APPLICATION OF A NOVEL TRANSACYLATION REACTION FOR THE SYNTHESIS OF NATURAL FLAVONOID GLYCOSIDES*

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We felt it was appropriate to commemorate the 100th anniversary of the establishment of the Faculty of Chemistry of our University with a talk about the synthesis of flavonoid glycosides, a field which had been opened by the late *Géza Zemplén*, professor of organic chemistry for more than fourty years at this Faculty.

Flavonoid glycosides is an exceptionally versatile class of compounds regarding either the many types of sugars and aglycons which are combined or the number, and points of attachment of the sugar units.

The crucial point in the selective synthesis of these glycosides is the elaboration of a partially blocked derivative of a polyhydroxy-flavonoid, which would couple with an acetobromosugar at only one of its hydroxyls to give a single glycoside of predetermined structure.

An efficient method to realise this aim is the transacylation reaction of flavonoid benzoates. Investigating the behaviour of the partial benzoates of apigenine a few years ago we have found that under the action of silver carbonate in dry pyridine benzoate groups migrate in such a way that in the outcome always the most acidic hydroxyl of the parent polyhydroxy-flavone becomes liberated [1]. This reaction can conveniently be interpreted in terms of the increased stability of esters with less acidic hydroxyls and salts with more acidic ones.

In the past few years the transacylation method was successfully applied to prepare various partially benzoylated derivatives of apigenine, luteolin, quercetine, as well as those of two isoflavones, daidzeine and genisteine.

Now this method will be exemplified by the transformations of quercetine leading to the selective synthesis of several natural quercetine glycosides.

Due to the conjugative effects of the pyron ring the C_7-hydroxyl and in a lesser degree the C_4-hydroxyl of quercetine are more acidic than those at other positions or than simple phenol itself. For this reason benzoyl groups

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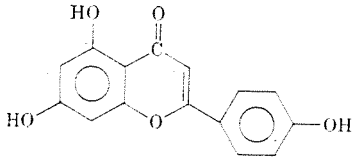
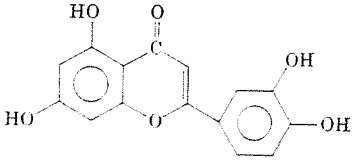
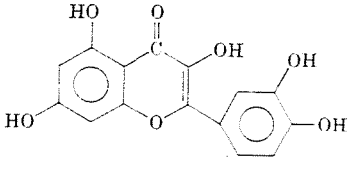
associated with these hydroxyls can easily be transferred in a base-catalysed ester exchange to hydroxyls of lower acidity. Thus, if pentabenzoyl quercetine (I) is reacted with two moles of phenol,* 3,3'5-tribenzoyl-quercetine (II) is formed in good yield. An equimolecular mixture of the dihydroxy compound (II) with the pentabenzoate (I) gives 2 moles of a monohydroxy-derivative with the free hydroxyl at C_7 (III). In this reaction the acidity difference of the C_4- and C_7-hydroxyls is operative. Coupling of (III) with acetobromoglucose and saponification accomplished the first synthesis of the long-known quercimeritrin [2] a constituent of *Gossipium harbaceum* [3].



