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The Absolute and Relative Stereochemical Correlation of Isoflavanone, Sophorol and Naturally-occurring Isoflavan Derivatives[1]

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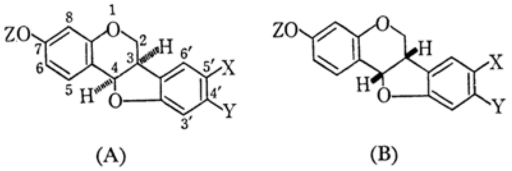
By rotatory-dispersion studies, it was confirmed that sophorol, (−) maackiain, pterocarpin, equol and homopterocarpin have the same absolute configuration at position 3. The results of the O. R. D. examination of (−) halostachine and pterocarpinoids allow us to assign the 3R, 4R configuration to pterocarpin and to the related compounds.

A number of natural isoflavanones have been discovered,[2] although sophorol[2a] is the only member of the group which has been isolated in an optically active state. In recent years, the existence of various chromanocoumarans*, which are closely related biogenetically to isoflavanones, has been disclosed. It is of interest to determine the stereochemical relationship between these compounds and their absolute configurations.

At present, nine chromanocoumarans, their glycosides (I—VIII)[3] and isoflavan equol (IX) are known; they have all been isolated in an optically active form.



(A) (B)

(I—V)

I (−) Homopterocarpin,[4] X=H; Y=OMe; Z=Me

II (−) Pterocarpin,[5] X and Y=methylenedioxy; Z=Me

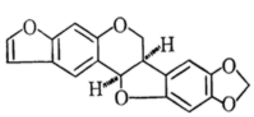
III (±) Maackiain,[6] X and Y=methylenedioxy; Z=H

(−) Maackiain[7] (Inermin), X and Y=methylenedioxy; Z=H

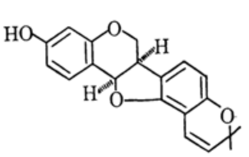
IV (−) Triforlirhizin,[8] X and Y=methylenedioxy; Z=-D-glucose

V (+) Sophojaponicin,[6] X and Y=methylenedioxy; Z=-D-glucose

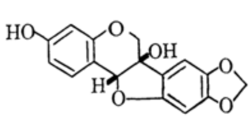
VI (−) Neodulin[9]



VII (−) Phaseolin[10]



VIII (+) Pisatin[11]



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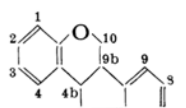
[1] Oxygen Heterocycles. X. The work has been interrupted since September, 1961 but is published now. A brief account of this paper has already been published. This Bulletin, **39**, 409 (1966).

[2] a) H. Suginome, *J. Org. Chem.*, **24**, 1655 (1959) and examples cited therein. b) L. Crombie and D. A. Whiting, *J. Chem. Soc.*, **1963**, 1569; S. Balakrishna, J. D. Ramanathan, T. R. Seshadri and B. Venkataramani, *J. Sci. Ind. Res.* (India), **20B**, 134 (1961).

* Group name "Pterocarpinoids" was suggested for the compounds.

[3] The numbering system of chromanocoumaran was chosen arbitrarily as derivative of isoflavones. However, an alternative numbering would be analogous



to the numbering of 6,12-dioxachrysene. The ring index, p. 708 (1960), American Chemical Society.

[4] E. Späth and J. Schläger, *Chem. Ber.*, **73**, 1 (1940).

[5] A. McGookin, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, **1940**, 787; J. B. Bredenberg and J. N. Shoolery, *Tetrahedron Letters*, **1961**, 285.

[6] S. Shibata and Y. Nishikawa, *Chem. and Pharm. Bull.*, **11**, 167 (1963).

[7] S. Shibata and Y. Nishikawa, ibid., **11**, 167 (1963); W. Cocker, T. Dahl, C. Dempsey and T. B. H. McMurry, *Chem. & Ind.*, **1962**, 216; H. Suginome, *Experientia*, **18**, 161 (1962).

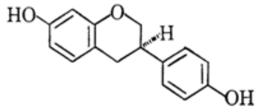
[8] J. B. Brendenberg and P. K. Hietala, *Acta Chem. Scand.*, **15**, 936, (1961).

[9] B. L. Van Duuren, *J. Org. Chem.*, **26**, 5013 (1961).

