THE ISOFLAVONOIDS OF DALBERGIA SISSOO

THE SYNTHESIS OF 7-METHYL-TECTORIGENIN*

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(Received November 7, 1963)

SESHADRI *et al.* [1] reported recently that from the extract of the flowers of Dalbergia sissoo they succeeded in isolating, besides the already known isoflavonoids biochanin A (5,7-dihydroxy-4'-methoxy-isoflavone) and tectorigenin (5,7,4'-trihydroxy-6-methoxy-isoflavone), an additional compound. According to their investigations, this proved to be a new isoflavonoid, 7-methyl-tectorigenin (5,4'-dihydroxy-6,7-dimethoxy-isoflavone).

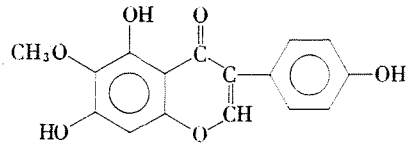
The present paper deals with the synthesis of this new isoflavone, as well as with the extension of our potassium-ethoxide induced ring-isomerization method, made possible by our investigation connected with the same synthesis.

The synthesis of this new natural product — 7-methyl-tectorigenin — is covered by the general method concerning the preparation of 5,7-dihydroxy--6-methoxy-isoflavones and their derivatives. This group comprises the following natural products:

Tectorigenin (I) 5,7,4'-trihydroxy-6-methoxy isoflavone;
7-Methyl tectorigenin (II) 5,4'-dihydroxy-6,7-dimethoxy-isoflavone;
Irigenin (III) 5,7,3'-trihydroxy-6,4',5'-trimethoxy isoflavone;
Caviunin (IV) 5,7-dihydroxy-6,2',4',5'-tetramethoxy isoflavone;
Podospicatin (V) 5,7,2'-trihydroxy-6,5'-dimethoxy-isoflavone.

An unambiguous and for preparative work suitable synthesis of this group of isoflavonoids was elaborated by FARKAS and VÁRADY [5]. The starting point of these investigations were some facts known since the beginning of this century, according to which flavonoids and isoflavonoids are subject to radical structural changes in alkaline media. On this basis some decomposition experiments were carried out on isoflavones by MAHESH, NARASIMHACHARI and SESHADRI [2, 3] which led to the following valuable conclusions. Isoflavones substituted in positions 5, 7 and 8 on treatment with alcoholic potassium hydroxide only partially underwent decomposition to the expected

* Prize award for Competition given by the Budapest Technical University.



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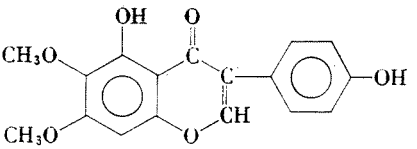

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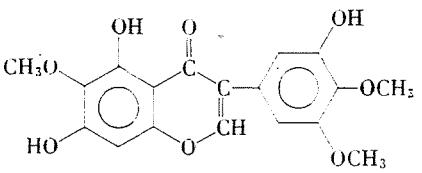

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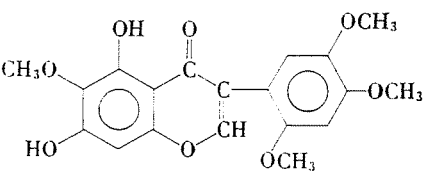

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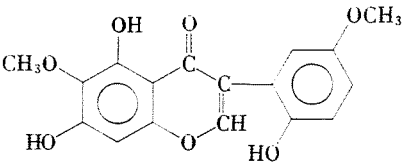

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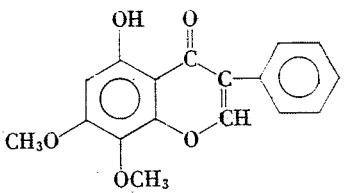

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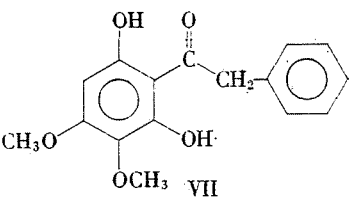

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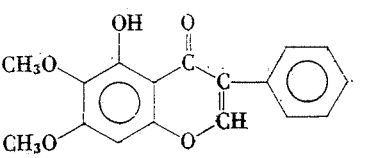


VIII

o-hydroxy-deoxybenzoines, the other part furnished a new isoflavone, namely an isomer of the parent compound substituted in positions 5,6 and 7.

