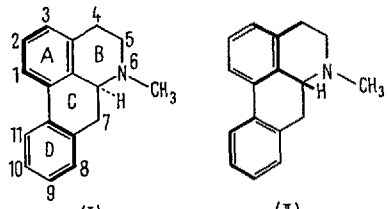
A Relationship between Ring Substituents and Absolute Configuration in the Aporphine Series[1]. The Structures of Thalicmidine and Argemonine

It has recently been found that all aporphine alkaloids possess a permanently twisted biphenyl system and that the sign of their specific rotation at 589 mμ is a true criterion of their absolute configuration[2-4]. Thus, if an aporphine is dextrorotatory its absolute configuration is as in (I), while if it is levorotatory the absolute configuration is represented by (II)[5].



(I) (II)

There are also certain other observations that can be made about this series of alkaloids. All naturally occurring aporphines are substituted at both C-1 and C-2[6]. Although positions C-9, C-10, and C-11 are the most commonly substituted positions besides C-1 and C-2, aporphines with substituents at either C-8 or C-3, such as stephanine and thalicmine, are also known. Furthermore, whenever both positions 1 and 11 are substituted, the magnitude of the specific rotation will always be large[3].

Even though any naturally occurring aporphine alkaloid may be found in a variety of different plants, the sign of its specific rotation at the sodium D line, and hence its absolute configuration, is always the same. For instance, laurotetanine is dextrorotatory, whether found in *Litsea chrysocoma* Blume (Lauraceae) or *Illigera pulchra* Blume (Combretaceae). This does not mean, however, that certain genera synthesize only aporphines of absolute configuration (I) while others produce only (II). To cite one example, *Neolitsea sericea* Blume (Lauraceae) produces both boldine which is dextrorotatory and roemerine which is levorotatory[7].

There appeared to be a possibility, therefore, that one could somehow relate the structures of the aporphines with their absolute configurations. Indeed, when such an attempt was made an interesting correlation became evident. If one considers only the substituents on ring D of the aporphines, regardless of the nature of ring A, it is found that certain substituents at particular positions can always be associated with a specific absolute configuration. For instance, the 10-methoxy-11-hydroxy combination which is present in isocorydine, norisocorydine, N-methylisocorydine chloride, corytuberine, magnoflorine iodide and bulbocapnine is always associated for biogenetic reasons with dextrorotatory bases of type (I). On the other hand, a completely unsubstituted ring D, as in roemerine, anonaine, and nuciferine, is associated with levorotatory bases of type (II).

In the Table are given different combinations of substituents for ring D, together with the aporphines and absolute configurations with which they can be associated. There is also listed a series of alkaloids each unique in the nature and positions of the ring D substituents, e.g., isothebaine, crebanine, laureline, pukateine, etc., which cannot be related at present with other known aporphines.

One wishes that more levorotatory aporphines were known to put the present correlation on a stronger basis. It is also worth noting that the extent of methylation on the nitrogen atom does not seem to affect the biosynthetic stereochemical destiny of an aporphine. For instance, isocorydine, norisocorydine, and N-methylisocorydine chloride all belong to the same absolute configuration (I) and exhibit positive rotations.

Regarding the biosynthetic process, one can state that even though the aporphines possess two centers of asymmetry, it is the asymmetric carbon atom that dominates the stereochemical picture. In other words, once the Mannich type (Pictet-Spengler) cyclization has occurred with formation of an optically active center, the two aromatic rings can be bonded together in only one stereochemical fashion. Thus, if the Mannich reaction yields an α-hydrogen on the asymmetric carbon atom, the two phenyl rings will link together as in expression (I), and conversely, if the hydrogen in question is β, the two phenyl rings will be bonded as in (II). This amounts to stating that no diastereoisomerism is possible in the aporphine series.

In the course of this correlation, there appeared to be one aporphine alkaloid which was delinquent. This is thalicmidine, a trimethoxymonohydroxyaporphine, to which YUNUSOV had assigned first structure (III)[8,9] and then structure (IV)[10,11]. On the basis of the present correlation both (III) and (IV) should be dextrorotatory. However, the Russian authors reported that thalicmidine is levorotatory, $[\alpha]_D - 84°$ (ethanol). A check on the structural determination of thalicmidine indicated that O-methylthalicmidine methiodide had been degraded to 2, 3, 5, 6-tetramethoxy-8-phenanthrenecarboxylic acid. No efforts were made actually to locate the specific position of the free hydroxy group. Now if thalicmidine is in actual fact levorotatory, a more logical structure for it on the basis of the present correlation, would be represented by the expression (V), which is related to levorotatory phanostenine in ring D.

