Studies of Synthetic Isoflavanones. VI. The Reaction of Isoflavan-4-ols with Acetic Acid[1]

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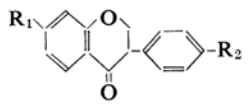
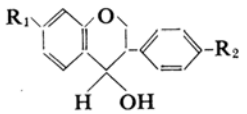
(Received June 11, 1963)

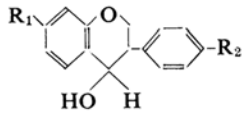
Bradbury and White[2] carried out the hydrogenation reaction of 7, 4'-dimethoxyisoflavanone (II) with platinum oxide in acetic acid to the corresponding isoflav-3-en (XI), but they did not isolate 7, 4'-dimethoxyisoflavan-4-ol (IX) and it is not clear whether or not 7, 4'-dimethoxyisoflavan was produced in their experiment. They hydrogenated 2-methyl-7, 4'-dimethoxyisoflavone by the method similar to the one used for the corresponding isoflavanone and obtained 2-methyl-7, 4'-dimethoxyisoflav-3-en, which was also obtained by the reduction of the same isoflavone with lithium aluminum hydride.



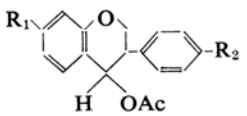
I, II, XIII



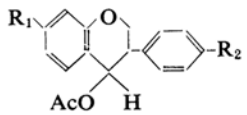
III, IX, XIV



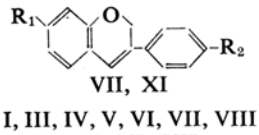
IV



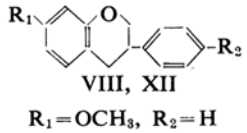
V, X



VI



VII, XI



VIII, XII

I, III, IV, V, VI, VII, VIII $R_1=OCH_3$, $R_2=H$
II, IX, X, XI, XII $R_1=R_2=OCH_3$
XIII, XIV $R_1=R_2=H$

It has been assumed that the isoflav-3-ens obtained in White's experiments were derived from the reduction products, isoflavan-4-ols, by dehydration with acetic acid. With a view to confirming this assumption, several experiments on isoflavan-4-ols were carried out. In the preceding paper of this series,[1] the author reported that 7-methoxyisoflavanone (I) was converted into 7-methoxyisoflavan-4β-ol (III, m.p. 144°C) by catalytic hydrogenation over Raney nickel or by the Meerwein-Ponndorf reduction and that 7-methoxyisoflavan-4α-ol (IV, m.p. 131°C) was obtained as a minor product, along with III, by the reduction of I with sodium borohydride. In order to obtain 7-methoxyisoflav-3-en (VII), III was heated on a water bath with dilute sulfuric acid, phosphoric acid, phosphoric anhydride in benzene, or formic acid. Treatment with all these reagents yielded an amorphous substance which was insoluble in ethanol. The treatment of III with concentrated sulfuric acid at room temperature gave the same result. However, when boiled with acetic acid III was converted into plate crystals (m.p. 108°C) whose ultraviolet absorption spectrum was similar to that of stilbene with absorption maxima at 335 mμ ($\log \varepsilon = 4.31$) and 245 mμ ($\log \varepsilon = 4.28$), as is shown in Fig. 1. The analytical values of this compound conformed with those of the anhydride of III. The product was hydrogenated over palladized charcoal to 7-methoxyisoflavan (VIII), which was also obtained by the Clemmensen reduction of I.[1] These results indicate that the compound with a m.p. of 108°C

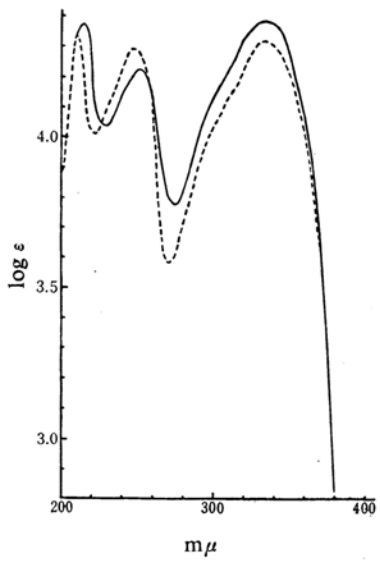
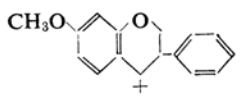


Fig. 1. Ultraviolet spectra of VII (——) and XI (·····) in ethanol.

