# Synthetic Studies of Sesamol Derivatives. VI.* The Synthesis of 6, 7 : 3′, 4′-Bismethylenedioxyisoflavone, an Isomer of the Maxima Substance A** and Related Compounds

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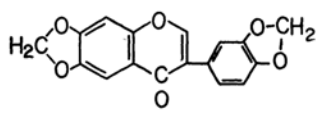
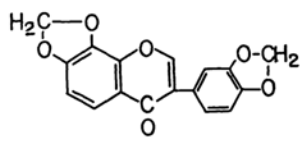
The maxima substance A was isolated from the root of *Tephrosia maxima Aers.* by Rangaswami and Sastry.[1] Their degradative experiments showed it to be 6, 7 : 3′, 4′-bismethylenedioxyisoflavone (I).[2] Up to now it has been the only known naturally-occurring isoflavone containing two methylenedioxy groups in the molecule. On the basis of further experiments, Kukla and Seshadri[3] proposed the revised formula of 7, 8 : 3′, 4′-bismethylenedioxyisoflavone (II) and confirmed its structure by synthesis. However, the isoflavone I has attracted increasing attention as it belongs to the same bismethylenedioxy skeleton. The present report will describe the synthesis of I and some related isoflavones.

The Hoesch condensation of sesamol with 3, 4-methylenedioxybenzyl cyanide (III) yielded 2-hydroxy-4,5-methylenedioxyphenyl 3,4-methylenedioxybenzyl ketone (IV). By a similar Hoesch reaction employing hydroxyhydroquinone, III was converted into 2, 4, 5-trihydroxyphenyl 3, 4-methylenedioxybenzyl ketone (V). The ketone IV was also obtained by the methylenation of V with methylene sulfate. The ketone V was partially methylated with diazomethane to 2, 5-dihydroxy-4-methoxyphenyl 3, 4-methylenedioxybenzyl ketone (VI), and with dimethyl sulfate to 2-hydroxy-4, 5-dimethoxyphenyl 3, 4 - methylenedioxybenzyl ketone (VII). On cyclization with ethyl orthoformate, IV afforded 6, 7 : 3′, 4′-bismethylenedioxyisoflavone (I), the melting point, of which 254—255°C, differed from the reported one, 227—229°C,[1,3] of the natural maxima substance A.



I



II

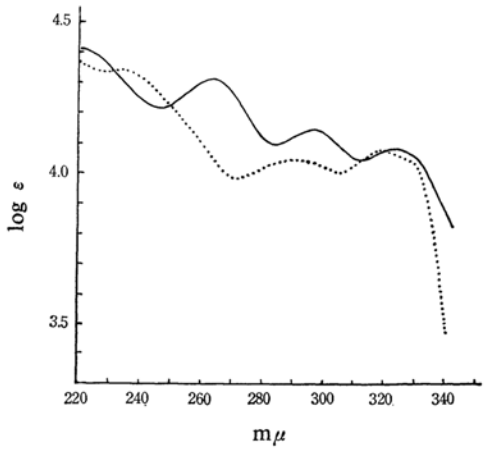



Fig. 1. Ultraviolet spectra of I (—) and XI (···) in ethanol.

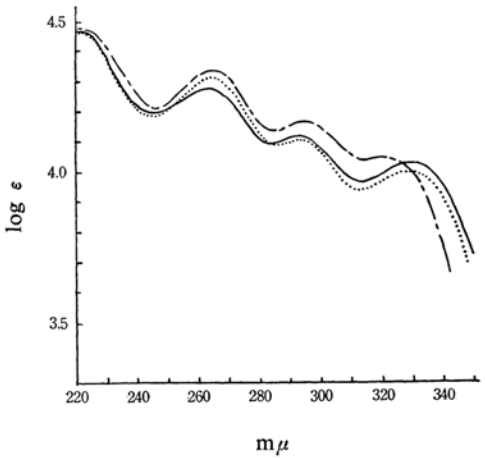



Fig. 2. Ultraviolet spectra of VIII(—), IX (···) and X(-·) in ethanol.