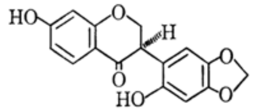
[10] D. R. Perrin, *Tetrahedron Letters*, **1964**, 29.

[11] D. R. Perrin and W. Bottomley, *Nature*, **191**, 76 (1961).

IX (−) Equol[12]



X (+) Sophorol



The absolute and relative stereochemical correlations between corresponding asymmetric centers of sophorol and those chromanocoumarans have not yet been defined, however. Therefore, the relative stereochemistry of these compounds has now been examined by rotatory-dispersion studies. The rotatory dispersion curves are recorded in Figs. 1 and 2.

Figure 1 shows the rotatory-dispersion curves of sophorol,[2a] the oxidation product of *O*-methyldihydropterocarpin obtained from pterocarpin by hydrogenolysis, followed by methylation and oxidation with potassium permanganate,[5] and *O*-dimethylsophorol.[2a] These three substances exhibit virtually identical plain positive dispersion curves throughout the spectral range under examination. This result can be taken as conclusive evidence of an identical absolute configuration at C^3 in sophorol and the corresponding asymmetric center of pterocarpin and related compounds; it confirms previous assumptions.[13]

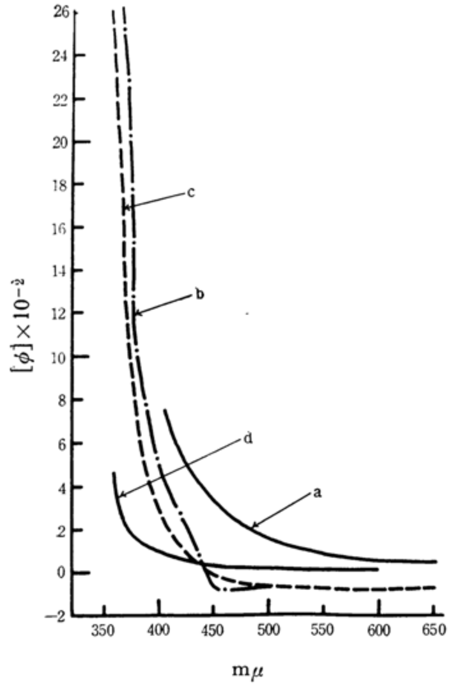


Fig. 1

a Sophorol in dioxane
b Potassium permanganate oxidation product
c Sophorol in ethanol
d *O*-Dimethylsophorol

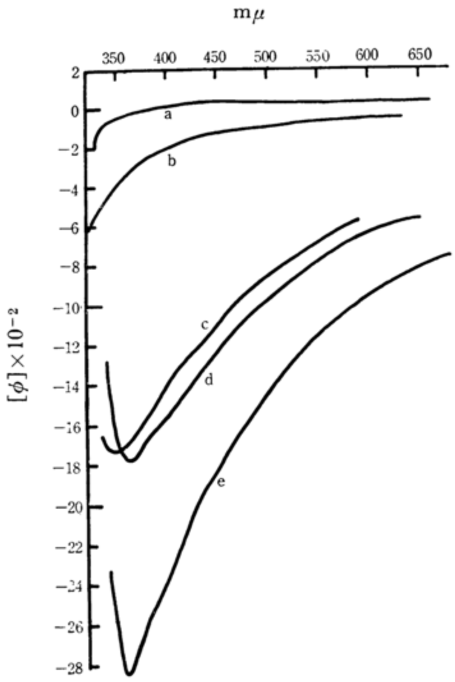


Fig. 2

a Dihydro-*O*-methylmaackiain-*O*-methylether
b Equol diacetate
c Homopterocarpin
d Pterocarpin
e Maackiain

In Fig. 2 are collected the rotatory-dispersion curves of homopterocarpin, pterocarpin, maackiain, equol diacetate and dihydro-*O*-methylmaackiain-*O*-methylether. Homopterocarpin, pterocarpin and maackiain all exhibit negative Cotton-effect curves. It is apparent from the figure that in these cases C^3 asymmetric carbon in the chromanocoumaran molecule makes a very weak negative contribution,[14] as is shown in the dispersion curves of dihydro-*O*-methylmaackiain-*O*-methylether. Therefore, the relatively strong negative rotation accompanying the Cotton effects in these compounds is probably produced by the C^4 asymmetric center with an aromatic ring and an ether linkage.

