BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1385—1387 (1968)

Total Synthesis of Nepseudin*[1]

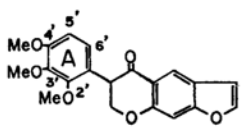
Kenji FUKUI and Mitsuru NAKAYAMA

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

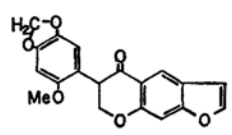
(Received December 1, 1967)

The Hoesch reaction of 6-hydroxy-2,3-dihydrobenzo[b]furan with 2,3,4-trimethoxyphenylacetonitrile yielded 6-hydroxy-5-(2,3,4-trimethoxyphenylacetyl)-2,3-dihydrobenzo[b]furan. The cyclization of the dihydrobenzofuran with ethyl orthoformate-pyridine-piperidine gave dihydrodehydronepseudin, an isoflavone. The dehydrogenation of the above isoflavone with N.B.S. or Pd-C yielded dehydronepseudin. Nepseudin was derived by the reduction of dehydronepseudin with sodium borohydride and by subsequent oxidation with the chromium trioxide-pyridine complex.

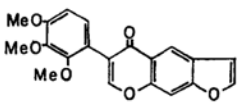
Nepseudin was isolated as colorless needles, along with neotenone, dolineone and pachyrrhizin, from the roots of *Neorautanenia pseudopachyrrhiza (Leguminosae)* by Crombie and Whiting.[1] On the basis of degradation experiments and spectral examinations, its structure was shown to be furano-(3'',2'' : 6,7)-2',3',4'-trimethoxyisoflavanone (I), which is very similar to that of neotenone (II).[1] However, the oxygenation pattern, 2',3',4', instead of the usual 2',4',5', is unique in the A ring of the isoflavonoid and rotenoid series. On dehydrogenation with manganese dioxide, I has been converted[1] into dehydronepseudin (III), a furanoisoflavone. In a previous paper,[2] the authors reported the synthesis of 7-hydroxy-2',3',4'-tritrimethoxyisoflavone (IV), which has the same oxygenation pattern as I and III. The present paper will describe the total synthesis of I *via* III, thus confirming the proposed structure.



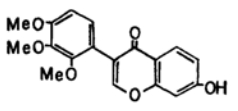
I



II



III



IV

The Hoesch reaction of 6-hydroxy-2,3-dihydrobenzo[b]furan (V)[3] with 2,3,4-trimethoxyphenylacetonitrile (VI)[2] yielded 6-hydroxy-5-(2,3,4-trimethoxyphenylacetyl)-2,3-dihydrobenzo[b]furan

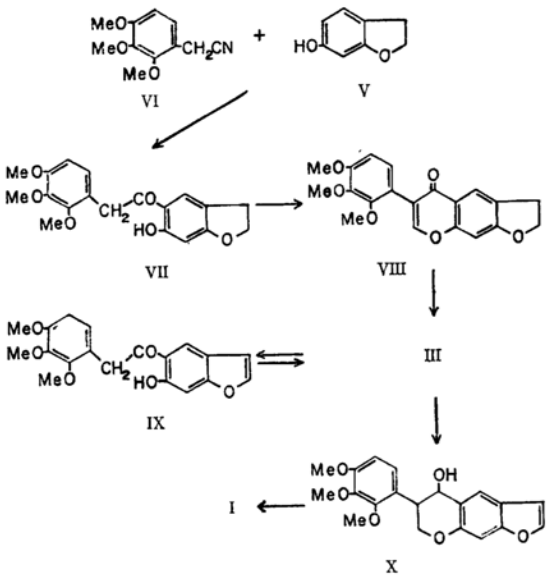
*1 Parts of this work have been briefly communicated: K. Fukui and M. Nakayama, *Experientia*, **19**, 621 (1963); *Chem. Ind. (London)*, **1963**, 1843.

1) L. Crombie and D. A. Whiting, *Tetrahedron Letters*, **1962**, 801; *Chem. Ind. (London)*, **1962**, 1946; *J. Chem. Soc.*, **1963**, 1569.

2) K. Fukui, M. Nakayama and N. Eto, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **84**, 752 (1963).

3) J. S. H. Davies, P. A. McCrea, W. L. Norris and G. R. Ramage, *J. Chem. Soc.*, **1950**, 3206.

