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MEDIUM RING COMPOUNDS PART II[1]

THE SYNTHESIS OF 6-KETODECANOLIDE.[2]

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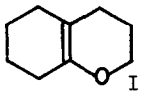
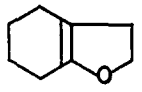
The synthesis of 6-ketononanolide from tetrahydrochroman (I) (1) has recently been described. The extension of this procedure to 6-ketodecanolide (VI) requires the synthesis of the hitherto unknown tetrahydrohomochroman (III). This compound should be available a priori via the reduction of homochroman or by an extension of the methods reported for the synthesis of I (3) and II (4). A modification of the latter methods was favored since it would more easily lend itself to the synthesis of larger rings.



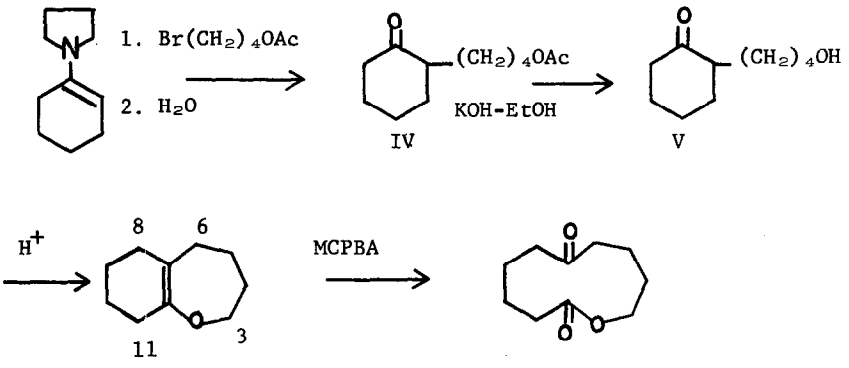
I



II

I and II have been prepared by the acid-catalysed cyclisation and dehydration of 2-(3'-hydroxypropyl)-cyclohexanone (3) and 2-(3'-hydroxypropyl)-cyclopentanone (4) respectively. The latter two compounds were prepared from the corresponding 2-carbethoxycycloalkanone by a rather long pathway in poor yield. The more direct route adopted in our

work employs the alkylation of the pyrrolidine enamine of cyclohexanone (5).



4-Bromobutyl acetate (6,7) was prepared from tetrahydrofuran and acetyl bromide. Previous workers (6,7) used an excess of acetyl bromide and obtained products which gave high bromine analysis. In this work a 50% excess of tetrahydrofuran was used and the product was obtained in 91% yield. (Anal. Calc. for $C_6H_{11}BrO_2$: Br, 40.97. Found: Br, 41.36).

The alkylation of the pyrrolidine enamine of cyclohexanone by 4-bromobutyl acetate was carried out in boiling toluene. 2-(4'-Acetoxybutyl)-cyclohexanone (IV) was obtained in 40-42% yield, B.P. 134°/.5 mm (Anal. Calc. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found; C, 68.12; H. 9.80).

Hydrolysis of IV by 7% ethanolic potassium hydroxide (4)

at room temperature for 24 hours gave V which cyclised to III on distillation. However the cyclisation of crude V, in boiling benzene containing a trace of p-toluenesulphonic acid by azeotropic removal of water, proceded more cleanly to give III in 74% yield (calculated from IV), B.P. 91-2°/11 mm. (Anal. Calc. for $C_{10}H_{16}O$: C, 78.89, H, 10.59. Found: C, 78.92; H, 10.73). The infrared spectrum of III (neat) exhibits a band at 5.94 μ , characteristic of an enol ether (8). The N.M.R. spectrum (neat) shows absorption centered at δ = 3.78 (triplet, $2C_3$ protons), 1.95 (multiplet, $6C_6$, C_8, C_{11} protons) and 1.58 (multiplet, 8 C_4, C_5, C_9, C_{10} protons).

The oxidation of tetrahydrochromans by monoperphthalic acid to 2-oxo-1, 6-dihydroxy- [4,4,0] -bicyclodecanes followed by oxidation by lead tetra-acetate to the ketolactone has been developed in this laboratory (9). This procedure gave VI in 52% overall yield. The oxidation of tetrahydrochroman (I) by m-chloroperbenzoic acid to 6-ketononanolide, in poor yield, has been previously reported (1). However, a three-fold excess of m-chloroperbenzoic acid has been found more recently to oxidise I to 6-ketononanolide in 90% yield (10). To a three-fold excess of m-chloroperbenzoic acid in methylene chloride was added III, with stirring, at such a rate as to maintain reflux conditions. The reaction mixture was stirred overnight and 6-ketodecanolide (VI)

was obtained in 71% yield, B.P. 105°/0.6 mm (Anal. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.05, H, 8.99). The N.M.R. spectrum of VI ($CDCl_3$) shows multiplets centered at δ=4.02 (2 C_{10} protons), 2.42 (6 C_2, C_5, C_6 protons) and 1.78 (8 C_3, C_4, C_8, C_9 protons).

The infrared spectrum of VI (neat) has carbonyl bands at 5.76 and 5.83 μ (corr).

This synthesis thus represents an overall conversion of the pyrrolidine enamine of cyclohexanone to VI in 22% yield. It would appear to be of greater synthetic value for the synthesis of middle ring ketolactones than our previous one derived from chromans. Extensions of this synthesis to related 10-to 12-membered ketolactones are in progress. Specifically this method is being utilized in the synthesis of 7-keto-undecanolide, the parent ring system of the macrolide antibiotic Methymycin (11).

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