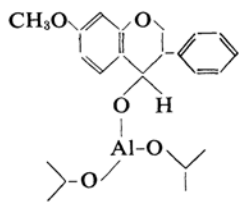
1) Presented at the 13th and 14th Annual Meetings of the Chemical Society of Japan, Tokyo, April, 1960 and 1961. Part V of this series: N. Inoue, This Bulletin, 37, 601 (1964).
2) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 1953, 871.

has the stilbene-type structure VII and that heating it with acetic acid did not cause any migration of the C_3 phenyl group.

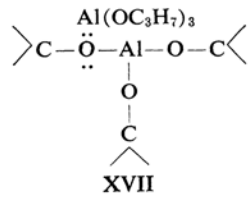
Considering the result of White's experiments, it was presumed that the dehydration of III might occur under milder conditions; therefore, III was treated with acetic acid at 50°C for one hour, by which method a compound with a m.p. of 111°C was obtained. The infrared spectrum of this substance indicated the absence of hydroxyl group and the presence of a carbonyl group ($\nu_{C=O}$ 1732 cm^{-1} in KBr), and its analytical results conformed with that of the acetate of 7-methoxyisoflavan-4-ol. Mixed melting point determination showed the product to be 4α-acetoxy-7-methoxyisoflavan (VI, m.p. 111°C). It is interesting that α-acetate was obtained by the treatment of the β-alcohol (III) with acetic acid. When III was allowed to stand overnight in acetic acid at room temperature, the starting material was recovered unchanged. 7-Methxyisoflavan-4α-ol (IV) was converted into VII on treatment with boiling acetic acid, and into VI on that with acetic acid at 50°C. In the preceding paper[1] it was reported that III and IV were acetylated with acetic anhydride and pyridine to 4β-acetoxy-7-methoxyisoflavan (V, m.p. 121°C) and 4α-acetoxy-7-methoxyisoflavan (VI, m.p. 111°C) respectively. Treatment with sodium methoxide in methanol gave III from V and IV from VI. Both V and VI were converted into VII by being boiled with acetic acid. These experimental results suggest that VI might be an intermediate product in the dehydration of III, IV, and V with boiling acetic acid.



