THE GINKGOLIDES, III\(^{1, 2}\). \hspace{1em} THE STRUCTURE OF THE GINKGOLIDES

M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods\(^*\) and K. Nakanishi

Department of Chemistry, Tohoku University, Sendai, Japan.

(Received 23 October 1966)

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 \(\text{C}_{20}\text{H}_{24}\text{O}_9\) 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 \(\text{C}_{20}\text{H}_{24}\text{O}_9\) 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/III\(a\) 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 III\(a\), 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/III\(a\)) 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

\(^*\) from Varian Associates.
No. 4

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 fully substituted and are not unique*.

* The unique carbons, 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), C₁ must overlap with C₆. Consequently both C₇ and C₄ must overlap with C₃ (or C₂), and this leads to structures V (i) and V (ii) which are the only possible structures derivable from a I/II/IIIa combination.

Similarly, a I/II/IIIb combination leads to only six possible structures. Since in this combination a total of twelve carbons are not involved in carbocyclic ring formation (Fig. 1), only eight carbons can be in the two carbocyclic rings 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.
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 C₄/C₅ and C₃/C₆ 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 IV⁵); the four structures are also incompatible with the intramolecular Overhauser effect (Part V⁴).

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 V⁴), 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 ketone¹ 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.

REFERENCES


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

