summary

S U M M A R Y

Isoflavones belong to the general class of the compounds known as benzo-γ-pyrones. They widely occur in nature in the form of glycones as well as glycosides. Isoflavones are exhibiting various physiological activities, as estrogenic, insecticidal, pesticidal and antifungal activity.

The present work deals with the synthesis of furo isoflavones, pyrano isoflavones and benzo furo isoflavones with different substituents on the furan and pyran ring.

Chapter - I

Synthesis of Furoisoflavones

Section - I : Allylation of isoflavones

7-Hydroxyisoflavone was condensed with allylbromide to furnish 7-allyloxy isoflavone which was further subjected to Claisen rearrangement by refluxing with N,N-dimethylaniline to obtain 7-hydroxy-8-allyl isoflavone. This on treatment with H_2SO_4 (80%) furnished cyclized product 2,3-dihydro-2-methyl-6-phenyl furo (2,3-h)-1-benzopyran-[7H]-one. Dehydrogenation of which was carried out by refluxing with Pd/C in diphenyl ether solvent.

Ozonolysis of 7-hydroxy-8-allylisoflavone was carried

out to obtain 7-hydroxy-8-(2-oxoethyl) isoflavone which was cyclized by treating with polyphosphoric acid to 6-phenylfuro (2,3-h)-1-benzopyran-[7H]-one.

Claisen rearrangements of 7-allyloxy-8-bromo, 7-allyloxy-8-iodo isoflavone gave 7-hydroxy-8-allylisoflavone while 7-allyloxy-6,8-dibromo isoflavone gave 8-allyl-6-bromo-7-hydroxy isoflavone.

Section - II Cinnamylation of isoflavones

7-Cinnamyloxy isoflavone was obtained by condensing 7-hydroxyisoflavone with cinnamyl chloride. It was subjected to Claisen rearrangement by refluxing with N,N-dimethyl-aniline. Two products were obtained 8-(1-phenyl-2-propenyl) 7-hydroxy isoflavone which was different from 8-(1-phenyl-1-propenyl)-7-hydroxy isoflavone reported by Jain and coworkers. 2,6-Diphenyl-3-methyl dihydrofuro (2,3-h) benzopyran-(7H)-one was also Dehydrogenation of the cyclized product was carried out by treating it with Pd/C. Position of double bond in the side chain was confirmed by subjecting it to ozonolysis and cyclization with PPA to obtain 3,6-diphenyl furo (2,3-h)benzopyran-(7H)-one. Stereochemistry of dihydrofuro isoflavones was established by studying NOE difference spectra and also by C^{13}nmr spectra.

Further, cyclization of 8-(1-phenyl-2-propenyl)-7-hydroxy isoflavone was carried out by refluxing with the mixture of acetic acid and hydrobromic acid. Isomeric product 3,6-diphenyl-2-methyl-2,3-dihydro furo (2,3-h) benzopyran-(7H)-one was obtained. Dehydrogenation was carried out treating with Pd/C in diphenyl ether.

Similarly, 7-Cinnamyloxy-8-methyl isoflavone, 7-cinnamyloxy-2-methyl isoflavone were subjected for Claisen rearrangement to obtain 2,7-dimethyl-3,6-diphenyl furo (3,2-g)benzopyran-(5H)-one, 2,5-dimethyl 3,6-diphenyl furo (2,3-h)benzopyran-(7H)-one and 3,5-dimethyl-2,6-diphenyl 2,3-dihydro furo (2,3-h)benzopyran-(7H)-one as the final product.

C-cinnamylation of 2,4-dihydroxy phenylbenzyl ketone was carried out by treating it with cinnamyl alcohol and formic acid solution. It furnished 2,4-dihydroxy-5-cinnamyl phenylbenzyl ketone. It was cyclized to 7-hydroxy-6-cinnamyl isoflavone by refluxing with the mixture of pyridine, piperidine and triethylorthoformate.

Similar C-cinnamylatin of 2,4-dihydroxy-3-methyl phenylbenzyl ketone was carried out to obtain 2,4-dihydroxy-3-methyl-5-cinnamyl phenylbenzyl ketone and was converted to 7-hydroxy-8-methyl-6-cinnamyl isoflavone.

Chapter - II

Synthesis of Pyranoisoflavone

7-Hydroxy-8-methylisoflavone was condensed with phenyl bromide to furnish 7-prenyloxy-8-methylisoflavone. Claisen rearrangement of it with N,N-dimethylaniline furnished deprenylated product.

