BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 233—236 (1969)

The Synthesis of 3-Hydroxy-8,9-dimethoxypterocarpan[*1]

Kenji FUKUI, Mitsuru NAKAYAMA and Teruo HARANO

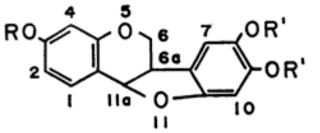
Department of Chemistry, Faculty of Science, Hiroshima University, Higashi Sendamachi, Hiroshima

(Received June 12, 1968)

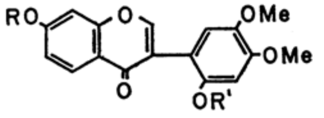
7,2′-Dihydroxy-4′,5′-dimethoxyisoflavone was obtained from 7-hydroxy-2′,4′,5′-trimethoxyisoflavone by selective demethylation with aluminum chloride in acetonitrile. By partial benzylation, the dihydroxyisoflavone then gave 7-benzyloxy-4′,5′-dimethoxy-2′-hydroxyisoflavone. The subsequent treatment of the latter with sodium borohydride afforded 3-hydroxy-8,9-dimethoxypterocarpan *via* its 3-benzyloxy-compound.

In connection with the investigation of the syntheses of natural pterocarpans (*e.g.*, (±)-maackiain (I)[1] and (±)-pterocarpin (II)[2]), the syntheses of the same oxygenated analogues and the spectral comparisons of these compounds were attempted. This paper will describe the syntheses of 3-hydroxy-8,9-dimethoxypterocarpan (III)[*2] and related compounds from 7-hydroxy-2′,4′,5′-trimethoxyisoflavone (IV).[3]

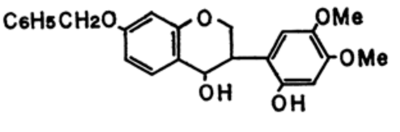
The selective demethylation at the 2′-position[4] of the 7-hydroxyisoflavone (IV) or of its 7-benzyl derivative (V) in acetonitrile with aluminum chloride afforded 7,2′-dihydroxy-4′,5′-dimethoxyisoflavone (VI) in a good yield; the product then gave a diacetate with acetic anhydride. The partial benzylation of VI at room temperature yielded 7-benzyloxy-4′,5′-dimethoxy-2′-hydroxyisoflavone (VII), which was then easily converted to a monoacetate by a usual method. The treatment of VII with sodium borohydride in absolute alcohol-tetrahydrofuran furnished a product (VIII), $C_{24}H_{22}O_5$, mp 142—143°C, in a good yield. This product (VIII) shows no infrared absorption due to hydroxyl or carbonyl groups (Fig. 1). A comparison of the NMR spectrum (Fig. 2, Table 1)[*3] of the product (VIII) with those of pterocarpan derivatives reported in the literature[5] indicates



I R = H R'-R' = CH2
II R = Me R'-R' = CH2
III R = H R' = Me
VIII R = C6H5CH2 R' = Me
X R = CH3CO R' = Me
XI R = R' = Me



IV R = H R' = Me
V R = C6H5CH2 R' = Me
VI R = R' = H
VII R = C6H5CH2 R' = H



IX

[*1] Presented at the 10th Symposium on the Chemistry of Natural Products, Tokyo, Oct., 1966. Symposium papers, p. 145.

[1] K. Fukui, M. Nakayama, H. Tsuge and K. Tsuzuki, *Experientia*, **24**, 536 (1968).

[2] K. Fukui and M. Nakayama, *Tetrahedron Letters*, **1966**, 1805.

[*2] The numbering of pterocarpan is according to S. H. Harper *et al.* (*Chem. Commun.*, **14**, 309 (1965).)

[3] K. Fukui, M. Nakayama, M. Hatanaka, T. Okamoto and Y. Kawase, This Bulletin, **36**, 397 (1963).

[4] a) K. Aghoiamurthy, A. S. Kukla and T. R. Seshadri, *J. Indian Chem. Soc.*, **38**, 914 (1961); b) V. K. Kalra, A. S. Kukla and T. R. Seshadri, *Indian J. Chem.*, **5**, 287 (1967); c) V. Chandrasheker, M. Krishnamurti and T. R. Seshadri, *Tetrahedron*, **23**, 2505 (1967); d) K. Fukui, M. Nakayama and T. Harano, *Experientia*, **23**, 613 (1967).

[*3] The NMR spectra were measured with a Varian A-60 and a Hitachi R-20 spectrometer, using tetramethylsilane as the internal standard (δ-value in $CDCl_3$).

