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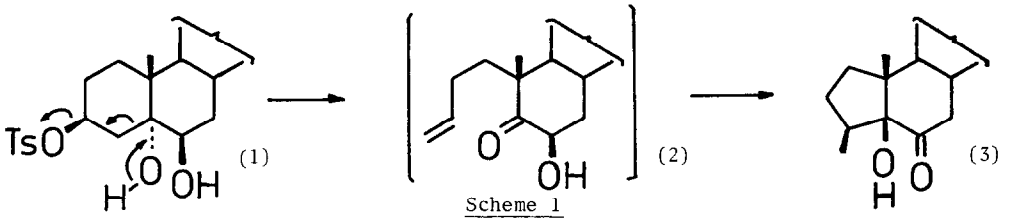
ENE REACTIONS OF UNSATURATED ACYLOINS†

Brian A. Marples* and Christopher D. Spilling
Department of Chemistry, The University of Technology,
Loughborough, Leicestershire, LE11 3TU

Summary Ene reactions of the unsaturated acyloins, 4,5-secocholest-3-en-6β-ol-5-one and 4,5-secocholest-3-en-5β-ol-6-one have been investigated.

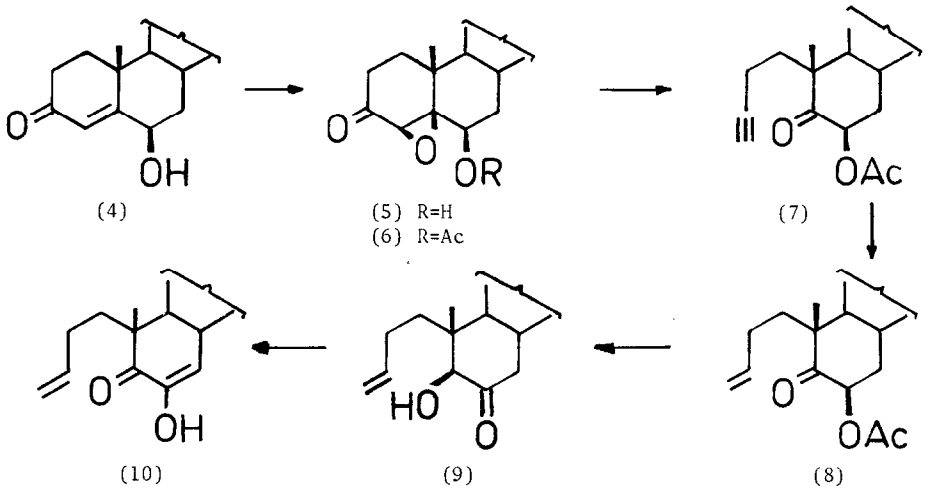
We recently reported[1] a by-product of the reaction of the tosyloxydiol (1) with Bu^tOK/Bu^tOH was 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3) and that it arose through an ene reaction of the unsaturated acyloin (2) believed to be formed by fragmentation of the tosyloxydiol (1) (Scheme 1). We report here the synthesis of the unsaturated acyloin (9), the regioisomer of (2), and an investigation of its ene reaction.



Scheme 1

Oxidation of 6β-hydroxycholest-4-en-3-one (4)[2] with $NaOH/H_2O_2$ gave the 4β,5β-epoxide (5), mp 174-176°, $[\alpha]_D$ +85°, which on acetylation gave the epoxy-acetate (6), mp 106-107°C, $[\alpha]_D$ +45°. Reaction of the epoxy-acetate (6) with toluene-p-sulphonyl hydrazine[3] gave the 4,5-secocholest-3-yn-5-one (7), an oil, $[\alpha]_D$ -42°. Partial hydrogenation of the acetylene (7) using $Pd/BaSO_4$ catalyst poisoned with quinoline gave the 4,5-secocholest-3-en-5-one (8), an oil, $[\alpha]_D$ -31° which on hydrolysis with aqueous ethanolic HCl gave the unsaturated acyloin (9), an oil, $[\alpha]_D$ +12° as the major product. If base-catalysed hydrolysis was used, it was necessary to use carefully deoxygenated solvent to avoid autoxidation to the diosphenol (10), mp 125-127°C, $[\alpha]_D$ -66°.

† Part of this work was presented at the Sixth East Midlands Regional Symposium of the Perkin Division of the Royal Society of Chemistry at Loughborough University of Technology, on 17th December, 1984.

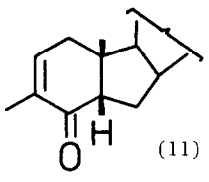


(4) (5) R=H (6) R=Ac (7) (8) (9) (10)

Spectroscopic data for compounds (5)-(10) were satisfactory. In particular, the terminal acetylene of compound (7) was apparent from the ir spectrum (ν_{max} 3300 and 2120 cm^{-1}) and the presence of the terminal alkene of compound (8) was supported by the ir (ν_{max} 3080 and 1640 cm^{-1}) and the ^1H nmr (δ 4.8-5.1, m, R-CH=C$\underline{H}_2$ and δ 5.6-6.0, m, R-C$\underline{H}$=CH_2) spectra. The unsaturated acyloin (9) is presumably more thermodynamically stable than (2) and it is assumed that the 5β-equatorial configuration would be preferred. Support for the assigned regiochemistry of compound (9) is evident in the ^1H nmr spectrum in which the 5-methine proton signal is a singlet at δ 4.08. A minor product of the acid-catalysed hydrolysis of (8) is the 6-epimer of the unsaturated acyloin (2).