C-prenylation of 2,4-dihydroxy-3-methylphenylbenzyl ketone was carried out by reacting it with BF -etherate, prenylalcohol in dioxan at rocm temperature. It gave two products, 7-hydroxy-8-methyl-6-phenylacetyl-2,2-dimethyl chroman and 2,4-dihydroxy-3-methyl-5-(3'-methyl-but-2'-enyl) phenylbenzyl ketone. Open chain product can be converted to chroman derivative by heating with formic acid. 7-Hydroxy-6-prenyl-8-methylisoflavone was synthesized from the ketone by heating it with the mixture of pyridine, piperidine and triethylorthoformate. Above isoflavone was further treated with DDQ to obtain 8,8,10-trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-(4H)-one.

Corresponding isoflavone 6,7-dihydro-8,8,10-trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-(4H)-one was preapred from 7-hydroxy-8-methyl-6-phenylacetyl 2,2-dimethylchroman by reacting it with pulverized sodium and ethylformate.

Further, 7-hydroxy-8-methylisoflavone was condensed with 3-chloro-3-methyl-but-1-yne and the corresponding ether was subjected to Claisen rearrangement. It furnished a novel product 1,2,3,7-tetrahydro-1,1,3-trimethyl-6-phenyl cyclopenta bezopyran-[2H,7H]-dione, along with expected product 8,8,10-trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-[4H]-one. Structures were established with the help of pmr and C^{13}nmr spectra.

Similar reaction was carried out for 7-hydroxy-2,8-dimethyl isoflavone to obtain 1,2,3,7-tetrahydro-1,1,3,5-tetramethyl-6-phenyl cyclopenta benzopyran-[2H,7H]-dione. 7-Hydroxy-8-allyl isoflavone gave 2,2-dimethyl-7-phenyl-3-(prop-2-enyl)pyrano (2,3-h)-1-benzopyran-[8H]-one while 7-hydroxy-8-cinnamyl isoflavone on similar treatment furnished 2,2-dimethyl-7-phenyl-10-(1-phenyl-prop-1-enyl) pyrano (2,3-g)-1-benzopyran-(6H)-one.

Chapter - III

Synthesis of benzofuroisoflavone

7-Hydroxyisoflavone was condensed with 2-bromocyclo-hexanone. Corresponding ether was subjected to cyclization by boiling with 0.1N alcoholic KOH solution. If furnished 5,6,7,8-tetrahydro-2-hydroxy-3-phenylacetyl dibenzofuran.

Corresponding isoflavone, 6,7,8,9-tetrahydro-3-phenyl-[4H]-benzofuro (3,2-g)-1-benzopyran-4-one, was synthesized by treating with pulverized sodium and ethylformate. Dehydrogenation was carried out by treating with palladized charcoal (10%), in refluxing diphenyl ether to otain 3-phenyl-[4H]-benzo furo (3,2-g)-1-benzopyran-4-one.

Similarly, 7-hydroxy-8-methyl isoflavone and 7-hydroxy-2-methyl isoflavone were condensed with 2-bromocyclohexanone and same series of reactions were carried out to obtain 1-methyl-2-hydroxy-3-phenyl acetyl dibenzofuran and 2-methyl-3-phenyl-[4H]-benzofuro (3,2-g)-1-benzopyran-4-one respectively.

2,4-Dihydroxy-3-methyl phenylbenzyl ketone was condensed with desyl chloride. Corresponding ether was obtained in the form of crude oil, hence it was directly subjected to cyclization with alkali without further purification. It furnished 2,3-diphenyl-6-hydroxy-7-methyl-5-phenylacetylbenzofuran. It was further treated with ethylformate and pulverized sodium to obtain corresponding isoflavone 2,3,6-triphenyl-9-methyl furo (3,2-g)-1-[5H] benzopyran-5-one. On tratment with acetic anhydride, ketone furnished 2,3,6-triphenyl-7,9-dimethyl furo (3,2-g)-1-[5H]-benzopyran-5-one. Corresponding coumarin derivative

diethyl carbonate and pulverized sodium with ketone to obtain 2,3,6-triphenyl-5-hydroxy-9-methyl furo (3,2-g)-1-[7H]-benzopyran-7-one.

