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Syntheses of Pterocarpans. II.*1 The Synthesis of (±)-Pterocarpin*2

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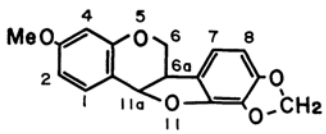
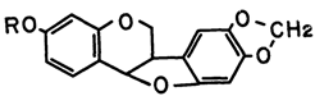
The reduction of medicagol methyl ether with lithium aluminum hydride in tetrahydrofuran yielded a diol. The dehydration of the diol in boiling diethylene glycol gave an ether (anhydropisatin, *O*-methyl anhydrosophorol). Then, the above ether was hydrogenated with 10% Pd-C to (±)-pterocarpin.

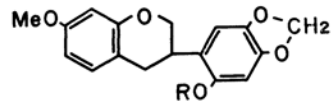
(−)-Pterocarpin was first isolated from the heartwood of the red sandalwood tree (*Pterocarpus santalinus*).[1] It was initially proposed by Robertson *et al.*[2] that in chemical structure it was a 3-methoxy-9,10-methylenedioxypterocarpan (I).*3 Lately, on the basis of NMR spectral analysis[3] and by a comparison[4] of synthetic (±)-dihydropterocarpin methyl ether ((±)-7,2′-dimethoxy-4′,5′-methylenedioxyisoflavan) (II) with the (−)-compound II derived from (−)-pterocarpin, the structure was revised and it was regarded as a 3-methoxy-8,9-methylenedioxypterocarpan (III).



I



III R=Me IX R=H



II R=Me X R=H XI R=CH_3CO

In a previous preliminary communication,[5] the present authors have already reported the total synthesis of (±)-pterocarpin*4 and confirmed the revised structure, III. The present paper will be concerned with providing a full account of the experiments. Another synthesis of (±)-pterocarpin *via* a different route has been reported.[7]

The reduction of the methyl ether (IV)[8] of medicagol (V),[9] which had been obtained by the procedure of Wanzlick's benzofurano(3′,2′ : 3,4)-coumarin synthesis,[10] with lithium aluminum hydride in tetrahydrofuran yielded 2-(2-hydroxy-4-methoxyphenyl)-3-hydroxymethyl-5,6-methylenedioxybenzo[*b*]furan (VI), with absorptions at 3350 and 3100 cm^{-1} in the infrared spectrum, in a 60% yield. This was readily transformed to a diacetate. The removal of water from the diol VI in boiling diethylene glycol gave a product (VII), $C_{17}H_{12}O_5$, which melted at 179—180°C, in a 83% yield. The

*1 Part 1: K. Fukui, M. Nakayama and T. Harano, This Bulletin, **42**, 233 (1969). Our previous paper entitled "The Synthesis of 3-Hydroxy-8,9-dimethoxypterocarpan" is included in this series.

*2 Presented at the 10th Symposium on the Chemistry of Natural Products, Tokyo, Oct., 1966. It has previously been reported in a preliminary form: K. Fukui and M. Nakayama, *Tetrahedron Letters*, **1966**, No. 16, 1805.

1) P. Cazeneuve, *Ber.*, **7**, 1789 (1874).

2) A. McGookin, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, **1940**, 787.

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

3) J. B.-S. Bredenberg and J. N. Shoolery, *Tetrahedron Letters*, **1961**, No. 9, 285.

4) H. Suginome, *Experientia*, **18**, 161 (1962); This Bulletin, **39**, 1529 (1966).

5) K. Fukui and M. Nakayama, *Tetrahedron Letters*, **1966**, No. 16, 1805.

*4 (±)-Pterocarpin was derived from (±)-maackiain, a naturally-occurring pterocarpan, which had been isolated from *Sophora japonica* by Shibata and Nishikawa.

6) S. Shibata and Y. Nishikawa, *Chem. Pharm. Bull.*, **11**, 167 (1963).

7) M. Uchiyama and M. Matsui, *Agr. Biol. Chem.*, **31**, 1490 (1967).

8) K. Fukui, M. Nakayama and H. Sesita, This Bulletin, **37**, 1887 (1964).