Above reaction is a first example of ring-isomerization in alkaline media of flavonoids and isoflavonoids. The obvious conclusion from the result of these experiments was to synthetise some natural isoflavones substituted

into positions 5, 6 and 7 via their more readily available isomers substituted in positions 5, 7 and 8.

Considering that the alkaline decomposition of isoflavonoids can not always be stopped at an intermediate deoxybenzoin stage, further, that free hydroxyls may have some importance in promoting or delaying these transformations, FARKAS and VÁRADY [4] investigated the decomposition of isotectorigenin, blocked by methylation in positions 7 and 4'. When — except for a milder effect — decomposition of this compound was attempted using potassium ethoxide, the product of this reaction was identical in every respect with 7,4'-dimethyl tectorigenin, thus proving unambiguously, that — if only the 5-hydroxyl is free — base-catalysed ring-isomerization is effected by this reagent.

This observation enabled FARKAS and VÁRADY to carry out the synthesis of tectorigenin [5], irigenin [6] and caviunin [7] on a preparative scale.

The synthesis of above mentioned three natural isoflavones is now completed by that of the recently discovered 7-methyl tectorigenin.

This compound was characterised by SESHADRI *et al.* as a substance crystallizing in pale yellow needles or thin plates of m. p. 227—228°. Its acetate was prepared and its ultraviolet spectrum compared with those of other isoflavones. Finally, with partial methylation of natural tectorigenin proved this as the new compound and established its structure as 7-methyl-tectorigenin.

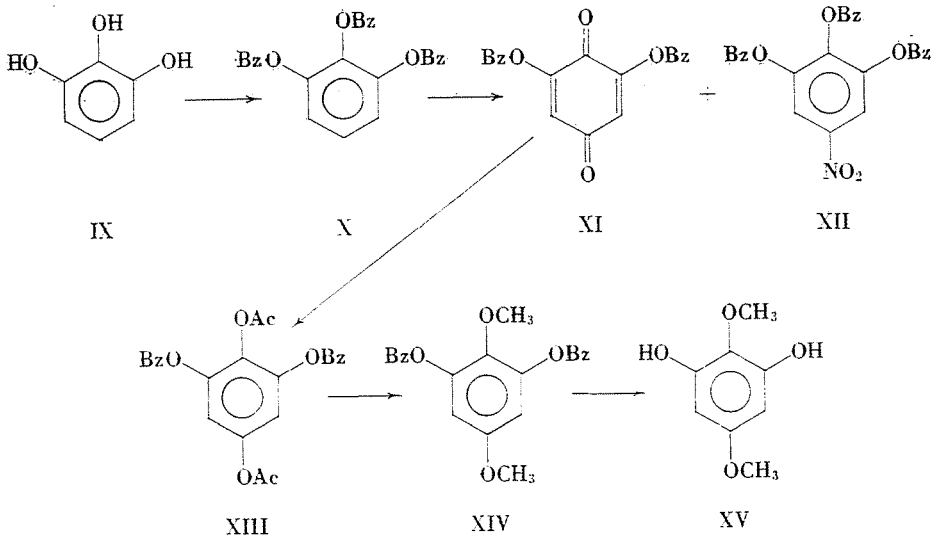
Present synthesis of 7-methyl tectorigenin was realised as follows.

The key intermediates of our synthesis were 1,3-dihydroxy-2,5-dimethoxy-benzene and 4-hydroxybenzyl cyanide.

1,3-Dihydroxy-2,5-dimethoxy benzene was prepared according to BAKER et al. [8] (see the following scheme): benzylation of pyrogallol was accomplished by the Baxter [9] method.

Benzylation of pyrogallol (IX) with benzyl chloride in dry acetone for 24 hours at a reflux temperature, in the presence of anhydrous potassium carbonate and sodium iodide gave tribenzyl pyrogallol (X), a 98% yield. After recrystallization from ethanol it was oxidized with nitric acid-acetic acid mixture. First 5-nitro-1,2,3-tribenzyloxy benzene (XII) formed as a side reaction precipitate, later a visibly deeper yellow substance, the 2,6-dibenzyloxy-benzochinon (XI). The two compounds were separated, based on their somewhat different solubility in acetone. XI was reduced with small portions of zinc dust in boiling acetic anhydride in the presence of fused sodium acetate. On pouring onto water 1,4-diacetoxy-2,6-dibenzyloxybenzene (XIII) separated. After recrystallization from acetone it was methylated in alkaline solution with dimethyl sulphate to yield 1,4-dimethoxy-2,6-dibenzyloxy benzene (XIV). Hydrogenation of an ethanolic solution of XIV in the presence of palladium on charcoal gave our phenol component, 1,3-dihydroxy-2,5-dimethoxy-benzene (XV).

