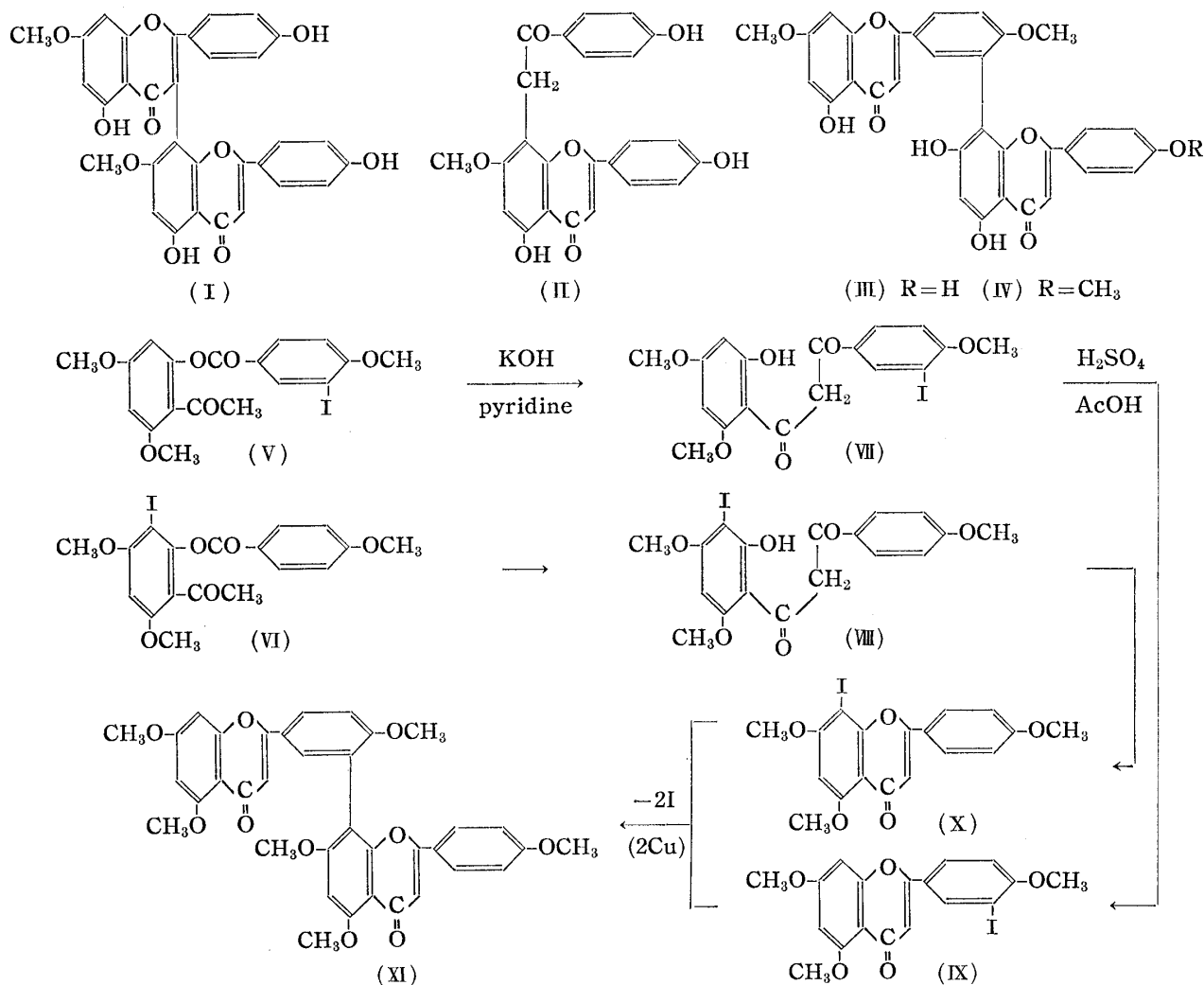


Synthesis of Ginkgetin Tetramethyl Ether

The writer gave in 1941 a formula $C_{32}H_{22}O_{10}$ for ginkgetin, a flavone compound isolated from the leaves of *Ginkgo biloba*, and suggested a structure of biflavonyl¹⁾ (I), coupling two 5,7,4'-trihydroxyflavone skeletons between 3- and 8-positions.

Later, oxoflavone (II) and its 6-substituted isomer were synthesized as permethylated ethers²⁾ which were not identical with methylated oxoflavone, a methylated product of the phenol component obtained by the alkaline hydrolysis of ginkgetin.

