans were synthesized according to the following reaction scheme. The catalytic hydrogenation of isoflavanone oxime (I) and 4',7-dimethoxyisoflavanone oxime (II) in acetic acid containing a small amount of perchloric acid in the presence of palladium on carbon produced the corresponding amines (IIIa and Va), which were then isolated as hydrochlorides (III and V), and the treatment of III and V with acetic anhydride and pyridine gave 4-acetamido derivatives (IIIb and Vb).

The stereochemistry of three 4-aminoisoflavans (IIIa, IVa, and Va) was determined on the basis of the NMR spectra. In the NMR spectra of these amines, the signals assigned to three protons of the 2- and 4-positions are observed around 4.0–4.9 ppm and overlap with each other. In the case of 4-acetamidoisoflavans (IIIb, IVb, and Vb), the proton signals of the 4-position shift to a lower field and appear quite broad. Therefore, it is difficult to determine the value of $J_{3H,4H}$ directly from the signals of the chroman-ring protons. As is shown in Table 1, the methyl proton signals of the acetyl group of 4-acetoxyflavan (*cis*, *trans*), 4-acetoxy-7-methoxyflavan (*cis*, *trans*), and *trans*-4-acetoxyisoflavans are observed at 2.02–2.07 ppm (Entries 1, 2, 3, 4, and 5). On the other hand, these signals of *cis*-4-acetoxyisoflavans shift to a field higher by approximately 0.19–0.22 ppm and appear at 1.83 ppm (Entries 3 and 4). In *cis*-4-acetoxyisoflavans, the

acetyl group is above the plane of the adjacent phenyl group at the 3-position (Fig. 1); consequently, the acetyl group suffers the shielding effect of the C₃ phenyl group and shifts to a higher field. This up-field shift seems to be characteristic of 3,4-*cis*-isoflavans. A quite similar phenomenon is observed in the NMR spectra of the 4-acetamidoisoflavans (IIIb, IVb, and Vb). The methyl proton signals of the acetyl group of these acetamido compounds appear at 1.83 ppm (Entries 6, 7, and 8 in Table 1). A comparison of these values with those of *cis*-acetoxyisoflavans suggests the *cis* configuration of IIIb, IVb, and Vb.

The above inference is also supported by the stereochemistry of the catalytic hydrogenation of cyclohexanone oximes⁴⁾ and isoflavanones.¹⁻³⁾ Furthermore, as will be shown in the Experimental part of this paper and as has been shown in a previous report,⁸⁾ in the reactions of 4-aminoisoflavan hydrochloride (III) and the 4-amino-7-methoxy derivative (IV) with nitrous acid, the yields of *trans*-isoflavan-4-ols (VI and VII) were as low as 26% and 15% respectively, and the 4-amino-4',7-dimethoxy derivative (V) gave only 4',7-dimethoxyisoflavene (VIII).⁵⁾ In view of the reported stereochemistry of the reaction of aminocyclohexanes with nitrous acid,⁶⁾ the results described above also support the *cis* configuration assigned to 4-aminoisoflavans.

The reaction of two 4-aminoisoflavan hydrochlorides (III and V) with nitrous acid was also carried out. From III, a compound with a mp of 97°C was obtained in a 26% yield; this compound had the molecular formula C₁₅H₁₄O₂, but it was not identical with *cis*-isoflavan-4-ol (IX).¹⁾ Therefore, the compound may be supposed to be *trans* alcohol (VI). This was confirmed by comparing the NMR

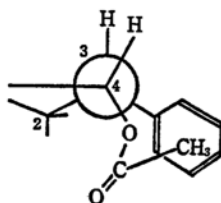


Fig. 1

4) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).5) R. B. Bradburry and D. E. White, *J. Chem. Soc.*, **1953**, 871.

6) a) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformation Analysis," Interscience Publishers, New York, N. Y. (1965), p. 89. b) M. Hannack, "Conformation Analysis," Academic Press, New York, N. Y. (1965).