Our basic nitrile component, 4-hydroxy-benzyl cyanide was prepared by PSCHOR et al. [10] from benzyl cyanide via nitration, reduction, diazotation and hydrolysis of diazonium salt.



In our laboratory the transformation of aromatic aldehydes by azlacton synthesis to the homologous benzyl cyanides (introduced by KROPP and DECKER [11]) was improved and adapted so as to furnish the necessary hydroxy- or benzyloxy-benzyl cyanides in a high yield.

The essence of KROPP and DECKER's procedure is the condensation of the appropriate aldehyde with hyppuric acid to the corresponding azlactone, the latter hydrolysed with alkali to a phenyl-pyruvic acid derivative. The by-product benzoic acid is separated and the phenyl-pyruvic acid transformed to its oxime, which on treatment with hot acetic anhydride gives the desired nitrile. The above mentioned authors separated the benzoic acid from the phenyl-pyruvic acid derivative by using a cumbersome and lengthy steam-distillation. This was later modified by HAWORTH, PERKIN and RANKIN [12] so that alkaline solution of the salt mixture, resulting from the hydrolysis of the azlactone was saturated with sulphur dioxide gas and the benzoic acid was filtered off the solution of the bisulphite compound of the phenyl-pyruvic acid. After acidification and boiling the ketonic acid-bisulphit decomposes, the sulphur dioxide is expelled from the solution and phenyl-pyruvic acid is obtained in the pure state. This method is made most inconvenient both by the long time required for sulphur dioxide inlet and decomposition of the complex, as well as by the unpleasant and deleterious properties of the sulphur dioxide itself.

Substituting benzyloxy benzaldehydes for hydroxy benzaldehydes, further: alkaline separation for sulphur dioxide treatment it became possible to extend this — otherwise efficient — synthesis also to the preparation of hydroxy- and benzyloxy-benzylcyanides.

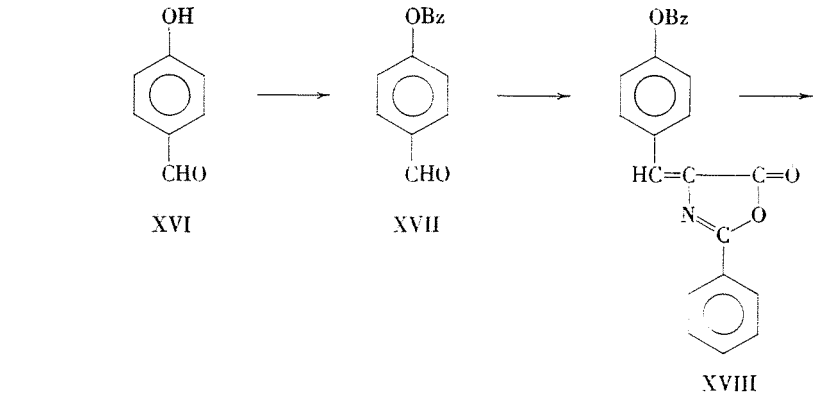
This alkaline separation essentially comprises the reaction of the mixture of phenyl-pyruvic acid and benzoic acid with hydroxyl amine, and subsequently with hot acetic anhydride, and the resulting mixture is only separated at this point by pouring onto aqueous alkali. The nitrile can be simply filtered off the aqueous solution of alkali benzoate or (if it is an oil) extracted with ether.

As in the subsequent step our intention was to use hydroxy nitrile in a Hoesch-reaction, it was not necessary to carry out debenzylation in a separate operation, though for the sake of completeness a sample of the benzyloxy nitrile had been catalytically debenzylated in a quantitive yield to the corresponding hydroxy-nitrile.