Quite recently, Baker³⁾ proposed for ginkgetin a new structure (III) coupling two flavone units between 3'- and 8-positions by the examination of oxidation, UV and IR absorptions, and biochemical considerations of ginkgetin, while, about the same time, Kawano also concluded the identical coupling positions of the two units by examination of oxidation of the alkaline hydrolysate of permethyl ether of sciadopitysin (a ginkgetin monomethyl ether) (IV) from the leaves of umbrella pine⁴⁾ (*Sciadopitys verticillata*).



1) K. Nakazawa : *Yakugaku Zasshi*, **61**, 174, 228(1941).

2) K. Nakazawa, S. Matsuura : *Ibid.*, **74**, 40(1954); **75**, 68, 467, 716(1955).

3) W. Baker, A. C. M. Finch, W. D. Ollis, K. W. Robinson : *Proc. Chem. Soc. (London)*, **1959**, 91.

4) N. Kawano : *Chem. & Ind. (London)*, **1959**, 368.

The writer has lately succeeded in the synthesis of methylated biflavonyl (XI), which was identical with ginkgetin tetramethyl ether. The course of the synthesis was as follows: 2-Acetyl-3,5-dimethoxyphenyl 3-iodoanisate (V) and 2-acetyl-6-iodo-3,5-dimethoxyphenyl anisate (VI) were respectively isomerized to the diketones (VII (40%), VIII (78%)) by potassium hydroxide in pyridine and then cyclized to the flavones (IX (91%), X (85%)) by sulfuric acid in acetic acid. The two iodinated flavones were finally condensed to biflavonyl (XI) by activated copper powder. In the condensation experiment, a mixture of equal moles of the iodo compounds and equal weight of copper powder to the above were heated in boiling dimethylformamide for 8 hours. To the filtrate of the reaction mixture several volumes of ethanol was added, when the sparingly soluble condensation compound (XI) separated in needles (28%), while 8,8- and 3',3'-bis compounds remained dissolved in the filtrate.

Biflavonyl compound (XI) obtained as above forms prismatic crystals (from dimethylformamide), m.p. 238°, scarcely soluble in methanol, ethanol, and dioxane. The dioxime, m.p. 252°. It was proved through elemental analysis, admixture of biflavonyls and their oximes, and infrared absorptions that the synthetic compound is identical with ginkgetin tetramethyl ether.

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On the Selenium-dehydrogenation of Cynanchogenin

A crystalline aglycone, cynanchogenin, m.p. 167°, $C_{28}H_{42}O_6$, which was isolated from the root of *Cynanchum caudatum* MAX. and gave desacylcynanchogenin ($C_{21}H_{32}O_6$, m.p. 242°) and 2,3-dimethylbutene-1-carboxylic acid¹⁾ on alkaline hydrolysis, was submitted to dehydrogenation with selenium. The aglycone (1.8 g.) was heated with selenium at 310° for 24 hours and the cooled mixture was extracted with ether. The extract was washed successively with dil. sodium hydrogen carbonate solution and water, and evaporation of ether left a neutral oily substance (200 mg.). The neutral portion of dehydrogenation product was chromatographed over neutral alumina and eluted with hexane and benzene to give two crystalline hydrocarbons.

One of them, m.p. 146~150°(A), showed ultraviolet absorption spectra ($\lambda_{\max}^{\text{cyclohexane}}$ m μ (log ϵ): 249.5 (4.50), 258 (4.85), 268 (5.02), 304 (4.33), 317 (4.32), 332 (3.37), 348 (2.88)) identical with that of the hydrocarbon first produced by the selenium-dehydrogenation of jervine and veratramine by Jacobs²⁾ and which was recently proved to be 7-ethyl-8-methyl-1,2-benzofluorene³⁾ (I). The other crystals (B), which seemed to be a mixture, gave a very similar UV curve to that of the oily hydrocarbon obtained from desisovaleryltetrahydrovogenin-A, $C_{22}H_{36}O_6$, which also gave Jacob's hydrocarbon as the main dehydrogenation product and was assured to have a hydrogenated benzofluorene skeleton.⁴⁾

- 1) The isolation and details of functional groups were reported at the 3rd Hokkaido Local Meeting of the Pharmaceutical Society of Japan, July 27, 1959.
- 2) W. A. Jacobs, L. C. Craig, G. Lavin: J. Biol. Chem., **141**, 51(1941); W. A. Jacobs, Y. Sato: *Ibid.*, **181**, 55(1949).
- 3) L. Keller, Ch. Tamm, T. Reichstein: Helv. Chim. Acta, **41**, 1633(1958).
- 4) R. E. Winkler, T. Reichstein: *Ibid.*, **38**, 721(1954).