[5] a) J. B-son Bredenberg and J. N. Shooley, *Tetrahedron Letters*, **1961**, 285; b) H. Suginome, This Bulletin, **39**, 1529 (1966); c) K. Fukui, M. Nakayam

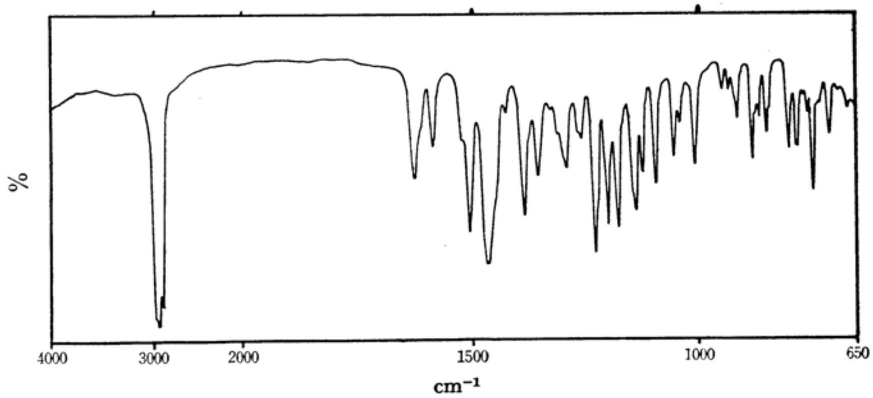


Fig. 1. IR spectrum of VIII (Nujol).

that the broad band at 5.35—5.55 (1H) is due to the C-11a proton, while the complex multiplet at from 3.5–4.5 (3H) surrounding the methoxy resonance is to be assigned to the C-6 protons and the C-6a proton. Accordingly, the structure of VIII is formulated as 3-benzyloxy-8,9-dimethoxypterocarpan. The reaction of the 2′-hydroxyisoflavone (VII) with sodium borohydride to the pterocarpan (VIII) can be postulated as proceeding through an intermediary, a 2′-hydroxyisoflavan-4-ol derivative, 7-benzyloxy-4′,5′-dimethoxy-2′-hydroxyisoflavan-4-ol (IX), followed by dehydration. Attempts to isolate the intermediate (IX) were, however, unsuccessful. The debenzylation of VIII with hydrogen afforded the desired pterocarpan, III, which was also obtained from the 7,2′-dihydroxyisoflavone (VI) by a similar method.

The structure of III is confirmed by the NMR spectra of III, its acetate (X), and methyl ether (XI), which were easily obtained by usual methods. These data are collected in Table 1. The representative NMR spectrum of the acetate (X) is shown in Fig. 3. The aromatic protons are assigned by comparing the data on them with the previously reported data on related compounds, the known values of substituent effects on chemical shifts in aromatic molecules,[6] and the characteristic magnitudes of the aromatic proton-proton splittings.[7]

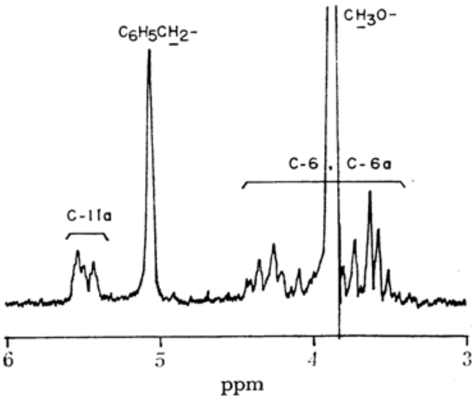


Fig. 2. NMR spectrum of VIII ($CDCl_3$).

TABLE 1. THE NMR SPECTRAL DATA OF PTEROCARPANS*[3,4]

Proton	Compound VIII	III	X	XI
Arom. C-1	7.45 d	7.33 d	7.51 d	7.40 d
C-2	6.68 q	6.45m (C-2, C-4)	6.78 q	6.62 q
C-4	6.53 d′		6.71	6.48 d′
C-7	6.82 s	7.08	6.83 s	6.82 s
C-10	6.50 s	6.80	6.50 s	6.50 s
C-11a	5.48m	5.55	5.48m	5.48m
C-6—C-6a	3.5—4.4m	3.5—4.4m	3.5—4.4m	3.5—4.4m
$C\underline{H}_3O$	3.84 s	3.92 s	3.81 s	3.77 s
	3.87 s		3.82 s	3.81 s
				3.83 s
$C_6\underline{H}_5CH_2$	7.39 s			
$C_6H_5C\underline{H}_2$	5.05 s			
$C\underline{H}_3CO$			2.26 s	

*4 s, singlet; d, doulet (J_{ortho}=8.5 Hz); d′, doublet (J_{meta}=2.5 Hz); q, quartet (J_{ortho}=8.5 Hz; J_{meta}=2.5 Hz); m, multiplet.

