

SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

Part XXII. Nitroflavones as Intermediates for the Synthesis of Hydroxy- and Hydroxymethoxyflavones

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Received July 25, 1947

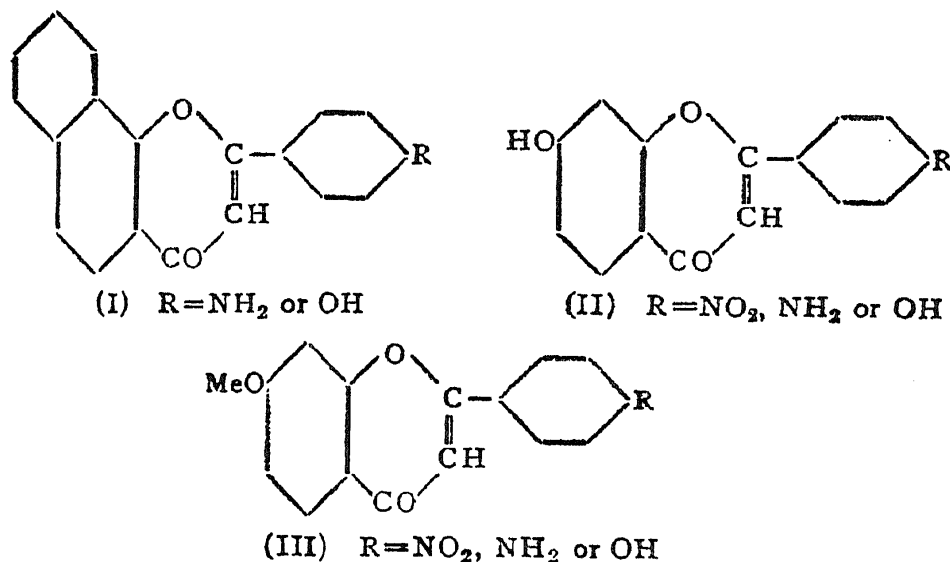
TAKING advantage of the easier removal of O-benzoyl and benzyl groups in comparison with the O-methyl group, partially methylated polyhydroxyflavones such as kæmpferide,¹ isorhamnetin,¹ myricetin,² diosmetin,³ tricetin,⁴ and rhamnazin⁵ have been prepared by using benzoyloxy or benzyloxy derivatives in the acetophenone or acid anhydride reactant, in the Robinson flavone synthesis. The observation,⁶ that by the action of aluminium chloride under specified conditions, preferential demethylation in the 5-position takes place in methylated polyhydroxyflavones, has been utilised for the synthesis of 5:8-dihydroxyflavone⁷ and several partially methylated polyhydroxyflavones, such as genkwanin,⁸ wogonin,⁹ tectochrysin¹⁰ and primetin-8-methyl ether.¹¹ Hydrobromic acid in acetic acid can also be used for the same purpose.¹² It has been found that the 3-methoxyl is also susceptible to demethylation by aluminium chloride and by hydrobromic acid in acetic acid,¹² and this has been used by Seshadri and Venkateswarlu¹³ for the synthesis of calycopterin. In connection with the work on calycopterin and rhamnazin, it was observed¹² that hydrobromic acid in acetic acid at room temperature attacked the 5-methoxyl in preference to the 3-methoxyl.

Naturally occurring colouring matters derived from resorcinol and phloroglucinol couple with diazonium salts, and Perkin¹⁴ obtained the disazo dyes. Mahal and one of us¹⁵ prepared from 6-hydroxy-flavone the 5-benzeneazo derivative, which has been reduced, diazotised and hydrolysed to the corresponding dihydroxy compound.¹⁶ While this method has obvious possibilities for the synthesis of polyhydroxyflavones and partially methylated polyhydroxyflavones, an alternative route to the intermediate amines would be through the corresponding nitroflavones. The introduction of a hydroxyl through the diazo coupling reaction has the limitation that the new group can only be located *ortho* or *para* to a hydroxyl group originally present in the 2-phenyl or the fused benzene ring of the flavone