Strong support for structure (V) is afforded by the following facts: (a) MARION[12] has recently characterized a new quaternary aporphine alkaloid from *Fagara tinguassoiba* Hoehne which is dextrorotatory and corresponds to structure (III) as the N-methyl quaternary salt. This alkaloid as the iodide is different from the methiodide salt of thalicmidine. (b) Structure (IV) corresponds to the well characterized alkaloid glaucentrine, and thalicmidine is clearly not glaucentrine from a comparison of physical properties. (c) The only remaining possibility for a 1, 2, 9, 10-tetraoxygenated aporphine possessing three methoxyl and one hydroxyl groups is represented by expression (VI)

[1] Part of a research program supported by grant G-10032 from the National Science Foundation.

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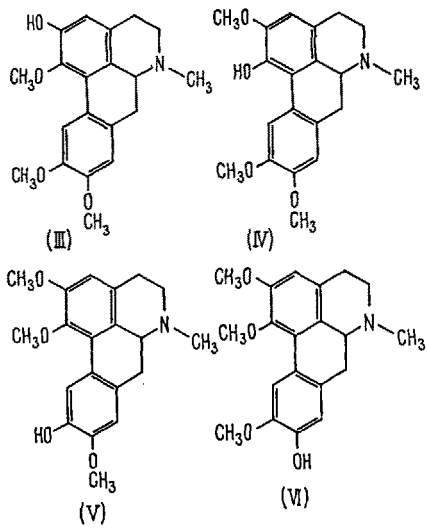
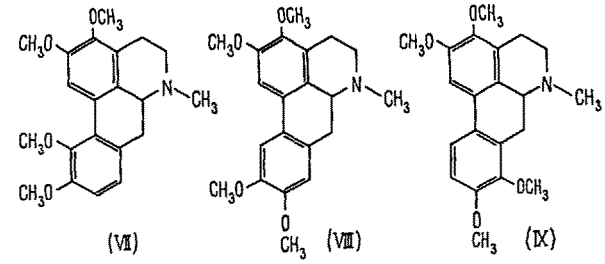


(III) (IV) (V) (VI)

which corresponds to N-methyllaurotetanine. Here again thalicmidine does not correspond to N-methyllaurotetanine. Hence the most probable structure for thalicmidine at present appears to be (V).

Another example of how the present correlation together with those previously made about the aporphines[2–4,6] can be used is in the case of argemonine, a tetramethoxyaporphine to whom SOINE has very tentatively assigned either structures (VII), (VIII), or (IX)[13].



(VII) (VIII) (IX)

Now argemonine has been found to be strongly levorotatory, $[\alpha]_D^{24} = -214°$ (ethanol). This would seem to eliminate structures (VII) and (VIII) as possibilities since, if the present correlation does hold, such structures would

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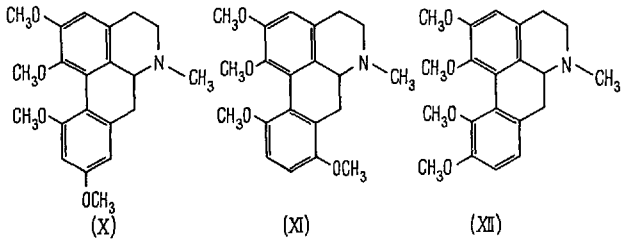
Positions of ring substituents and signs of optical rotations for the aporphines

