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STEREOSPECIFIC ALKYLATIONS OF A GAMMA-LACTONE

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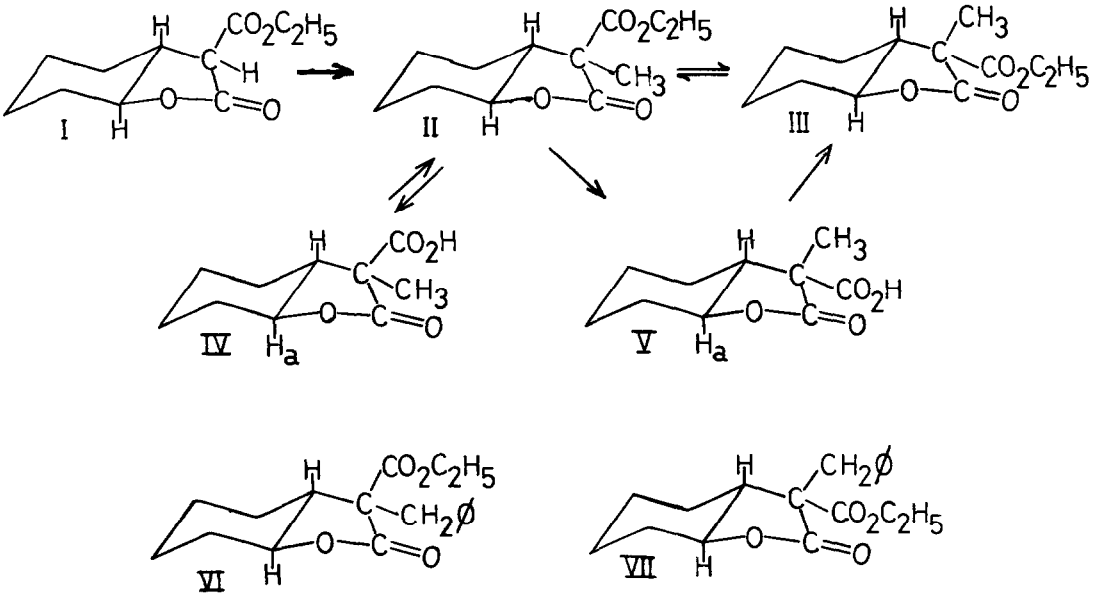
The α-methyl-γ-butryolactone structural unit occurs in many sesquiterpene lactones, and particular interest has been shown in the stereochemistry of model lactones (1,2) related to the controversial α- and β-santonin series (3). We wish to report the stereospecific alkylation of the lactone I and the stereoselective conversion of II, at will, either to the lactono-acid IV or to its stereoisomer V.



Previous syntheses of the lactono-acids IV and V (4) and of closely related α-methyl-lactono acids (5) led to mixtures of stereoisomers of indeterminate configuration.

When the dry sodium enolate salt of I (6) was heated with methyl iodide in dry aprotic solvents (benzene or N,N-dimethylformamide (D.M.F.) at 80°, or tetrahydrofuran (T.H.F.) under reflux), proton magnetic resonance spectroscopy (n.m.r.) showed, even in the crude oily product,

the presence of only one stereoisomer (τ-CH_3, 8.64). Its structure was II, the methyl group having been introduced into a pseudo-axial position trans to the adjacent ring proton. When II was heated with excess ethanolic potassium hydroxide, and the product acidified, there was formed the lactono-acid IV (τ-CH_3, 8.64), accompanied by less than 5% of its isomer V. From this, II was regenerated with diazoethane; thus II and IV had the same configuration. With diazomethane, IV gave the corresponding methyl ester as beautiful long needles, m.p. 62.8-63.2°.