9) a) K. Fukui, M. Nakayama, H. Tsuge and K. Tsuzuki, *Experientia*, **24**, 536 (1968); b) A. L. Livingston, S. C. Witt, R. E. Lundin and E. M. Bickoff, *J. Org. Chem.*, **30**, 2353 (1965).

10) H. W. Wanzlick, R. Gritzky and H. Heidepriem, *Chem. Ber.*, **96**, 305 (1963).

absence of a hydroxyl band in its infrared spectrum, and the close similarity of its ultraviolet spectrum (Fig. 1) of those of anhydrosophorol[11] and anhydropisatin[12] previously reported, indicated that this compound was an ether derivative. Moreover, the NMR spectrum*5 (Table 1) of VII suggested the presence of aromatic protons (5H, complex peaks from 6.5 to 7.4), methylenedioxyl protons (2H, 5.97), and methoxyl protons (3H, 3.78). The singlet peak at 5.51 (2H) is due to the ring protons. Accordingly, the structure VII is formulated: 3-methoxy-8,9-methylenedioxy-6*a*,11*a*-dehydropterocarpan (anhydropisatin,[12] *O*-methyl anhydrosophorol[13]). The identity of this product with *O*-methyl anhydrosophorol,*6 which had been obtained from sophorol (VIII)[11] by the action of acid, followed by methylation, was confirmed by a mixed-melting-point determination and by spectral comparisons. Then, VII was hydrogenated over 10% palladium-charcoal in acetic acid; this produced a product in a 60% yield. The synthetic product was found to be identical with (±)-maackiain methyl ether ((±)-pterocarpin) (III)*7 which had

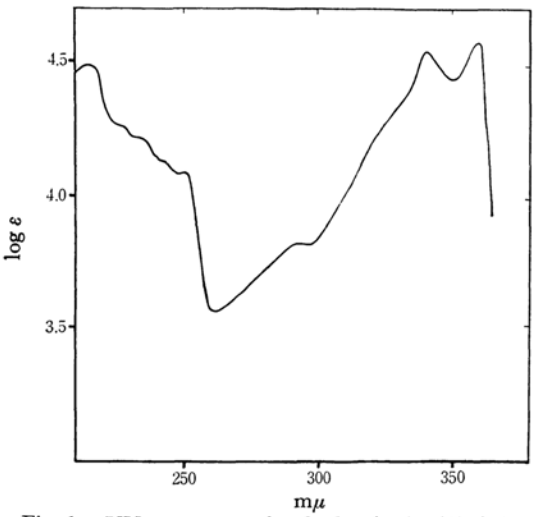


Fig. 1. UV spectrum of anhydropisatin (VII) in ethanol.

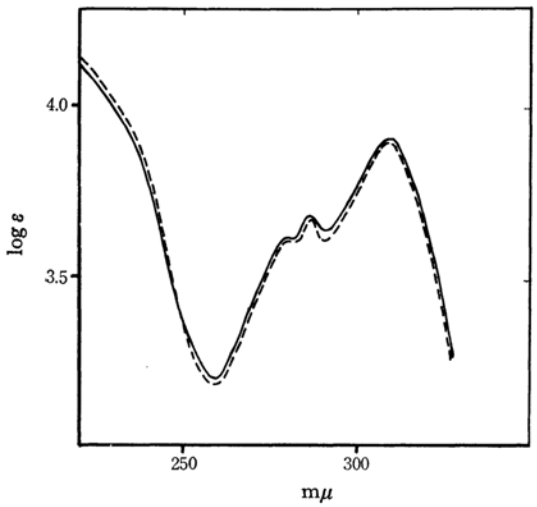


Fig. 3. UV spectra of synthetic (——) and natural (·····) (±)-pterocarpin (III) in ethanol.