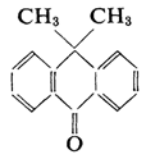
XV



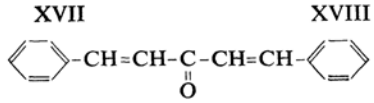
XVI



XVII

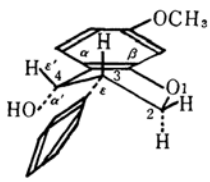


XVIII

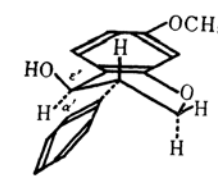


XIX

In the conversion of III to the epimeric acetate VI by treatment with the acetic acid, a proton from acetic acid is thought to be added to the C_4 hydroxyl group, followed by the elimination of water from the oxonium ion to give the carbonium ion (XV), which then reacts with acetic acid to yield the epimeric acetate VI. This is a solvolysis reaction of the S_N1 type in acetic acid. In a previous paper, the author assigned trans configuration to 7-methoxyisoflavan-4α-ol (IV) and a cis to 4β-ol (III) on the basis of the stereochemistry of the transition state of the Meerwein-Ponndorf reduction[3] and Mitsui's theory for catalytic hydrogenation.[4,5] As III' and IV' show, the perferred conformation of the C_3 phenyl group of 7-methoxyisoflavan-4-ol is equatorial and that of C_3 hydrogen atom, axial. The C_4 hydroxyl group could be either quasi-axial (a') or quasi-equatorial (e'), and the C–H bond and C–O bond projected from C_4 are inclined at the same angle to the plane in which C_α, C_β, O_1, and C_4 exist. The catalytic hydrogenation and Meerwein-Ponndorf reduction of I gave III with a quasi-axial C_4 hydroxyl group which is cis to the C_3 equatorial phenyl group (III'). On the other hand, the IV formed as a minor product by the reduction of I with sodium borohydride is a trans compound with a quasi-equatorial C_4 hydroxyl group (IV').



cis
III'



trans
IV'

Because of its quasi-equatorial conformation and trans configuration, the α-compound IV is considered to be more stable than the β-compound III. Therefore, the reactions which proceed through the planar sp^2 form of the C_4 of isoflavan would give the trans or α-type compound. As has been described above, the reaction between III and acetic acid thus proceeds via the C_4 carbonium ion, with sp^2 hybridization, to give a more stable α-acetate. This conclusion suggests that when the carbonium ion XV reacts with water instead of acetic acid, the stereoisomeric alcohol IV will be produced. Therefore, III was dissolved in a dioxane-water mixture with one drop of concentrated sulfuric acid or hydrochloric acid

3) L. M. Jackman, A. K. Macbeth and J. A. Mills, ibid., 1953, 871.

4) S. Mitsui and K. Kasahara, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **79**, 1382 (1958); **81**, 1583 (1960).

5) S. Mitsui and S. Imaizumi, ibid., **77**, 1516 (1956).

and the solution was set aside overnight. The desired alcohol IV was obtained as expected. When pure dioxane was used as the solvent instead of a dioxane-water mixture, an amorphous compound was obtained.

7, 4'-Dimethoxyisoflavan-4-ol (IX), which had been obtained by the hydrogenation of 7, 4'-dimethoxyisoflavanone (II) over Raney nickel or by its reduction with aluminum isopropoxide or with sodium borohydride, was treated with acetic acid at 50°C and was converted into 7, 4'-dimethoxyisoflav-3-en (XI) in one experiment and into 4-acetoxy-7,4'-dimethoxyisoflavan with a m. p. of 123°C in another. As has been reported in the preceding paper, the acetylation of IX with acetic anhydride and pyridine gave the acetate (X) with a m. p. of 128°C, which was different from the acetate (m. p. 123°C) obtained above (mixed melting point determination).

Bradbury and White[2] hydrogenated II with platinum oxide in acetic acid to 7, 4'-dimethoxyisoflav-3-en (XI). It was assumed that XI would be derived from the primary reduction product, IX, through reaction with acetic acid. The experimental results mentioned above support this assumption. The reaction of IX with boiling acetic acid gave isoflav-3-en XI, which was then converted into 7, 4'-dimethoxyisoflavan (XII) by catalytic hydrogenation over palladized charcoal. XII was prepared from II by the Clemmensen reduction.

Unlike III and IX, the isoflavan-4-ol (XIV) obtained by the reduction of isoflavanone (XIII) was not converted into 4-acetoxyisoflavan with acetic acid at 50°C, but was recovered unchanged. As has been mentioned above, the conversion of isoflavan-4-ols to 4-acetoxyisoflavans could go through the transition state in which C_4 is a carbonium ion. The resonance stabilization of the carbonium ion might affect the rate of this reaction. A methoxyl group in the 7-position will facilitate the formation of this transition state, and, consequently, the acetylation of the 4-hydroxyl with acetic acid will proceed smoothly. The lack of a electron-releasing substituent in this position makes the transformation of the starting substance into this transition state difficult; in the case of unsubstituted isoflavan-4-ol, acetylation with acetic acid does not occur.