TABLE 2. NMR SPECTRA OF ISOFLAVAN-4-OLS AND THEIR DERIVATIVES

Compound	Position of peaks in ppm	No of protons (assignment)	Remarks	Configuration
Isoflavan-4-ol (IX) ^{1,2,3)}	4.60	1 (4-H)	Doublet $J_{3,4}=2.9$ Hz	3(ax), 4(eq) cis
Acetate ²⁾	6.16	1 (4-H)	Doublet $J_{3,4}=3.0$	3(ax), 4(eq) cis
Isoflavan-4-ol (VI)	4.92	1 (4-H)	Doublet $J_{3,4}=8.0$	3(ax), 4(ax) trans
Acetate	6.19	1 (4-H)	Doublet $J_{3,4}=6.0$	3(ax), 4(ax) trans
4',7-Dimethoxyisoflavan-4-ol (XI) ²⁾	4.66	1 (4-H)	Doublet $J_{3,4}=2.9$	3(ax), 4(eq) cis
4',7-Dimethoxyisoflavan-4-ol (XIV)	4.82	1 (4-H)	Quartet $J_{3,4}=7.9$	3(ax), 4(ax) trans
Acetate	6.06	1 (4-H)	Doublet $J_{3,4}=5.0$	3(ax), 4(ax) trans

spectra of VI and its acetate with those of *cis*-isoflavan-4-ol (Table 2). The reaction between V and nitrous acid at room temperature gave an olefinic compound with a mp of 161°C which was identified as VIII.⁵⁾ Even the reaction at a lower temperature (ice-cooling) gave no expected *trans*-4',7-dimethoxyisoflavan-4-ol (XIV); rather, the starting amine was recovered, together with VIII.

The synthesis of *trans*-isoflavan-4-ols by the hydroboration of isoflavenes was attempted next. The hydroboration of substituted double bonds and subsequent oxidation by hydrogen peroxide has been reported to lead to *cis*-type hydration, following the anti-Markownikoff rule.⁷⁾ Therefore, it was anticipated that the application of this reaction to isoflavenes would result in the formation of *trans*-isoflavan-4-ols. 7-Methoxyisoflavene (XIII) and

VIII were prepared from the corresponding *cis* alcohols (X and XI) by heating in acetic acid. Isoflavene (XII) was prepared by refluxing a solution of the *cis* alcohol (IX) in acetic acid containing a small amount of concentrated hydrochloric acid.

A 1-mol equivalent of diborane (2.0 M equivalent in BH_3) and a 2.51-mol equivalent of XIII were allowed to react in tetrahydrofuran. At appropriate intervals of time, samples were withdrawn and analysed for remaining XIII by measuring the extinction at 333 μ . The amounts of remaining unreacted XIII observed 30 min, 2 hr, and 17 hr after the beginning of the reaction were 65%, 35%, and 10% respectively. In order to transform the remaining XIII into the organoborane completely, a diborane-THF solution was then added until the molar ratio of XIII and diborane became 1.62:1. The XIII disappeared 70 min after the addition of the final diborane solution.

It has been reported⁷⁾ that, in the hydroboration of trisubstituted olefins such as α -pinene, the reaction proceeds rapidly to the dialkylborane stage. In our experiment, however, when the molar ratio of XIII (trisubstituted olefin) to diborane was 2.5:1, unreacted XIII was detected, but when the ratio was 1.62:1, no XIII was detected. The above experimental results indicate that the reaction proceeds predominantly to the monoalkylborane. After the usual treatment, a compound with a mp of 131°C was obtained in a 44% yield; this compound was identical with *trans*-7-methoxyisoflavan-4-ol (VII).¹⁻³⁾ A similar reaction of XII gave *trans*-isoflavan-4-ol (VI) in a 73% yield. A compound (XIV) with a mp of 124°C was obtained in a 66% yield from VIII. It was different from *cis*-4',7-dimethoxyisoflavan-4-ol (XI)^{1,2)} and may, therefore, be supposed to be a *trans* modification. The NMR spectra of XIV and its acetate (Table 2) support the *trans* configuration.

In conclusion, the hydroboration of isoflavenes seems valuable as a general method of synthesizing *trans*-isoflavan-4-ols.

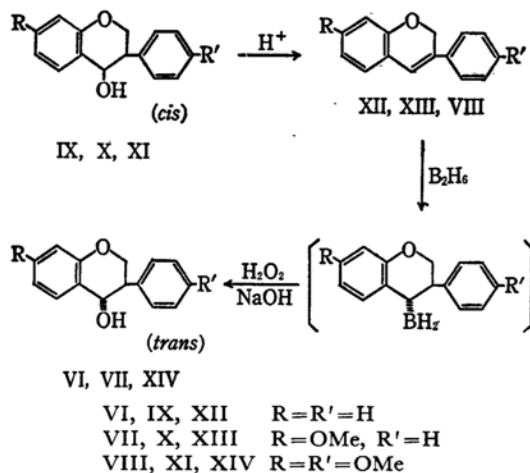


Chart 2

7) a) H. C. Brown, "Hydroboration," Benjamin Inc., New York, N. Y. (1962). b) H. C. Brown and J. Zweifel, "Organic Reaction," Vol. 13, ed. by R. Adams, John Wiley & Sons, Inc., New York, N. Y. (1963), p. 1.