A novel methyl migration in the Claisen rearrangement of 3-(1,1-dimethylprop-2-ynyloxy)-4-methylxanthone and 7-(1,1-dimethylprop-2-ynyloxy)-8-methylisoflavone

260

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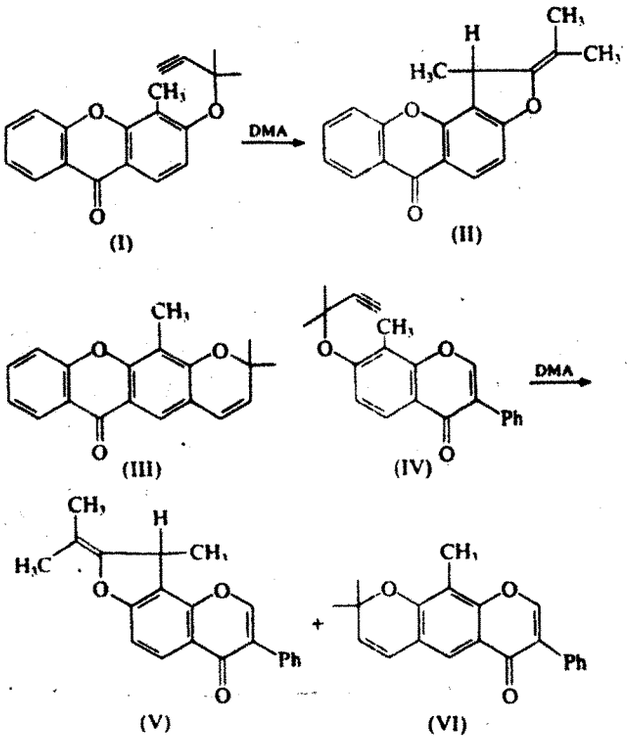
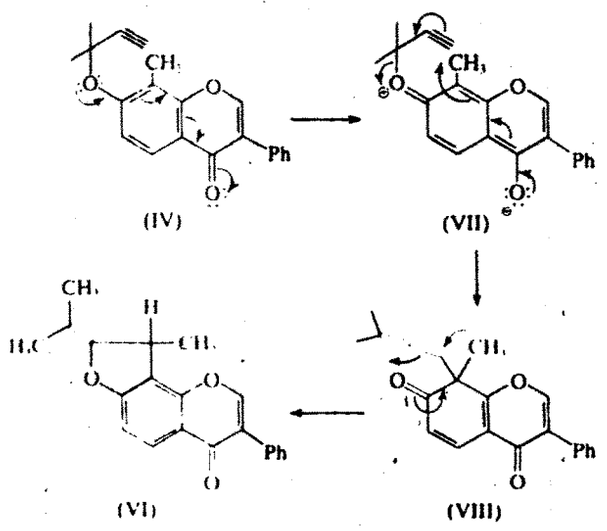
he interesting results obtained for the Claisen arrangement of 3-allyloxy-4-bromo or iodoxanthone[1] and ,4-dibromo-3-allyloxyxanthone,[2] make it of interest to tudy the effect on Claisen rearrangements of a methyl oup at position 4 instead of a bromo or iodo substituent. Condensation of 3-hydroxy-4-methylxanthone with -chloro-3-methylbut-1-yne in the presence of potassium rbonate and potassium iodide gave 3-(1,1-dimethylprop--ynyloxy)-4-methylxanthone (I), m p 159°C; n.m.r. DCl$_3$):δ1.75 (*s*,6H, =C(C*H*$_3$)$_2$), 2.4 (*s*, 3H, ArCH$_3$), 2.6 , 1H, -C≡C*H*), 7.3-7.7 (*m*, 4H, H-2, H-5, H-6 and H-7), .1 (*d*, 1H, *J* 9Hz, H-1), 8.25 (*dd*, 1H, *J* 9, 2Hz, H-8). ompound (I) on Claisen rearrangement in *N,N*-dimethyl- iline gave the abnormal product (II), the n.m.r. spectrum f which shows a doublet, *J* 9Hz at δ8.25 for the *peri* roton H-1, indicating that migration has not taken place at sition 2 but at position 4 with the simultaneous igration of a methyl group from the phenyl ring to osition 4 of the furan ring. This was further confirmed by quartet with *J* 9Hz at δ 3.87 for one proton and a doublet ith *J* 9Hz at 1.68 for a methyl group at position 4' of the ran ring. The structure 4,6',6'-trimethylpyrano 3',2':2,3)xanthone (III) is eliminated by the absence of two oublets, *J* 10Hz in the region δ5.5-7.0 for unsaturated pro- ons at positions 3' and 4'. Thus, the abnormal product is '-methyl-5'-dimethylmethylene-4'-*H*-furano(2',3':3,4)- nthone (II), m p 165°C; n.m.r. (CDCl$_3$):δ1.4 and 1.38 2x*s*, each 3H, =C(C*H*$_3$)$_2$), 1.68 (*d*, 3H, *J* 9Hz, 4'-CH$_3$), .87 (*q*, 1H, *J* 9Hz, 4'-H), 7.28 (*d*, 1H, *J* 9Hz, H-2),



7.35-7.42 (*m*, 2H, H-5 and H-7), 7.7 (*td*, 1H, *J* 9, 9, 2Hz, H-6), 8.25 (*d*, *J* 9Hz, H-1), 8.3 (*dd*, *J* 9, 2Hz, H-8).