As reported in the previous paper,[1] the Meerwein-Ponndorf reduction of I and II gave isopropyl ethers of the corresponding isoflavan-4-ols. This fact can be explained by the carbonium ion-intermediate theory as follows. The aluminum atom of excess aluminum isopropoxide would combine with the oxygen atom of the intermediate aluminum compound of I or II (XVI) as Lewis acid (XVII), and the oxygen atom in C_4 is likely to be eliminated from C_4, thus forming the carbonium ion XV. Then the carbonium ion would react with isopropanol to give the isopropyl ether of the isoflavan-4-ol. The carbonyl carbons of all the compounds which have been reported to give isopropyl ethers by the Meerwein-Ponndorf reduction[6] have a stable structure when they form carbonium ions (XVIII, XIX). As has been shown above, I and II have the structure which can produce a stable carbonium ion and give isopropyl ether in the Meerwein-Ponndorf reduction.

Experimental*

The Reaction of 7-Methoxyisoflavan-4β-ol (III) with Acetic Acid. — *1) In the Boiling State.* — A solution of III (500 mg.) in acetic acid (10 ml.) was refluxed for one hour. After the acetic acid had been removed under reduced pressure, water (30 ml.) was added to the residue and the mixture was allowed to stand for several hours. The precipitate formed was collected and recrystallized from ethanol in the form of plates (VII) (m. p. 108°C). Yield, 300 mg.

UV: λ_{max}^{EtOH} mμ (log ε): 335 (4.31), 245 (4.28).
Found: C, 80.55; H, 6.09. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%.

2) At 50°C. — A solution of III (100 mg.) in acetic acid (10 ml.) was heated at 50°C for one hour. After the acetic acid had been removed below 50°C under reduced pressure, water (30 ml.) was added to the residue and the mixture was set aside for several hours. The product formed was collected and recrysallized from ethanol, giving plates with a m. p. of 111°C (70 mg.) which showed no depression of melting point when admixed with 4α-acetoxy-7-methoxyisoflavan (VI).

The Reactions of 7-Methoxyisoflavan-4α-ol (IV) with Acetic Acid.—*1) In the Boiling State.*—A solution of IV (50 mg.) in acetic acid (5 ml.) was refluxed for one hour. The reaction mixture, when worked up as described for III, gave VII (55 mg., m. p. and mixed m. p. 108°C).

2) At 50°C. — A solution of IV (100 mg.) in acetic acid was heated at 50°C for one hour. After the acetic acid had been removed under reduced pressure, the residue was recrystallized from ethanol in the form of plates with a m. p. of 111°C, either alone or mixed with 4α-acetoxy-7-methoxyisoflavan (VI).

The Reactions of 4β-Acetoxy-7-methoxyisoflavan (V) with Acetic Acid.—*1) In the Boiling State.*—A solution of V (100 mg.) in acetic acid (10 ml.) was refluxed for one hour. The reaction mixture, when worked up as described for III, gave VII (m. p. and mixed m. p. 106°C).

2) At 50°C.—A solution of V (100 mg.) in acetic acid (10 ml.) was heated at 50°C for one hour.

6) A. L. Wild in "The Organic Reactions," Ed. by R. Adams, Vol. II, John Wiley & Sons, New York (1944), p. 190.

* All melting points are uncorrected.

The reaction mixture, when worked up as described for III, gave VI (55 mg., m. p. and mixed m. p. 108°C).

The Reaction of 4α-Acetoxy-7-methoxyisoflavan (IV) with Boiling Acetic Acid.—A solution of VI (100 mg.) in acetic acid (10 ml.) was refluxed for one hour. When the reaction mixture was worked up as described for III, it gave VII (70 mg., m. p. and mixed m. p. 108°C).

The Hydrolysis of 4β-Acetoxy-7-methoxyisoflavan (V).—A mixture of V (100 mg.), N/2 methanolic sodium methoxide (1.0 ml.), and methanol (20 ml.) allowed to stand for 24 hr. at room temperature. After dilution with water (100 ml.), the precipitate formed was separated, dried, and recrystallized from ethanol to III (60 mg., m. p. and mixed m. p. 143°C).

