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structural formula of 2,6-diphenyl-3,7-dioxabicyclo[3,3,0]octane derivatives with substituents R^1, R^2, R^3, R^4, and X

Figure 1: structural formula of 2,6-diphenyl-3,7-dioxabicyclo[3,3,0]octane derivatives with substituents R^1, R^2, R^3, R^4, and X

Abstract

Full Text

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ABSOLUTE CONFIGURATION OF LIGNANS OF THE 2,6-DIPHENYL-3,7-DIOXABICYCLO[3,3,0]OCTANE GROUP

At the present time, 11 natural lignans are known that are derivatives of 2,6-diphenyl-3,7-dioxabicyclo[3,3,0]octane, namely: pinoresinol, (+)-, (−)-, and (±)-sesamins, (+)- and (−)-asarinin, eudesmin, simplexoside, phillyrin, liriodendrin, and gmelinol ([1–3]). For all the compounds listed, the structural formulas (Ia)–(Iz) have been established for a comparatively long time, and many stereochemically important transformations have been studied; however, the spatial structure (in particular, the absolute configuration) has been elucidated only in part. This situation was caused by the absence of a critical analysis of the scattered experimental data available in the literature, although, as will be shown below, on the basis of the available material it is possible easily to derive the complete spatial formulas of most lignans of this group.

(Ia),	pinoresinol:	$X = \mathrm{H},\ R^1 = R^2 = R^4 = \mathrm{H},\ R^3 = \mathrm{Me}$;
(Ib),	sesamin:	$X = \mathrm{H},\ R^1 = \mathrm{H},\ R^2 + R^3 = R^3 + R^4 = \mathrm{CH_2}$;
(Iv),	asarinin:	$X = \mathrm{H},\ R^1 = \mathrm{H},\ R^2 + R^3 = R^3 + R^4 = \mathrm{CH_2}$;
(Ig),	eudesmin:	$X = \mathrm{H},\ R^1 = \mathrm{H},\ R^2 = R^3 = R^4 = \mathrm{Me}$;
(Id),	simplexoside:	$X = \mathrm{H},\ R^1 = \mathrm{H},\ R^2 = \mathrm{H},\ R^3 = \mathrm{Me},\ R^4 = \beta$-glucosyl;
(Ie),	phillyrin:	$X = \mathrm{H},\ R^1 = \mathrm{H},\ R^2 = R^3 = \mathrm{Me},\ R^4 = \beta$-glucosyl;
(Izh),	liriodendrin:	$X = \mathrm{H},\ R^1 = R^3 = \mathrm{Me},\ R^2 = R^4 = \beta$-glucosyl;
(Iz),	gmelinol:	$X = \mathrm{OH},\ R^1 = \mathrm{H},\ R^2 = R^3 = R^4 = \mathrm{Me}$.

All compounds of this series possess a cis fusion of the tetrahydrofuran rings. This follows from the fact that optically active dilactones of dioxymethylsuccinic acid (and not the corresponding meso compounds) are formed upon cleavage of

six stereochemical formulas labeled (IIa), (IIIa), (IVa), (IIb), (IIIb), and (IVb), showing relative configurations with Ar and H substituents

Figure 2: six stereochemical formulas labeled (IIa), (IIIa), (IVa), (IIb), (IIIb), and (IVb), showing relative configurations with Ar and H substituents

optically active natural lignans and a number of their derivatives with nitric acid ([2–6]). It should also be noted that the corresponding trans-fused compounds must be highly strained and, apparently, cannot be formed ([7]). With such cis fusion, the existence of three relative configurations is possible for the 2,6-diaryl-substituted derivatives under consideration: (II), (III), and (IV).

Earlier, when considering the question of the symmetry of some of these compounds, the conclusion had already been drawn that pinoresinol and sesamin possess an axis of symmetry of the second order, whereas the aglucone of phillyrin (phillygenol) must be asymmetric, as a result of which it (and therefore the glucoside itself—phillyrin) should be assigned the relative configuration (II) ([2,5,6,8–10]). At the same time, study of the composition of the equilibrium mixtures formed upon epimerization of (+)-sesamin and (−)-asarinin ([11]) led to the conclusion that sesamin has the relative configuration (III), and asarinin the configuration (II). The relative configuration of the remaining compounds of this group had not previously been established.

Since it is known that the methyl ether of phillygenol is the optical antipode of the dimethyl ether of simplexigenol (the aglucone of simplexoside) ([12–14]), and that eudesmin is the optical antipode of the dimethyl ether of pinoresinol ([8,13–15]), it may be asserted that simplexigenol and simplexoside have the asymmetric structure (II), while eudesmin has a symmetric structure similar to that of pinoresinol.

Vigorous hydrolysis of the methylenedioxy groups of (+)-sesamin and subsequent methylation lead to the formation of a mixture of the dimethyl ether of pinoresinol and the methyl ether of phillygenol ([13,14,16]). By an analogous route, from (−)-asarinin a mixture of eudesmin and the dimethyl ether of simplexigenol was obtained ([13,14]). The same mixtures of two isomers are also formed upon epimerization (under the action of alcoholic HCl) of the methyl ether of phillygenol or of the dimethyl ethers of pinoresinol and simplexigenol ([9,14,16,17]). The fact that a third pair of isomers was not detected in these mixtures may be regarded as evidence of the instability of the latter, as would be expected for compounds of type (IV). Consequently, pinoresinol and eudesmin must be assigned the remaining symmetric structure (III).