molecule. Proceeding through a nitroflavone there will be a greater latitude regarding the position of the hydroxyl group to be introduced. The exploratory experiments described in the present paper have shown that the method may be utilised for synthesis in the flavone and *iso*-flavone series. Bogert¹⁷ nitrated α -naphthaflavone to a mixture of the 2'-, 3'- and 4'-nitroflavones, which were separated as their amines, the latter being then characterised after diazotisation as their β -naphthol dyes. He also prepared 2'-hydroxy- α -naphthaflavone from the corresponding amine, *via*. the diazo salt. Sugasawa¹⁸ prepared 5-amino-6-hydroxyflavone from the corresponding acetamido compound, but failed to hydrolyse it to the dihydric phenol. Virkar,¹⁹ in a study of the rearrangement of nitroaryl esters, prepared some nitroflavones, which were reduced to the corresponding amines. We have now synthesised 4'-hydroxy- α -naphthaflavone, 7:4'-dihydroxyflavone, 4'-hydroxy-7-methoxyflavone (*isoprato*l) and 5:4'-dihydroxy-7-methoxyflavone (*genkwanin*), by hydrolysis of the corresponding aminoflavones through the diazo salts, the amines being obtained by the reduction of the nitroflavones.

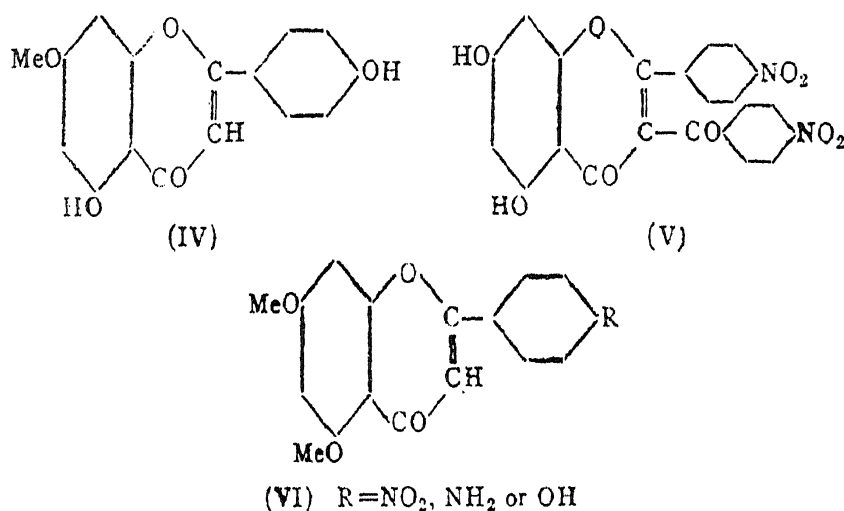
The diazo salt of 4'-amino- α -naphthaflavone (I, R = NH₂) could be hydrolysed to 4'-hydroxy- α -naphthaflavone (I, R = OH) only by boiling with 30 per cent. sulphuric acid after the complete removal of free nitrous acid.

O-Di-*p*-nitrobenzoyl-resacetophenone was rearranged by potassium carbonate and toluene²⁰ to the diketone, which on cyclisation gave 4'-nitro-7-hydroxyflavone (II, R = NO₂). It was reduced to the amine (II, R = NH₂), which on diazotisation and hydrolysis as in the previous case, gave 7:4'-dihydroxyflavone (II, R = OH). 4'-Nitro-7-methoxyflavone (III, R = NO₂), prepared by methylation of the corresponding hydroxyflavone, was reduced



to the amine (III, R = NH₂), which was diazotised and hydrolysed to 4'-hydroxy-7-methoxyflavone (III, R = OH) (*isoprato*l).

With a view to applying this method for the synthesis of genkwanin (IV), the tri-(*p*-nitrophenyl)-ester of phloracetophenone, prepared by condensing *p*-nitrobenzoyl chloride and phloracetophenone in pyridine under specific conditions, was submitted to rearrangement with potassium carbonate in toluene;²⁰ but subsequent treatment with concentrated sulphuric acid in the cold, gave 3-*p*-nitrobenzoyl-4'-nitro-5:7-dihydroxyflavone (V), which could not be hydrolysed to 4'-nitro-5:7-dihydroxyflavone. When the rearrangement was carried out with sodium ethoxide in alcohol²¹ the ester was merely hydrolysed.