Consequently our need concerning the second key-intermediate has been modified; instead of preparing 4-hydroxy-benzyl cyanide we terminated the synthesis sequence at the 4-benzyloxy-benzyl cyanide stage, as follows:

In the possession of the two key-intermediates, i.e. 1,3-dihydroxy-2,5-dimethoxy benzene (XV) and 4-benzyloxy-benzyl cyanide (XXII) we were able to accomplish the synthesis of 7-methyl tectorigenin along the following sequence:

1,3-Dihydroxy-2,5-dimethoxy benzene (XV) was reacted with 4-benzyloxy-benzyl cyanide (XXII) in dry ether in the presence of fused zinc chloride and dry hydrogen chloride gas. The resulting 2,4-dihydroxy-3,6-dimethoxy-phenyl-(4-hydroxy-benzyl-) ketone (XXIII) was formylated with freshly distilled ethyl orthoformate in pyridine, in the presence of piperidine, followed by acidification with hydrochloric acid, effecting ring closure to 7,4'-dihydroxy-5,8-dimethoxy isoflavone (XXIV). Partial methylation of the latter was successfully carried out by treatment with dimethyl sulphate in dry boiling acetone for 20 hours, in the presence of sodium hydrogen carbonate and furnished 4'-hydroxy-5,7,8-trimethoxy isoflavone (XXV). Partial demethylation with aluminium chloride in nitrobenzene gave 5,4'-dihydroxy-7,8-dimethoxy isoflavone (7-methyl-isotectorigenin, XXVI). The success of the partial demethylation depended greatly on temperature. Demethylating for 90 minutes at the usual 105°, the starting material was recovered unchanged; at 118—120° a gelous reaction-mixture was obtained, indicating the predominance of excessively demethylated products. The desired 7-methyl-isotectorigenin was only available if the reaction was conducted at 112—113°. The latter compound can be prepared alternatively by demethylating first 7,4'-dihydroxy-5,8-dimethoxy isoflavone (XXIV) in the usual manner with aluminium chloride at 105° to 5,7,4'-trihydroxy-8-methoxy isoflavone (XXVII), followed by partial methylation of the latter to XXVI.



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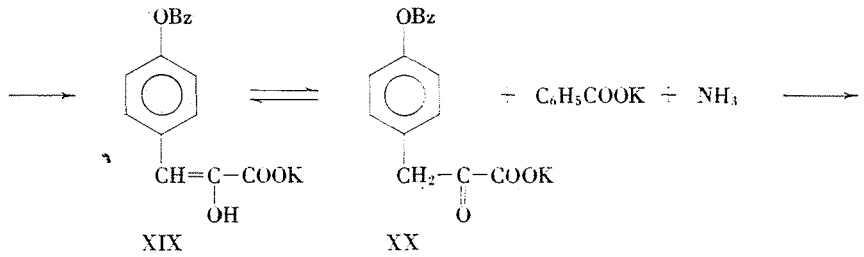
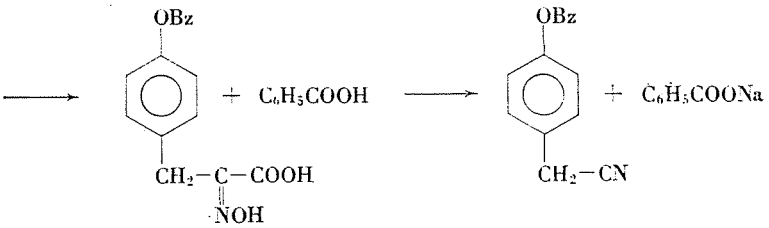