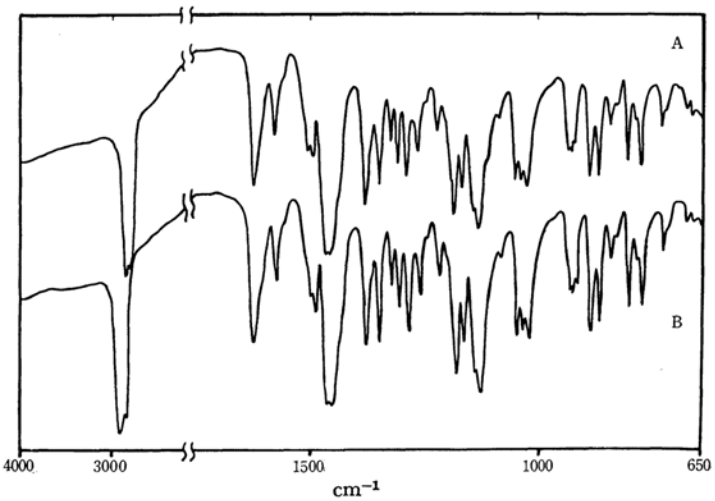


Fig. 2. IR spectra of synthetic (A) and natural (B) (±)-pterocarpin (III) in Nujol.

11) H. Suginome, *J. Org. Chem.*, **24**, 1655 (1959).

12) D. R. Perrin and W. Bottomley, *J. Am. Chem. Soc.*, **84**, 1919 (1962); D. D. Perrin and D. R. Perrin, *ibid.*, **84**, 1922 (1962).

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

13) H. Suginome, This Bulletin, **39**, 1525 (1966).

*6 *O*-Methyl anhydrosophorol was kindly supplied by Dr. Hiroshi Suginome, Hokkaido University.

*7 (±)-Maackiain methyl ether was kindly supplied by Professor Shoji Shibata, Tokyo University.

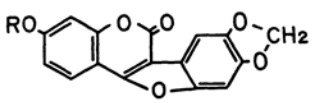
TABLE 1. THE NMR SPECTRAL DATA*5,*8

Protons	Compounds				
	(±)-Pterocarpin	(±)-Pterocarpin[3]	VII	(±)-II	(±)-XI
Arom.					
C-1	7.37 d	7.41 d	7.38 d	6.97 d[a]	6.97 d[a]
C-2	6.60 q	6.65 q	6.51 q	6.60 q	6.63 q
C-4	6.43 d′	6.48 d′	6.49 d′	6.41 d′	6.43 d′
C-7	6.68 s	6.72 s	6.98 s	6.64 s	6.67 s
C-10	6.40 s	6.43 s	6.70 s	6.56 s	6.59 s
Ring					
C-11*a*	5.45m	5.48m	5.51 s[b]	2.8—4.4m[c]	2.8—4.4m[c]
C-6—C-6*a*	3.35—4.20m	3.35—4.20m			
O–CH_2–O	5.87 s	5.92 s	5.97 s	5.89 s	5.95 s
OCH_3	3.75 s	3.78 s	3.78 s	3.78 s[d]	3.81 s
CH_3CO					2.30 s

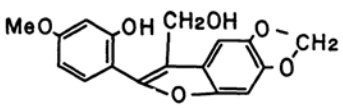
been derived from natural (±)-maackiain (IX)[6] by a mixed-melting-point determination and by infrared, ultraviolet, and NMR spectral comparisons. The infrared and ultraviolet spectra of synthetic and natural (±)-pterocarpin are superimposable, as is shown in Figs. 2 and 3. The data of the NMR spectra was in good accordance with those of (−)-pterocarpin reported by Bredenberg and Shoolery (Table 1).

The catalytic hydrogenolysis of III with either 15% palladium-charcoal or 10% palladium-charcoal at an elevated temperature in acetic acid gave (±)-2′-hydroxy-7-methoxy-4′,5′-methylenedioxyisoflavan ((±)-dihydropterocarpin (X). An acetate (XI) of X was easily prepared. Also, the methyl ether of X is identical with (±)-II reported earlier by Suginome.[4] The NMR spectra of II and XI were assigned as is shown in Table 1.

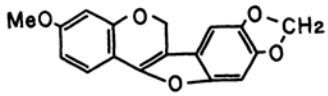
The partial synthesis of the racemate of (−)-pisatin (XII)[12] has been carried out from (−)-



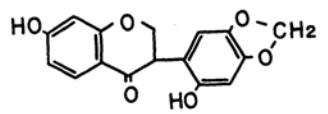
IV R=Me V R=H



VI

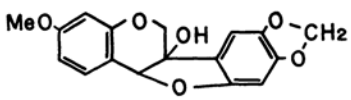


VII



VIII

pterocarpin by Bevan *et al.*[14] Thus, the synthesis of (±)-XII has been now totally accomplished.