The *p*-nitrobenzoyl ester of 4:6-*o*-dimethylphloracetophenone was then prepared; it could not be rearranged to the diketone by means of potassium carbonate²⁰ or atomic sodium²² in toluene, the ester remaining unaffected, but gave the diketone when treated with sodamide²³ in benzene or toluene. This on cyclicisation gave 4'-nitro-5:7-dimethoxyflavone (VI, R = NO₂), which crystallised in dimorphic forms; on reduction both gave the same 4'-amino-5:7-dimethoxyflavone (VI, R = NH₂). Diazotisation of the amine and hydrolysis gave the 5-monomethyl ether of genkwanin (VI, R = OH), which on treatment with aluminium chloride⁶ in nitrobenzene led to 4':5-dihydroxy-7-methoxyflavone (IV) (genkwanin).

The probability that puddumetin, isolated by Chakravarti and Ghosh,²⁴ from the bark of *Prunus puddum* is identical with genkwanin, has been suggested by one of us.²⁵ The identity has now been confirmed by taking a mixed melting point of puddumetin and genkwanin synthesised by us.

EXPERIMENTAL

4'-Nitro- α -naphthylflavone (I, R = NO₂)

2-Aceto-1-naphthol-*p*-nitrobenzoate, obtained by heating acetone-naphthol (10 g.) in pyridine (40 c.c.) and *p*-nitrobenzoyl-chloride (1 mol., 10 g.) for half an hour on the water-bath, crystallised from alcohol or benzene in light

yellow thick needles (16 g.), m.p. 151–52° (Found: N, 4.4. $C_{19}H_{23}O_5N$ requires N, 4.2%) (Virkar,¹⁹ m.p. 151°). The ester (4 g.) in toluene (30 c.c.) and freshly ignited potassium carbonate (12 g.) was refluxed for eight hours, with mechanical stirring, toluene filtered off, the orange red mass washed with benzene, dried and stirred into dilute acetic acid, and the diketone collected (3 g.). It crystallised from acetic acid in yellow thin long needles or from acetone in yellowish orange needles, m.p. 222° (Found: N, 4.0 $C_{19}H_{23}O_5N$ requires N, 4.2%) (Virkar,¹⁹ m.p. 222°). 4'-Nitroflavone, obtained by diluting a solution of the diketone (1 g.) in concentrated sulphuric acid (20 c.c.) after having been kept overnight, crystallised from acetic acid in long thin light yellow plates, m.p. 293° (Found: N, 4.5. $C_{19}H_{11}O_4N$, requires N, 4.4%) (Virkar,¹⁹ m.p. 293°).

4'-Amino- α -naphthaflavone (I, R = NH₂)

To a boiling solution of the nitroflavone (0.5 g.) in acetic acid (5 c.c.), iron powder (0.5 g.) was added in about one hour's time, refluxed for another half an hour, the unreacted iron filtered, the dark brown solution diluted, and the greenish yellow amine collected. It was crystallised as its hydrochloride from water containing hydrochloric acid in bunches of small orange needles (0.4 g.); when heated it discolours and melts at 250–51° (Found: N, 4.4. $C_{19}H_{14}O_2NCl$ requires N, 4.3%). The amine obtained by neutralising a solution of the hydrochloride with sodium carbonate crystallised from dilute alcohol in long thin light yellow plates, m.p. 265° (Virkar,¹⁹ m.p. 265°, non-crystalline). The yellow solutions in alcohol and in sulphuric acid exhibit a bright green fluorescence.

4'-Hydroxy- α -naphthaflavone (I, R = OH)

The amine (0.1 g.) was dissolved in water (50 c.c.) containing hydrochloric acid, cooled and diazotised by sodium nitrite (0.03 g.). After keeping at 0–5° for ten minutes, excess of nitrous acid was destroyed by urea, and the diazo solution slowly added to thirty per cent. boiling sulphuric acid (100 c.c.), when some frothing due to the evolution of nitrogen took place, and the diazo solution was almost immediately hydrolysed as shown by testing with alkaline β -naphthol. If a higher concentration of acid was used or there was free nitrous acid, only bye-products were formed. On cooling the solution, light yellow bunches of short needles separated, which were collected, washed free from acid and crystallised from alcohol and acetic acid mixture in small colourless needles (0.05 g.), m.p. 315–16° (Found: C, 78.8; H, 3.9. $C_{19}H_{12}O_3$ requires C, 79.2; H, 4.0) (Kostanecki,²⁶ m.p. 315–16°). It does not give any colour with ferric chloride, and is turned yellow with concentrated sulphuric acid, giving an almost colourless solution

with a bright green fluorescence, as described by Kostanecki²⁴ for 4'-hydroxy- α -naphthaflavone.