* Part V: K. Fukui and T. Matsumoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **85**, 793 (1964).

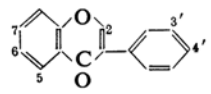
** Recently named maxima isoflavone A by Seshadri et al.[3]

1) S. Rangaswami and B. V. R. Sastry, *Curr. Sci.*, **23**, 397 (1954); *Chem. Abstr.*, **49**, 8568 (1955).

2) S. Rangaswami and B. V. R. Sastry, *Proc. Indian Acad. Sci.*, **44A**, 279 (1956).

3) A. S. Kukla and T. R. Seshadri, *Tetrahedron*, **18**, 1443 (1962).

TABLE I. ULTRAVIOLET SPECTRA OF SOME 3′,4′-METHYLENEDIOXYISOFLAVONES IN ETHANOL



| | Substituent | | | | | $\lambda_{max}$, mμ (log ε) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | OH | AcO | MeO | Me | O-$CH_2$-O | | | | | | |
| I | | | | | 3′, 4′<br>6, 7 | 264 | (4.31) | 296 | (4.14) | 323 | (4.08) |
| VIII | 6<br>7 | | | | 3′, 4′ | 263.5 | (4.28) | 294 | (4.12) | 329 | (4.03) |
| IX | 6 | | 7 | | 3′, 4′ | 264.5 | (4.31) | 293.5 | (4.10) | 329 | (4.00) |
| X | | | 6<br>7 | | 3′, 4′ | 265 | (4.34) | 295 | (4.16) | 320 | (4.05) |
| XI | | | | 2 | 3′, 4′<br>6, 7 | 235 | (4.34) | 291 | (4.05) | 319 | (4.80) |
| XII | | 6<br>7 | | 2 | 3′, 4′ | — | | 294 | (4.03) | — | |
| XIII | 6<br>7 | | | 2 | 3′, 4′ | — | | 290 | (4.80) | 325 | (4.03) |
| XIV | | 6 | 7 | 2 | 3′, 4′ | 248* | (4.34) | 296 | (4.20) | — | |
| XV | 6 | | 7 | 2 | 3′, 4′ | — | | 288 | (4.06) | 324 | (4.03) |
| XVI | | | 6<br>7 | 2 | 3′, 4′ | — | | 290 | (4.11) | 316 | (4.08) |

* Inflexion point

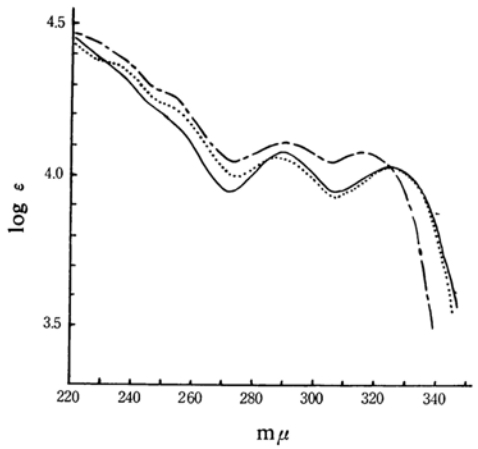
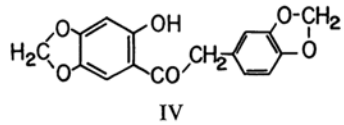



Fig. 3. Ultraviolet spectra of XIII(—), XV(···) and XVI(--) in ethanol.

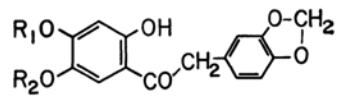
By a similar reaction, the ketones V, VI and VII were converted into 6, 7-dihydroxy- (VIII), 6-hydroxy-7-methoxy- (IX) and 6, 7-dimethoxy-3′, 4′-methylenedioxyisoflavone (X) respectively. X was also obtained by the methylation of VIII or IX with dimethyl sulfate.