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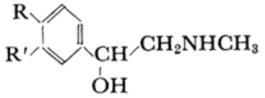
[12] G. F. Marrian and D. Beall, *Biochem. J.*, **29**, 1586 (1935); R. Suemitsu, M. Hiura and M. Nakajima, *J. Agr. Chem. Soc. Japan*, **29**, 591 (1955).

[13] W. B. Whalley, "The Chemistry of Flavonoid Compounds," T. A. Geissman ed., Pergamon Press, London, (1962), p. 441.

[14] The formation of ring compounds from open chains is accompanied by an increase in optical rotation.[16] Needless to say, no Cotton effect will be produced by C3 center after ring formation to chromanocoumaran.

Lyle reported that the compounds of the XI, XII, XIII, (−) ephedrine and (−)-*ψ*-ephedrine types showed negative Cotton effects of a similar shape; he also identified the absolute configuration of (−) halostachine (XI) as R on the basis of an unequivocal chemical correlation.15)



(XI) R=R'=H
(XII) R=H, R'=OH
(XIII) R=R'=OH

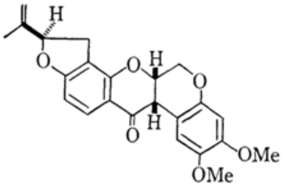
Attention must be paid to the structural similarity between the asymmetric center of halostachine (XI) and the environment of the corresponding asymmetric center of pterocarpin.

Although in the present series of compounds, the aromatic ring is not free to rotate, and the enhancement of optical activity can be observed,16) the negative Cotton effects of the asymmetric center of the R configuration in halostachine (XI) and the C^4 environment of pterocarpin are strong evidence for assuming that the asymmetric centers of these compounds have the same absolute configuration R.

Since the B/C ring junction in pterocarpin is cis,17) pterocarpin is represented as having the C^4R, C^3R, configuration IIA. Consequently, all the other chromanocoumarans which have been reported to exhibit a negative rotation can be identified as having the C^4R, C^3R configuration, IA, IIA, IVA, VIA, VIIA. Since it is apparent from Fig. 2 that C^3 in equol and the corresponding asymmetric center of dihydro-*O*-methylmaackiain-*O*-methylether have the same absolute configuration, the R configuration is assigned to be the C^3 center of equol. Then sophojaponicin8) must have the C^4S, C^3S configuration (VB). Pisatin is of particular interest in that there is an extra hydroxyl function in the angular position.

This situation leads to two benzyl alcoholic functions in a molecule which would cause a stronger rotation than in pterocarpin. The reported $[\alpha]_D$ of pisatin is +280° (pterocarpin, −230°). It is considered that an asymmetric center with an angular hydroxyl group is much less effective in causing a negative rotation because of the free rotation of the hydroxyl group. Since C^3 hydroxyl and C^4 hydrogen have cis interrelationship,17a) the C^4S, C^3S configuration (VIII) is also assigned to pisatin.

Furthermore, it follows that the absolute configuration of C^3 of sophorol is (R) (X). It is perhaps surprising that sophorol has an opposite absolute configuration in the corresponding asymmetric center of rotenone and the rotenoids, which was assigned the 4b(s) 9b(s) configuration (XIV).18)



(XIV)

Although no isoflavanone of the s-configuration has yet been found in nature, apparently two enzymatic reactions which lead to a pair of enantiomers of the isoflavanone, as shown by the coexistence of *d*-maackiain and *l*-maackiain,6) operate in plants.

The present assignment of the absolute configuration should be examined further by unequivocal chemical correlation.*

Experimental

All measurements of rotation were made on a Rudolph Model 200S, 80, photoelectricspectropolarimeter with an oscillating polarizer prism, using zirconium arc.

Sophorol.—R. D. (Fig. 1) in ethanol (*c* 0.22) 22.5°: $(\phi)_{589}$ −70°: $(\phi)_{500}$ −56°: $(\phi)_{450}$ −10°: $(\phi)_{430}$ +79°: $(\phi)_{410}$ +194°: $(\phi)_{400}$ +301°: $(\phi)_{390}$ +464°: $(\phi)_{380}$ +752°: $(\phi)_{355}$ +2726°: R. D. (Fig. 1) in dioxane (*c* 0.29) 24.5°: $(\phi)_{700}$ +41°: $(\phi)_{650}$ +54°: $(\phi)_{589}$ +65°: $(\phi)_{500}$ +161°: $(\phi)_{450}$ +332°: $(\phi)_{408}$ +710°.