The *acetate*, prepared by refluxing with acetic anhydride and pyridine, crystallised from acetic acid in long thin colourless needles, m.p. 214° (Found: C, 76.8; H, 4.2. $C_{21}H_{14}O_4$ requires C, 76.4; H, 4.2) (Kostanecki,²⁶ m.p. 215°). It shows the same behaviour as the hydroxyflavone towards concentrated sulphuric acid.

2-Hydroxy-4-(p-nitro) benzyloxy-4'-nitrodibenzoylmethane

Resacetophenone-di-(*p*-nitro) benzoate, prepared as in the last case, from resacetophenone and *p*-nitrobenzoyl chloride, was obtained as an amorphous solid from benzene, alcohol or acetic acid, m.p. 151–52° (Found: N, 5.9. $C_{22}H_{14}O_9N_2$ requires N, 6.2%). 2-Hydroxy-4-(*p*-nitro) benzoyloxy-4'-nitrodibenzoylmethane (14 g.) obtained by the rearrangement of the ester (20 g.), as in the last case, crystallised from acetone in yellow plates, m.p. 225–26° (Found: N, 6.0. $C_{22}H_{14}O_9N_2$ requires N, 6.2%).

This on treatment with glacial acetic acid cyclicised, 7-*p*-nitrobenzyloxy-4'-nitroflavone thus obtained crystallised from acetic acid in bunches of colourless needles, m.p. 294–95° (Found: N, 6.3. $C_{22}H_{12}O_8N_2$ requires N, 6.4%).

4'-Nitro-7-hydroxyflavone (II, R = NO₂)

The diketone (2 g.) was dissolved in concentrated sulphuric acid (20 c.c.), left overnight, poured over chipped ice, the flavone thus obtained was collected, washed with cold alcohol and crystallised from acetic acid in light yellow, long thin plates (1.0 g.), m.p. 310–11° (Found: N, 5.1. $C_{15}H_9O_5N$ requires N, 4.9%). It gives a reddish brown colour with ferric chloride.

7: 4'-Dihydroxyflavone (II, R = OH)

7-Hydroxy-4'-aminoflavone, obtained by reduction of the nitro flavone (0.5 g.) with iron and acetic acid, as in the last case, crystallised from dilute alcohol in bunches of light yellow curved needles (0.3 g.), m.p. 338–40°, after darkening at 310° (Found: N, 5.4. $C_{15}H_{11}O_3N$ requires N, 5.5%) Its alcoholic solution exhibits a blue fluorescence, and it dissolves in concentrated sulphuric acid, giving an almost colourless solution with a strong blue fluorescence.

7: 4'-Dihydroxyflavone, obtained by diazotisation and hydrolysis of the amine (0.35 g.) with 30 per cent. boiling sulphuric acid, crystallised from alcohol in bunches of light yellow needles (0.2 g.), m.p. 315°, not depressed when admixed with a sample which had been prepared by Mahal and

Venkataraman²⁵. (Kostanecki and Osius,²⁸ m.p. 315°) (Found: C, 70·7; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%). It agrees with all its properties with those described for 7:4'-dihydroxyflavone by Kostanecki and Osius.²⁸

The *diacetate*, obtained by refluxing with acetic anhydride and pyridine, crystallised from alcohol in colourless needles, m.p. 184° (Kostanecki and Osius,²⁸ m.p. 184°) (Found: C, 67·4, H, 4·1. $C_{19}H_{14}O_6$ requires C, 67·4; H, 4·1%).

4'-Nitro-7-methoxyflavone (III, $R = NO_2$)

4'-Nitro-7-methoxyflavone, obtained by methylation of 4'-nitro-7-hydroxyflavone (1 g.), with alkali and dimethyl sulphate in the cold, crystallised from acetic acid in light yellow needles (0·85 g.), m.p. 216–17° (Found: N, 5·0. $C_{16}H_{11}NO_5$ requires N, 4·7%).

