Spectroscopic Properties of Two Nonenolizable α-Keto-γ-lactones, Dehydroginkgolide A and 3,3-Dimethyl-2-oxo-γ-butyrolactone

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Summary Dehydroginkgolide A (IIa) is converted into a 4:1 mixture of the ester hemiacetal (IIb) and ester aldehyde (IIc) in 30 min. when dissolved in methanol, whereas 3,3-dimethyl-2-oxo-γ-butyrolactone (IV) rapidly adds methanol to give (V).

DURING structural studies on ginkgolides, a group of diterpenes with unique cage structures,[1a-g] it was found that sodium bichromate oxidation of ginkgolide A (GA) (I) gave dehydro-GA (IIa), [1b] i.r. (MeCN) 1803, 1780 cm.$^{-1}$, which, in addition to its unexpected and easy conversion into photodehydro-GA,[1d] exhibited very confusing spectroscopic properties.‡ The λ_{max} around 400 nm vanishes after 30 min. and is replaced by maxima at 333 nm and 264 nm [curve (ii) Figure 1];‡ an isosbestic point is present at 357 nm at a concentration of $1{\cdot}06 \times 10^{-2}$ M. The peaks at 409 and 388 nm disappear very rapidly in more dilute solution ($1{\cdot}3 \times 10^{-3}$ M) leaving one peak at 333 nm (ϵ 40); after 70 min. curve (ii), accompanied by an isosbestic point at 313 nm. The c.d. curve remains unchanged in tetrahydrofuran [curve (iii)]; however, it changes in methanol and after 30 min. gives curve (iv), Figure 1. The intensity of the broad 1790 cm^{-1} i.r. band (MeOH) decreases with time and shoulders appear at 1750 and 1713 cm^{-1}. These

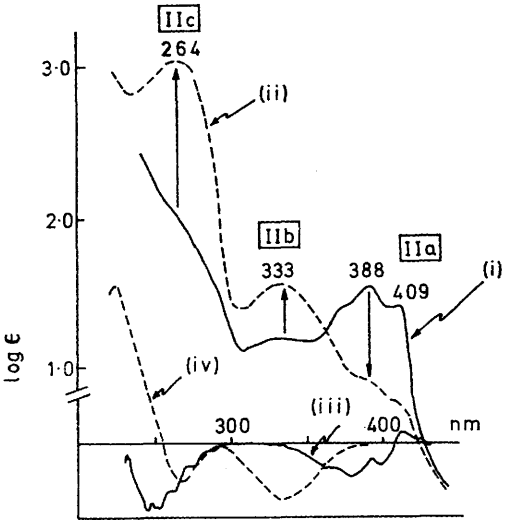

FIGURE 1. *U.v. and c.d. of* (IIa), (IIb), and (IIc) (i): *u.v. in methanol immediately after preparation of solution*; (ii): *u.v. in methanol after* 30 *min.* (*equilibrium*); (iii): *c.d. in tetrahydrofuran*; $\Delta\epsilon_{414}$ + 0·12, $\Delta\epsilon_{401}$ − 0·23, $\Delta\epsilon_{380}$ − 0·36, $\Delta\epsilon_{253}$ − 0·76; (iv): *c.d. in methanol after* 30 *min.* (*equilibrium*); $\Delta\epsilon_{335}$ − 0·47, $\Delta\epsilon_{264}$ − 0·35, $\Delta\epsilon_{220}$ + 5·46.

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‡ It is now clear that in the Figure on p. 307 in ref. 1b, the u.v. curve in methanol is that of the equilibrium mixture of (IIb) and (IIc); on the other hand, the o.r.d. curve in tetrahydrofuran is that of dehydro-GA (IIa). See also p. 317 in ref. 1d and footnote in ref. 1f.

spectral changes also occur in ethanol but not in t-butyl alcohol.

This behaviour can be ascribed to the equilibria between (IIa), (IIb), and (IIc) (Chart). Furthermore the ring-cleaved compounds yield interesting photochemical products.[2] The methanolysis product (IIb) was isolated in powder form by dissolving (IIa) in methanol, and after 2 hr., evaporating the solvent and drying the residue at 120° for 4 hr. [i.r. (MeCN) 1788, 1745, 1710 cm^{-1}]; (IIa) was recovered upon recrystallization from acetone–water. The u.v. and c.d. curves of (IIb) in tetrahydrofuran [Figure 2, curves (i) and (iii)] changed to those of (IIa) after 24 hr. [Figure 2, curve (ii), and Figure 1, curve (iii), respectively]. Conversely, in methanol, they changed to curves (ii) and (iv) in Figure 1. The cleaved keto-ester structure rests on the n.m.r. data: (in deuterioacetone) 3·79 (s, OMe), 6·14 (d, *J* 4·5, 12-H), 7·46 p.p.m. (d, *J* 4·5, sec-OH). Moreover, it was fully confirmed by the u.v. [λ_{max} (MeOH) 334 nm. (ϵ 34)] and o.r.d. [Φ_{368} (MeOH) -880, Φ_{246} (MeOH) $+8600$] of the ester acetal (III), m.p. 240°, which were almost identical with those of (IIb) in methanol (immediately after preparation). Derivative (III) was prepared by treatment of GA (I) with Me_2SO_4 (opening of ring C and methyl acetal formation), followed by CH_2N_2 (methylation) and then cupric acetate (oxidation of 10-OH). It is therefore clear that the 409—388 nm. peak and the 333 nm. peak (Figure 1) owe their geneses, respectively, to the nonenolizable keto-lactone[3] in (IIa) and the keto-ester in (IIb).