Treatment of the unsaturated acyloin (9) with Bu^tOK in deoxygenated Bu^tOH at 50°C did not give the A-nor-compound (3) and only the starting material was isolated. However, when a decalin solution of the unsaturated acyloin (9) was heated in a sealed tube at 200°C in an argon atmosphere the B-norcholest-2-en-4-one (11) (26%), mp 83-84°C, $[\alpha]_D$ +146°, and 5-hydroxy-5β-cholestan-6-one (12)[4] (13%) were isolated after preparative tlc. The latter compound was identical with an authentic sample.[4] For the former compound, the ir (ν_{max} 1665 cm^{-1}) and uv (λ_{max} 240 nm, ε 9820) spectra confirmed the presence of the α-substituted α,β-unsaturated ketone as did the ^1H nmr spectrum (δ 6.50, m, R-C$\underline{H}$=CMe-C=O and δ 1.80, brs, RCH=C$\underline{Me}$-C=O). Double irradiation of the methyl signal at δ 1.80 caused the multiplet at δ 6.50 to collapse to a double doublet (J 5.8 and 2.8 Hz) illustrating the spin-spin coupling between the C-2 and C-1 protons. Further evidence in support of the structure (11) was the observation that a maximum incorporation of 3-deuterium atoms (at C1 and C5) was attained when it was treated with NaOD/D_2O/dioxan. The 5β-configuration is assumed on the basis of thermodynamic stability. Interestingly, the A-nor-compound (3) was not obtained but on heating it in solution in decalin under similar conditions it was partially converted to the B-nor-compound (11).

It is presumed that the unsaturated acyloin (9) is converted to the dienediol which reacts in the conformations (13) and (14) to give respectively the A-nor-compound (3) and 6β-hydroxy-4(5-6α)abeo-cholestan-5-one (15) as primary products (Scheme 2). Under the reaction conditions the primary products are further modified to give the B-nor-compound (11) and 5-hydroxy-5β-cholestan-6-one (12). It is conceivable that acid catalysis on the glass tube surface is important in the modification of the primary products. Such catalysis may be similarly important in the enolisation of unsaturated ketones (or acyloins) prior to their high temperature ene reactions.[5]



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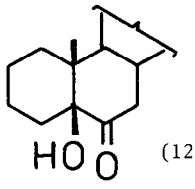

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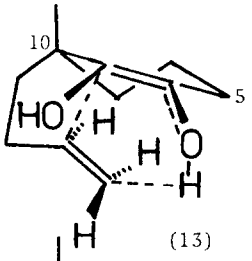
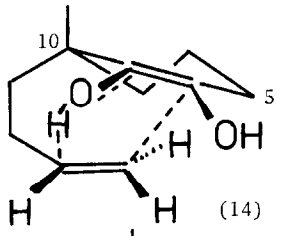


(13)

(2) or (9)



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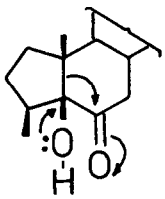

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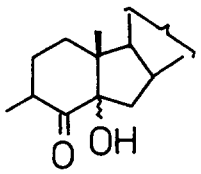

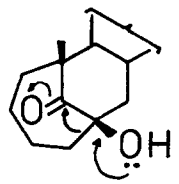

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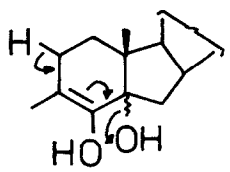
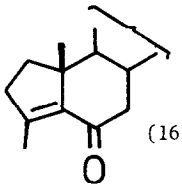
(11)



(12)

Scheme 2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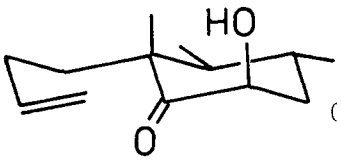

(17)

We have shown that the A-nor-compound (3) is susceptible to acid-catalysed rearrangement since on treatment with toluene-p-sulphonic acid in benzene solution it was converted to the B-nor-compound (11) (49%) and the A-nor-α,β-unsaturated ketone (16) (32%), mp 80-81°C, $[\alpha]_D$ +56°, which were separated by preparative tlc. The ir (ν_{max} 1680 and 1625 cm^{-1}), uv (λ_{max} 260 nm, ε 11500) and ^1H nmr (δ 2.03, brs, $R^1CMe{=}CR^2{-}C{=}O$) spectra of the A-nor-α,β-unsaturated ketone were in accord with the assigned structure.

The observed ene reaction of the unsaturated acyloin (9) occurs at relatively low temperature compared with unsaturated ketones and it is unusual in that one of the products (15) is formed by carbon-carbon bond formation to the terminal carbon atom of the olefin. We suggest the unsaturated acyloin (2) also undergoes the ene reaction when it is formed in situ by fragmentation of the tosyloxydiol (1). The failure of the isomeric unsaturated acyloin (9) to react in Bu^tOK/Bu^tOH may be a function of the difficulty of attaining the appropriate reacting conformation (13) of the dienediol. This difficulty may be surmounted at high temperatures or by forming the unsaturated acyloin (and dienediol) in situ in a conformation (eg 17) which requires minimum bond rotations for this to be achieved. The view that the A-nor-compound (3) arises from the unsaturated acyloin (2) is further supported by the observation that the reaction of the tosyloxydiol (1) with Bu^tOK/Bu^tOH in the presence of air leads to the diosphenol (10) in yields (typically ca 15%) approximating to those of the A-nor-compound (3) obtained in the absence of air. Thus, the unsaturated acyloin (2) is efficiently trapped by oxygen under these conditions.

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