Pottasium Permanganate Oxidation Product of *O*-Methyldihydropterocarpin.—R. D. (Fig. 1) in dioxane (0.024) 4.5°: $(\phi)_{665-475}$ −63°: $(\phi)_{450}$ −74°: $(\phi)_{425}$ +243°: $(\phi)_{400}$ +506°: $(\phi)_{375}$ +1212°: $(\phi)_{360}$ +4175°: $(\phi)_{350}$ +5672°.

***O*-Dimethylsophorol.**—R. D. (Fig. 1) in dioxane (*c* 0.11) 24.5°: $(\phi)_{587-475}$ +33°: $(\phi)_{450}$ +38°: $(\phi)_{400}$ +101°: $(\phi)_{368}$ +254°: $(\phi)_{359}$ +467°.

Dihydro-*O*-methylmaackiain-*O*-methylether.—R. D. (Fig. 2) in dioxane (*c* 0.15) 24.5°: $(\phi)_{650-450}$ +31°: $(\phi)_{415}$ +14°: $(\phi)_{385}$ −4.1°: $(\phi)_{355}$ −40°: $(\phi)_{340}$ −71°: $(\phi)_{330}$ −167°.

Pterocarpin.—R. D. (Fig. 2) in dioxane (*c* 0.055) 24.5°: $(\phi)_{700}$ −400°: $(\phi)_{589}$ −662°: $(\phi)_{500}$ −976°: $(\phi)_{425}$ −1396°: $(\phi)_{375}$ −1702°: $(\phi)_{365}$ −1786°: $(\phi)_{360}$ −1789°: $(\phi)_{355}$ −1786°: $(\phi)_{350}$ −1666°: $(\phi)_{340}$ −1276°.

Maackiain.—R. D. (Fig. 2) in dioxane (*c* 0.044) 24.5°: $(\phi)_{680}$ −757°: $(\phi)_{589}$ −983°: $(\phi)_{500}$ −1431°: $(\phi)_{425}$ −2030°: $(\phi)_{375}$ −2628°: $(\phi)_{365}$ −2695°: $(\phi)_{360}$ −2852°: $(\phi)_{355}$ −2771°: $(\phi)_{350}$ −2632°: $(\phi)_{345}$ −2472°: $(\phi)_{340}$ −2290°.

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15) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

16) W. J. Kauzmann, J. E. Walter and H. Eyring, *Chem. Revs.*, **26**, 339 (1940).

17) H. Suginome, *Experientia*, **18**, 163 (1962).

17a) C. W. L. Bevan, A. J. Birch, B. Moore and S. K. Mukerjee, *Tetrahedron Letters*, **1962**, 673.

18) G. Büchi, L. Crombie, P. J. Godin, J. S. Kalternbronn, K. S. Siddalingaiah and D. A. Whiting, *J. Chem. Soc.*, **1961**, 2843; C. Dierassi, W. D. Ollis and R. C. Russell, ibid., **1961**, 1448.

* After this paper was prepared, Professor S. Ito informed us that he and his colleagues had assigned C^4R, C^3R as the absolute configuration of trifolirhizin on the basis of the chemical correlation.

Homopterocarpin.—R. D. (Fig. 2) in dioxane (*c* 0.16) 24.5°: $(\phi)_{700}$ −403°: $(\phi)_{589}$ −579°: $(\phi)_{500}$ −856°: $(\phi)_{425}$ −1240°: $(\phi)_{360}$ −1699°: $(\phi)_{350}$ −1735°: $(\phi)_{340}$ −1701°: $(\phi)_{355}$ −1650°.

Equol Diacetate.—R. D. (Fig. 2) in dioxane (*c* 0.16) 24.5°: $(\phi)_{693}$ −23°: $(\phi)_{589}$ −65°: $(\phi)_{500}$ −108°: $(\phi)_{425}$ −163°: $(\phi)_{375}$ −274°: $(\phi)_{330}$ −548°: $(\phi)_{320}$ −649°.

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The author is also grateful to the following for kindly supplying samples. Dr. J. W. W. Morgan (Pterocarpin and homopterocarpin), Professor W. B. Whalley (an oxidation product of dihydropterocarpin *O*-methyl ether), and Professor Rikisaku Suemitsu (equol diacetate). Rotatory dispersions were measured through the courtesy of Professor Yuji Tonomura of the Research Institute of Catalysis Hokkaido University, in the summer of 1961.