The reaction of the ketone IV with acetic anhydride in the presence of sodium acetate[4] gave a 2-methyl derivative (XI) of the isoflavone I. 2-Methylisoflavone XI was also obtained from V by the following process. The reaction of V with acetic anhydride gave a cyclized diacetate XII which could easily be

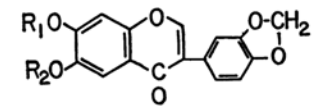
4) W. Baker and R. Robinson, *J. Chem. Soc.*, **127**, 1981 (1925).



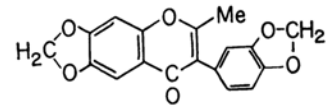
IV



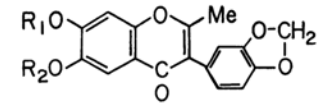
V $R_1=R_2=H$
VI $R_1=Me$ $R_2=H$
VII $R_1=R_2=Me$



VIII $R_1=R_2=H$
IX $R_1=Me$ $R_2=H$
X $R_1=R_2=Me$



XI



XII $R_1=R_2=Ac$
XIII $R_1=R_2=H$
XIV $R_1=Me$ $R_2=Ac$
XV $R_1=Me$ $R_2=H$
XVI $R_1=R_2=Me$

hydrolyzed to 6, 7-dihydroxy-3', 4'-methylenedioxy-2-methylisoflavone (XIII) under mild conditions. The methylenation of XIII with methylene sulfate afforded XI. A similar acetylation of VI gave a cyclized acetate XIV which could be converted into 6-hydroxy-7-methoxy-3', 4'-methylenedioxy-2-methylisoflavone (XV) by alkaline hydrolysis. XIII and XV were methylated with dimethyl sulfate to 6, 7-dimethoxy-3', 4'-methylenedioxy-2-methylisoflavone (XVI), which was then changed to the ketone VII by the alkaline hydrolysis.

The ultraviolet absorption spectra of these synthetic isoflavones are recorded in Figs. 1—3 and Table I.

In most cases there are three characteristic peaks, at ca. 265 (band I), ca. 295 (band II) and ca. 325 mμ (band III). The methylation of the 6-position (IX—X and XV—XVI) or the and 6-7-positions (VIII—X and XIII—XVI) has little effect on bands I and II, but it causes a hypsochromic shift of 8—9 mμ in band III, as has been reported previously.[5] A similar shift (6 mμ) in band III is also observed by the methylenation of two vicinal hydroxy groups (VIII—I and XIII—XI). The replacement of the 2-position with a methyl unit causes a displacement (4—5 mμ) of bands II and III towards a shorter wave length.

## Experimental***

**2, 4, 5-Trihydroxyphenyl 3, 4-Methylenedioxybenzyl Ketone (V).**—A mixture of hydroxyhydroquinone (50 g.), 3,4-methylenedioxybenzyl cyanide (6.5 g.) and anhydrous zinc chloride (3.0 g.) in dry ether (5.0 ml.) was saturated with dried hydrogen chloride in an ice bath and allowed to stand overnight. The ether solution was then decanted from the ketimine hydrochloride which had separated. The residue was heated on a steam bath in water (30 ml.) for 1 hr. The precipitates were collected, washed with water, and recrystallized from aqueous methanol to give V; m. p. 206—208°C (yellow needles); yield, 4.9 g. It gave a dark green color with an alcoholic ferric chloride solution and was soluble in an aqueous potassium carbonate solution. UV $\lambda_{max}^{EtOH}$ mμ (log ε): 241 (4.13), 287 (4.13), 354 (3.89).

Found: C, 62.29; H, 4.31. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20%.

