Tetrahedron Letters No. 8, pp. 317-319, 1962. Pergamon Press Ltd. Printed in Great Britain.

# SYNTHESIS OF GINKGETIN

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(Received 21 March 1962)

GINKGETIN is a flavone isolated from the leaves of Ginkgo biloba by one of us (K. N.) who suggested a biflavonyl structure for it.[1] Baker et al. assigned it the structure of 7,4'-dimethoxy-5,5",7",4"-tetrahydroxybiflavonyl-(3',8") (I),[2] a bisflavone in which two 5,7,4'-trihydroxyflavone (apigenin) skeletons linked each other at 3'- and 8"-positions. The coupling positions of the two flavone units have been confirmed by the synthesis of ginkgetin di- and tetramethyl ethers, II and III.[3]

This paper deals with the total synthesis of ginkgetin by the condensation of 3'- and 8"-iodinated flavones, VII (or VI) and XIV (or X), by means of activated copper powder in the absence of solvent followed by removal of the protecting groups.

Partial demethylation of 3'-iodo-5,7,4'-trimethoxyflavone (IV)[3] with aluminium chloride in nitrobenzene gave 5-hydroxy compound (V) (m.p. 217°, 64%), which was benzoylated to give the benzoate (VII) (m.p. 236°, 95%). Meanwhile, 5,7,4'-tribenzyloxyflavone (IX) (m.p. 161°, 85%) obtained readily from 5,7,4'-trihydroxyflavone (apigenin) (VIII) by benzylation with benzyl chloride and potassium carbonate in dimethylformamide was iodinated to give 8"-iodinated compound (X) (m.p. 179°, 83%). The position of iodine

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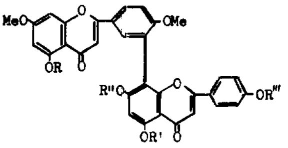
[1] K. Nakazawa, Yakugaku Zasshi 61, 174, 228 (1941).

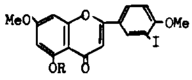
[2] W. Baker, A.C.M. Finch, W.D. Ollis and K.W. Robinson, Proc. Chem. Soc. 91 (1959).

[3] K. Nakazawa, Chem. Pharm. Bull. 6, 748 (1959).

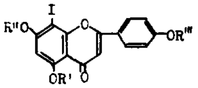
was confirmed by the fact that debenzylation of X with 10 per cent sulphuric acid in acetic acid followed by methylation gave the known 8-iodo-5,7,4'-trimethoxyflavone (XII) (m.p. 236°).[3] Partial debenzylation of X with 10 per cent phosphoric acid in acetic acid led to the formation of 5-hydroxy compound (XIII) (m.p. 202°, 72%), which was benzoylated to give the benzoate (XIV) (m.p. 205°, 93%).



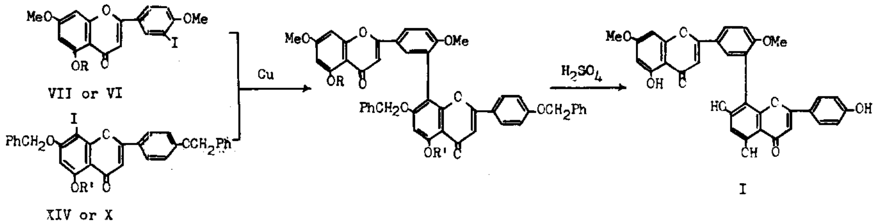
I $R=R'=R''=R'''=H$
II $R=R'=H$, $R''=R'''=Me$
III $R=R'=R''=R'''=Me$
XV $R=R'=COPh$, $R''=R'''=CH_2Ph$



IV $R=Me$
V $R=H$
VI $R=CH_2Ph$
VII $R=COPh$



VIII $R'=R''=R'''=I=H$
IX $R'=R''=R'''=Ch_2Ph$, $I=H$
X $R'=R''=R'''=CH_2Ph$
XI $R'=R''=R'''=H$
XII $R'=R''=R'''=Me$
XIII $R'=H$, $R''=R'''=CH_2Ph$
XIV $R'=COPh$, $R''=R'''=CH_2Ph$



The condensation of the two components, VII and XIV, obtained above was carried out at 225-230° for 40 min by means of activated copper powder in the absence of solvent. Chloroform extract of the resinous and dark brown colored reaction mixture was treated with 10 per cent sulphuric acid in acetic acid to hydrolyse benzyl and benzoyl groups, dissolved in a mixture of dioxane and ether and shaken with 10 per cent potassium carbonate to deposit yellow, sandy crystals of potassium salt[1] of ginkgetin, which were purified by recrystallization from the carbonate solution, decomposed with dilute sulphuric acid and the free ginkgetin (I) thus obtained was retrystallized from methyl ethyl ketone to form pale yellow, small plates melting at 336° (21%). Its acetate forms colorless needles, m.p. 259°. It was proved through elemental analysis, m.p.s.,[4] mixed m.p.s. and infrared spectra that synthetic ginkgetin and its acetate were resp. identical with materials of natural origin.

The benzoate VII can be replaced by the benzyl ether (VI) (m.p. 228°) and XIV by the tribenzyl ether (X) as components in the condensation reaction. Yield of ginkgetin varied according to the combination of the two components, the highest yield (21%) being obtained from the condensation of VII and XIV and the lowest (6%) from VI with X.

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[4] The m.p. of natural ginkgetin became higher (336°) than already reported[1] after regeneration via its acetate and recrystallization from methyl ethyl ketone.