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SYNTHESIS AND STUDY OF ISOFLAVAN-4-OLS

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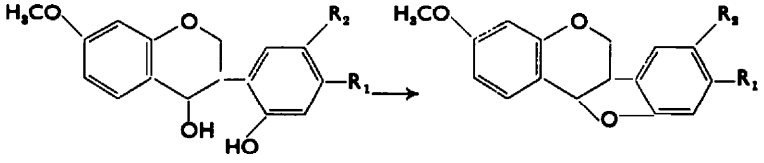
Abstract—The action of $NaBH_4$ on some typical isoflavones yields isoflavan-4-ols in 70–85% yields. 2-Methylisoflavones are resistant to this reduction. The isoflavan-4-ols undergo dehydration to isoflavens in presence of protonic reagents suggesting a *quasi-trans* relationship between the *quasi-equatorial* 4-OH and 3-H, proposed by Micheli *et al.*[3] and based on NMR evidence.

ALTHOUGH isoflavan-4-ols have not been found in nature pterocarpin (IIa) and homopterocarpin (IIb) from *Pterocarpus indicus*[1] may be derived from the corresponding isoflavan-4-ols (I) by a process of dehydration between the 4-OH and 2′-phenolic OH. Or alternatively, the oxide bridge may have been produced by dehydrogenation (oxidative linkage) between the 4-OH and 2′-H, as the latter is fairly active.



I II

(a) $R_1 - R_2$, $O{-}CH_2{-}O$
(b) R_1, OCH_3; R_2, H

In connection with the study of the oestrogenic activity of isoflavanones and isoflavens, Bradbury and White[2] and Micheli *et al.*[3] reduced isoflavones using $Pt{-}H_2$ in acetic acid. The isoflavone is always accompanied by small quantities of isoflavan-4-ol, isoflaven and isoflavan. Other reagents like Grignard reagents,[4] Pd on charcoal,[5] sodium metabisulphite,[6] LAH,[2] Rhodium-alumina[3] and Birch reduction[7] have limited applicability.

The action of $NaBH_4$, extensively used for the reduction of flavanones to flavan-4-ols,[8] has now been extended to isoflavones. In the synthesis of homopterocarpin (IIb) and its analogue, Seshadri *et al.*[9] and Suginomi and Iwadara[10] noticed that the reduction of 2′-hydroxyisoflavones with $NaBH_4$ resulted in the formation of 2′-hydroxyisoflavan-4-ols (I) which readily undergo cyclodehydration in acid.

[1] A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1440 (1954).
[2] R. B. Bradbury and D. E. White, *J. Chem. Soc.* 871 (1953).
[3] R. A. Micheli, A. N. Booth, A. L. Livingstone and M. E. Bickoff, *J. Medicinal Pharm. Chem.* **5**, 321 (1961).
[4] W. Lawson, *J. Chem. Soc.* 4448 (1954).
[5] E. Breitner, E. Roginski and P. N. Rylander, *J. Org. Chem.* **24**, 1855 (1959).
[6] N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **35A**, 202 (1952).
[7] A. J. Birch and H. Smith, *Quart. Rev.* **12**, 17 (1958).
[8] L. R. Row and G. P. Sastry, P. V. S. Rao and M. G. Rao, *J. Ind. Chem. Soc.* **40**, 311 (1963).
[9] K. Aghoramurty, A. S. Kukla and T. R. Seshadri *Curr. Sci.* **30**, 218 (1961).
[10] H. Suginomi and T. Iwadara, *Bull. Chem. Soc. Japan* **33**, 567 (1960).