**2-Hydroxy-4, 5-methylenedioxyphenyl 3, 4-Methylenedioxybenzyl Ketone (IV).**—*From Sesamol.*—A mixture of sesamol (11.0 g.), 3,4-methylenedioxybenzyl cyanide (13.0 g.) and anhydrous zinc chloride (6.0 g.) in dry ether (150 ml.) was treated with a method similar to that used for V. The product was recrystallized from acetone to give IV; m. p. 172—173°C (yellow needles); yield, 3.0 g. It gave a green color with an alcoholic ferric chloride solution. IR: 1636 (C=O), 1031 (=C-O-C), 916 $cm^{-1}$ (O-$CH_2$-O). UV $\lambda_{max}^{EtOH}$ mμ (log ε): 240 (4.24), 281 (3.98), 353 (3.96).

Found: C, 64.08; H, 4.15. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

*From V.*—Into a mixture of the ketone V (1.1 g.), ethanol (10 ml.) and potassium hydroxide (1.4 g.) in water (10 ml.), air being excluded by a current of nitrogen, methylene sulfate (0.9 g.) in acetone (15 ml.) was stirred at 45—50°C. After the stirring had been continued another 70 min., the solvent was removed in vacuo. After the residue had been dissolved in water, the solution was saturated with carbon dioxide. The brown precipitates were collected, washed with water, and recrystallized from aqueous acetone to give IV; m. p. 172—173°C (yellow needles); yield, 100 mg. This substance was identified with the above sample by a mixed fusion and a comparison of the infrared spectra.

**6, 7 : 3', 4'-Bismethylenedioxyisoflavone (I).** — A mixture of the ketone IV (1.5 g.), freshly-distilled ethyl orthoformate (5.0 ml.), dry pyridine (6.0 ml.) and piperidine (1.0 ml.) was refluxed for 8 hr. The crystals which separated on cooling were recrystallized from acetic acid to give I; m. p. 254—255°C (colorless needles); yield, 1.1 g. This substance was soluble in concentrated sulfuric acid to a green solution. IR: 1641 (C=O), 1037 (=C-O-C), 931 $cm^{-1}$ (O-$CH_2$-O).

Found: C, 65.90; H, 3.50. Calcd. for $C_{17}H_{10}O_6$: C, 65.81; H, 3.25%.

**2, 5-Dihydroxy-4-methoxyphenyl 3, 4-Methylenedioxybenzyl Ketone (VI).** — To a solution of the ketone V (1.0 g.) in acetone (30 ml.) was added an ethereal diazomethane solution; the mixture was then allowed to stand overnight at room temperature. After the excess diazomethane had been destroyed with acetic acid, the solvent was evaporated and the residue was recrystallized from methanol to give VI; m. p. 194—196°C (pale yellow needles); yield, 0.8 g.. It gave a green color with an alcoholic ferric chloride solution. UV $\lambda_{max}^{EtOH}$ mμ (log ε): 240 (4.17), 283.5 (4.10), 355 (3.77).

Found: C, 63.39; H, 4.86. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67%.

**2-Hydroxy-4, 5-dimethoxyphenyl 3, 4-Methylenedioxybenzyl Ketone (VII).** — A mixture of the ketone V (230 mg.), anhydrous potassium carbonate (3.0 g.) and dimethyl sulfate (0.2 ml.) in anhydrous acetone (40 ml.) was refluxed for 6 hr. The reaction mixture was then treated in a usual manner. Recrystallization from aqueous acetone give VII in the form of colorless plates; m. p. 153—154°C; yield, 100 mg. It gave a green color with an alcoholic ferric chloride solution. IR: 1625 (C=O), 1033 (=C-O-C), 920 $cm^{-1}$ (O-$CH_2$-O). UV $\lambda_{max}^{EtOH}$ mμ (log ε): 237.5 (4.24), 280 (4.12), 346 (3.92).

Found: C, 65.41; H, 4.94. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10%.

**6, 7-Dihydroxy-3', 4'-methylenedioxyisoflavone (VIII).** — A mixture of the ketone V (800 mg.), ethyl orthoformate (2.0 ml.), dry pyridine (2.0 ml.) and piperidine (0.3 ml.) was refluxed for 4 hr.