D-Ring substituents and positions	Sign of $[\alpha]_D$	Alkaloids	
9,10-Dimethoxy	+	Glaucine:	1,2,9,10-Tetramethoxyaporphine
	+	Dicentrine:	1,2-Methylenedioxy-9,10-dimethoxyaporphine
	+	Glaucentrine:	1-Hydroxy-2,9,10-trimethoxyaporphine[14]
	+	Methochloride of 1,9,10-trimethoxy-2-hydroxyaporphine from *Fagara tinguassoiba*[12]	
9-Hydroxy-10-methoxy	+	Boldine:	1,10-Dimethoxy-2,9-dihydroxyaporphine
	+	Laurotetanine:	1,2,10-Trimethoxy-9-hydroxynoraporphine
	+	N-Methyllaurotetanine:	1,2,10-Trimethoxy-9-hydroxyaporphine
	+	Actinodaphnine:	1,2-Methylenedioxy-9-hydroxy-10-methoxyaporphine
	+	Laurifoline chloride:	1,9-Dihydroxy-2,10-dimethoxyaporphine methochloride[15]
10-Methoxy-11-hydroxy	+	Isocorydine:	1,2,10-trimethoxy-11-hydroxyaporphine
	+	Norisocorydine:	1,2,10-Trimethoxy-11-hydroxynoraporphine
	+	N-Methylisocorydine chloride:	1,2,10-Trimethoxy-11-hydroxyaporphine methochloride[16]
	+	Corytuberine:	1,11-Dihydroxy-2,10-dimethoxyaporphine
	+	Magnoflorine iodide:	1,11-Dihydroxy-2,10-dimethoxyaporphine methiodide[17]
	+	Bulbocapnine:	1,2-Methylenedioxy-10-methoxy-11-hydroxyaporphine
10,11-Dimethoxy	+	Corydine:	1-Hydroxy-2,10,11-trimethoxyaporphine
	+	Thalicmine:	1,2-Methylenedioxy-3,10,11-trimethoxyaporphine[18]
9,10-Methylenedioxy	+	Domesticine:	1-Hydroxy-2-methoxy-9,10-methylenedioxyaporphine
	+	Nantenine:	1,2-Dimethoxy-9,10-methylenedioxyaporphine
11-Methoxy	+	Isothebaine:	1-Hydroxy-2,11-dimethoxyaporphine
Unsubstituted ring D	–	Roemerine:	1,2-Methylenedioxyaporphine
	–	Anonaine:	1,2-Methylenedioxynoraporphine
	–	Nuciferine:	1,2-Dimethoxyaporphine[19]
9-Methoxy-10 hydroxy	–	Phanostenine:	1,2-Methylenedioxy-9-methoxy-10-hydroxynoraporphine[20]
	–	Thalicmidine:	1,2,9-Trimethoxy-10-hydroxyaporphine
8,9-Dimethoxy	–	Crebanine:	1,2-Methylenedioxy-8,9-dimethoxyaporphine
10-Methoxy	–	Laureline:	1,2-Methylenedioxy-10-methoxyaporphine
11-Hydroxy	–	Pukateine:	1,2-Methylenedioxy-11-hydroxyaporphine
9-Hydroxy	–	Anolobine:	1,2-Methylenedioxy-9-hydroxynoraporphine
8-Methoxy	–	Stephanine:	1,2-Methylenedioxy-8-methoxyaporphine
9-Methoxy	–	Xylopine:	1,2-Methylenedioxy-9-methoxynoraporphine
10-Hydroxy	–	Tuduranine:	1,2-Dimethoxy-10-hydroxynoraporphine
10,11-Methylenedioxy	–	Laurepukine:	1,2-Dihydroxy-10,11-methylenedioxyaporphine

be expected to be dextrorotatory. Furthermore, the high rotation of this base indicates that it must be substituted both at positions 1 and 11[3]. If argemonine is in reality an aporphine alkaloid as SOINE with good reasons believes a perhaps more logical structure for it would be represented by either expressions (X) or (XI).



(X) (XI) (XII)

Both of the above two structures fit a basic fact about the chemistry of argemonine, namely that on oxidation with manganese dioxide in sulfuric acid argemonine yields 4,5-dimethoxy-N-methylphthalimide[13]. Furthermore, (X) and (XI), being substituted at both C-1 and C-11 would be expected to have a high specific rotation and a relatively low intensity ultraviolet absorption[3]. Argemonine has indeed been found to exhibit a relatively low absorption, $\log \varepsilon = 4.01$, at 287 mμ, and as has been mentioned previously, it is strongly levorotatory[13]. Finally, structures (X) and (XI) would not violate the biogenetic rule[6] that all natural aporphines are substituted at both C-1 and C-2.

Structure (XII) is eliminated as a possibility for argemonine since: (a) The present correlation would predict that such an aporphine would be strongly dextrorotatory. (b) Argemonine has been found not to correspond to dimethylcorytuberine which is represented by structure (XII)[13].