The Hydrolysis of 4α-Acetoxy-7-methoxyisoflavan (VI).—A mixture of VI (50 mg.), N/2 methanolic sodium methoxide (0.5 ml.), and methanol (20 ml.) was allowed to stand for 12 hr. at room temperature. On treatment as described above, IV (28 mg.) was obtained (m. p. and mixed m. p. 130°C).

The Reactions of 7-Methoxyisoflavan-4β-ol (III) with Mineral Acid.—Two drops of concentrated sulfuric acid or hydrochloric acid were added to a solution of III (50 mg.) in hydrous dioxane (1 : 1, 40 ml.). The solution was then allowed to stand for 48 hr. at room temperature. After dilution with water (200 ml.), the precipitate formed was recrystallized from ethanol to IV (20 mg., m. p. and mixed m. p. 129°C).

The Reaction of Isoflavan-4-ol (XIV) with Acetic Acid.—A solution of XIV (50 mg.) in acetic acid (10 ml.) was heated at 50°C for one hour. The usual after-treatment of the mixture gave XIV unchanged.

The Reactions of 7, 4'-Dimethoxyisoflavan-4-ol (IX) with Acetic Acid.—*1) At 50°C.*—A solution of IX (50 mg.) in acetic acid (10 ml.) was heated at 50°C for one hour. The reaction mixture, when worked up as described for III, gave 7, 4'-dimethoxyisoflav-3-en (XI) (m. p. 161°C). Yield, 20 mg.

UV: λ_{max}^{EtOH} mμ (log ε): 335 (4.38), 250 (4.22). (Found: C, 75.87; H, 6.09%.)

2) At 50°C.—A solution of IX (100 m.) in acetic acid (10 ml.) was heated at 50°C for one hour. The usual after-treatment gave crystals with a m. p. of 123°C. Yield, 30 mg.

Found: C, 69.63; H, 6.15. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%.

IR (KBr): 1728 cm^{-1}.

3) In the Boiling State.—A solution of IX (100 mg.) in acetic acid (20 ml.) was refluxed for one hour. The usual treatment of the reaction mixture gave XI (60 mg., m. p. and mixed m. p. 161°C).

7-Methoxyisoflavan.—*The Catalytic Hydrogenation of the VII Obtained by the Reaction of III with Boiling Acetic Acid.*—A mixture of VII (500 mg.) in acetic acid (140 ml.) and palladized charcoal (20%, 500 mg.) was shaken with hydrogen at 30°C until the absorption of hydrogen stopped. One mole of hydrogen had been absorbed. The catalyst was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol in the form of plates with a m. p. of 106°C (300 mg.). The product was identified, by mixed melting point determination, to be the same compound prepared by the Clemmensen reduction of I[1].

7, 4'-Dimethoxyisoflavan (XII).—*1) The Catalytic Haydrogenation of the XI Obtained by the Reaction of IX with Acetic Acid.*—A mixture of XI (500 mg.) in acetic acid (150 ml.) and palladized charcoal (5%, 1.0 g.) was shaken with hydrogen at 20°C until the absorption of hydrogen stopped. One mole of hydrogen (46 ml.) had been absorbed. Upon working up the product in the usual manner, XII (200 mg., m. p. 113°C (from ethanol)) was obtaind. (Found: C, 75.69; H, 6.78%.)

2) The Clemmensen Reduction of II.—A mixture of II (250 mg.), amalgamated zinc dust (3.6 g.), concentrated hydrochloric acid (5 ml.), and acetic acid (30 ml.) was allowed to stand for 24 hr. at room temperature. The mixture was then poured into water (200 ml.). The recrystallization of the precipitate from ethanol gave a product with a m. p. 114°C (150 mg.) which showed no depression of the melting point when admixed with XII prepaped as above.

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