(VII) (mp 129—130°C). The cyclization of dihydrobenzofuran VII with ethyl orthoformate-pyridine-piperidine gave dihydrodehydronepseudin (VIII) (mp 143—144°C). By dehydrogenation either with *N*-bromosuccinimide in carbon tetrachloride or with 10% palladium on a carbon catalyst in diphenyl ether, the dihydrocompound VIII was converted into dehydronepseudin (III) (mp 164—165°C). III was identical with the isoflavone obtained from natural nepseudin by Crombie and Whiting.[1] On alkaline hydrolysis, III gave 6-hydroxy-5-(2,3,4-trimethoxyphenylacetyl)benzo[b]-furan (IX) (mp 118°C). III was resynthesized from IX with ethyl orthoformate-pyridine-piperidine. The isoflavone III, when reduced with sodium borohydride, gave furano-(3'',2'' : 6,7)-2',3',4'-trimethoxyisoflavan-4-ol (X) (mp 161—162°C), presumably a product of 1,4-addition to the γ-pyrone system, followed by further reduction.[1,4]



On oxidation with the chromium trioxide-pyridine complex, isoflavanol X gave the desired isoflavanone I (mp 114—115°C); its identity with natural nepseudin was confirmed by mixed-melting-point, infrared, and ultraviolet spectral comparisons (Figs. 1 and 2).

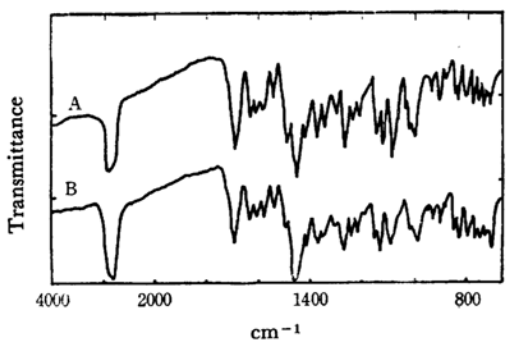


Fig. 1. IR spectra of synthetic (A) and natural (B) nepseudin in Nujol.

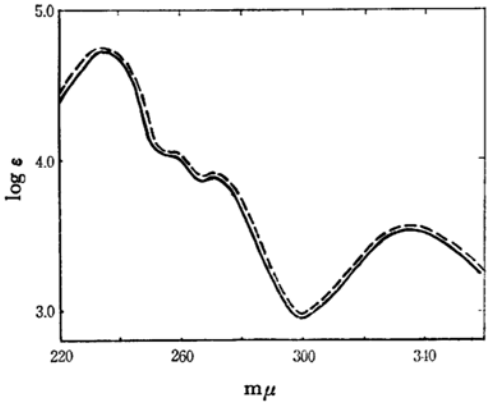


Fig. 2. UV spectra of synthetic (——) and natural (----) nepseudin in ethanol.

Experimental*2

6-Hydroxy-5-(2,3,4-trimethoxyphenylacetyl)-2,3-dihydrobenzo[b]furan (VII). A mixture of 6-hydroxy-2,3-dihydrobenzo[b]furan (V)[3] (5.0 g), 2,3,4-trimethoxyphenylacetonitrile (VI)[2] (5.0 g), and fused zinc chloride (4.0 g) in dry ether (150 m*l*) was saturated with dried hydrogen chloride for 4 hr at 0°C and then allowed to stand 2 days. The ethereal solution was decanted from the ketimine hydrochloride which had separated. The residue was washed twice with dry ether, and then heated on a steam bath with water (100 m*l*) for an hour. The resulting precipitates were collected and recrystallized from ethanol to give VII as colorless needles, mp 129—130°C, which gave a dark-brown ferric chloride reaction in ethanol; yield, 4.6 g (55%). IR: 1637 (C=O) cm^{-1}. UV: λ_{max} mμ (log ε); 281 (4.11), 330 (4.02).

Found: C, 66.37; H, 5.99%. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%.

Dihydrodehydronepseudin (4'',5'' - Dihydrofurano(3'',2'' : 6,7)-2',3',4' - trimethoxyisoflavone) (VIII). To a solution of VII (1.8 g) and ethyl orthoformate (8 m*l*) in pyridine (30 m*l*), piperidine (2 m*l*) was added; the mixture was then refluxed for 24 hr. The cooled reaction mixture was poured into ice-cooled dilute hydrochloric acid, and the resulting precipitates were colected. After being washed with water, the residue was recrystallized from ethanol to give VIII as colorless needles, mp 143—144°C; yield, 1.4 g (76%). IR: 1628 (γ-pyrone) cm^{-1}. UV: λ_{max} mμ (log ε); 240.5 (4.42), 310 (4.11).

Found: C, 67.87; H, 5.22%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.

4) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958); H. Suginome and T. Iwadare, This Bulletin, **39**, 1536 (1966); K. Fukui, M. Nakayama, T. Harano and H. Tsuge, The Chemistry of Natural Products, Symposium Papers, **10**, Tokyo (1966), p. 145.