In the present study, nine different isoflavones (IIIa–f and IVa–c) with various substituents have been reduced with $NaBH_4$ and isoflavan-4-ols (Va–f and VIa–c R = H) obtained in good yield (70–85%). The reduction proceeds readily even in the absence of boric acid which is, therefore, superfluous. The isoflavan-4-ols (Table 1)

TABLE 1

No.	Isoflavan-4β-ol	m.p.	Mol. formula	Requires C	Requires H	Found C	Found H
1.	7-Methoxy	138–140°	$C_{16}H_{16}O_3$	75·01	6·25	74·66	7·12
	... acetate	116–118°	$C_{18}H_{18}O_4$	72·49	6·04	72·95	6·57
2.	7,4′-Dimethoxy	141–143°	$C_{17}H_{18}O_4$	71·32	6·29	71·50	6·37
	... acetate	121–123°	$C_{19}H_{20}O_5$	69·50	6·09	69·93	6·83
3.	7,3′,4′-Trimethoxy	120–122°	$C_{18}H_{20}O_5$	68·35	6·33	68·14	5·94
	... acetate	130–132°	$C_{20}H_{22}O_6$	67·15	6·15	67·17	6·60
4.	7,4′. Dimethoxy 2-methyl	144–146°	$C_{18}H_{20}O_4$	72·00	6·66	71·85	6·45
	... acetate	164–166°	$C_{20}H_{22}O_5$	70·17	6·43	70·05	6·25
5.	*(4′,5′) Dihydro furano (6,7,3′,2′)	160–162°	$C_{17}H_{16}O_3$	76·12	5·97	76·05	6·19
	... acetate	147–148°	$C_{19}H_{18}O_4$	70·39	5·80	70·25	6·20
6.	(4′,5′) Dihydro furano-(6,7,3′,2′) 4″-methoxy	160–162°	$C_{18}H_{18}O_4$	72·49	6·01	72·34	6·44
	... acetate	130–132°	$C_{20}H_{20}O_5$	70·59	5·90	70·45	6·21
7.	(4′,5′) Dihydro furano (6,7,3′,2′) 3″,4″-dimethoxy	197–198°	$C_{19}H_{20}O_5$	69·50	6·00	69·50	6·47
	... acetate	132–134°	$C_{21}H_{22}O_6$	68·10	5·95	67·94	6·25

* The isoflavone was prepared according to the method of S. K. Pavanaram, T. R. Seshadri and L. R. Row, *J. Sci. Ind. Res.* **15B**, 495 (1956).

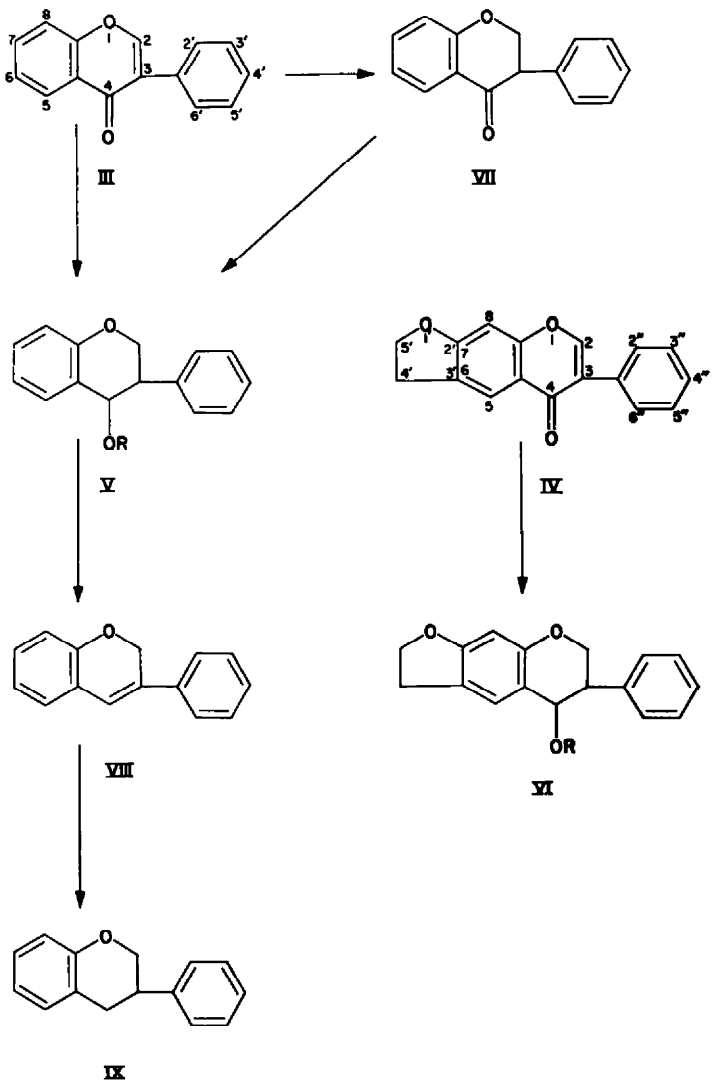
are colourless crystalline solids and readily yield crystalline acetates (Va–d and VIa–c R = Ac). 7-Methoxy-, 3′,4′-methylenedioxy- and 7,2′-dimethoxyisoflavan-4-ols (Ve, f R = H) were obtained as colourless liquids. These develop an orange red colouration in conc. H_2SO_4, while the parent isoflavones yield only yellow solutions. Since, $NaBH_4$ is known to reduce the pyrone double bond,[9,10] the isoflavones (IIIa, b) were first reduced to the corresponding isoflavanones (VIIa, b) and then subjected to $NaBH_4$ treatment. The resulting isoflavan-4-ols (Va, b) were identical with those obtained directly from isoflavones (IIIa, b).

