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# REACTION OF GRIGNARD REAGENTS WITH A STEROIDAL A-RING LACTONE AND PERACID OXIDATION OF A RESULTANT 6-PHENYL-2,3-DIHYDROPYRAN

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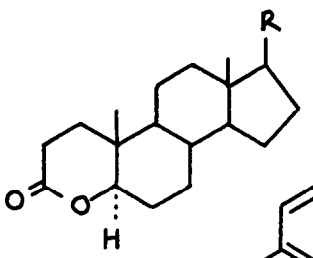
The reactions of Grignard reagents with lactones are commonplace. However, few examples of their reactions with saturated steroidal lactones are reported,[1] although recent interest has been shown in their reactions with A-ring enol lactones.[2] The reaction of phenylmagnesium bromide with the δ-lactone (1; R=$CHOHCH_3$) is reported[1b] to give the anomalous product (2; $R^1$=H. $R^2$=$CHOHCH_3$). We have found that the δ-lactone (1; R=$C_8H_{17}$)[3] reacts in a similar manner with phenylmagnesium bromide, giving the dihydropyran (2; $R^1$=H, $R^2$=$C_8H_{17}$) (50%) but somewhat differently with p-methoxyphenyl magnesium bromide, giving the tetrahydropyran (3) (35%), the hydroxyolefin (4) (16%), and the dihydropyran (2; $R^1$=OMe, $R^2$=$C_8H_{17}$) (8%). In addition, we find that the dihydropyran (2; $R^1$=H, $R^2$=$C_8H_{17}$) may be oxidised with excess monoperphthalic acid to the hemiacetal ketones (5; R=H) and the hydroxyolefin (4) is rearranged, with acid, to the saturated ketone (6; R=O).

The dihydropyran (2; $R^1$=H, $R^2$=$C_8H_{17}$) crystallised readily from the crude Grignard reaction product, and was identified from its $^1$H n.m.r. [τ4.72 (t, 2-H) and 6.42 (q, 5-H)] and its u.v. ($\lambda_{max.}$ 264 nm, ε9250) spectra. Preparative t.l.c. of the crude product of the reaction between the δ-lactone (1; R=$C_8H_{17}$) and p-methoxyphenylmagnesium bromide gave the dihydropyran (2; $R^1$=OMe, $R^2$=$C_8H_{17}$), the tetrahydropyran (3) and the hydroxyolefin (4). The spectroscopic data for the dihydropyran (2; $R^1$=OMe, $R^2$=$C_8H_{17}$) were similar to those for the dihydropyran (2; $R^1$=H, $R^2$=$C_8H_{17}$). The occurrence of two singlets [τ6.17 and 6.25 (2 x MeO)] and an 8 proton multiplet [τ2.5-3.4] in the $^1$H n.m.r. spectrum of the tetrahydropyran (3) confirmed the presence of two aryl groups and a multiplet at τ6.96 was assigned to the 5α-H. The structure of the tetrahydropyran (3) was further supported by its Pd/C/$H^+$-catalysed hydrogenolysis to the saturated alcohol (6; R=β-OH,H) which was also obtained by the hydrogenation of the hydroxyolefin (4). The $^1$H n.m.r. spectrum of the latter confirmed the presence of two aryl groups [τ6.2 and 6.27 (s, 2 x MeO), 2.8-3.4 (m, 8 protons)] and the 2,3-double bond [τ4.1 (t, 2-H)]. The structure of the



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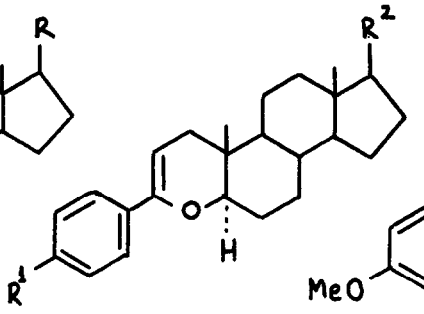