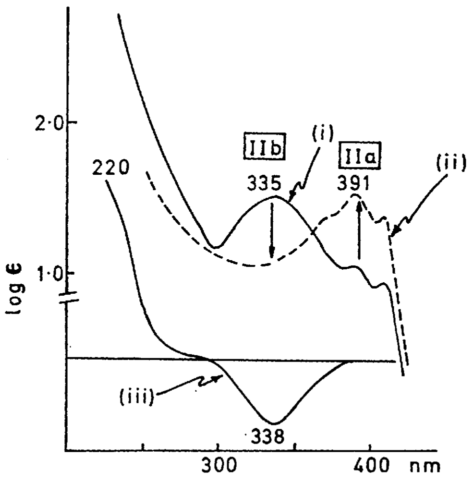
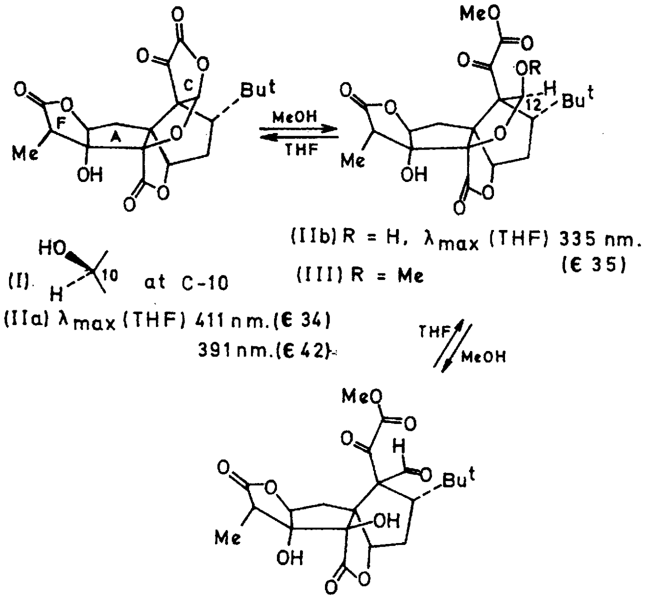


FIGURE 2. *U.v. and c.d. of* (IIa) *and* (IIb): (i): *u.v. in tetrahydrofuran immediately after preparation of solution*; (ii): *u.v. in tetrahydrofuran after* 1 *day*; (iii): *c.d. in tetrahydrofuran immediately after preparation of solution*; $\Delta\epsilon_{338}$ − 0·66, $\Delta\epsilon_{220}$ + 5·30.

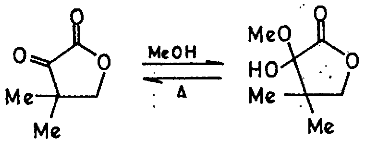
The aldehyde ester (IIc) could not be isolated as a single compound, but gave a 4:1 mixture of (IIb) and (IIc) (based on intensity of the n.m.r. aldehyde proton at 8·05 p.p.m. in CD_3OD) upon evaporation of a methanol solution of (IIa) after 2 hr., and drying the residue at room temperature; u.v. and c.d. (tetrahydrofuran, immediately after preparation) 335 (ϵ 36, $\Delta\epsilon$ −0·45), 265 (ϵ 1200, $\Delta\epsilon$ −0·27), 224 nm ($\Delta\epsilon$ +5·60, lactones). The changes in the u.v. and c.d. curves in tetrahydrofuran and in MeOH were similar to those of (IIb). The 265 nm. peak of (IIc) (ϵ *ca.* 4400, estimated from intensity of n.m.r. aldehyde proton and ϵ in MeOH) may be caused by interaction between the aldehyde and keto-ester functions: otherwise its origin is obscure.[4]

The properties of the simplest nonenolizable α-keto-γ-lactone (IV) were studied for comparison. Oxidation of 3,3-dimethyl-2-hydroxy-γ-butyrolactone[5] with chromic acid–acetic acid gave the keto-lactone (IV), m.p. 63—64°: i.r. ($CHCl_3$) 1797, 1786 cm^{-1}: u.v. ($CHCl_3$) 382 (29); (cyclohexane) 219 nm. (193); n.m.r. ($CDCl_3$) 1·32 (s, Me), 4·47 p.p.m. (s, CH_2). U.v. (MeOH, 2 min. after preparation) has peaks at 368 (16) and 215 nm. (ϵ 170), which on the basis of the solvent shifts are assignable, to a first approximation, to $n \rightarrow \pi^*$ transitions of the ketone and lactone groups, respectively; however, after 20 min. the spectrum shows only one peak at 219 nm. Similarly, the i.r. spectrum of lactone (IV) in MeOH shows an intense band at 1784 cm^{-1} which shifts to 1780 cm^{-1} with a decrease in intensity during measurement; its n.m.r. (MeOH) has two methyl singlets at 1·02 and 1·03 p.p.m. These spectroscopic properties indicate that methanol rapidly adds to the ketone group to give adduct (V) and that the equilibrium is almost exclusively in favour of the adduct. The starting lactone (IV) is recovered upon evaporation of solvent.



(IIc) λmax (MeOH) 265 nm. (calcd. ε 4400)

CHART



(IV) (V)

The transformations in methanol are most probably caused by the dipole–dipole interaction and ring strain due to the cisoid α-dicarbonyl functions. In dehydro-GA, methanol attacks the lactone carbonyl rather than the ketone at C-10 because of the severe crowding imposed on this centre by ring F and the Bu^t group.[6]

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[6] The steric crowding is evidenced by the 30% NOE observed with the 10-H n.m.r. signal in GA (I) upon irradiation of the Bu^t group. [1e,1f]