4'-Hydroxy-7-methoxyflavone (Isoprato) (III, $R = OH$)

The amine, obtained by reduction of the nitroflavone (0·7 g.) with acetic acid and iron powder, crystallised from dilute alcohol in thin light yellow needles (0·5 g.), m.p. 201–02° (Found: N, 5·5. $C_{16}H_{13}O_3N$ requires N, 5·3%). Its light yellow solution in alcohol exhibits a bluish fluorescence, and it dissolves in concentrated sulphuric acid giving an almost colourless solution with a blue fluorescence.

The amine (0·5 g.) dissolved in water (25 c.c.) containing hydrochloric acid, was diazotised and hydrolysed by adding to thirty per cent. boiling sulphuric acid in the usual manner. It crystallised from alcohol in light yellow needles (0·37 g.), m.p. 260°, not depressed by admixture with a sample which had been prepared by Mahal and Venkataraman²⁷ (Found: C, 71·8; H, 4·4. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5). The melting point of the substance in Mahal and Venkataraman's paper²⁷ should read as 260°. The alcoholic solution gives brown colour with ferric chloride, and its light yellow solution in concentrated sulphuric acid exhibits a blue fluorescence. On demethylation with hydriodic acid in acetic anhydride it gave 7:4'-dihydroxyflavone.

7:4'-Dimethoxyflavone, obtained by methylating with dimethyl sulphate in alkaline solution in the cold crystallised from alcohol in long thin colourless needles, m.p. 149–50° (Kostanecki and Osius²⁶, m.p. 149°) (Found: C, 72·5; H, 5·2. $C_{17}H_{14}O_4$ requires C, 72·3; H, 4·9%).

7-Methoxy-4'-acetoxyflavone obtained by refluxing with acetic anhydride and pyridine crystallised from alcohol in colourless needles, m.p. 155°C. (Found: C, 69·8; H, 4·6. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%).

Tri-o-(p-nitro)-benzoyl phloracetophenone

Phloracetophenone (3.4 g.) was dissolved in pyridine (40 c.c.) and *p*-nitrobenzoyl chloride (3 mole., 11.5 g.) was added in small quantities, with good shaking so that the temperature did not rise above 50°; it was then left overnight, when a yellow mass separated, which was poured on to crushed ice and hydrochloric acid. The product separated as a white amorphous solid from benzene (6 g.), m.p. 195–97° (Found: N, 6.9. $C_{29}H_{17}O_{13}N_3$ requires N, 6.8 per cent.).

3-p-Nitrobenzoyl-4'-Nitro-5:7-dihydroxyflavone (V)

The ester, on rearrangement with potassium carbonate (6 g.) and toluene, gave a cream coloured compound (4.5 g.), m.p. 272–73°, which was very insoluble in organic solvents and could not be crystallised. It is insoluble in aqueous alkali in the cold. On warming with two per cent. sodium hydroxide or by treatment with concentrated sulphuric acid in the cold, it gave 3-(*p*-nitro) benzoyl-4'-nitro-5:7-dihydroxyflavone, which crystallised from alcohol in light yellow needles, m.p. 279° (Found: N, 6.1. $C_{22}H_{12}O_9N_2$ requires N, 6.25%). Its alcoholic solution gives a violet colour with ferric chloride.

The 3-benzoyl group could not be removed; when treated with hydriodic acid in acetic anhydride, it remained unaffected and when treated with 10 per cent. alcoholic or 10 per cent. aqueous alkali, and acidified, an orange compound which did not melt was obtained.

2-p-Nitrobenzoyl-4: 6-dimethyl phloracetophenone

Phloracetophenone-4: 6-dimethyl ether was prepared by the method of Seshadri and Rao.²⁹ Its *p*-nitrobenzoate, prepared in the usual manner from the dimethyl ether of phloracetophenone (2.5 g.) and *p*-nitrobenzoyl chloride (2.5 g.) in pyridine, crystallised from alcohol in colourless needles (3 g.), m.p. 152–53° (Found: N, 4.3. $C_{17}H_{15}O_7N$ requires N, 4.1%).

