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SYNTHESIS OF 4-HYDROXY-2-CYCLOPENTEN-1-ONES VIA 1,3-DITHIANES

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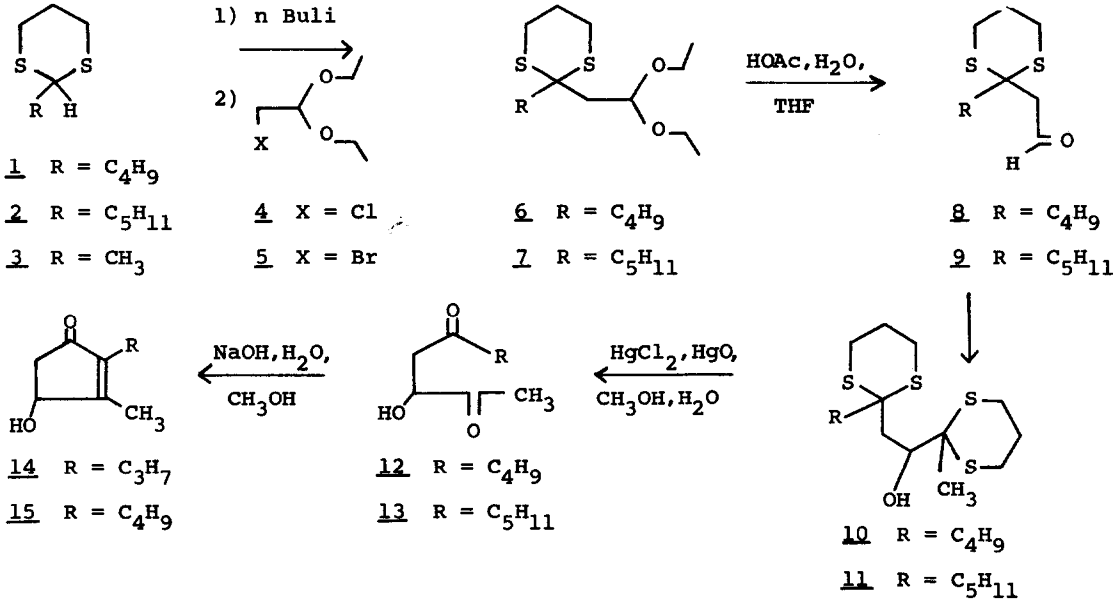
Recently there has been considerable interest in developing routes for the synthesis of the title compounds as they constitute the main structural feature of several important biologically active natural products and related compounds. Previous efforts in this area were directed toward the rethrolones[1,4] and the prostaglandins.[5,6] In connection with our work on prostaglandins we report here a route which is easy to effect in good overall yield.



1 R = C_4H_9
2 R = C_5H_{11}
3 R = CH_3

4 X = Cl
5 X = Br

6 R = C_4H_9
7 R = C_5H_{11}

8 R = C_4H_9
9 R = C_5H_{11}

10 R = C_4H_9
11 R = C_5H_{11}

12 R = C_4H_9
13 R = C_5H_{11}

14 R = C_3H_7
15 R = C_4H_9

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Reaction of 2-n-butyl-1,3-dithiane (1) (prepared from pentanal, propane-1,3-dithiol and hydrogen chloride[7]) with n-butyllithium in tetrahydrofuran at -20° for 5 hr followed by treatment with chloroacetaldehyde diethyl acetal (4)[8] (56 hr at -20°, 85.5 hr at 0° then 3.25 hr at 25°) gave the substituted acetal 6 in a crude yield of 68.1% after recovery of excess 4 by vacuum distillation, nmr ($CDCl_3$): δ 0.92 (t, 3H, J = 6Hz), 1.18 (t, 6H, J = 7Hz), 2.28 (d, 2H, J = 5Hz), 4.78 (t, 1H, J = 5Hz). In a similar reaction, homolog 7 was obtained in 68.8% yield.

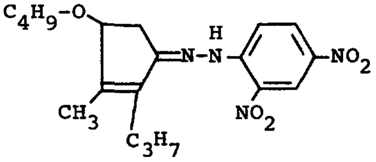
Acetal 6 was hydrolyzed in a mixture of acetic acid-water (65:35) and tetrahydrofuran at 34° for 13.5 hr to give an oily product which was purified by thin-layer chromatography. In this manner aldehyde 8 was obtained in 69% yield, ir ($CHCl_3$): 5.85, 10.98 (dithiane)μ; nmr ($CDCl_3$): δ 9.81 (t, 1H, J = 3Hz).[9] Aldehyde 9 was similarly obtained in 68.1% yield.[9]

Addition of 8 to a tetrahydrofuran solution of the lithio anion of 3 at -20° followed by reaction at 0° for 65 hr and at 25° for 4 hr gave a high yield of crude 10. This could be purified by thin-layer chromatography but the sequence was more efficient if purification was done at a later stage, ir ($CHCl_3$): 2.88, 10.98μ; nmr ($CDCl_3$): δ 0.92 (t, 3H, J = 6Hz), 1.36 (S, 3H).

Hydrolysis of the dithiane rings was accomplished by refluxing in aqueous methanol in the presence of mercuric chloride and mercuric oxide under a nitrogen atmosphere. Thus, after 19 hr, crude 10 gave the unstable hydroxy-diketone 12 in high yield, ir ($CHCl_3$): 2.90, 5.85μ; nmr ($CDCl_3$): δ 0.90 (t, 3H, J = 7Hz), 2.22 (S, 3H), 4.42 (t, 1H, J = 6Hz). This could also be purified by chromatography but was unstable and cyclization was thus carried out immediately. Crude 12 was stirred at 25° for 3.5 hr with methanolic 0.5N sodium hydroxide in the presence of a small amount of hydroquinone[2] under nitrogen. The oily product was purified by thin-layer chromatography to give pure dihydroallethrolone (14) in 32.2% yield from 8, ir ($CHCl_3$): 2.95, 5.90, 6.05μ; nmr ($CDCl_3$): δ 0.90 (t, 3H, J = 6.5 Hz), 2.06 (S, 3H), 4.78 (d,d, 1H, J = 6, 2.5 Hz). In our hands, recrystallization of the 2,4-dinitrophenylhydrazone from n-butanol yielded a melting point differing from the literature value (mp. 133-133.5°, lit 203-204° [10]). The nmr spectrum and chemical analysis[9] clearly indicated that this compound was the DNP of the butyl ether (16).

Similarly, dihydrocinerone (15) was formed from 9 in 44.2% yield, ir ($CHCl_3$): 2.95, 5.92, 6.05µ; nmr ($CDCl_3$): δ 0.90 (t, 3H, J = 6.5 Hz), 2.08 (s, 3H), 4.73 (d, d, 1H, J = 6, 2.5 Hz).[9] The DNP of 15 (mp, 119.5-120.5°; lit 140.5-141.5[11]) also proved to be the butyl ether derivative.[9] The nmr spectra of 14 and 15 compare closely with those for similar compounds.[12]

It is instructive to note that when the initial alkylation was conducted using the bromo acetal 5, yields of 6 were much lower (36%) and the product was accompanied by a 45% yield of the dimer of 1 (17). This compound was identified by comparison with authentic material prepared by us previously[13] by coupling lithio-1 with 1,2-dibromoethane. This apparently similar coupling with the bromo acetal is completely avoided by using the less reactive[14] chloro derivative.



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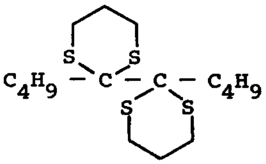

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