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THE GINKGOLIDES. III[1, 2]. THE STRUCTURE OF THE GINKGOLIDES

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In the two preceding communications[1, 3], we have shown that Ginkgolide A (GA) must contain the partial structures I, II and III (a or b). By considering the various ways in which these partial structures can be combined to give a $C_{20}H_{24}O_9$ molecule, and by eliminating those structures which are obviously inconsistent with the properties of the ginkgolides and their derivatives, the unique " planar" structure V (i) can be derived for GA.

Since GA has no double bond, the molecular formula $C_{20}H_{24}O_9$ requires it to be either a cyclic ether with two carbocyclic rings or an acyclic ether with three carbocyclic rings. The only acyclic ether which can be constructed from I, II and III (a or b) is one containing a tert-butoxy grouping, and this is not in accord with the formation of pivalic acid in the Kuhn-Roth oxidation. Therefore rings A and B (Fig. 1) are the only two carbocyclic rings in GA.

The combination I/II/IIIa contains a total of eleven carbons (Fig. 1) which cannot be involved in carbocyclic rings, hence the two carbocyclic rings (i. e., rings A and B in II and IIIa, respectively,) must contain a maximum of nine carbons. This and the known substitution patterns of rings A and B require these two rings to form a spiro[4, 4]nonane system which, moreover, can only be formed through overlap of C_5 with C_2 or C_3. This combination (I/II/IIIa) contains 17 unique carbons (Fig. 1). Moreover, the three carbons, C_1, C_2 and C_3, cannot overlap with one another, which means that all 20 carbons have now been defined. Carbon C_4 (and similarly C_6 and C_7) must therefore be identical with either C_1 or C_3 (or C_2, depending on whether C_5 overlaps with C_2 or C_3). Since C_1/C_4 and C_1/C_7 overlaps are forbidden (they would lead to a tert-Bu ether or pivalic acid ester, neither of which is the

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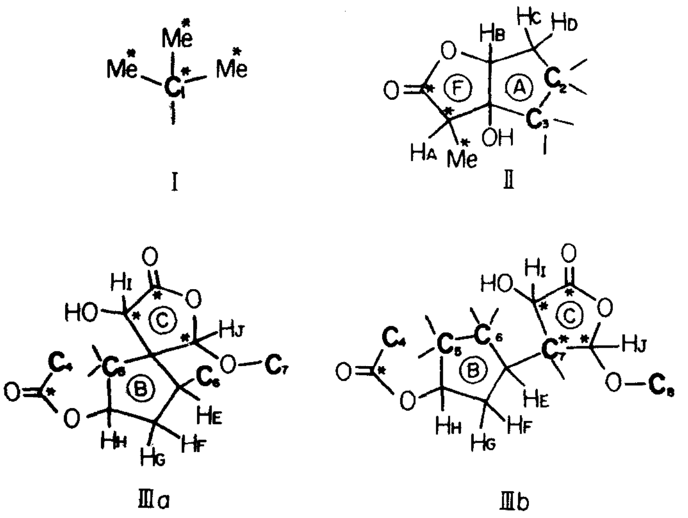
* from Varian Associates.



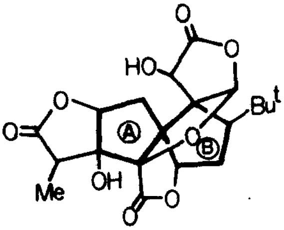
	I	II	IIIa	IIIb
No. of unique✦ carbons	3	6	8	7
No. of carbons which cannot be in carbocyclic rings (carbons marked *)	4	3	4	5

Carbons numbered 1 to 8 are <u>fully substituted</u> and are not unique✦.

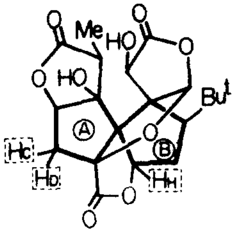
✦ The <u>unique carbons</u>, which include all the unnumbered carbons in I, II and III (a or b), cannot be identical with any other carbon in these partial structures.

Fig. 1

case), C_1 must overlap with C_6. Consequently both C_7 and C_4 must overlap with C_3 (or C_2), and this leads to structures V (i) and V (ii) which are the only possible structures derivable from a I/II/IIIa combination.



V(i)

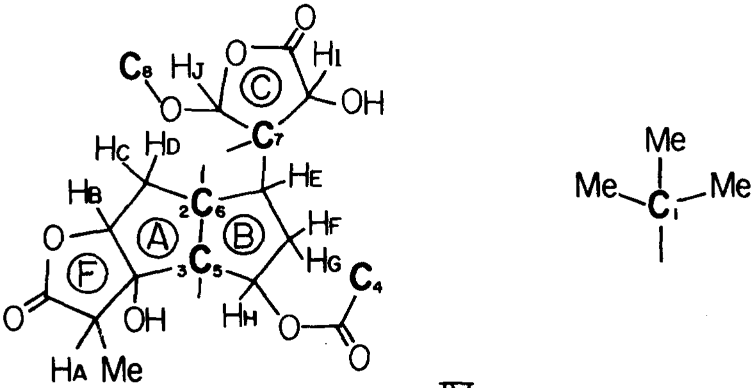


V(ii)

Similarly, a I/II/IIIb combination leads to only six possible structures. Since in this combination a total of twelve carbons are <u>not</u> involved in carbocyclic ring formation (Fig. 1), only <u>eight carbons can be in the two carbocyclic rings</u> A and B, which cannot be spiro and therefore must form a bicyclo[3, 3, 0]octane system; the substitution pattern of these two rings

(rings A and B in II and IIIb, respectively) excludes a bridged-ring system. Fusion of rings A and B must involve a C_2/C_6 and C_3/C_5 or C_2/C_5 and C_3/C_6 overlap, and, since the difference between these two alternatives in no way affects the remainder of this argument, only the former alternative IV (C_2/C_6 and C_3/C_5 overlaps) will be considered.