XIX XX

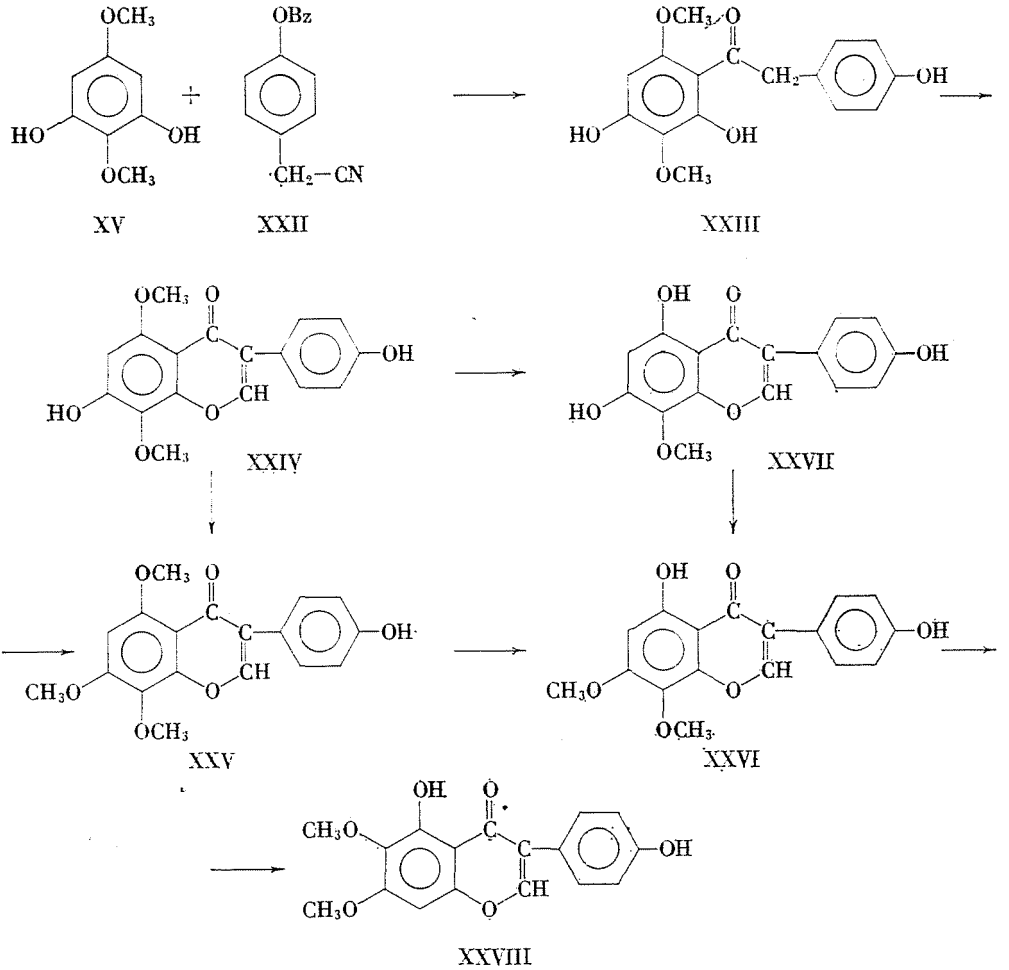


XXI XXII

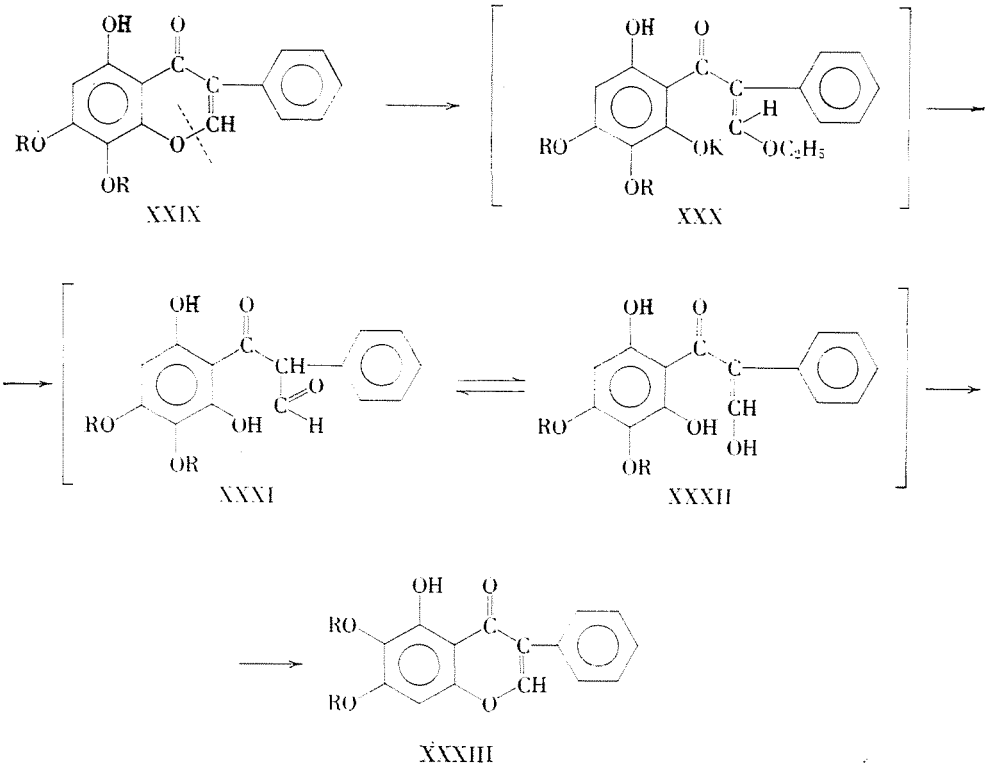
At a last stage our synthesis was concluded with potassium ethoxide catalysed isomerization in order to change the substitution of our isoflavone from 5,7,8,4' to 5,6,7,4'.