XII

Experimental*9

2-(2-Hydroxy-4-methoxyphenyl)-3-hydroxymethyl-5,6-methylenedioxybenzo[*b*]furan (VI). A suspension of medicagol methyl ether (1.0 g) (mp 269—270°C)[8] (V) in absolute tetrahydrofuran (150 m*l*) was stirred into a suspension of lithium aluminum hydride (600 mg) in absolute tetrahydrofuran (150 m*l*); the mixture was then refluxed for 3 hr. The excess lithium aluminum hydride was destroyed by the careful addition of ethyl acetate (2 m*l*) and water (50 m*l*). The cooled mixture was acidified with dilute hydrochloric acid and extracted with ether. After the removal of the solvent under diminished pressure, the resulting solid was recrystallized from benzene to give colorless prisms of VI; mp 186—187°C; yield, 600 mg (60%). IR: 3350, 3100 (OH); 1026, 941 cm^{-1} (O–CH_2–O). UV: λ_{max} mμ (log ε); 271 (4.11), 322 (4.36).

*8 s, singelt; d, doublet (J_{ortho}=8.5 Hz); d′, doubelt (J_{meta}=2.5 Hz); q, quartet (J_{ortho}=8.5 Hz; J_{meta}=2.5 Hz); m, multiplet.

a) The protons of C-1, 2, 4, 7 and 10 in pterocarpan is corresponding with those of C-5, 6, 8, 3′ and 6′ in isoflavan.

b) Protons (2H) of C-6.

c) Protons (5H) of C-2, 3 and 4 in isoflavan ring.

d) $OCH_3 \times 2 = 6H$.

14) C. W. L. Bevan, A. J. Birch, B. Moore and S. K. Mukerjee, *J. Chem. Soc.*, **1964**, 5991.

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

Found: C, 65.03; H, 4.64%. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%.

The diacetate: acetic anhydride-pyridine method or hot acetic anhydride-sodium acetate method; mp 134—135°C (colorless prisms from methanol). IR: 1757, 1738 (C=O); 1025, 937 cm^{-1} (O-CH_2-O). UV: λ_{max} mμ (log ε); 274 (4.15), 320 (4.34). NMR:[*5,8] 7.52_d (C-6'), 7.03_s (C-7), 6.94_s (C-4), 6.89_q (C-5'), $6.73_{d'}$ (C-3'), 5.96_s (2H) (O-CH_2-O), 5.23_s (2H) (CH_2OH), 3.87_s (3H) (CH_3O), 2.20_s (3H) (CH_3CO), 2.11_s (3H) (CH_3CO).

Found: C, 63.27; H, 4.60%. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55%.

3-Methoxy-8,9-methylenedioxy-6*a*,11*a*-dehydropterocarpan (Anhydropisatin, *O*-Methyl Anhydrosophorol) (VII). A solution of VI (1.2 g) in pure diethylene glycol (35 m*l*) was refluxed for 10 min. During boiling, a slow separation of the water was noted. The mixture was then cooled, diluted with water (100 m*l*), extracted with ether, and washed with a 5% aqueous sodium hydroxide solution. After the ether had been removed under diminished pressure, the resulting solid was recrystallized from ethanol to give colorless needles of VII, mp 179—180°C (lit. mp 179—180°C[12]; mp 187—188°C[13]; mp 179—180°C[14]); yield, 1.0 g (83%). IR: 1658, 1619, 1570, 1518, 1500 (C=C, aromatic); 1023, 920 cm^{-1} (O-CH_2-O). UV: λ_{max} mμ (log ε); 215 (4.49), 232_i (4.22),[*10] 243_i (4.13), 251 (4.09), 294 (3.82), 340 (4.54), 359 (4.57). (lit.[12] 215 (4.49), 234 (4.30), 244 (4.2), 257 (4.1), 291 (3.8), 339 (4.58), 358 (4.60)).

Found: C, 69.02; H, 4.14%. Calcd for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08%.

This substance was found, by mixed-melting-point measurements and by ultraviolet spectral comparison, to be identical with the *O*-methyl anhydrosophorol supplied by Suginome.