T. Harano and H. Tsuge, 10th Symposium on the Chemistry of Natural Products, Oct., 1966. Symposium papers, p. 145; d) K. G. R. Pachler and W. G. E. Underwood, *Tetrahedron,* **23**, 1817 (1967).

6) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book, Co., New York (1959), p. 259.

7) H. S. Gutowsky, C. H. Holm, A. Saika and G. A. Williams, *J. Am. Chem. Soc.,* **79**, 4596 (1957); G. A. Williams and H. S. Gutowsky, *J. Chem. Phys.,* **25**, 1288 (1956).

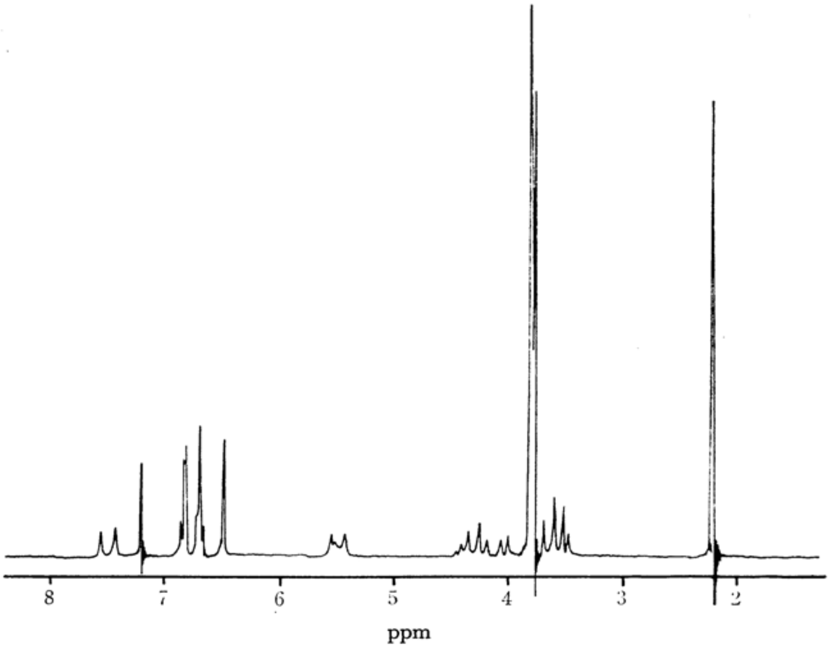


Fig. 3. NMR spectrum of X ($CDCl_3$).

Experimental[*5]

7-Benzyloxy-2′,4′,5′-trimethoxyisoflavone (V). A mixture of the isoflavone IV[3)] (1.5 g), anhydrous potassium carbonate (5.0 g), and benzyl chloride (1.0 g) in anhydrous acetone (80 m*l*) was refluxed for 6 hr. The reaction mixture was then treated in a usual manner. The resulting solid was collected and recrystallized from ethanol to give colorless plates of V, mp 143—144°C (lit.[8)] mp 144—145°C); yield, 1.5 g. IR: 1641 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 247.5 (4.40), 296.5 (4.32).

Found: C, 71.81; H, 5.43%. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30%.

7,2′-Dihydroxy-4′,5′-dimethoxyisoflavone (VI). *a) From IV.* A mixture of IV (1.2 g) and anhydrous aluminum chloride (4.0 g) in anhydrous acetonitrile (30 m*l*) was refluxed for 12 hr. After the solvent had been removed, the residue was treated with 10% hydrochloric acid. The resulting solid was collected, washed with water, and recrystallized from ethanol to give light yellow needles of VI, mp 236—237°C; yield, 1.0 g. IR: 3460 (OH), 1619 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 249_i (4.30),[*6] 265_i (4.22), 301 (4.28).

Found: C, 64.74; H, 4.58%. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%.

The diacetate: hot acetic anhydride-anhydrous sodium acetate method; mp 152—153°C (colorless needles from ethanol). IR: 1755, 1640 cm^{-1} (C=O). UV: λ_{max} mμ (log ε): 245.5_i (4.38), 290 (4.06).