Résumé. L'auteur démontre qu'il existe, d'une manière générale, un rapport entre les substituants du cycle D des aporphines et la configuration absolue de ces alkaloïdes. De nouvelles structures ont été proposées pour la thalicmidine et l'argémonine.

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Triterpenoid XIII. The Constitution of Barringtogenol D

The isolation of barringtogenol D, a new triterpenoid sapogenol (m.p. 305–310°, $[\alpha]_D$ + 57° (dioxane)) from the fruits of *Barringtonia acutangula* Gaertn. was reported earlier[1]. This communication deals with its complete structural elucidation.

Barringtogenol D ($C_{30}H_{48}O_4$) formed a triacetate ($C_{36}H_{54}O_7$, m.p. 233–234°, $[\alpha]_D$ + 74° ($CHCl_3$)) which accounts for three oxygen atoms in the original alcohol. The presence of an oxide linkage, indicated by a band at 1150 cm^{-1} in the IR-spectrum of barringtogenol D and its triacetate was confirmed by opening the oxide linkage of the latter with *p*-toluene sulphonic acid and acetic anhydride[2] when a crystalline tetraacetate ($C_{38}H_{58}O_8$, m.p. 284–285° $[\alpha]_D$ – 12.5°, ($CHCl_3$)) was obtained, in which the IR-band at 1150 cm^{-1} was absent (Anal. calc. for $C_{38}H_{58}O_8$: C, 71.02; H, 9.04; found: C, 70.91; H, 8.99). The same tetraacetate was also obtained by treatment of the triacetate in acetic anhydride with dry hydrogen chloride. The tetraacetate on hydrolysis gave a tetrol ($C_{30}H_{50}O_4$, m.p. 293–295°, $[\alpha]_D$ + 48° ($CHCl_3$); Anal. calc. for $C_{30}H_{50}O_4$: C, 75.90; H. 10.62; found: C, 75.80; H, 10.55).

The ethylenic linkage in barringtogenol D, indicated by tetranitromethane colour, is hindered. The triacetate could neither be hydrogenated over Adams' catalyst nor did it react with selenium dioxide[3], but it consumed nearly 1 mole of perbenzoic acid extremely slowly. Evidence for the typical 12:13 double bond was obtained by oxidation of the triacetate with CrO_3 to yield an $\alpha\beta$-unsaturated ketone (m. p. 256–258°, λ max 241 mμ ($\log \varepsilon$ 4.1)) which is at a slightly lower wave length than is usually observed for 11-keto Δ^{12}-triterpenes[4] of the β-amyrin series. The tetraacetate consumed 1 mole of perbenzoic acid at a rate typical of the triterpenes of the β-amyrin group. The unusually hindered nature of the ethylenic linkage in barringtogenol D is probably due to the shielding effect of the oxide bridge[5,6].

The ready formation of the triacetate (at room temperature) indicated the hydroxyl groups to be primary and/or equatorially oriented secondary hydroxyl functions[7]. Barringtogenol D did not react with periodic acid but readily formed a monoacetonide ($C_{33}H_{52}O_4$, m.p. 233–236°, $[\alpha]$. + 33° ($CHCl_3$); Anal. calc. for $C_{33}H_{52}O_4$: C, 77.29; H, 10.22; found: C, 77.25; H, 10.21). The acetonide formation showed the presence of a 1:3 glycol system. Oxidation of the acetonide by SARETT's method[8] furnished a colourless crystalline product ($C_{33}H_{50}O_4$, m.p. 212–213°, $[\alpha]_D$ + 57° ($CHCl_3$); Anal. calc. for $C_{33}H_{50}O_4$: C, 77.60; H, 9.86; found: C, 77.59; H, 9.42). It has been characterized as a 3-keto derivative by Zimmerman's test and optical rotatory dispersion curve (through the courtesy of Prof. C. DJERASSI of Stanford University, USA). Further, we have evidence for believing that barringtogenol D contains no other substituents except the 3β-hydroxyl group in ring A. The 3β-configuration was confirmed by the molecular rotational data[9]. The secondary hydroxyl group of the 1:3 glycol, which of necessity should be in D/E ring, was unusually hindered toward chromic acid oxidation under varied conditions. The sapogenol, when treated with chromium trioxide-sulphuric acid in acetone[10], gave neutral and acid products. The ester of the acid on chromatographic resolution furnished two colourless crystalline compounds, characterized as methyl di-

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