2-Methylisoflavones could not be reduced under these conditions; but when refluxed for 6 hr with $NaBH_4$ 7,4′-dimethoxy-2-methylisoflavan-4-ol (Vc R = H) was obtained in 20% yield. This resistance to $NaBH_4$ reduction is probably due to the conjugation of the methyl group with the pyrone carbonyl. Similar resistance was also noticed with 7-methoxyflavone[11] where the 2-phenyl group is similarly conjugated to the pyrone carbonyl.

Action of Al—Hg[12] on 7-methoxy- and 7,4′-dimethoxyisoflavones (IIIa, b) and isoflavanones (VIIa, b) in aqueous ethanol has been studied; but no reduction was noticed in either case.

[11] L. R. Row, A. S. R. Anjaneyulu and C. S. Krishna, *Curr. Sci.* **32**, 67 (1963).

[12] R. Bognar, M. Rakosi, H. Fletcher, D. Kehoe, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **18**, 135 (1962).



a. 7-OCH_3 b. 7,4'-OCH_3
c. 7,4'-OCH_3; 2-CH_3
d. 7,3',4'-OCH_3 e. 7,2'-OCH_3
f. 7-OCH_3; 3',4'-O—CH_2—O

a. Unsubstituted
b. 4''-OCH_3
c. 3'',4''-OCH_3

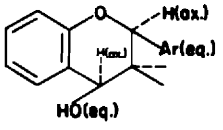
Isoflavan-4-ols (Va–d, R = H) undergo *trans* elimination of H_2O with the formation of isoflavens (VIIIa–d, Table 2) in 70–75% yield in the presence of (a) glacial acetic acid at 100°, (b) acetic acid containing a drop of HCl at 50° or (c) $POCl_3$–pyridine at 28°. But during pyrolysis at 160°, the isoflavan-4-ol acetates are recovered unchanged. These dehydrations suggest that the 4-OH is *trans* situated to the 3-H (X).

Recently, Inoue[13] recorded the formation of the same isoflavan-4-ols from isoflavanones when reduced with Raney Ni, $NaBH_4$ or aluminium isopropoxide. The

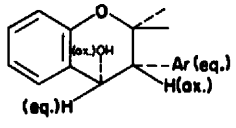
[13] N. Inoue, *Bull. Chem. Soc. Japan* 37, 601, 606 (1964); N. Inoue, S. Yamaguchi and S. Fujiwara, *Bull. Chem. Soc. Japan* 37, 588 (1964).

action of $NaBH_4$ on 7-methoxyisoflavanone (VIIa), however, produced a mixture of the isomeric 4-α-ol (m.p. 131°) and 4-β-ol (m.p. 144°). The latter compound agrees with the isoflavan-4-ol obtained by us from 7-methoxyisoflavone (IIIa). 7,4'-Dimethoxyisoflavanone (VIIb) yielded only the β-ol and no α-ol as did the isoflavones in our experiments. The hydroxyl in 7-methoxyisoflavan-4-ol (m.p. 144°) is considered *axial*[13] as its acetate is less stable and quickly changes to the epimeric acetate at 50°.