The combination I/II/IIIb with a C_2/C_6 and C_3/C_5 overlap (IV) contains 16 unique carbons and, since C_1, ${}_2C_6$, ${}_3C_5$ and C_7 cannot overlap with one another, accounts for all twenty carbon atoms. C_4 and C_8, neither of which can be identical with C_1, must therefore overlap with two of the carbons, C_7, ${}_2C_6$, ${}_3C_5$, the remaining one being linked to C_1. This leads to the following combinations.

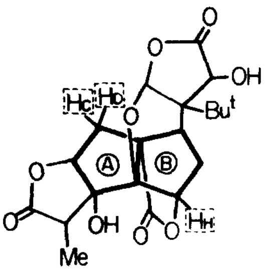


IV

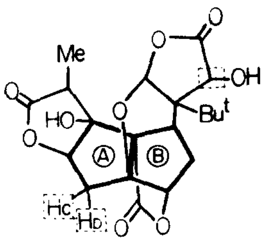
(1) C_1-C_7 + $C_4/{}_2C_6$ + $C_8/{}_3C_5$ = Structures VI (i) and (ii)
(2) C_1-C_7 + $C_8/{}_2C_6$ + $C_4/{}_3C_5$ (Note 1)
(3) C_1-${}_2C_6$ + C_4/C_7 + $C_8/{}_3C_5$ = Structures VI (i) and (ii)
(4) C_1-${}_2C_6$ + C_8/C_7 + $C_4/{}_3C_5$ (Notes 1 and 2)
(5) C_1-${}_3C_5$ + C_4/C_7 + $C_8/{}_2C_6$ = Structures VIII (i) and (ii)
(6) C_1-${}_3C_5$ + C_8/C_7 + $C_4/{}_2C_6$ (Note 2)

Note 1. The $C_4/{}_3C_5$ overlap results in a four-membered lactone ring which is not in accord with the IR spectra or ease of relactonization of the ginkgolides nor with the NMR spectrum of the "triether" (Part $V^{4)}$) which shows $J_{e,e'}$ = 10.5 cps. Structures containing a $C_4/{}_3C_5$ overlap may therefore be neglected.

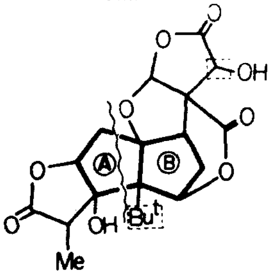
Note 2. A C_8/C_7 overlap would mean the ginkgolides contain an epoxy-α-hydroxylactone, which is most unlikely in view of the behaviour of the ginkgolides with alkali (Part $IV^{5)}$).



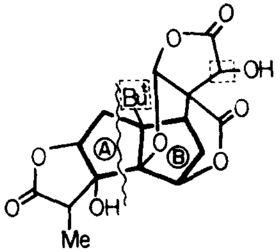
VI(i)



VI(ii)



VII(i)



VIII(i)

Arrangements (1), (3) and (5) correspond to structures VI (i and ii), VII (i and ii), and VIII (i and ii), respectively; the second structure in each pair results from the alternative mode of fusion of rings A and B (i. e., a C_2/C_5 and C_3/C_6 overlap). Of the eight possible structures V to VIII derived for GA, VII (i) and (ii), and VIII (i) and (ii) do not have the tert-Bu and the carbonyl (from oxidation of the ring C hydroxyl) in dehydro-GA sufficiently close to permit the photochemical ring closure (Part IV[5)]); the four structures are also incompatible with the intramolecular Overhauser effect (Part V[4)]).

Structures V (ii) and VI (i) can also be eliminated, since the separation between proton H and proton D in these structures is too great to account for the deshielding of proton H (at 5. 04 ppm in GA) observed in GB (5. 73 ppm), GC (5. 60 ppm) and GM (5. 49 ppm) which have a hydroxyl group in place of proton D.

Finally, structure VI (ii) can be discarded for the following reason. In the "triether" (Part V[4)]), a GA derivative in which all the lactone carbonyls have been reduced to methylenes without any skeletal change, oxidation of the sec-OH to a ketone[1)] causes protons C and D to undergo up-field shifts of 0. 34 and 0. 61 ppm. A dehydro-GA triether derived from structure VI (ii) cannot account for this shielding of protons C and D by the ketone grouping.

There remains only one possible structure for GA, namely V (i), which can account satisfactorily for all the known chemical and spectroscopic properties of the ginkgolides.

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1) Part II. M. Maruyama, A. Terahara, Y. Itagaki and K. Nakanishi, Tetrahedron Letters, this issue.

2) Supported by the National Institutes of Health, Public Health Service Research Grant No. CA08394.

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