Omitting here detailed theoretical considerations, the course of base-catalysed ring-isomerization of isoflavones can be summarised as follows: the γ-pyron ring of isoflavones is split by the nucleophilic attack of the ethoxide ion to yield the potassium salt of an enol ether, that has not yet been isolated. On acidification in aqueous solution hydrolysis of the latter takes place and a tautomeric mixture of β-keton aldehyde —α-hydroxy-methylene keton (XXXI, XXXII) with the predominant participation of

the enolic form is formed. If the parent isoflavone had a free hydroxyl in position 5, the postulated intermediate (XXXII) may undergo rotation around its free axis, followed by ring closure with the more reactive hydroxyl on C—6, accompanied by proton migration and elimination of water resulting in an isoflavone with 5,6,7-substitution pattern (XXXIII).

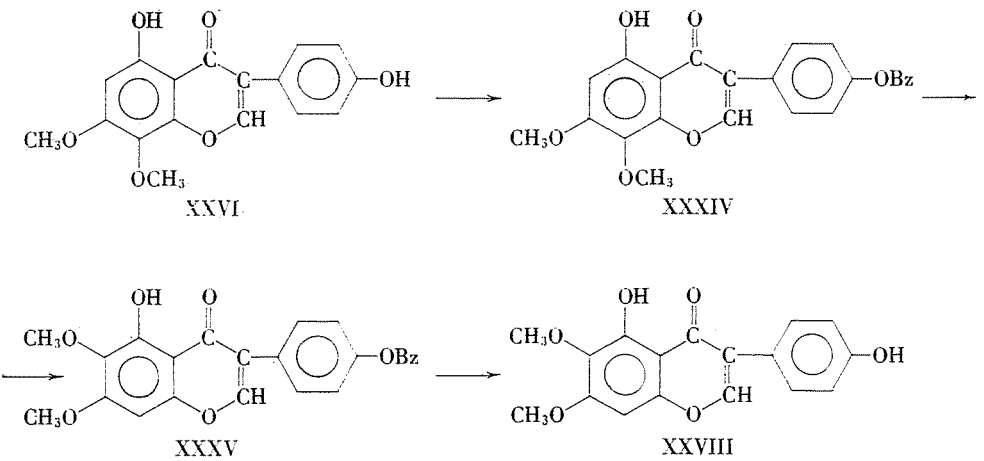


According to our previous investigations, this isomerization is only feasible if there are no free hydroxyls on the isoflavone skeleton but in position 5. Thus, in the case of isotectorigenin, where an abundance of electrons is induced in the γ-pyron ring by free hydroxyls in positions 7 and 4', no change was observable when boiled with 2% potassium ethoxide of the usual 10 minutes and not even on treatment with a 5% solution for 30 minutes. Isomerization of 4'-methyl isotectorigenin resulted in a mixed product. For



this reason it seemed necessary to block interfering hydroxyls with easily removable benzyl groups.

In the present synthesis the following reaction sequence was accomplished:



Benzylation was carried out with benzyl chloride in boiling acetone in the presence of potassium carbonate and sodium iodide. 7-Methyl-4'-benzyl isotectorigenin (XXXIV) was boiled for 12 minutes with 2% potassium ethoxide to yield 7-methyl-4'-benzyl tectorigenin (XXXV), that was debenzylated to 7-methyl tectorigenin (XXVIII) by hydrogenation in the presence of palladium on charcoal.

By this step the synthesis of this recently discovered natural isoflavone was accomplished.

As mentioned above, ring-isomerization could not have been successfully carried out with isoflavones containing free hydroxyls (except that in position 5). Some modification of this statement became necessary in connection with experiments on 7-methyl isotectorigenin (XXVI.) This compound viz., if subjected to the usual conditions of isomerization with potassium ethoxide gave a product that was in every respect identical with 7-methyl tectorigenin (XXVIII), i.e. isomerization took place.

Besides the synthesis of 7-methyl tectorigenin, this work enabled us to extend the scope of potassium ethoxide catalysed isomerization to cover compounds bearing more than one hydroxyl in certain positions. This observation, if completed by further experiments, may have great importance for investigating reaction mechanism, not taking into account the simplification of syntheses.

Summary

Synthesis of the recently isolated 7-methyl tectorigenin was accomplished by potassium ethoxide catalysed isomerization of 7-methyl isotectorigenin. The synthetic product was in every respect identical with the natural product.

By this synthesis potassium ethoxide catalysed isomerization was extended to isoflavones having a free hydroxyl group in a certain position (besides that in position 5).

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