(±)-Pterocarpin ((±)-Maackiain Methyl Ether) (III). A mixture of VII (500 mg) and 10% palladium-charcoal (300 mg) in acetic acid (300 m*l*) was shaken in an atmosphere of hydrogen until 1.1 mol of hydrogen had been absorbed. After the subsequent separation of the catalyst, the filtrate was evaporated under diminished pressure and the residue dissolved in ether. The ether solution was washed with a 5% aqueous sodium hydroxide solution and then with water. After the ether had been removed, the resulting solid was recrystallized from methanol to give colorless leaflets of III; mp 185—186°C (mp 185—186°C[*11]; lit. mp 185—186°C[6]); yield, 300 mg (60%). IR: 1634, 1585, 1503, 1493 (aromatic); 1027, 930 cm^{-1} (O-CH_2-O) (1634, 1586, 1500, 1491, 1026, 929 cm^{-1}[*11]; lit. 1620, 1589, 1037, 942 cm^{-1} ($CHCl_3$)[6]). UV: λ_{max} mμ (log ε); 281 (3.60), 287 (3.66), 311 (3.89) (281 (3.60), 287 (3.67), 311 (3.88)[*11]; lit. 280 (3.58), 286 (3.65), 310 (3.87)[6]).

Found: C, 68.55; H, 4.79%. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

This substance was found, by mixed-melting-point measurements and by infrared and ultraviolet comparisons, to be identical with the natural (±)-peterocarpin supplied by Shibata.

Hydrogenolysis of (±)-III. a) A mixture of (±)-III (500 mg) and 15% palladium-charcoal (500 mg) in acetic acid (200 m*l*) was shaken in an atmosphere of hydrogen until 1.1 mol of hydrogen had been absorbed. The reaction mixture was then treated in the usual manner. The product was recrystallized from ethanol to give colorless needles of (±)-2'-hydroxy-7-methoxy-4',5'-methylenedioxyisoflavan ((±)-dihydropterocarpin) (X); mp 177—178°C (lit. mp 176—178°C[14]); yield, 300 mg (60%). IR: 3330 (OH); 1613, 1583, 1496 (aromatic); 1025, 934 cm^{-1} (O-CH_2-O). UV: λ_{max} mμ (log ε); 287 (3.79), 297.5 (3.78).

Found: C, 68.27; H, 5.48%. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%.

The acetate (XI): acetic anhydride-pyridine method; mp 118—119°C (colorless needles from methanol). IR: 1759 (C=O); 1036, 935 (O-CH_2-O) cm^{-1}. UV: λ_{max} mμ (log ε); 284 (3.85).

Found: C, 66.63; H, 5.23%. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

b) From a mixture of (±)-III (500 mg) and 10% palladium-charcoal (500 mg) in acetic acid (200 m*l*), hydrogenolysis was carried out at 90—95°C. Recrystallization from ethanol gave (±)-X; mp 177—178°C; yield, 150 mg (30%).

(±)-7,2'-Dimethoxy-4',5'-methylenedioxyisoflavan (II). A mixture of X (300 mg), methyl iodide (2.0 g), and anhydrous potassium carbonate (5.0 g) in anhydrous acetone (100 m*l*) was refluxed for 6 hr, and then the acetone was evaporated. The resulting solid was recrystallized from methanol to give colorless needles of (±)-II; mp 117—118°C (lit. mp 111—113°C[4]; mp 110—111°C[14]); yield, 250 mg (83%). IR: 1613, 1576, 1505 (aromatic); 1033, 939 cm^{-1} (O-CH_2-O). UV: λ_{max} mμ (log ε): 291 (3.86), 301 (3.82).

Found: C, 68.73; H, 5.89%. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%.

The authors are grateful to Professor Shoji Shibata, Tokyo University, for supplying the (±)-maackiain methyl ether, and to Dr. Hiroshi Suginome, Hokkaido University, for supplying the *O*-methyl anhydrosophorol. They are also indebted to Professor Shô Itô, Tohoku University, for measuring the NMR spectra, and to Professor Tetsuo Mitsui, Kyoto University, for his elemental analyses. This work was supported in part by a grant-in-aid from the Ministry of Education.

[*10] i=Inflection point.

[*11] The natural (±)-pterocarpin was measured in this laboratory.