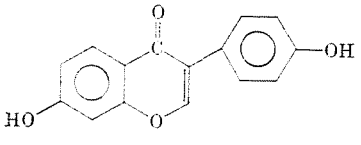
Apigenine



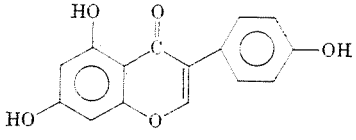
Luteolin



Quercetine



Daidzeine



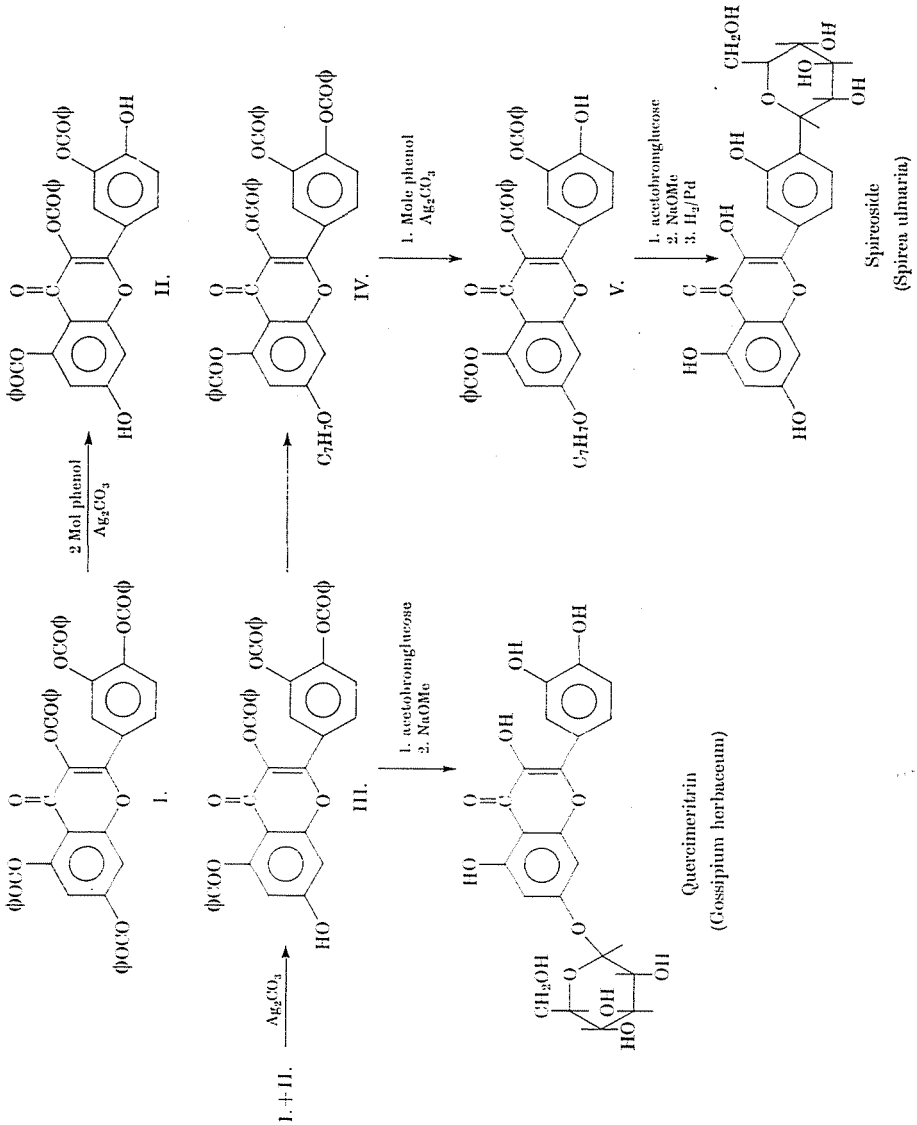
Genisteine

By benzylation and repeated transacylation with one mole of phenol compound (IV) can easily be transformed to a key intermediate (V) which is suitable for the synthesis of 4'-substituted quercetine derivatives.

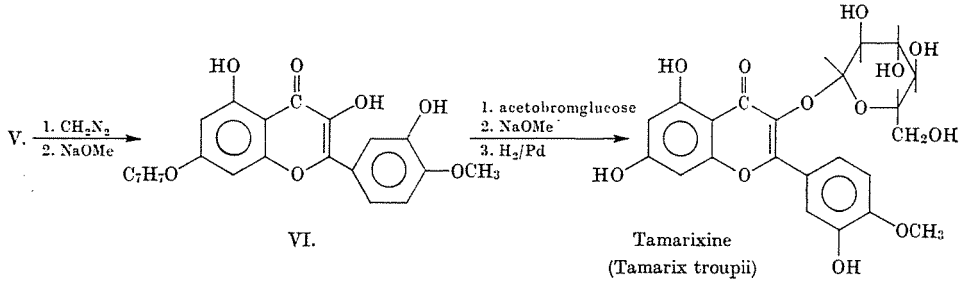
Coupling of this 4'-monohydroxy aglycon (V) with acetobromoglucose gave after elimination of the blocking groups quercetine-4'-glucoside (spiraeoside) [4], which was first isolated from *Spirea ulmaria* [5].

Methylation of (V) with diazomethane gave a compound which served after saponification as aglycon (VI) for the synthesis of tamarixine [6] the

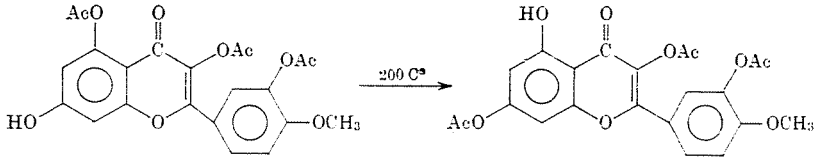
* Reactions were invariably carried out in pyridine at room temperature in the presence of a large excess of silver carbonate.