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

Dehydronepseudin (Furano(3'',2'' : 6,7)-2',3',4'-trimethoxyisoflavone) (III). *a) N. B. S.* A mixture of VIII (1.0 g), *N*-bromosuccinimide (500 mg), and benzoyl peroxide (50 mg) in dry carbon tetrachloride (60 m*l*) was refluxed gently for an hour. The precipitates which separated on cooling were filtered off. The resulting filtrate was washed with a 5% sodium bisulfite solution and dried with anhydrous calcium chloride. The evaporation of the solvent under reduced pressure left a light yellow residue. After the addition of acetic acid (30 m*l*) and potassium acetate (5.0 g), the mixture was refluxed for an hour and then poured into water (300 m*l*). The resulting precipitates were collected and recrystallized from methanol to give III as colorless prisms, mp 164—165°C; yield, 550 mg (55%) (lit.[1] mp 158—160°C). IR: 1649 (γ-pyrone) cm^{-1} (lit.[1] 1647). UV: λ_{max} mμ (log ε); 244 (4.59), 324 (3.86) (lit.[1] λ_{max} mμ (log ε); 245 (4.64), 325 (3.92)).

Found: C, 67.96; H, 4.61%. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58%.

b) 10% *Pd-C.* A mixture of VIII (1.0 g), 10% palladium on a carbon catalyst (700 mg), and diphenyl ether (20 m*l*) was refluxed for 10 hr. The catalyst was then filtered off, and the solvent removed by steam distillation. The resulting precipitates were collected and recrystallized from methanol to give III (mp 164—165°C), which was identical with the above sample; yield, 740 mg (74%).

6-Hydroxy-5-(2,3,4-trimethoxyphenylacetyl)benzo[b]furan (IX). A mixture of III (300 mg), a 5% aqueous sodium hydroxide solution (15 m*l*), and ethanol (20 m*l*) was refluxed for 3 hr on a steam bath. After the solvent had been evaporated, the residue was extracted with ethyl acetate. The resulting precipitates were recrystallized from methanol to give IX as pale yellow plates, mp 118°C, which gave a dark-green ferric chloride reaction; yield, 200 mg (69%) (lit.[1] mp 118—119°C). IR: 1639 (C=O) cm^{-1} (lit.[1] 1645). UV: λ_{max} mμ (log ε); 236 (4.76), 258.5 (4.07), 272.5 (3.97), 345 (3.71); (lit.[1] 235 (4.66), 258 (4.00), 270 (3.86), 345 (3.60)).

Found: C, 66.69; H, 5.40%. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

The Cyclization of IX to III. By a reaction similar to that used for VII, III was prepared from IX (70 mg), ethyl orthoformate (3 m*l*), pyridine (10 m*l*), and piperidine (5 drops). Recrystallization from methanol gave III (mp 163—164°C), which was identical with the above sample; yield, 50 mg (69%).

Furano(3'',2'' : 6,7)-2',3',4'-trimethoxyisoflavan-4-ol (X). III (400 mg) in tetrahydrofuran (30 m*l*) was treated at 60°C for 90 min with sodium borohydride (300 mg) in 70% aqueous ethanol (30 m*l*) containing potassium hydroxide (30 mg). The mixture was kept at 20°C for 30 min and then diluted with a saturated ammonium chloride solution and extracted with ether. After the solvent had been evaporated, the residue was recrystallized from methanol to give X as colorless prisms, mp 161—162°C; yield, 200 mg (50%). IR: 3400 (broad) (OH) cm^{-1}.

Found: C, 67.23; H, 5.47%. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66%.

Nepseudin (I). Chromium trioxide (300 mg) was added to dry pyridine (3 m*l*); the mixture was swirled until it turned to an orange paste, and then X (100 mg) was added. The mixture was allowed to stand overnight at room temperature. After the addition of water, the resulting mixture was extracted with ether. The ether layer was washed with dilute hydrochloric acid, water, and a dilute sodium hydroxide solution, and finally dried over anhydrous potassium carbonate. After the solvent had been evaporated, the residue was recrystallized from methanol to give I as colorless prisms, mp 114—115°C; yield, 300 mg (75%) (lit. mp 115—116°C[1]; mp 115°C[*3]). IR: 1688, 1630, 1603, 1581, 1544, 1502 cm^{-1} (lit. 1686, 1631, 1605, 1585, 1541, 1490[1]; 1688, 1630, 1602, 1580, 1544, 1500[*3] cm^{-1}). UV: λ_{max} mμ (log ε); 235 (4.73), 257_i[*4] (4.03), 272.5 (3.88), 336 (3.56) (lit. 235 (4.74), 257_i (4.08), 272 (3.94), 335 (3.61)[1]; 235 (4.78), 257_i (4.06), 272.5 (3.91), 336 (3.60)[*3]). It was found, by mixed-melting-point measurement and by infrared and ultraviolet spectral comparisons, to be identical with the natural nepseudin supplied by Crombie.

Found: C, 67.94; H, 5.41%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.

The authors are grateful to Professor L. Crombie, King's College, University of London, for his gift of natural nepseudin. Grateful acknowledgement is also made to Professor Tetsuo Mitsui, Kyoto University, for his microanalyses. This work was supported by a grant-in-aid from the Ministry of Education.

*3 The natural nepseudin kindly supplied by Professor Crombie was measured in this laboratory.

*4 i=Inflection point.