A completely different steric course was followed when II was carefully treated with one equivalent of potassium hydroxide, followed by acidification. The only product was the stereoisomeric acid V (τ-CH_3, 8.53), which with diazoethane gave III (τ-CH_3, 8.53). Though both acids were crystalline solids of m.p. 146-147° (lit. 151-152°) (4), their mixture melting point was 122-129°. Presumably the remarkable influence of the amount of alkali upon the stereochemistry of ring closure was partly due to closure occurring with a carboxyl group to give IV, and with a carbethoxyl group to give V.

Nuclear Overhauser experiments gave conclusive proof that the above assignments of structure were correct. Irradiation of IV at the resonance frequency of the α-methyl group produced an increase in intensity of 15% in the signal due to H_a, but of only 8% with V, relative to the signal from irradiation at a "distant" frequency. Furthermore, the effect of the ring protons, geometrically near H_a, spectroscopically near the methyl peak, and common to both IV and V, was removed by varying the irradiation frequency, with IV, but not at all with V, there was a sharp increase in the intensity of the H_a peak as the irradiation frequency passed through the methyl resonance.

Alkylation in ethanol-benzene as solvent was not stereospecific: a mixture of II and III being obtained. Isomer III was slightly the more stable thermodynamically. when either II alone or a mixture of II and III was heated in ethanol-benzene with a trace of the sodium salt of I, compound III predominated over II approximately in the ratio 1.5:1 (by n.m.r.). A similarly equilibrated mixture of methyl esters resulting from an alkylation in methanol-benzene showed the same preponderance of the isomer corresponding to III. Although this difference in stability is in the same direction as in the santonin series (the larger group preferring the pseudo-equatorial position or cis to the adjacent ring proton), it is small, and we urge caution in the application of the qualitative arguments that have been used in this series (7).

Much larger and more striking differences between the results of rate control of the stereochemistry of alkylation in aprotic solvents and of equilibrium control in ethanol-benzene were observed when the sodium salt of I was heated with benzyl chloride. With T.H.F. (at reflux) or D.M.F. (at 100°) as solvent, the crude product consisted mainly of VI, and stereoisomers were absent. (A fast moving by-product, perhaps due to O-benzylation, and about 10% of slow-moving starting compound were separated from VI by column chromatography on silica gel with petroleum ether-ethyl acetate 4:1). Equilibration of VI in ethanol-benzene with the sodium salt of I gave complete conversion (n.m.r.) to its stereoisomer VII. Thus the difference in stability of the two isomers was much greater than with the methyl analogues II and III, and (as was not true for the methyl analogues), Dreiding models left no doubt that the ester of structure VII was the more stable. This seemed to be confirmed by the greater chemical shift difference of the benzyl protons in the compound thought to be VI ($\Delta\tau$ = 0.38, J = 14 Hz) than in that thought to be VII ($\Delta\tau$ = 0.13, J = 14 Hz), in agreement with the much more restricted conformational occupancies possible to the benzyl group in VI. Some support to the assignments of structure was also given by the relative chemical shifts of two poorly resolved parts of the spectra. The signal for H_a in VI was upfield from that of VII by approximately 0.2 τ, very similar to the difference observed for the methyl analogues, and presumably due to the relative positions of the carbethoxyl group. Similarly, a major lobe due to alicyclic hydrogens in VII was upfield from any part of the corresponding signal of VI, consistent with the shielding positions of the benzene ring possible in some conformations of VII, but not of VI, an effect not seen in the methyl series.

Alkylation in aprotic solvents led exclusively to the less stable axial product in our examples. We agree with Kuehne and Nelson (8) as to the main factor responsible for this result in the two possible transition states, there is greater ease in maintaining the coplanarity of the carbanion in the one leading to the axial product. Our examples seem to be more free from other effects than theirs, and have the advantage of making clear that the steric course is rate-controlled and not stability-controlled.

All new compounds have been characterized by n.m.r., infra-red, T.L.C. or m.p., and II, IV, V, VI, and VII by satisfactory elemental analysis. We thank the National Research Council of Canada for financial support.

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