Isomerisation In Isoflavones

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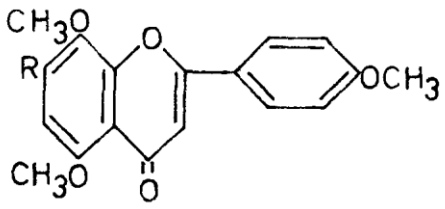
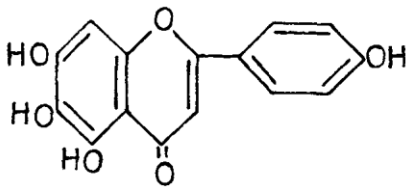
In the synthesis of most flavones and isoflavones, demethylation is an essential step and hydriodic acid is the reagent most commonly used. During hydriodic acid demethylation rearrangement of a 5, 7, 8 to 5, 6, 7- trihydroxy flavone was observed by Wessely and Moser, who obtained 5, 6, 7, 4'-tetra- hydroxy flavone (LXV) (scutellarein) from 7-hydroxy-5, 8, 4'-trimethoxy flavone (LXIV; R = OH). The view was later confirmed by Wessely and Kallab who found that contrary to the result of Hattori, 5, 7, 8, 4' -tetramethoxy flavone (LXIV; R = OMe) on treatment with hydriodic acid suffers isomeric change to scutellarein (LXV).



LXIV

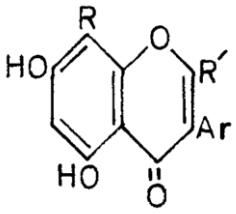


LXV

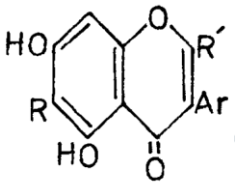
This important type of rearrangement of a 5, 8- to 5, 6-orientation during demethylation under the influence of hydriodic or hydrobromie acids is known as Wessely-Moser rearrangement and was for the first time observed in flavones. The rearrangement is not only confined to flavones but is exemplified by most of the compounds related to flavones e.g. flavonols, flavanones, chromones, chromonols, xanthones and isoflavones.

The rearrangement of 5, 8- to 5, 6-dihydroxy flavones and chromones under the corri.itions of demethylation with hydrobromic or hydriodic acids is well established and is due to the hydrolytic opening of the pyrone ring and closure in the alternative direction involving the hyiroxyl group initially in position -5. Baker et al. observed that 5, 7, 8-trihydroxy-2- methyl isoflavone (LXVI; R = OH, R' = Me, Ar = Ph) when boiled for eight hours in acetic acid,

containing hydrobromic acid, gave the corresponding 5, 6, 7-isomer (LXVII; R = OH, R' = Me, Ar = Ph). Similarly demethylation of 5, 7-dihydroxy-8, 3', 4', 5'-tetramethoxy iso-flavone (LXVI ; R = OMe, R' = H, Ar = 3, 4, 5-trimethoxy phenyl) gave irigenol, 5, 6, 7, 3, 4 ,5-tri-hexahydroxy isoflavone (LXVII; R = OH, R' = H, Ar = 3, 4, 5-tri-hydroxy phenyl). The conditions of the reaction are the deciding factor in controlling whether or not the rearrangement occurs. Thus 5, 7, 8-trimethoxy iso-flavone and its 2-methyl derivative, methyl genistein and methyl isogenistein have been demethylated with hydriodic acid without change of

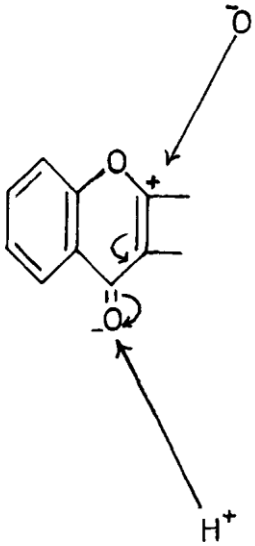


LXVI

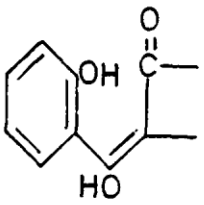


LXVII

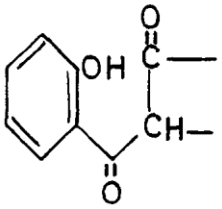
orientation. Mukerjee et al. have advanced an explanation as to why flavonol, chromonol, and iso-flavones do not undergo isomerisation under the usual conditions of demethylation. According to them the electrophilic activity of the 2-position is consi-dered to be mainly responsible for this reaction and the ring opens out to form a diketone or its equivalent. The hydroxyl group in the 8-position may have some effect in encouraging the ring fission but does not seem to be absolutely essential since this iso-meric charge is found to take place even in 6- and 8-niethyl compounds. But the presence of substituents hydroxyl (methoxyl) and phenyl in the 3-position is of importance. They seem to inhibit ring opening and this is attributed to their capacity to reduce the electrophilic activity of the 2-position by an electromeric mechanism.