Experimental

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

4',7-Dimethoxyisoflavanone Oxime (II). A solution of 2.2 g of 4',7-dimethoxyisoflavanone⁸⁾ and 2.2 g of hydroxylamine hydrochloride in a mixture of 22 ml of pyridine and 22 ml of ethanol was refluxed for 10 hr. The reaction mixture was then poured into water to precipitate crystals. The recrystallization of the crystals from ethanol gave 1.7 g (74% yield) of crystals, mp 142–143°C.

Found: C, 68.47; H, 5.43; N, 4.65%. Calcd for $C_{17}H_{17}O_5N$: C, 68.21; H, 5.73; N, 4.68%.

4-Aminoisoflavan (IIIa). A solution of 3 g of isoflavanone oxime (I)⁹⁾ in 200 ml of acetic acid containing 0.5 ml of 70% perchloric acid was hydrogenated under atmospheric pressure in the presence of 3 g of 5% palladium on carbon.*¹ After 2.43 mol of hydrogen had been absorbed at room temperature (18°C), the catalyst was filtered off. The acetic acid was removed under reduced pressure, and 6 N hydrochloric acid was added to the residue, thus affording crystals. Recrystallization from ethanol gave 2 g (64% yield) of 4-aminoisoflavan hydrochloride (IIIa), mp 243–245°C (decomp.) ν_{N^+-H} 3200–2700 cm^{-1} (KBr). pK_a^{10} 7.67 (in H_2O); 7.25 (in 34% aqueous ethanol).

Found: C, 68.71; H, 5.98; N, 5.54%. Calcd for $C_{15}H_{16}ONCl$: C, 68.83; H, 6.16; N, 5.35%.

The crystals obtained by the neutralization of an aqueous solution of 300 mg of III with 5% sodium hydroxide were recrystallized from dilute methanol to give 150 mg of 4-aminoisoflavan (IIIa), mp 74–76°C.

Found: C, 79.69; H, 6.73; N, 6.01%. Calcd for $C_{15}H_{16}ON$: C, 79.97; H, 6.71; N, 6.22%.

4-Acetamidoisoflavan (IIIb). A solution of 100 mg of III in pyridine was acetylated with acetic anhydride by the usual method. Recrystallization from diluted ethanol then gave 70 mg of the acetate (IIIb), mp 182–183°C. ν_{NH} 3260 cm^{-1} (KBr), $\nu_{C=O}$ 1660 cm^{-1} (KBr).

Found: C, 76.74; H, 6.45; N, 5.13%. Calcd for $C_{17}H_{17}O_5N$: C, 76.38; H, 6.41; N, 5.24%.

Reaction of 4-Aminoisoflavan Hydrochloride (III) with Nitrous Acid. To a swirling solution of 1 g of III in 80 ml of 50% acetic acid, there were added, drop by drop and under cooling with ice, 25 ml of an aqueous solution containing 700 mg of sodium nitrite. After the stirring had continued for 1 hr under cooling, and then a further 30 min at room temperature, the reaction mixture was poured into water, and subsequently extracted with ether. The extract was washed with a sodium hydrogen carbonate aqueous solution and with water, dried on sodium sulfate, and distilled. The

recrystallization of the residue from petroleum ether gave *trans*-isoflavan-4-ol (VI), mp 96–97°C, in a 26% yield. The NMR spectrum of VI shows a signal of the C_4 proton at 4.92 ppm as a doublet, $J_{3H,4H}$ 8.0 Hz, ν_{OH} 3350 cm^{-1} (KBr).

Found: C, 76.32; H, 6.43%. Calcd for $C_{15}H_{14}O_2$: C, 76.62; H, 6.24%.

***trans*-4-Acetoxyisoflavan.** A solution of 100 mg of *trans*-isoflavan-4-ol (VI) in pyridine was acetylated with acetic anhydride by the usual method. The recrystallization of the crude product from diluted ethanol gave 70 mg of acetate, mp 72–73°C. $\nu_{C=O}$ 1739 cm^{-1} .

Found: C, 75.95; H, 6.24%. Calcd for $C_{17}H_{16}O_5$: C, 76.10; H, 6.01%.