In order to develop this novel observation, the reaction was extended to the isoflavone ring system. Thus, 7-(1,1-dimethylprop-2-ynyloxy-8-methyl-isoflavone(IV), m p 150°C, when heated under reflux in *N,N*-dimethylaniline gave a similar product, 4'-methyl-5'-dimethylmethylene-4'-*H*-furano(2',3':7,8)isoflavone (V), m p 165°C, together with the linear compound 6',6',8-trimethylpyrano(5',6':6,7)isoflavone (VI), m p 136-40°C, in poor yields. The structure of compound (V) was confirmed by n.m.r. spectral measurements (CDCl$_3$): δ1.4 and 1.38 (2x*s*, each 3H, C(C*H*$_3$)$_2$), 1.65 (*d*, 3H, *J* 9Hz, 4'-CH$_3$), 3.8 (*q*, 1H, *J* 9Hz, 4'-H), 7.2 – 7.5 (*m*, 6H, aromatic protons), 8.25 (*d*, 1H, *J* 9Hz, H-5), 8.0 (*s*, 1H, H-2). The structure of compound (VI) was also confirmed on the basis of its n.m.r. spectrum (CDCl$_3$): δ 1.6 (*s*, 6H, 2 x-CH$_3$), 2.5 (*s*, 3H, ArCH$_3$), 5.85 (*d*, 1H, *J* 10Hz, H-3'), 6.5 (*d*, 1H, *J* 10Hz, H-4'), 7.3 – 7.7(*m*, 5H, aromatic protons), 7.85 (*s*, 1H, H-2), 8.1 (*s*, 1H, H-5).

The formation of compound (V), and presumably compound (III), can be explained as suggested in Scheme 1. Compound (IV) on Claisen rearrangement gives the



Scheme 1

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Studies in the Synthesis of Furochromones: Part VIII† — Synthesis of Furoisoflavones

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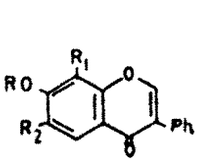
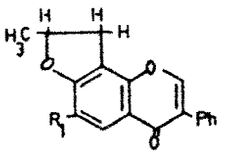
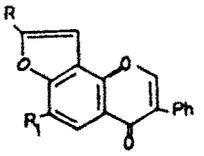
7-Hydroxyisoflavone (Ia) on allylation and Claisen migration gives 8-allyl-7-hydroxyisoflavone (Ic) which undergoes cyclization and dehydrogenation affording 8-methyl-3-phenylfuro[2,3-*h*]-1-benzopyran-4(*H*)-one (IIIa). Compound Ic on ozonolysis and cyclization with PPA gives 3-phenylfuro [2,3-*h*]-1-benzopyran-4(*H*)-one (IIIb). 7-Allyloxy-8-methylisoflavone (Ig) on a similar series of rections furnishes 2,9-dimethyl-6-phenylfuro [3,2-*g*] -1-benzopyran-5(*H*)-one (V), while 7-allyloxy-6,8-dibromoisoflavone (Ii) gives 6-bromo-8,9-dihydro-8-methyl-3phenylfuro [2,3-*h*]-1-benzopyran-4(*H*)-one (IIb).

Naturally occuring linear furochromones such as Khellins and Visanagin possess several pharmaceutical properties such as antispasmodic[2-4], vasodilatory[5-7] and hypertensive[8] activities, etc. In view of this and in continuation of our work on the synthesis of furobenzopyrans[9,10], we report herein the synthesis of linear furoisoflavones and also the angular furoisoflavones.