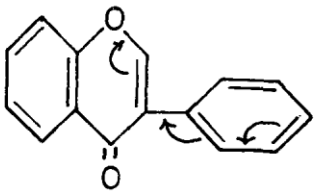
LXVIII



LXIX



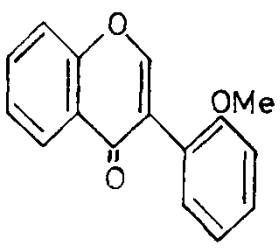
LXX



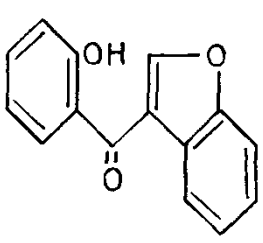
LXXI

More recently Wheeler et al. and Baker et al. have shown that under drastic conditions flavonols, chromonols and isoflavones also can be made to undergo the isomeric change. Mukerjee and Seshadri hold that the explanation advanced by Mukerjee et al. is still valid because under ordinary eoraiitions, the change does not take place and hence resistance to ring fission is definite though not absolute. But Whalley's report of isomerisation of methyl isogenistein by boiling with "stabilised" hydriodic acid only for forty five minutes and our observations for methyl isogenistein and 5, 7-dimethoxy- 8-methyl isoflavone undergoing isomerisation under normal conditions as prescribed by Seshadri et al. are not in agreement with the explanation of Mukerjee. et al.

The demethylati on of 2'-methoxy isoflavones (LXXII) by acidic reagents leads to extensive resini fication and it is suggested that this is due to their transformation into acid-sensitive 3-aroylbenzfurans (3-aroylcommarones) (LXXIII).

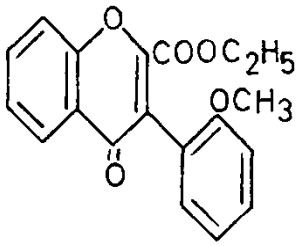


LXXII

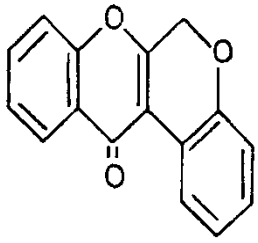


LXXIII

Similarly action of hydrobromic and acetic acids on 2-carbethoxy-2'-methoxy isoflavone (LXXIV) is reported to cause hydrolysis of the ester group and lactonisation to (LXXV).

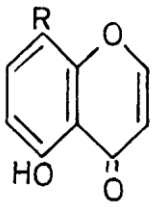


LXXIV

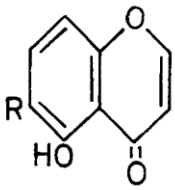


LXXV

The reverse change i.e. the rearrangement of compounds of type (LXXVII) to those of type (LXXVI) has not been previously reported in any series of such compounds with the exception of only one example in chromone series.

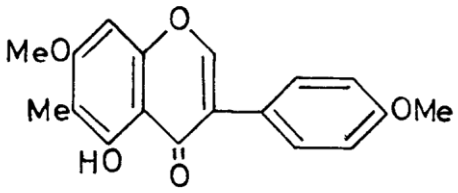


LXXVI

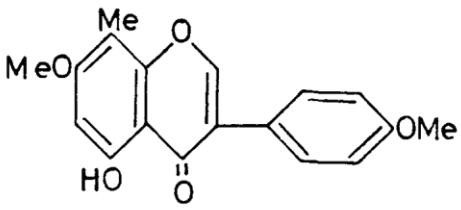


LXXVII

The reverse type of change has now for the first time been reported in isoflavone series, when 5-hydroxy- 7, 4'-dimethoxy-6-methyl isoflavone (LXXVIII) on deme-thylation with hydriodic acid furnished two distinct products isolated after reuBthylation i.e. (a) 5-hy-droxy -7, 4' -dime thoxy -6-methyl isoflavone (LXXVIII) and (b) 5-hyiroxy-7, 4'-dimethoxy-8-methyl isoflavone (LXXIX). This suggests that these rearrangements, occur under equilibration conditions and the relative proportions of the two isomers depend upon their relative thermodynamic stabilities.



