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THE NOVEL SYNTHESIS AND LACK OF REACTIVITY OF ETHYL N-2[1-HYDROXY-2-METHYLPROPYL]-3,3'-IMINO-2,2,2',2'-TETRAMETHYLDIPROPIONATE-ε-LACTONE

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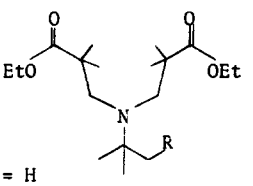
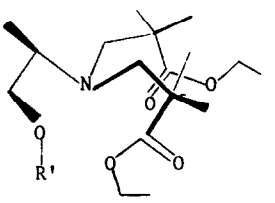
Recently we reported the surprising anti-neoplastic properties of the hindered amino diester 1.[1] Inspection of this molecule suggested its possible mode of action as a "β-lactam ion" dialkylator One also notices that the transport properties of this molecule in an aqueous system could be poor since there are no readily available functional groups on the molecule to help solubilize it in vivo

As the anti-neoplastic activity of growth inhibitors of the nitrogen mustard type have been shown to be greatly enhanced when they are introduced in vivo as the water soluble glucuronic acid or ethereal phosphate derivatives of a hydroxylated form of the drug,[2] we have undertaken the synthesis of 2, a hydroxylated form of amino diester 1 in order to use it as a precursor for the syntheses of water soluble salts of 1 in hopes of increasing the specific activity of this new class of anti-neoplastics

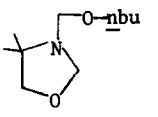


1 R = H

2 R = OH



2a R' = H



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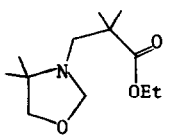
Hydroxy amino diester 2[3] was to be synthesized by a simple, but novel procedure The mixed amino diacetal 3, which was prepared in 73% yield by reaction of 2-methyl-2-amino-1-propanol, formaldehyde, and n-butyl alcohol, was reacted with two equivalents of the Grignard reagent generated at 0° in ether from ethyl α-bromoisobutyrate and magnesium While we did not obtain 2 as expected from this reaction, we did obtain a good yield, 52% after two-recrystallizations (mp 76-77°), of the titled lactone 5 as well as the mono adduct, 4 (34%). Lactone 5 was identified by its spectra[4] ir (CCl_4) 1730, 1715 cm^{-1}, nmr (100 megacycle, 58°, CCl_4/tms)[5] δ 1 01 (s,6), 1 13 (s,6), 1 18 (s,6), 1 23 (t,3), 2 51 (s,2), 2 63 (s,2), 3 85 (s,2), 4 05 (q,2), mass spect (70 eV, rel intensity) m/e 299 (8,m^+), 184 (100), 112 (47), and 84 (85) The products are shown in Figure 1.

Presumably lactone 5 was formed as a result of ring opening attack by the Grignard reagent on the initially formed mono adduct 4 leaving a magnesium alkoxide in a partially frozen conformation

which is extremely favorable for attack on the ester carbonyl (Structure 2a, R' = $Mg^{+}Br$) resulting in the formation of the lactone instead of the desired hydroxy diester 2.



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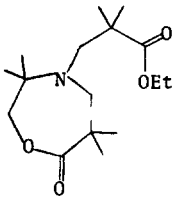

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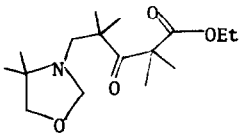

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Lactone 5 is an extremely stable molecule, remaining untouched by refluxing ethanol (24 hr) using either acid or base catalysis. The apparent ease of formation of the seven-membered ring lactone and its lack of reactivity to ethanol can only be accounted for by hinderedness of the system and the favorability as a result of steric factors of the U conformational relationship between the nitrogen and the ester carbonyl groups. This favorable relationship not only results in the close proximity of the nitrogen and carbonyl groups but also in the hydroxy (alkoxide) and carbonyl groups, in the latter case leading to reaction between them These results add chemical credibility to the idea of nitrogen-carbonyl interaction as an important factor in possible "β-lactam ion" formation in vivo as postulated.[1]

When THF was used as the solvent the major product, isolated as a liquid in 57% yield, was the isobutyrisobutyrate mono adduct 6 along with mono adduct 4 (26%).

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References

1. P Y Johnson and I. Jacobs, Chem. Commun , 925 (1972).
2. M A Bukhari, J. L. Everett and W. C Ross, Biochem Pharmacol., 21, 963 (1972).
3. Model studies of 1, 2 and 5 show these molecules to be more or less conformationally frozen. This is verified by low temperature nmr studies (see ref. 5). Figure 2a represents a preferred conformation of 2.
4. Proper analyses have been obtained on 4 and 5.
5. The lactone $-CH_2-$ singlets show considerable peak broadening at 25° due to hindered rotation of the ester group about the N–C bond. The temperature dependent NMR spectra of 1, 5 and hopefully 2 will be presented at a later time.