4-Acetamido-7-methoxyisoflavan (IVb). A solution of 100 mg of 4-amino-7-methoxyisoflavan hydrochloride³⁾ (pK_a 7.45 in 34% aqueous ethanol) in pyridine was acetylated with acetic anhydride by the usual method. The recrystallization of the product from ethanol gave 80 mg of acetate, mp 238–239°C. ν_{NH} 3250 cm^{-1} (KBr), $\nu_{C=O}$ 1640, 1665 cm^{-1} (KBr).

Found: C, 73.08; H, 6.66; N, 4.65%. Calcd for $C_{18}H_{19}O_5N$: C, 72.70; H, 6.44; N, 4.71%.

4-Amino-4',7-dimethoxyisoflavan (Va). A solution of 1.5 g of 4',7-dimethoxyisoflavanone oxime (II) in 250 ml of acetic acid containing 2 ml of 70% perchloric acid was hydrogenated in the presence of 1.5 g of 5% palladium on carbon under atmospheric pressure. After the solution had absorbed 2.20 mol of hydrogen at room temperature (17°C), the catalyst was filtered off and the solvent was removed under reduced pressure. To the residue, 6 N hydrochloric acid was added to give crystals. Recrystallization from ethanol gave 700 mg (45% yield) of 4-amino-4',7-dimethoxyisoflavan hydrochloride (V), mp 213–215°C (decomp.). ν_{N^+-H} 3200–2700 cm^{-1} (KBr). pK_a 7.50 in 34% aqueous ethanol.

Found: C, 63.62; H, 6.12; N, 4.13%. Calcd for $C_{17}H_{20}O_5NCl$: C, 63.41; H, 6.23; N, 4.35%.

The neutralization of an aqueous solution of 200 mg of the hydrochloride (V) with 5% sodium hydroxide afforded a crystalline material, which was then recrystallized from diluted ethanol to give 100 mg of 4-amino-4',7-dimethoxyisoflavan (Va), mp 89–90°C.

Found: C, 71.34; H, 6.79; N, 4.77%. Calcd for $C_{17}H_{19}O_5N$: C, 71.56; H, 6.71; N, 4.91%.

4-Acetamido-4',7-dimethoxyisoflavan (Vb). A solution of 100 mg of V in pyridine was acetylated with acetic anhydride in the usual manner. Recrystallization from ethanol gave 70 mg of acetate (Vb), mp 240–242°C. ν_{NH} 3250 cm^{-1} (KBr), $\nu_{C=O}$ 1643, 1665 cm^{-1} (KBr).

Found: C, 69.92; H, 6.35; N, 4.17%. Calcd for $C_{19}H_{21}O_5N$: C, 69.70; H, 6.47; N, 4.28%.

Reaction of 4-Amino-4',7-dimethoxyisoflavan Hydrochloride (V) with Nitrous Acid. To a swirling solution of 500 mg of the hydrochloride (V) in 60 ml of 50% acetic acid, there was added, drop by drop and under cooling with ice, a solution of 300 mg of sodium nitrite in 20 ml of water. After it had then been allowed to stand for 2 hr under the cooling and a further hour at room temperature, the reaction mixture was poured into water and subsequently extracted with ether. The extract was washed with a sodium hydrogen carbonate solution and with water, and dried on anhydrous sodium sulfate. The residue remaining after the removal of the ether was recrystallized from ethanol to yield 150 mg

8) N. Inoue, *Nippon Kagaku Zasshi* (J. Chem. Soc. Japan, Pure Chem. Sect.), **79**, 215 (1958).

9) N. Inoue, *Sci. Repts. Tohoku Univ., First Ser.* **XLV**, 63 (1961).

*¹ Five percent palladium on carbon, obtained from the Kawakami Research Institute, was used in all the following experiments.

10) K. Nakanishi, "Yuki Kagaku no Shinpo," Vol. 12, ed. by M. Murakami, Kyoritsu Shuppan, Tokyo, Japan (1957), p. 19.

(36% yield) of crystals, mp 160–161°C, which were identified as 4',7-dimethoxyisoflavene (VIII). When V was treated with nitrous acid for 2 hr under milder reaction conditions (ice cooling), the expected *trans*-4',7-dimethoxyisoflavan-4-ol (XIV) was not obtained, but 50 mg of VIII and 200 mg of unreacted V were recovered.