7-Hydroxyisoflavone (Ia) on allylation with allyl bromide gave 7-allyloxyisoflavone (Ib) which on Claisen rearrangement in refluxing N,N-dimethylaniline furnished 8-allyl-7-hydroxyisoflavone (Ic), as TLC-pure product. The PMR spectrum of Ic exhibited doublets at δ 7.9 and 7.0 for protons at C-5 and C-6 respectively indicating that migration took place at position-8 rather than at position-6 of the isoflavone ring. This is because of the fact that there is fixation of double bond between positions 7 and 8 of the isoflavone ring, and is supported by the work of Rangaswami and Seshadri[11] who reported the analogous migration of 7-allyloxyflavone giving 8-allyl-7-hydroxyflavone. The allylisoflavone Ic on trituration with sulphuric acid (80%) furnished 8-, 9-dihydro-8-methyl-3-phenylfuro[2, 3-*h*]-1-benzopyran-4(*H*)-one (IIa), the structure of which was established by PMR spectrum ($CDCl_3$) exhibiting signals at δ 1.5 (3H, *dd*, *J*=7Hz, C_8-CH_3), 3.0 (1H, *dd*, *J*=18, 8Hz, C_9-H), 3.5



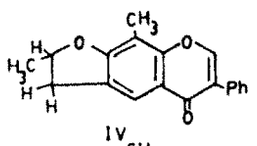




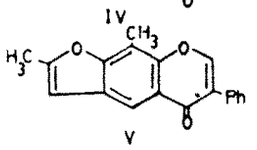
Ia R = R_1 = R_2 = H
Ib R = $CH_2CH=CH_2$ R_1 = R_2 = H
Ic R = R_2 = H R_1 = $CH_2CH=CH_2$
Id R = $CH_2CH=CH_2$ R_1 = Br R_2 = H
Ie R = R_1 = H R_2 = $CH_2CH=CH_2$
If R = R_2 = H R_1 = CH_2CHO
Ig R = $CH_2CH=CH_2$ R_1 = CH_3 R_2 = H
Ih R = H R_1 = CH_3 R_2 = $CH_2CH=CH_2$
Ii R = $CH_2CH=CH_2$ R_1 = R_2 = Br
Ij R = H R_1 = $CH_2CH=CH_2$ R_2 = Br

IIa R_1 = H
IIb R_1 = Br

IIIa R = CH_3 R_1 = H
IIIb R = H R_1 = H
IIIc R = CH_3 R_1 = Br



IV



V

†For part VII of the series, see ref. 1.

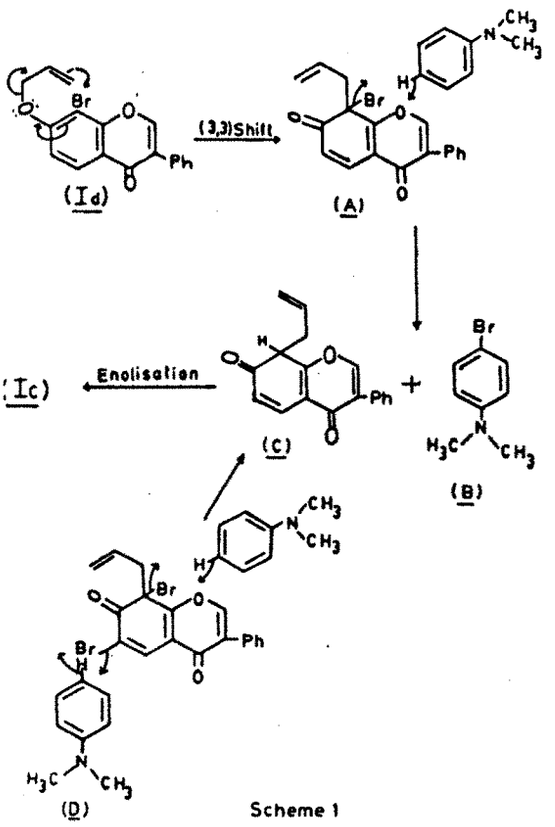
(1H, *dd*, *J*=18, 8Hz, C_9-H), 5.2 (1H, m, C_8-H), 6.95 (1H, *d*, *J*=9Hz, C_6-H), 7.5 (5H, *m* Ar-*H*), 7.9 (1H, *s*, C_2-H), 8.15 (1H, *d*, *J*=9Hz, C_5-H). The compound IIa was also obtained when Ic was heated with a mixture of acetic acid and hydrobromic acid followed by cyclization with K_2CO_3 and acetone. Compound IIa when refluxed with diphenyl ether with Pd/C (10%) underwent dehydrogenation to furnish 8-methyl-3-phenylfuro[2,3-*H*]-1-benzopyran-4(*H*)-one (IIIa), the structure of which was established by PMR spectrum ($CDCl_3$) exhibiting signals at δ 2.6 (3H, *s*, C_8-CH_3), 6.8 (1H, *s*, C_9-H), 7.35 (1H, *d*, *J*=8Hz, C_6-H), 7.5 (5H, *m*, Ar-*H*), 8.1 (1H, *s*, C_2-H), 8.2 (1H, *d*, *J*=9Hz, C_5-H).

