The Structure of Ginkgolide A, a Novel Diterpenoid Trilactone

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GINKGOLIDE A is one of the bitter principles[1] from *Gingko biloba* L., which is a gymnospermous tree and a single surviving species of the family *Ginkgoaceae*, comprising Mesozoic plants. In this Communication we report the isolation of the three diterpenoids, their chemical and physical properties and the *X*-ray analysis of a mono-*p*-bromobenzoate of ginkgolide A.

The aqueous extracts of the leaves were treated with charcoal, which absorbed bitter principles effectively. The collected charcoal was washed with hot acetone. Concentration of the acetone extract gave crude crystalline bitter principles. Three crystalline compounds were obtained as ethanolates in pure form by fractional crystallization from ethanol: (1) ginkgolide A (I): m.p. *ca.* 300° (decomp.), $C_{20}H_{24}O_9$,* $[\alpha]_D^{24} -53{\cdot}4°$ (*c* 1, EtOH); (2) ginkgolide B (II): m.p. *ca.* 300° (decomp.), $C_{20}H_{24}O_{10}$,* $[\alpha]_D^{24} -52{\cdot}6°$ (*c* 1, EtOH); (3) ginkgolide C (III): m.p. *ca.* 300° (decomp.), $C_{20}H_{24}O_{11}$,* $[\alpha]_D^{24} -14{\cdot}7°$ (*c* 1, EtOH); The n.m.r. spectrum (in deuterioacetone) of (I) showed signals at 1·28 p.p.m. (3H, doublet, J = 7 c./sec.) due to a secondary methyl group and at 1·17 p.p.m. (9H, singlet) arising from three tertiary methyl groups. The presence of two hydroxyl groups in (I) was revealed by the formation of a diacetate, $C_{24}H_{28}O_{11}$, m.p. 291°, ν_{max} (KBr) 1805, 1795 cm.$^{-1}$, on treatment with acetic anhydride and pyridine under reflux for 2 hr. and also by the signals of the n.m.r. spectrum at 5·12 p.p.m. (1H, singlet) and at 5·79 p.p.m. (1H, doublet, J = 5 c./sec.), which disappeared on addition of deuterium oxide. Potentiometric titration of (I) showed three lactones, the γ-lactonic nature of which was detected by strong absorption bands at 1802, 1780, and 1773 cm.$^{-1}$ in the infrared spectrum (KBr). Chemical correlation of (I) and (II) was achieved: treatment of (I) with acetic anhydride and sodium acetate gave an $\alpha\beta$-unsaturated γ-lactone monoacetate, $C_{22}H_{24}O_9$, m.p. 297° (decomp.), λ_{max} (EtOH) 216 mμ (log ϵ, 4·07), ν_{max} (KBr) 1793, 1778, and 1760 cm.$^{-1}$, which, by catalytic hydrogenation with palladium in ethanol with the uptake of one mole of hydrogen, afforded a saturated monoacetate, $C_{22}H_{26}O_9$, m.p. 300° (decomp.), ν_{max} (KBr) 1800, 1785, and 1765 cm.$^{-1}$. This compound was also obtained from (II) by the same two-step reactions as in (I).† On oxidation with chromic acid in acetic acid, (II) gave pivalic acid, indicating the presence of a t-butyl group.‡ From the chemical correlation of (I) and (II), together with the isolation of pivalic acid by the oxidation of (II), it is evident that (I) also has a t-butyl group.

From the chemical and spectral data described above, it is concluded that (I) contains a secondary methyl group, three tertiary methyl groups which constitute a t-butyl group, two hydroxyl groups, and three γ-lactones.

This Communication describes the complete structure and stereochemistry of (I), including the absolute configuration as determined by the *X*-ray crystallographic analysis of its *p*-bromobenzoate.

Treatment of ginkgolide A, which has two hydroxyl groups, with sodium hydride and *p*-bromobenzoyl chloride in tetrahydrofuran,§ gave two mono-*p*-bromobenzoates. They were separated by chromatography on silica gel and recrystallized from ethanol to give white needles and prisms. The prismatic crystals were studied by *X*-ray analysis.