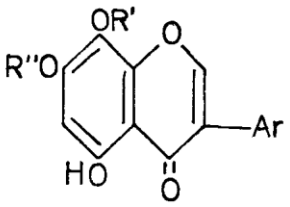
LXXVIII



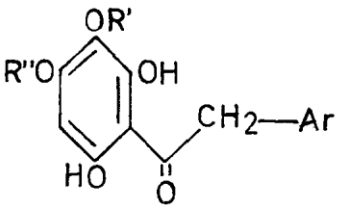
LXXIX

Whalley has observed that in case of 5, 7, 2- or 5, 7, 4-trimethoxy-8-methyl isoflavones demethylation with aluminium chloride in dry benzene yields a mixture of products having 8- and 6- C-methyl orientations. Wheeler et al. have suggested that as no rearrangement has yet been observed during demethylation by aluminium chloride, the production of 6-isomer by the reagent might be due to the direct migration of methyl group rather than to ring opening followed by cyclisation to and alternate position.

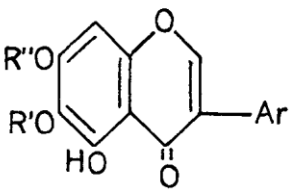
In all the above discussions isomeric changes took place in acid media. Alkaline solution could not be used because decomposition sets in. A special case was observed when the isomeric change took place to some extent in alkaline medium. It was observed that 5-hydroxy-7, 8-dimethoxy isoflavone (LXXX; R' = R" = Me = Ar = Ph) undergoes fission with 8% alcoholic alkali to give the corresponding deoxy-benzoin (LXXXI; R' = R" = Me, Ar = Ph) and a small quantity of the isomeric isoflavone (LXXXII; R' = R" Me. Ar = Ph).



LXXX



LXXXI



LXXXII

This constitutes the first example of isomeric change of isoflavone in alkaline meditim.

Later on, Mahesh and Seshadri and Dhar and Seshadri showed that 5-hydroxy-7, 8-dimethoxy iso-flavone (LXXX; R' = R" = Me, Ar = Ph) may be converted into the isomeric 5-hydroxy-6, 7-dimethoxy Isoflavone (LXXXII; R' = R" = Me, Ar = Ph) by treatment with 2% alcoholic potash. This method was found useful as the former could be prepared easily. Recently Dhar and Seshadri have applied this method for the preparation of 5, 6-dihydroxy-

7-methoxy (LXXXII; R' = H, R" = Me, Ar = Ph), 6-benzyloxy-5-hydroxy-7-methoxy- (LXXXII; R' = CH_2. Ph, R" = Me, Ar = Ph), 6,4'-dihenzyloxy-5-hydroxy- 7-mthoxy (LXXXII; R' = CH2. Ph, R" = Me, Ar = p-Ph.CH_3O-C_6H_4) and 5,7-dihyiroxy-6-methoxy- (LXXXII; R' = Me, R" = H, Ar = Ph) isoflavones. However, they could not synthesisetectoregenin (LXXXII; R' = Me, R" = H, Ar =p-HO.C_6H_4) by this method. They have reported better yields when the isomerisation was bourght about in the atmosphere of hydrogen.

Very recently Farkas Varady have also been suecessful in bringing about the isomerisation of isoflavones from 5, 7, 8-orientation of substituents to the corresponding 5, 6, 7-isomers in alkaline medium. They have used 2% potassium ethoxide [prepared by dissolving metallic potassium (2 g.) in absolute ethanol (100ml.)] for studying the isomerisation. A synthesis of tectorigenin and its 7, 4'-dimethyl ether has now been achieved by the potassium ethoxide isomerisation of 7, 4'-dibenzyl- and 7, 4'-dimethyl ethers of 5, 7, 4'-trihydroxy-8-methoxy isoflavone (LXXX; R' = Me, R" = H, Ar = p-OH•C_6H_4). Farkas and Varady have also been successful in synthesising irigenin (LXXXII; R' = Me, R" = H, Ar = 3- hydroxy-4,5-dimethoxy phenyl) and caviunin (LXXXII; R' = Me, R" = H, Ar = 2, 4, 5-trimethoxy phenyl).

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