Isoflavene (XII). A solution of 1 g *cis*-isoflavan-4-ol (IX) in 30 ml of acetic acid containing 2 drops of concentrated hydrochloric acid was refluxed for 1 hr. After the removal of the acetic acid under reduced pressure, 50 ml of water were added. The crystals thus obtained were recrystallized from methanol to give 0.8 g of the crystals (XII), mp 90–91°C.

Found: C, 86.32; H, 5.92%. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81%.

Preparation of the Diborane-Tetrahydrofuran Solution⁷. All the reactions were carried out under a nitrogen atmosphere. To a swirling solution of 3 g of sodium borohydride in 18 ml of diglyme (dried on calcium hydride and then on lithium aluminum hydride, and subsequently distilled), there were added, drop by drop over a period of 30 min under cooling with ice, 15 ml of boronfluoride etherate (distilled under reduced pressure after adding anhydrous ethyl ether and calcium hydride). The stirring was then continued for 30 more min, after which the mixture was heated at 110°C for 1 hr for the complete generation of diborane. The generated diborane was cooled by dry ice-acetone to remove the ether, and then passed through 15 ml of THF (dried on lithium aluminum hydride and distilled) containing 0.2 g of sodium borohydride in order to remove the borontrifluoride. Then the diborane was introduced to 25 ml of THF in an absorption bottle cooled by ice water. The concentration of diborane in the diborane-THF solution was determined from the volume of the hydrogen generated by pouring a constant volume of the solution into a mixture of water-diglyme-THF.

***trans*-7-Methoxyisoflavan-4-ol (VII).** To a solution of 635 mg (2.67 mmol) of 7-methoxyisoflavene³ (XIII) in 10 ml of THF, there were added 1.60 ml (1.06 mmol) of a diborane-THF solution (concentration 0.66 mol/l) with stirring and under cooling with ice. Every hour, a small portion of the solution was taken up in order to determine the unreacted XIII by means of the change in the absorption intensity at 333 m μ by reference to a previously-prepared calibration curve. The flask was permitted to remain for 2 hr at 0°C, and then kept for 15 hr at room temperature. After 17 hr, 0.9 ml (0.59 mmol) of the diborane-THF solution was added.

After it had been confirmed that the unreacted XIII had disappeared after 70 min, 5 ml of THF and 0.5 ml of water were carefully added with stirring and under cooling with ice in order to decompose the excess diborane. To the above solution, there were then added, drop by drop, 1.25 ml of 3 N sodium hydroxide over a period of approximately 3 min and then 0.32 ml of 30% hydrogen peroxide over a period of about 2 min. The stirring was continued for 1 hr under cooling with ice, and then for 1 more hr at room temperature, after which the solution was poured into water and extracted with ether. In order to remove any phenolic substances, the extract was washed with 1 N sodium hydroxide and with water, dried on sodium sulfate, and distilled under reduced pressure. The residual oil was crystallized by the addition of ethanol, which afforded 300 mg (44% yield) of crystals, mp 130–131°C. The melting point of this compound was not depressed on admixture with authentic *trans*-7-methoxyisoflavan-4-ol.

***trans*-Isoflavan-4-ol (VI).** To a swirling solution of 1.0 g of isoflavene (XII) in 7 ml of THF, there were added 4.0 ml of the diborane-THF solution under cooling with ice. The reaction mixture was then worked up in a manner similar to that of Experiment XIII described above. After the ether had been removed, 5 ml of *n*-hexane were added to the residual oil, giving 0.8 g (73% yield) of crystals. Recrystallization from *n*-hexane-benzene afforded crystals, mp 97–97.5°C, which did not show any depression of melting point on admixture with authentic *trans*-isoflavan-4-ol.

***trans*-4',7-Dimethoxyisoflavan-4-ol (XIV).** To a solution of 700 mg of 4',7-dimethoxyisoflavene (VIII)³ in 15 ml of THF, 2.2 ml of the diborane-THF solution were added under cooling with ice. The crystals obtained by the usual treatment were recrystallized from benzene to give 490 mg (66% yield) of crystals, mp 123.5–124°C. This compound (XIV) was not identical with the reduction product of 4',7-dimethoxyisoflavanone. $J_{3H,4H}$ 7.9 Hz.

Found: C, 71.87; H, 6.44%. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

By the usual manner, the acetate of XIV was prepared by reaction with pyridine-acetic anhydride, mp 131–132.5°C. $J_{3H,4H}$ 5.0 Hz.

Found: C, 69.77; H, 6.09%. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%.

The authors wish to express their sincere thanks to Professor Yoshio Kitahara for his making convenient the NMR spectra measurements.