Ozonolysis of Ic followed by hydrogenation furnished 7-hydroxy-8-(2'-oxoethyl)isoflavone (If) which was cyclized with polyphosphoric acid to give 3-phenylfuro[2,3-*h*]-1-benzopyran-4(*H*)-one (IIIb); PMR ($CDCl_3$): δ 7.1 (1H, *d*, *J*=3Hz, C_9-H), 7.4 (6H, *m*, Ar-*H* + C_6-H), 7.7 (1H, *d*, *J*=3Hz, C_8-H), 8.0 (1H, *s*, C_2-H), 8.1 (1H, *d*, *J*=9Hz, C_5-H).

Pardanani and Trivedi[12] have reported that 7-allyloxy-8-bromocoumarin on Claisen rearrangement gives 7-hydroxy-6-allylcoumarin with simultaneous elimination of bromine from position-8. In analogy with this observation, Claisen rearrangement of 7-allyloxy-8- bromoisoflavone (Id) was carried out in N,N-dimethylaniline as well as in decalin, and it gave Ic and *p*-bromo-N,N-dimethylaniline and not 6-allyl-7-hydroxyisoflavone (Ie). This shows that the reaction followed the path suggested in Scheme 1.

7-Allyloxy-8-iodoisoflavone also gave Ic along with *p*-iodo-N,N-dimethylaniline.

Claisen rearrangement of 7-allyloxy-6,8-dibromoisoflavone (Ii) in N,N-dimethylaniline also gave Ic. Elimination of bromine from positions 6 and 8 takes place by the base N,N-dimethylaniline because both are adjescent to the carbonyl group in the dienone structure (D) which makes them labile (Scheme 1). Thus, both bromine atoms were eliminated during migration. When migration was carried out using decalin as solvent, it furnished 8-allyl-6-bromo-7-hydroxyisoflavone (Ij), which was cyclized with 80% H_2SO_4 to obtain 6-bromo-8,9-dihydro-8-methyl-3-phenylfuro[2,3*h*]-1-benzopyran-4 (*H*)-one (IIb), the structure of which was proved by comparison with the product obtained by bromination of IIa. The PMR ($CDCl_3$) spectrum of IIb exhibited signals at δ 1.55 (3H, *d*, *J*=8Hz, C_8-CH_3), 3.0 (1H, *dd*, *J*=18, 8Hz, C_9-H), 3.5 (1H, *dd*, *J*=18, 8Hz, C_9-H, 5.2 (1H, *m*, C_8-H), 7.4 (5H, *m*, Ar-*H*), 7.8 (1H, *s*, C_5-H), 8.15 (1H, *s*, C_2-H). Dehydrogenation of IIb with Pd/C (10%) in diphenyl ether gave IIIa and not IIIc, bromine being eliminated during the course of the reaction. Compound Ii when heated in Vacuum (5 mm) at 140° for 2 hr underwent Claisen rearrangement followed by cycliation to give IIb, one bromine being eliminated during the course of the reaction.



Scheme 1

As the synthesis of linear furoisoflavone could not be achieved by blocking the 8th position by bromine or iodine in the isoflavone ring, it was thought of interest to block it by methyl group. Thus, the Claisen rearrangement of 7-allyloxy-8-methylisoflavone in N,N-dimethylaniline gave 6-allyl-7-hydroxy-8-methylisoflavone (Ih), which was cyclized with HOAc-HBr mixture to 2,9-dimethyl-2,3-dihydro-6-phenylfuro[3,2-*g*]-1-benzopyran-5(*H*)-one (IV). Dehydrogenation of IV with Pd C (10%) afforded 2,9-dimethyl-6-phenylfuro[3,2-*g*]-1-benzopyran-5(*H*)-one (V).

Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded on a 90 MHz Perkin-Elmer R-32 Spectrometer, using TMS as internal standard. Silica gel of 60-120 mesh was used for column chromatography.

7-Allyloxyisoflavone (Ib)

A mixture of 7-hydroxyisoflavone (Ia; 2.4 g, 0.01 mol), allyl bromide (1.2 g, 0.01 mol) and anhyd.

UGC, New Delhi for the award of a research fellowship.

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