5) K. Fukui and T. Matsumoto, *J. Sci. Hiroshima Univ., Ser. A-II*, **28**, 47 (1964).

*** All melting points are uncorrected. The infrared spectra were measured in Nujol.

The reaction mixture was then poured into dilute hydrochloric acid. The precipitates were collected, washed with water, and recrystallized from aqueous pyridine to give VIII; m. p. 308—310°C (decomp.) (colorless needles); yield, 380 mg. It gave a green color with an alcoholic ferric chloride solution and was soluble in concentrated sulfuric acid to a green solution and in an aqueous sodium carbonate solution to a yellow solution.

Found: C, 64.55; H, 3.55. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38%.

The diacetate was prepared by the pyridine-acetic anhydride method; m. p. 190.5—191.5°C (colorless needles). UV: $\lambda_{max}^{EtOH}$ mμ (log ε): 263 (4.31), 293 (4.14).

Found: C, 63.01; H, 3.88. Calcd. for $C_{20}H_{14}O_8$: C, 62.83; H, 3.69%.

**6-Hydroxy-7-methoxy-3′, 4′-methylenedioxyisoflavone (IX).** — From the ketone VI (1.2 g.), ethyl orthoformate (3.0 ml.), dry pyridine (4.0 ml.) and piperidine (1.0 ml.), synthesis was carried out by a method similar to that used for I. Recrystallization from aqueous pyridine yielded IX; m. p. 250—252°C (colorless needles); yield, 0.5 g. It gave a negative color with an alcoholic ferric chloride solution and was soluble in concentrated sulfuric acid to a green solution.

Found: C, 65.05; H, 3.88. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87%.

**6,7-Dimethoxy-3′,4′-methylenedioxyisoflavone (X).**—*From IX.* — A mixture of the isoflavone IX (200 mg.), anhydrous potassium carbonate (5.0 g.) and dimethyl sulfate (0.2 ml.) in dry acetone (100 ml.) was refluxed for 20 hr. The product was recrystallized from aqueous acetic acid to give X; m. p. 237—238°C (colorless needles); yield, 170 mg. It was soluble in concentrated sulfuric acid to a green solution. IR: 1644 (C=O), 1033 (=C-O-C), 926 $cm^{-1}$ ($O-CH_2-O$).

Found: C, 66.34; H, 4.60. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32%.

*From VIII.* — A mixture of the isoflavone VIII (100 mg.), anhydrous potassium carbonate (5.0 g.) and dimethyl sulfate (0.2 ml.) in dry acetone (100 ml.) was treated in a method similar to that used above. Recrystallization from aqueous acetic acid yielded X; m. p. 236—237°C (colorless needles). This substance was identified with the above sample by mixed fusion and a comparison of the infrared spectra.

*From VII.*—A mixture of the ketone VII (0.9 g.), ethyl orthoformate (3.0 ml.), pyridine (4.0 ml.) and piperidine (0.5 ml.) was treated in a method similar to that used for I. Recrystallization from acetone yielded X; m. p. 237—238°C (colorless needles); yield, 0.3 g. This was identical with the above sample.

**6,7-Diacetoxy-3′,4′-methylenedioxy-2-methylisoflavone (XII).** — A mixture of the ketone V (4.0 g.) and anhydrous sodium acetate (7.0 g.) in acetic anhydride (70 ml.) was refluxed for 16 hr., and then the excess acetic anhydride was removed in vacuo. The residue was washed with water and recrystallized from methanol to give XII; m. p. 146—147°C (colorless needles); yield, 4.2 g..

Found: C, 63.77; H, 4.27. Calcd. for $C_{21}H_{16}O_8$: C, 63.63; H, 4.07%.

**6,7-Dihydroxy-3′,4′-methylenedioxy-2-methylisoflavone (XIII).**—A mixture of the diacetate XII (3.8 g.), sodium hydroxide (1.2 g.), water (5.0 ml.) and methanol (80 ml.) was refluxed for 30 min.