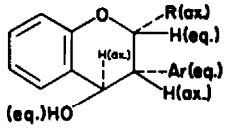
The conformation of the heterocyclic ring systems in chromans and flavans has been discussed by several workers.[12,14] The 4-OH of flavan-4β-ol[15] (XI) is *cis* situated with regard to the 2-phenyl group. By analogy, the 3-phenyl and 4-OH groups in isoflavan-4-ols would both be *equatorial* causing the 3-H and 4-H to be *trans-axial* (XII R = H). This view is supported by Micheli *et al.*[3] who showed that the spin couplings of 2,3,4 protons in 7,4'-diacetoxy 2-methylisoflavan-4-ol (XII R = CH_3) are $J_{2,3}$ 2·1 c/s and $J_{3,4}$ 7·71 c/s which indicates an *axial–axial* configuration for 3,4 protons and *axial–equatorial* configuration for 3,2 protons.



XI



X



XII

These considerations support an equatorial configuration for the 4-OH and although this apparently conflicts with the chemical evidence, the *equatorial* 4-OH and 3-H in the isoflavan-4-ol may be regarded as possessing a *quasi–trans* relationship in which proton catalysed *trans* elimination takes place readily.

EXPERIMENTAL

7-Methoxyisoflavan-4β-ol (Va)

(A) The following represents a general method for the preparation of isoflavan-4β-ols. A solution of 7-methoxyisoflavone (500 mg) and boric acid (120 mg) in 95% EtOH (50 ml) was treated with $NaBH_4$ (235 mg) in small portions at room temp. After 3 hr it was neutralized with dil. acetic acid and the isoflavan-4β-ol separated and crystallized from EtOH as colourless needles (400 mg), m.p. 138–140°. It exhibits a yellow colour with green fluorescence in conc. H_2SO_4.

The acetate (pyridine–Ac_2O at room temp), colourless micro needles from EtOH m.p. 116–118°.

(B) 7-Methoxyisoflavanone m.p. 98° (from isoflavone by Pt—H reduction; 200 mg) in EtOH (20 ml) was reduced with $NaBH_4$ (45 mg). The isoflavan-4β-ol crystallized from EtOH as colourless needles m.p. and m.m.p. with the above sample, 138–140°.

5-(ω-p-methoxyphenyl) acetyl 6-hydroxycoumaran

A solution of 6-hydroxycoumaran (2·0 g) and *p*-methoxyphenyl acetonitrile (2·2 g) in dry ether (75 ml) containing fused $ZnCl_2$ (2·0 g) was saturated with dry HCl gas at 0°. After 24 hr at 0°, the ketimine hydrochloride in water (100 ml) was heated at 90° for 1 hr. The ketone crystallized from EtOH as pale brown plates (0·9 g), m.p. 108–110°. (Found: C, 72·06; H, 6·03; $C_{17}H_{16}O_4$ requires C, 71·83; H, 5·63%.) It gives a reddish brown colour with $FeCl_3$.

[14] J. W. Clark-Lewis, *Rev. Pure Appl. Chem.* **12**, 96 (1962); J. W. Clark-Lewis, L. M. Jackman and T. M. Spotswood, *Austr. J. Chem.* **17**, 632 (1964).

[15] J. W. Clark-Lewis, T. M. Spotswood and L. R. Williams, *Proc. Chem. Soc.* 20 (1963).

4″-Methoxy (4′,5′)-dihydrofurano-(3′,2′,6,7)isoflavone

The above ketone (1 g) in ethyl formate (30 ml) at 0° was added dropwise with shaking during 30 min to a suspension of powdered Na (1 g) in ethyl formate (10 ml) at −5°. After 30 hr, the isoflavone was separated as usual and crystallized from MeOH as pale brown needles (0·5 g), m.p. 222–224°. (Found: C, 73·23; H, 6·3; requires: C, 73·48; H, 6·8%.)