2 Mol phenol
Ag_2CO_3
1. Mole phenol
Ag_2CO_3
1. acetobromglucose
2. NaOMe
1. acetobromglucose
2. NaOMe
3. H_2/Pd
Ag_2CO_3
Quercimeritrin
(Gossipium herbaceum)
Spiroside
(Spiraea ulmaria)

3-glucoside of 4'-methyl-quercetine (tamarixetine). This glucoside was first isolated from an Indian tamariscus species [7], but its structure was later contested by American workers [8]. Now we proved the correctness of the first structural assignment.

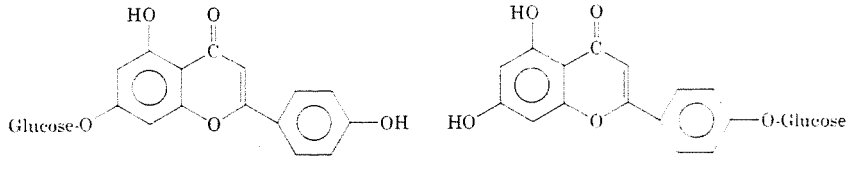


An interesting counterpart of the base catalysed transacylation was found in the thermolysis of (VII) leading to (VIII). This migration is catalysed by glass surface and results in the liberation of the hydrogen bonded C_5-hydroxyl.



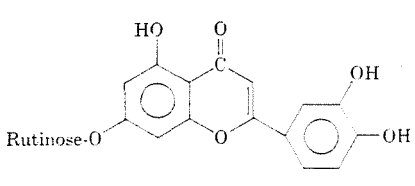
VII. VIII.

The example of quercetine illustrates well the usefulness of this approach, which has by now been applied to the synthesis of cosmosiin (apigenin-7-glucoside) (1) apigenin-4'-glucoside (9) and luteolin-7-rutinoside (10).



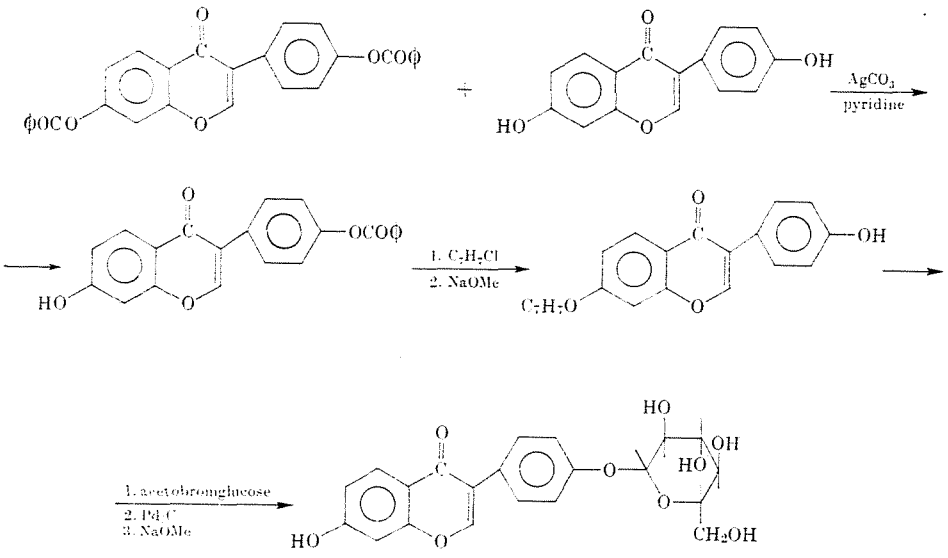
Cosmosiin
(Cosmos bipinnatus)

Apigenin-4'-glucoside
(Dhalia variabilis)



Luteolin-7-rutinosid (Scolymosid)
(Cynara scolymus)

The same principle can also be applied to isoflavones. Earlier this was demonstrated on the example of genisteine benzoates (11) and now the synthesis of daidzein-4'-glucoside by the transacylation method is presented (see formulae).



Daidzein-4 -glucoside
(Phaseolus dureus Roxb.)

Summary

A selective transacylation of flavonoid-benzoates and its utilisation for the selective synthesis of flavonoid glycosides in described.

References

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