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CYANURIC CHLORIDE, A USEFUL REAGENT FOR MACROCYCLIC LACTONIZATION[1]

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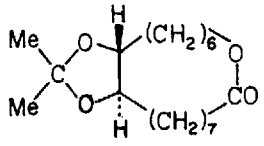
Abstract: Six ω-hydroxy acids have been converted to macrocyclic lactones by treatment with cyanuric chloride and triethylamine in acetone at room temperature. The mechanism apparently involves activation of both the carboxyl and hydroxyl groups.

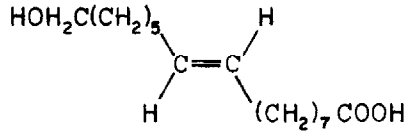
In an excellent review of "the synthesis of macrocyclic lactones (approaches to complex macrolide antibiotics)" Back has discussed seven available routes classified according to the starting materials[2]. The most commonly used are ω-hydroxycarboxylic acids, lactonized by seven methods, and the technique of "double activation" of the hydroxyl and carboxyl groups via the 2-pyridinethiol esters (I), by which Corey[3] has achieved the synthesis of several complex macrolides, is relevant to our work on cyanuric chloride (CC).[4] CC has no action on alcohols under the conditions specified by us,[4] although replacement of one or more Cl in CC by alkoxyl groups occurs in refluxing acetone and triethylamine (TEA) or in presence of sodium bicarbonate or carbonate at room temperature. We have now found that CC and TEA in acetone at room temperature (about 25°) smoothly convert six ω-hydroxy acids immediately available to us into the corresponding lactones. The general procedure is to dissolve the acid (0.01 mole) in dry acetone (100 ml) by warming on the water-bath if necessary, cool to room temperature, and under magnetic agitation add CC (0.01 mole), followed by TEA (0.02 mole) when a clear solution is obtained. A precipitate appears after about 20 minutes and gradually increases in bulk. After 6 hours when no CC remains in solution, the precipitate of chlorohydroxytriazine and TEA hydrochloride is removed, the filtrate diluted with water and extracted with chloroform. After washing with 10% aqueous sodium bicarbonate, the lactone recovered from the chloroform solution is substantially pure (TLC, NMR and mass spectra). Thus 12-hydroxystearic, 15-hydroxypentadecanoic, 16-hydroxypalmitic and 18-hydroxystearic acids gave the 13-, 16-, 17- and 19-membered lactones[5,6,7] in isolated yields of 70, 68, 85 and 33% respectively, not taking recoverable acid into account. The conversion of 15-hydroxypentadecanoic acid to exaltolide was carried out only on 90 mg, the available quantity. Good solubility in acetone or acetonitrile, the two most suitable solvents, is desirable for these CC reactions,[4]

and the poor yield of the lactone from 18-hydroxystearic acid is due to its sparing solubility; further, troublesome emulsions were formed in the routine work-up, but by concentrating the acetone filtrate, adsorbing on a short silica gel column, and eluting with benzene, the crystalline lactone, m.p. 36-37°, was obtained from the benzene solution.

Aleuritic acid (9,10,16-trihydroxypalmitic acid), a commercially available shellac constituent, has not been lactonized so far. In acetone solution this acid, occurring in the threo-configuration,[8] gave the lactone-acetonide (II), b.p. 227° (bath)/0.1 mm, in 86% yield; IR, CCl_4, 1740 cm^{-1} for lactone CO; M^+ in the MS at 326 and fragments at m/e 311 and 269 corresponding to successive loss of CH_3 and CH_2CO characteristic of acetonides of 1,2-glycols,[9] in addition to fragments at m/e 325, 298 and 296 showing loss of H, CO and CH_2O from the lactone part of the molecular ion[10]; NMR, CCl_4, δ 1.28 (6H, s, CMe_2), 3.53 (2H, m, -CH-CH- of acetonide ring).[11] Replacing acetone by acetonitrile, the 17-membered lactone with the vicinal glycol group intact was obtained in 51% yield; b.p. 165° (bath)/0.7 mm (considerable loss on distillation because of polymerisation); M^+ 286; IR, $CHCl_3$, 3380, 3200 (OH) and 1725 (lactone CO); NMR, CCl_4, δ 3.43 (2H, m, CH-CH of glycol).



(II)

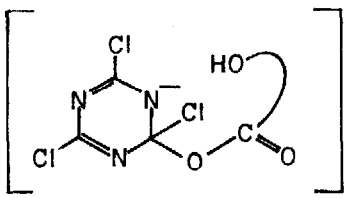


(III)

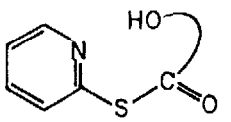
Trans-16-hydroxy-9-hexadecenoic acid (III) gave the lactone (isoambrettolide, b.p. 135-6°/0.1 mm)[12] in 70% yield. The appearance of the -CH=CH- protons at 5.3(m) in the NMR spectrum (CCl_4) shows that the trans-orientation of the olefine remains unchanged by lactonization; in the cis-isomer of the acid this signal is a t at 5.27.[13]

The Corey procedure involves the preparation of the thiol ester (I) from the hydroxy carboxylic acid by Mukaiyama's oxidation-reduction[3] using di(2-pyridyl) disulphide and triphenylphosphine. In our method no separate derivatization of the acid is necessary. The σ-adduct (IV) is formed in the course of the reaction with CC and TEA, but instead of breaking down to the acid chloride[4] it leads to the lactone (V) and the triazine derivative (VI) by the indicated double-activation mechanism. Except for the olefine (III), which gives a trace of the diolide detected by the MS, the lactone is the only product found in the acetone or acetonitrile solution; Corey

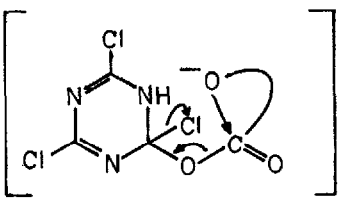
and Nicolaou[3] obtained lactone yields of 71, 8, 47, 66, 68 and 80%, together with the diolide (7,41,30,7,6 and 5%) respectively, from $HO(CH_2)_n$-COOH (n = 5,7,10,11,12 and 14). The vital role of the entropy factor in the adduct (IV) favouring lactonization is shown by the fact that no methyl ester is isolable when aleuritic acid in acetone is treated successively with methanol (6 mols.), CC and TEA under the usual experimental conditions; the product, obtained in low yield (20%) as the result of solvation of the ω-hydroxyl group by methanol, is the lactone-acetonide (II).

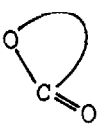


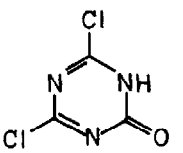
(IV)



(I)







(V) (VI)

Mukaiyama et al.[14] have described a method, apparently not involving "double activation", in which ω-hydroxy acids, $HO(CH_2)_n$-COOH, in acetonitrile were refluxed for 9 hours with 2-chloro-1-methylpyridinium iodide and TEA. The yield varied from 3% (n = 31) to 93% (n = 15).

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