2-Hydroxy-4: 6-dimethoxy-4'-nitrodibenzoylmethane

The ester (2 g.) was dissolved in benzene or toluene (30 c.c.) sodamide (2 g.) added, and refluxed for two hours. The deep red compound that separated was filtered, washed with benzene, and acidified with dilute acetic acid, the diketone collected and crystallised from acetic acid (40 c.c.) in bunches of small thin yellow needles (0.4 g.), m.p. 220–22° (Found: N, 4.2. $C_{17}H_{15}O_7N$ requires N, 4.1%).

4'-Nitro-5:7-dimethoxyflavone (VI, R = NO₂)

The flavone, obtained by treating the diketone (0.6 g.) with concentrated sulphuric acid in the cold crystallised from acetic acid in light yellow, long

thin plates (0.4 g.), m.p. 262° (Found: N, 4.3. $C_{17}H_{13}O_6N$ requires N, 4.3%). The flavone also crystallised as yellow needles, m.p. 235° (Found: N, 4.5. $C_{17}H_{13}O_6N$ requires N, 4.3%). Crystallised again from acetic acid, the first fraction had m.p. 235°, but on dilution the filtrate gave a light yellow crystalline precipitate, m.p. 262°. Both these dimorphic forms on reduction gave the same amine.

4'-Hydroxy-5:7-dimethoxyflavone (VI, R = OH)

The amine, obtained by the reduction of the nitroflavone (0.5 g.) with acetic acid and iron, crystallised from alcohol in shining yellow needles (0.30 g.), m.p. 212°. Its alcoholic solution exhibits a blue fluorescence (Found: N, 4.5. $C_{17}H_{17}O_4N$ requires N, 4.7%).

4'-Hydroxy-5:7-dimethoxyflavone, obtained by diazotisation and hydrolysis of the amine (0.3 g.) with boiling thirty per cent. sulphuric acid, crystallised from alcohol in long, light yellow needles (0.2 g.), m.p. 294–95° (Mahal and Venkataraman⁹, m.p. 298°) (Found: C, 68.2; H, 4.8. $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.7%). Its alcoholic solution exhibits a very weak blue fluorescence.

The *acetate* prepared by boiling with acetic anhydride and pyridine crystallised from alcohol in colourless needles, m.p. 220° (Mahal and Venkataraman,⁹ m.p. 220°) (Found: C, 67.4; H, 4.7. $C_{19}H_{16}O_6$ requires C, 67.1; H, 4.7%).

4:5-Dihydroxy-7-methoxyflavone (Genkwanin) (IV)

The above methyl ether (0.2 g.), aluminium chloride (0.4 g.) and nitrobenzene (4 c.c.) were heated on the water-bath for one hour, ice and hydrochloric acid added, and nitrobenzene steam distilled; the yellow residue crystallised from alcohol in bright yellow needles (0.13 g.), m.p. 284–85° not depressed when admixed with a genuine sample of puddumetin (Tseng²⁸, m.p. 285°, Mahal and Venkataraman,⁹ m.p. 285–86°) (Found: C, 67.4; H, 4.2. $C_{18}H_{12}O_5$ requires C, 67.5; H, 4.2%). It gives a brownish violet colour with ferric chloride.

The *diacetate* obtained by refluxing with acetic anhydride and pyridine crystallised from alcohol in long thin colourless needles, m.p. 197–98° (Tseng,²⁹ m.p. 196°; Mahal and Venkataraman,⁹ m.p. 197–98°) (Found: C, 65.2; H, 4.3. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%).

We are greatly indebted to Dr. D. Chakravarti of Calcutta University for a sample of puddumetin and to Mr. T. S. Gore for carrying out the microanalyses.

SUMMARY

Hydroxyflavone can be prepared from nitroflavone by reduction, diazotisation and hydrolysis. The utility of this general procedure has been shown by the synthesis of 4'-hydroxy- α -naphthaflavone, 7:4'-dihydroxyflavone, 4'-hydroxy-7-methoxyflavone and 5:4'-dihydroxy-7-methoxyflavone (genkwanin). Puddumetin, isolated from *Prunus puddum*, has been proved to be identical with genkwanin.

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