Found: C, 63.26; H, 4.60%. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55%.

b) From V. By a reaction similar to that described above, V (1.2 g), anhydrous aluminum chloride (4.0 g), and anhydrous acetonitrile (30 m*l*) gave VI, mp 236—237°C, which was identical with the sample derived by the above-described method a); yield, 0.85 g.

7-Benzyloxy-2′-hydroxy-4′,5′-dimethoxyisoflavone (VII). Dihydroxyisoflavone VI (0.4 g), benzyl chloride (0.15 g), and anhydrous acetone (100 m*l*) were kept at room temperature for 32 hr while being stirred. After the potassium salts and acetone had then been removed, the water was added to the residue. The resulting solid was collected and recrystallized from ethanol to give yellow needles of VII, mp 172—173°C; yield, 0.3 g. IR: 1622 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 245_i (4.35), 267 (4.27), 299 (4.32).

Found: C, 70.97; H, 4.98%. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99%.

The acetate: hot acetic anhydride - anhydrous sodium acetate method; mp 154—155°C (colorless needles from ethanol). IR: 1750, 1640, 1630 cm^{-1} (C=O). UV: λ_{max} mμ (log ε); 248 (4.40), 293.5 (4.19), 304_i (4.12).

Found: C, 70.13; H, 5.03%. Calcd for $C_{26}H_{22}O_7$: C, 69.94; H, 4.97%.

3-Benzyloxy-8,9-dimethoxypterocarpan (VIII). A solution of sodium borohydride (0.4 g) in absolute ethanol (10 m*l*) was added, drop by drop to a solution of the isoflavone VII (0.3 g) in anhydrous tetrahydrofuran (50 m*l*). The reaction mixture was then kept for 50 hr at room temperature while being stirred. After acetone (20 m*l*) had been added to decompose the excess reducing agent, the solvent was removed under reduced presusre, and 10% hydrochloric acid was added. The separated solid was collected, washed with water, and recrystallized from ethanol to give colorless plates of VIII, mp 142—143°C; yield, 0.22 g. IR: 1627, 1583, 1505 cm^{-1}

[*5] All the melting points are uncorrected; the infrared spectra were measured in Nujol, while the ultraviolet spectra were measured in an ethanol solution.

8) K. Fukui and M. Nakayama, This Bulletin, **38**, 1803 (1965).

[*6] i=inflection point.

(phenyl). UV: λ_{max} mμ (log ε); 287 (3.88), 298 (3.85).

Found: C, 73.99; H, 5.63%. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68%.

3-Hydroxy-8,9-dimethoxypterocarpan (III). *a) From VIII.* A solution of VIII (0.1 g) in acetic acid (40 m*l*) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (10%: 0.04 g). After the catalyst had been filtered out, the filtrate was evaporated under reduced pressure; the residue was then recrystallized from dilute ethanol to give colorless crystals of III, mp 209—211°C; yield, 0.06 g. IR: 3460 (OH), 1625, 1595, 1515, 1495 cm^{-1} (phenyl). UV: λ_{max} mμ (log ε); 288 (3.85), 298 (3.85).

Found: C, 65.91; H, 5.68%. Calcd for $C_{17}H_{16}O_5 \cdot \frac{1}{2}H_2O$: C, 66.01; H, 5.54%.

b) From VI. By a reaction similar to that described above, VI (0.6 g) and sodium borohydride (0.7 g) were treated in ethanol - tetrahydrofuran for 60 hr, giving III, mp 209—211°C, which was identical with a sample derived by the above-described method a); yield, 0.5 g.

The acetate (X): hot acetic anhydride - anhydrous sodium acetate method; mp 146—147°C (colorless crystals from ethanol). IR: 1757 (C=O), 1620, 1592, 1501 cm^{-1} (phenyl). UV: λ_{max} mμ (log ε); 288$_i$ (3.76), 300 (3.83).

Found: C, 66.63; H, 5.33%. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

The methyl ether (XI): methyl iodide - anhydrous potassium carbonate-acetone method; mp 136—137°C (colorless needles from ethanol). IR: 1616, 1570, 1505, 1492 cm^{-1} (phenyl). UV: λ_{max} mμ (log ε); 288 (3.83), 300 (3.83).

Found: C, 68.49; H, 5.82%. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%.

The authors wish to express their thanks to Professor Shô Itô, Tohoku University, for his NMR spectra measurements. This work was supported in part by a grant-in-aid from the Ministry of Education.