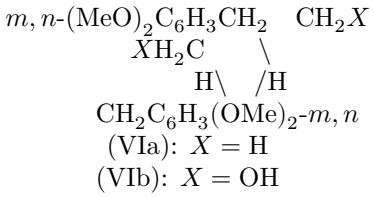
Similarly, in considering the results of acid hydrolysis of liriodendrin, it should be noted that in this case a mixture of two aglucones is obtained, isomeric with the aglucone formed upon enzymatic hydrolysis (liriioresinol C) ([3]); the latter is evidently an unstable isomer. Since the data on the molecular rotation of the corresponding derivatives show ([3]) that one of the aglucones formed upon

acid hydrolysis of liriodendrin (liriioresinol A) corresponds in configuration to phillygenol, and the other (liriioresinol B) to pinoresinol, it follows, therefore, that liriioresinol C and liriodendrin possess the configuration (IV).

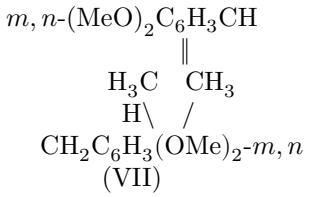
The data on the configuration of gmelinol are less definite, but in this case too a number of assumptions is permissible. Thus, the probable strain, or even impossibility of existence, of the corresponding trans-fused bicyclic systems, as well as the almost complete identity of the UV spectra of gmelinol and the dimethyl ether of pinoresinol ([18]), make it possible to suppose that gmelinol has the cis-configuration of the dioxabicyclooctane nucleus. The fact that upon epimerization of gmelinol the mixture contains only two of the three possible isomers—gmelinol and isogmelinol ([18,19])—allows one to assert that gmelinol cannot possess an unstable configuration of type (IV). The choice between the remaining possible configurations of types (II) and (III) can be made indirectly on the basis that isogmelinol, unlike gmelinol, is incapable of forming derivatives at the tertiary hydroxyl group ([20]). This may be regarded as evidence of steric hindrance to reactions in the case of isogmelinol, whence for gmelinol one may propose structure (Va) or (Vb).

[[chemical structures labeled (Va) and (Vb); two dioxabicyclooctane skeletal formulas with substituents Ar, H, OH/HO, and O atoms as shown in the source image]]

The conclusions available in the literature and those drawn by us concerning the relative configuration of natural compounds of the 2,6-diphenyl-3,7-dioxabicyclo-[3,3,0]-octane group make it possible to proceed to a discussion of their absolute configuration. It is known that catalytic hydrogenation of the dimethyl ether of pinoresinol in the presence of Pd gives (−)-diol (VIb), which can be converted into the dimethyl ether of (−)-dihydroguaiaretic acid (VIa) ([21]). Consequently, both asymmetric centers of the latter correspond to centers 1 and 5 in pinoresinol. The absolute configuration of ether (VIa) can in turn be deduced from the fact that it is formed (together with the corresponding meso compound) on reduction of the ether of (−)-guaiaretic acid (VII) ([22]), the configuration of the single asymmetric atom of which has recently been established ([23]). Knowledge of the relative configuration of all centers of pinoresinol thus makes it possible to represent its absolute configuration by formula (IIIa) and to describe pinoresinol in modern notation ([24]) as $(1R, 2S, 5R, 6S)$-2,6-diaryl-3,7-dioxabicyclo-[3,3,0]-octane. The same configuration (IIIa) is possessed by (+)-sesamin, whereas (−)-sesamin and eudesmin (the optical antipode of the dimethyl ether of pinoresinol) must possess the antipodal $(1S, 2R, 5S, 6R)$-configuration (IIIb).



(VIa): $X = \mathrm{H}$
(VIb): $X = \mathrm{OH}$



(VII)

(+)-Asarinin differs from (+)-sesamin in the configuration of only one center, C_2; therefore its absolute configuration, as well as the configuration of phillyrin, may be described as $(1R, 2R, 5R, 6S)$ and represented by formula (IIa). In accordance with this, (−)-asarinin and simplexoside must have the $(1S, 2S, 5S, 6R)$-configuration (IIb). Since the configuration of atoms C_1 and C_5 in liriodendrin must be the same as in pinoresinol, it may be assigned the $(1R, 2R, 5R, 6R)$-configuration, represented by formula (IVa). Finally, for gmelinol we consider it possible to propose the $(1S, 2S, 5R, 6R)$-configuration (Va). This assumption is based on the fact that gmelinol, isogmelinol, and a number of their derivatives have positive rotation ([18], [20]). Since the lignans described above and their derivatives, possessing structures (IIa) and (IIIa), also rotate to the right, this may serve as an indication that centers 1 and 5 of gmelinol have a similar configuration, whence formula (Va) may be assigned to it. It is true that this supposition agrees poorly with the data on the shift of optical rotation for some derivatives of gmelinol and isogmelinol ([18]).

The analysis of the experimental data carried out by us allows the absolute configuration of pinoresinol, (+)- and (−)-sesamins, (+)- and (−)-asarinins, eudesmin, and simplexosidegenol to be regarded as proven. The absolute configuration of liriodendrin may be accepted with a high degree of reliability. Since in the case of gmelinol the relative configuration has not been strictly proven, the absolute configuration proposed by us is to a certain extent hypothetical. Finally, the absolute configurations of phillyrin and simplexoside can be described only in general form—respectively by formulas (IIa) and (IIb)—since these lignans have nonequivalent aryl radicals, the positions of which have not been established. However, in the case of simplexoside the matter is somewhat simplified by the fact that the aryl residues in its aglycone are equivalent and, consequently, the absolute configuration of the latter is proven.

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Note: Figure translations are in progress. See original paper for figures.