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SYNTHESIS OF HINOKIFLAVONE

Koichi Nakasawa

Gifu College of Pharmacy, Gifu, Japan

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In recent years a number of bisflavones having the skeleton of 4',5,7-trihydroxyflavone (apigenin) have been isolated from the leaves of Coniferae. They are classified into bisflavonyls (ginkgetin, sciadopitysin, etc.) and bisflavonyl ethers (hinokiflavone (1) and its methyl ethers (2)). Structure for ginkgetin (I) was already confirmed by synthesis (3). This communication deals with a synthesis of hinokiflavone, a bisflavone from the leaves of Chamaecyparis obtusa ENDL., for which a unique structure of a bisapigenyl ether (II, R=R'=H) was proposed.

The key-intermediate for the synthesis was permethylated 3'-nitrobisapigenyl ethers II ($R=CH_3$, $R'=NO_2$) and III ($R=CH_3$, $R'=NO_2$) readily accessible by coupling of phenolic components VI (R'=H) and VIII (R'=H), respectively, with 3'-nitroactivated 4'-iodo-5,7-dimethoxyflavone VII in DMSO in the presence of K_2CO_3.

Synthesis of 4',8"-bisflavonyl ether II ($R=CH_3$, R'=H). 2,3-Dihydroxy-4,6-dimethoxyacetophenone (IV, R=R'=H, $R''=CH_3$) was prepared from 3,6-dihydroxy-2,4-dimethoxyacetophenone (IV, $R=CH_3$, $R'=R''=H$) (4) by monoacetylation (IV, $R=CH_3$, $R'=COCH_3$, R"=H), methylation with dimethyl sulfate in boiling acetone in the presence of K_2CO_3 (IV, $R=R''=CH_3$, $R'=COCH_3$), partial demethylation with aluminum chloride in nitrobenzene at 100° for 10 min. (IV, R=H, $R'=COCH_3$, $R''=CH_3$) followed by saponification. The phenolic component was anisoylated (IV, $R=R'=COC_6H_4OCH_3$ (p) $R''=CH_3$), isomerized to diketone V with KOH in pyridine, cyclized and saponified to produce flavone VI (R'=H). 4'-Iodo-5,7-dimethoxy-3'-nitroflavone (VII) was obtained from 2-hydroxy-4,6-dimethoxyacetophenone by 4-iodo-3-nitrobenzoylation, diketonization and cyclization.

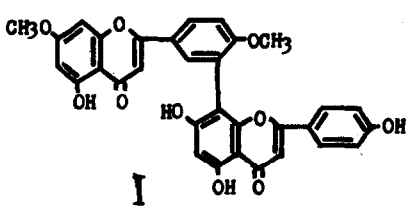
The condensation of VI (R'=H) and VII was carried out by heating them in DMSO in the presence of K_2CO_3 at 110 for 1 hr. to give II ($R=CH_3$, $R'=NO_2$) (m.p. 275°, 85%). The 3'-

nitrobisflavonyl ether was reduced to amine II ($R=CH_3$, $R'=NH_2$) by $Na_2S_2O_4$ in aqueous DMF, diazotised and decomposed with 50% H_3PO_2 to give II ($R=CH_3$, $R'=H$) (m.p. 288°, 45%), which was proved to be different from pentamethyl ether of natural hinokiflavone.

Synthesis of 4',6"-bisflavonyl ether III ($R=CH_3$, $R'=H$) and its demethylation product, hinokiflavone (III, $R=R'=H$) An alternative bisflavonyl ether having the 4'6"-ether linkage has now been synthesized by a similar route described above. Thus, the 3'-nitro-bisflavonyl ether III ($R=CH_3$, $R=NO_2$) (m.p. 283°, 80%) obtained by the condensation of 6-hydroxy-4',5,7-trimethoxyflavone (VIII, $R'=H$) (5), with VII was reduced, diazotised and decomposed to give permethylated 4',6"-bisflavonyl ether III ($R=CH_3$, $R'=H$) (m.p. 288°, 34%), which was identical with pentamethyl ether of natural hinokiflavone (m.p., mixed m. ps. and IR spectra). The synthesized methyl ether upon demethylation by means of HI·Ac_2O at 130° ~ 140° for 3 hrs. finally gave 4',6"-bisapigenyl ether (III, $R=R'=H$) (m.p. 343°) identical with natural hinokiflavone. Structure of hinokiflavone has now been established.

Demethylation of 4',8"-bisflavonyl ether with simultaneous rearrangement to 4',6"-isomer

4',8"-Bisflavonyl ether II ($R=CH_3$, $R'=H$) was converted into the bisflavone identical with natural hinokiflavone, when demethylated by means of HI·Ac_2O as above, under conditions which may be expected to bring about a Wessely-Moser rearrangement in flavonoids, coumarins, xanthones, etc.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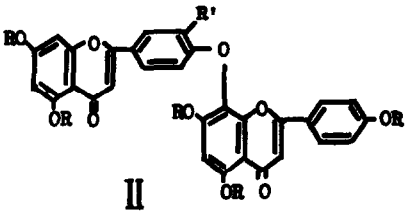
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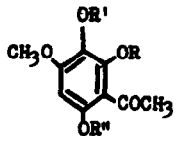
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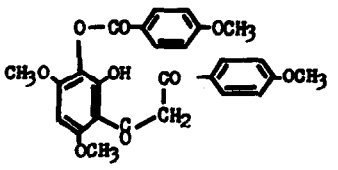
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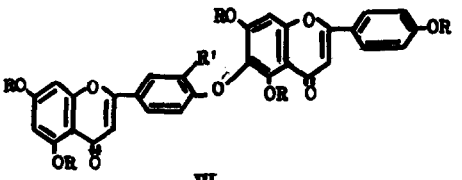
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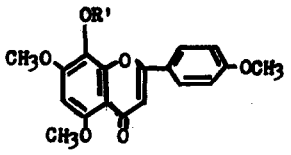
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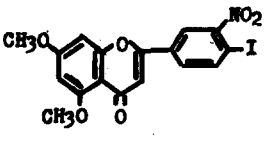
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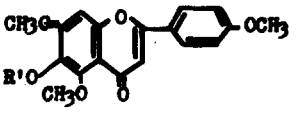
VIII

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References

1. H. Miura and N. Kawano, J. Am. Chem. Soc. 81, 6331 (1959). N. Kawano and Y. Fukui, Yakugaku Zasshi, 80, 749 (1960). Y. Fukui, ibid. 80, 752, 756 (1960).
2. H. Miura, N. Kawano and A. C. Waiss, Jr., Chem. Pharm. Bull. 14, 1404 (1966). H. Miura, Yakugaku Zasshi, 87, 871 (1967).
3. K. Nakazawa and M. Ito, Chem. Pharm. Bull. 11, 283 (1963).
4. F. Mauthner, J. prakt. Chem. 147, 288 (1936).
5. M. G. Stout, H. Reich and M. N. Huffman, J. Pharm. Sci. 53, 192 (1964).