Crystal data were: $C_{27}H_{27}O_{10}Br,2C_2H_5OH$; M = 591·44 + 92·14; monoclinic, a = 12·54 ± 0·03, b = 12·69 ± 0·03, c = 11·52 ± 0·03 Å, β = 57°49′; Z = 2, D_m = 1·46, D_c = 1·463 g.cm.$^{-3}$; space group $P2_1$; absorption coefficient for *X*-rays (λ = 1·542 Å) μ = 25·5 cm.$^{-1}$.

Small crystals which were covered by collodion to prevent the loss of ethanol molecules, were employed for the intensity measurement and no corrections for absorption were applied. Intensity

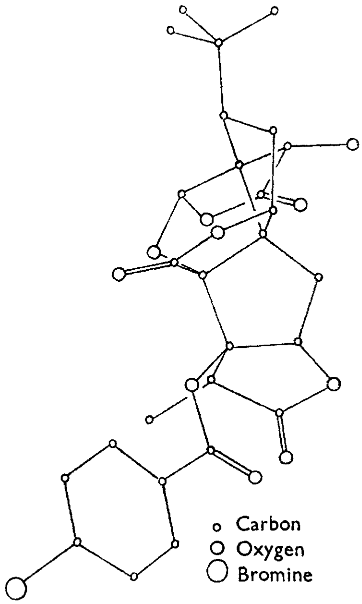

FIGURE 1. *Molecular structure projected along the* b-*axis.*

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* Satisfactory analyses were obtained for the samples prepared by heating under reduced pressure to remove ethanol from the crystals.

† In the first step, (II) afforded an $\alpha\beta,\gamma\delta$-unsaturated γ-lactone monoacetate, $C_{22}H_{22}O_9$, m.p. *ca.* 300°(decomp.), λ_{max} (EtOH) 284 mμ (log ϵ, 4·10), ν_{max} (KBr) 1790 br, 1760, 1685, and 1640 cm.$^{-1}$. This was reduced by catalytic hydrogenation with the uptake of two moles of hydrogen to give the saturated monoacetate.

‡ On oxidation of (I) under the same conditions as those used in (II), an unusual oxidation involving the t-butyl group occurred.

§ In this procedure the normal *O*-benzoylation occurs without any structural changes; ginkgolide A is recovered unchanged after treatment with sodium hydride in tetrahydrofuran.

data were taken with Cu-K_{α} radiation from equi-inclination Weissenberg photographs of layers $0kl \rightarrow 4kl$ and $h0l \rightarrow h6l$ by using multiple film technique. The relative intensities were estimated visually by comparison with a standard chart, and relative values of the observed structure factors of 2228 independent reflections were converted to the absolute scale.

The co-ordinate of the bromine atom was determined from a three-dimensional sharpened Patterson synthesis. Using the co-ordinate of the bromine atom, the three-dimensional minimum function method was used for obtaining the positions of the light atoms. The whole structure was elucidated by successive application of the Fourier syntheses and the least-squares method. The final molecular structure projected along the b-axis is illustrated in Figure 1. The reliability factor, R, was converged to a rather high value ($R = 19{\cdot}02$). This may be due to the fact that the ethanol molecules were lost gradually, in spite of the crystals being covered by collodion, resulting in large temperature factors.

The absolute configuration of this compound has been determined by the method of Bijvoet, Peerdeman, and van Bommel (1951). Thus the complete chemical formula and absolute configuration of ginkgolide A was deduced as shown in Figure 2.

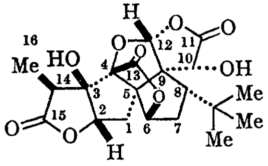

FIGURE 2. *The complete chemical formula and absolute configuration of ginkgolide A.*

Ginkgolide A has a novel structure, in which the carbon skeleton is spiro[4,4]nonane, with a t-butyl substituent. These features have not previously been encountered in diterpenoid chemistry. Moreover it has three γ-lactones and a five-membered-ring acetal, and they form a complicated molecular skeleton.

The calculations were performed on the NEAC-2206 electronic computer using our own programs.

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[1] (a) S. Furukawa, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1932, **19**, 27; (b) K. Nakanishi, "IUPAC Symposium on the Chemistry of Natural Products", Stockholm, 1966, p. 9. (c) K. Maruyama, *et al.*, *Tetrahedron Letters*, 1967, 299, 303, 309 and 315.