2-Methyl 4″-methoxy-(4′,5′)-dihydrofurano-(3′,2′,6,7)isoflavone.

The above ketone (500 mg) was refluxed with Ac_2O (15 ml) and fused NaOAc (1 g) for 20 hr at 185–190°. The 2-methylisoflavone crystallized from alcohol as fine needles (250 mg), m.p. 162–164°. (Found: C, 73·66; H, 5·60; $C_{19}H_{16}O_4$ requires: C, 74·01; H, 5·19%.)

3″,4″-Dimethoxy-(4′,5′)-dihydrofurano-(3′,2′,6,7)isoflavone.

An ice cold solution of 5-(w-3′, 4′-dimethoxyphenyl)acetyl 6-hydroxycoumaran[16] (1·0 g) in ethyl formate (25 ml) was carefully added dropwise to a suspension of powdered Na (1 g) in ethyl formate (10 ml) at −5° during 30 min. After 24 hr at 0°, the isoflavone was separated and crystallized from EtOH as micro-needles (600 mg) m.p. 180–182°. (Found: C, 70·05; H, 5·26; $C_{19}H_{18}O_6$ requires: C, 70·37; H, 4·94%.)

7-Methoxyisoflaven

(a) 7-Methoxyisoflavan-4-ol (100 mg) was dissolved in glacial HOAc (5 ml) and heated at 100° for 1 hr. After the usual procudure, the isoflaven crystallized from EtOH as colourless needles (70 mg), m.p. 105–107°. It exhibits light violet fluorescence in EtOH and acetone.

(b) The isoflavan-4-ol (100 mg) in HOAc (3 ml) was heated with a drop of conc. HCl at 50° for 10 min. After 1 hr at room temp water was added to separate the isoflaven. It crystallized from EtOH as colourless needles (70 mg), m.p. and m.m.p. with the above sample 105–107°.

(c) $POCl_3$-*Pyridine*: The isoflavan-4-ol (100 mg) in pyridine (2 ml) was treated with freshly distilled $POCl_3$ (2 drops). After 12 hr at room temp, water was added and the separated solid crystallized from EtOH as colourless needles (65 mg), m.p. and m.m.p. with isoflaven 105–107°.

(d) *Pyrolysis of the acetate.* The acetate of 7-methoxyisoflavan-4-ol (100 mg) was heated in an oil-bath at 160° for 1 hr *in vacuo*. The residue crystallized from EtOH as colourless needles (80 mg), m.p. 116–118° unchanged by the starting acetate.

TABLE 2

No.	Isoflaven	m.p.	Mol. formula	Requires C	Requires H	Found C	Found H
1.	7-Methoxy	105–107°	$C_{16}H_{14}O_3$	80·68	5·88	81·04	6·17
2.	7,4′-Dimethoxy	159–161°	$C_{17}H_{16}O_3$	76·12	5·97	75·73	6·25
3.	7,4′-Dimethoxy 2-methyl	125°	$C_{18}H_{18}O_3$	76·60	6·38	76·40	6·12
4.	7,3′,4′-Trimethoxy	112–114°	$C_{18}H_{18}O_4$	72·48	6·04	72·55	5·90

Isoflavans

The isoflavens were hydrogenated in acetic acid in presence of Adam's catalyst at room temp and press. to give isoflavans.

TABLE 3

No.	Isoflavan	m.p.	Mol. formula	Requires C	Requires H	Found C	Found H
1.	7-Methoxy	98°	$C_{16}H_{16}O_3$	80·00	6·67	79·85	6·50
2.	7,4′-Dimethoxy	105–107°	$C_{17}H_{18}O_3$	75·55	6·66	75·45	6·45
3.	7,3′,4′-Trimethoxy	92–94°	$C_{18}H_{20}O_4$	72·00	6·66	71·85	6·45

Acknowledgements—Two of us (A. S. R and C. S. K) wish to express our grateful thanks to the University Grants Commission and The Council of Scientific and Industrial Research for the award of Fellowships respectively.

[16] S. K. Pavanaram and L. R. Row, *J. Sci. Ind. Res.*, **17B**, 272 (1958).