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THE SYNTHESIS AND SUBSEQUENT OXIDATION OF TETRAHYDROCHROMAN. A NEW LACTONE SYNTHESIS.

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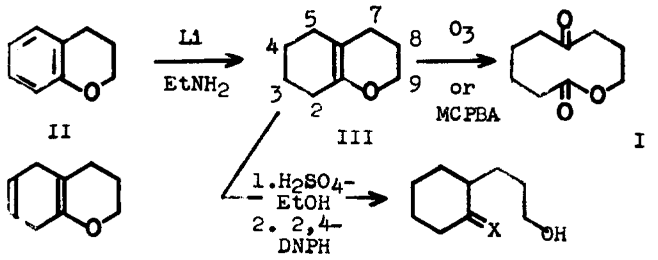
In this initial phase of a program involving the synthesis of middle-ring ketolactones related to the macrolide antibiotics, we wish to report the synthesis of 6-ketononanolide (I) as illustrated.



II

III

I

V

IV a: X = 2,4-DNP

b: X = O

FIG. I

The reduction of chroman (II)[1] with a six-fold excess of lithium in ethyl amine[2] has been found to give tetrahydrochroman (III) (51%) as the major component (85%) of a mixture, b.p. 80-83°/ 15 mm., as determined by gas chromatography.[3]

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The structure of III follows from the following data. The infrared spectrum of the above mentioned mixture exhibits a maximum at 5.95 μ (corr.), characteristic of an enol ether.[4] The N. M. R. spectrum ($CDCl_3$) shows absorption at $\tau = 8.35$ (multiplet, 4 C_3, C_4 protons), 8.10 (multiplet, 8 protons including those of C_2, C_5, C_7 and C_8) and 6.05 (triplet, 2 C_9 protons next to oxygen).[5] No olefinic or aromatic proton absorption is found. Reaction of II with warm 95% ethanol containing a few drops of conc. sulfuric acid, followed by the addition of 2,4-dinitrophenylhydrazine in sulfuric acid-ethanol-water gives the red-orange 2,4-dinitrophenylhydrazone of 2-(3'-hydroxypropyl)-cyclohexanone (IVa) (58%), m.p. 126-128°; lit.: m.p. 126-127°.[6] (Anal. Calcd. for $C_{15}H_{20}O_5N_4$: C, 53.56; H, 5.99; N, 16.66. Found: C, 53.71; H, 6.05; N, 16.50).

Reaction of III with 1.1 equivalents of meta-chloroperbenzoic acid (MCPBA)[7] in chloroform at room temperature leads directly to 6-ketononanolide (I) (17%) as a white crystalline solid, m.p. 69-71° (corr.). (Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29; mol. wt., 170. Found: C, 6360; H, 8.08; mol. wt. (ebulliscopic and mass-spec.), 170. The N. M. R. spectrum ($CDCl_3$) shows absorption at $\tau = 8.22$ (sextet, 4 C_3, C_4 protons), 7.70 (multiplet, 8 C_2, C_5, C_7 and C_8 protons) and 5.75 (triplet, 2 C_9 protons).

The infrared spectrum of I ($CHCl_3$) has carbonyl bands at 5.75 and 5.83 μ (corr.). The ultraviolet spectrum (95% ethanol) exhibits a broad maximum at 278 mμ (18). The yellow 2, 4-dinitrophenylhydrazone of I (94%) has an infrared absorption band ($CHCl_3$) at 5.78 μ indicating that the lactone is still present. (Anal. Calcd for $C_{15}H_{18}O_6N_4$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.57; H, 5.43; N, 15.80).

The nature of the other products formed in the reaction of III with meta-chloroperbenzoic acid is being investigated.

Ozonolysis of III in methylene chloride with zinc-acetic acid workup also gives I (15%).

Further work on improving the yield of formation of I is in progress. That there should probably be nothing unusual in the ozonolysis of an enol ether such as III is borne out by the successful ozonolysis of ethoxycyclohexene[8] to give the half aldehyde half ethyl ester of succinic acid, isolated as the diethyl acetal.

The mass spectrum of I exhibits a parent molecular ion peak at m/e 170 and has a fragmentation pattern consistent with the assigned structure.[9] A full analysis of this spectrum and those of related compounds will be given at a later date.

The reduction of chroman II to tetrahydrochroman III with excess lithium in ethylamine was anticipated in view of the reported reduction of II with sodium in liquid ammonia to a dihydrochroman, presumably V (Figure 1).[10]

We are investigating the possibility that the direct formation of I from III upon treatment with meta-chloroperbenzoic acid occurs via reaction of the initially formed epoxide VI with excess peracid as shown in Figure II.

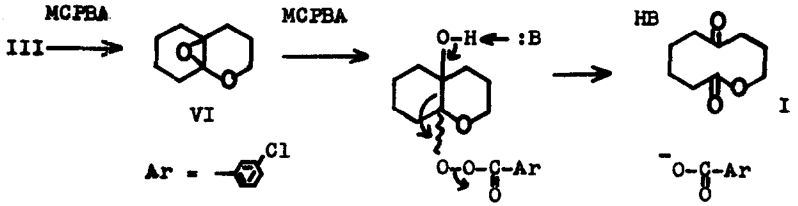

Fig. II

Tetrahydrochroman III has been synthesized previously by the acid catalyzed dehydration of the cyclic hemiketal in equilibrium with 2-(3'-hydroxypropyl)-cyclohexanone (IVb).[5]

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7. Obtained in 85% purity from FMC Research and Development, Princeton, New Jersey.

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9. The mass spectrum of I was taken on a modified Consolidated Electrodynamics Model 21-103C mass spectrometer.

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