After the solvent had been distilled off in vacuo, the residue was dissolved into water and the solution was acidified. The precipitates were collected, washed with water, and then recrystallized from ethanol to give XIII; m. p. 293—294°C (colorless needles); yield, 2.8 g. It gave a green color with an alcoholic ferric chloride solution and was soluble in aqueous sodium carbonate to a yellow solution.

Found: C, 65.14; H, 4.07. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87%.

**6,7 : 3′,4′-Bismethylenedioxy-2-methylisoflavone (XI).**—*From IV.*—From a mixture of the ketone IV (600 mg.) and anhydrous sodium acetate (0.8 g.) in acetic anhydride (10 ml.), synthesis was carried out by a method similar to that used for XII. Recrystallization from aqueous acetic acid gave XI; m. p. 219—220°C (colorless needles); yield, 450 mg.. It was soluble in concentrated sulfuric acid to a green solution. IR: 1637(C=O), 1037 (=C-O-C), 934 $cm^{-1}$ ($O-CH_2-O$).

Found: C, 66.59; H, 3.70. Calcd. for $C_{18}H_{12}O_6$: C, 66.67; H, 3.73%.

*From XIII.* — From a mixture of the isoflavone XIII (1.0 g.), potassium hydroxide (680 mg.), ethanol (10 ml.), water (10 ml.) and methylene sulfate (650 mg.) in acetone (15 ml.), synthesis was carried out by a method similar to that used for IV. The product was recrystallized from aqueous acetic acid to give XI; m. p. 218—219°C (colorless needles); yield, 160 mg. It was identified with the above sample by mixed fusion and a comparison of the infrared spectra.

**6-Acetoxy-7-methoxy-3′,4′-methylenedioxy-2-methylisoflavone (XIV).** — From the ketone VI (1.8 g.), anhydrous sodium acetate (5.0 g.) and acetic anhydride (50 ml.), synthesis was carried out by a method similar to that used for XII. Recrystallization from aqueous acetone gave XIV; m. p. 217—218°C (colorless needles); yield, 1.6 g.

Found: C, 65.17; H, 4.36. Calcd. for $C_{20}H_{16}O_7$: C, 65.21; H, 4.38%.

**6-Hydroxy-7-methoxy-3′,4′-methylenedioxy-2-methylisoflavone (XV).**—From the isoflavone XIV (1.1 g.), sodium hydroxide (0.5 g.), water (5.0 ml.) and ethanol (100 ml.), reaction was carried out by a method similar to that used for XIII. Recrystallization from aqueous pyridine gave XV; m. p. 244—245°C (colorless prisms); yield, 0.9 g. It was soluble in concentrated sulfuric acid to a green solution.

Found: C, 66.10; H, 4.39. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32%.

**6,7-Dimethoxy-3′,4′-methylenedioxy-2-methylisoflavone (XVI).**—*From XIII.*—A mixture of the isoflavone XIII (2.0 g.), anhydrous potassium carbonate (15.0 g.), dimethyl sulfate (4.0 ml.) and dry acetone (190 ml.) was treated by a method similar to that used for VII. Recrystallization from ethanol gave XVI; m. p. 214.5—215°C (colorless microneedles); yield, 2.1 g. IR: 1639

(C=O), 1026 (=C-O-C), 921 $cm^{-1}$ ($O-CH_2-O$).

Found: C, 67.02; H, 4.51. Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75%.

*From XV.* — The methylation of isoflavone XV (470 mg.) was carried out by the same procedure; yield, 430 mg.

A mixture of the isoflavone XVI (1.5 g.), sodium hydroxide (1.5 g.), water (10 ml.) and ethanol (150 ml.) was refluxed for 2 hr. under the stream of nitrogen. After the solvent had been removed in vacuo, the residue was dissolved in water and the solution was acidified. The precipitates were collected, washed with water, and recrystallized from aqueous acetone to give colorless plates; m. p. 153—154°C; yield, 1.3 g. This substance was identified with VII by mixed fusion and a comparison of the infrared spectra.

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