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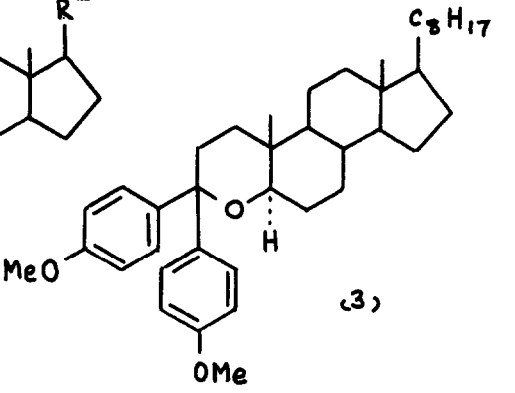

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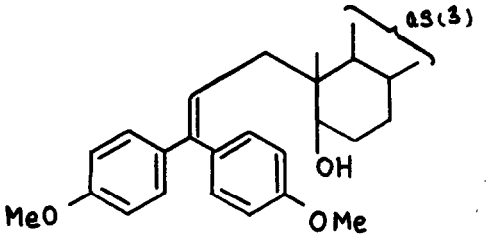

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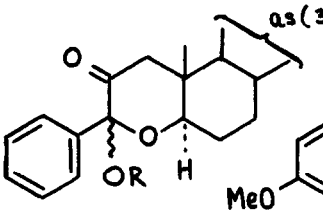

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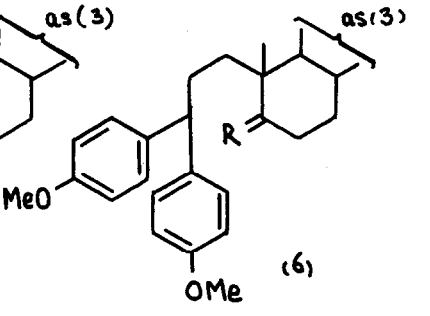

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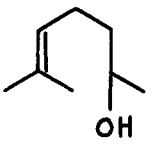

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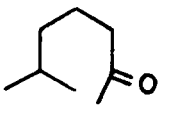

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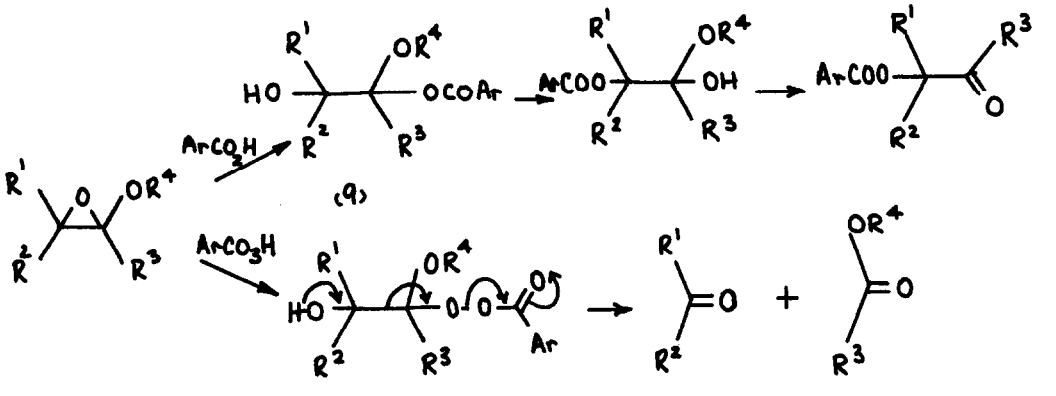

Scheme 1

hydroxyolefin (4) was further supported by its toluene-p-sulphonic acid-catalysed rearrangement to the ketone (6; R=O) ($\nu_{max.}$ 1706 cm.$^{-1}$). This rearrangement, which presumably involves a hydride shift from C(5) to C(3), appears to be novel in steroids, although the similar rearrangement of (7) to (8) has been reported.[4]

Essentially two processes have been reported for the reactions of enol ethers with peracids.[5-8] The initially formed epoxides are attacked by the carboxylate or peroxycarboxylate ion to give the intermediates (9) or (10) respectively which either rearrange or fragment as shown (Scheme 1). The production of the hemiacetal ketones (5; R=H) appears to represent a new type of reaction of enol ether epoxides. The composition of the epimeric mixture of the hemiacetal ketones (5; R=H) was variable but the i.r. spectrum confirmed the presence of the carbonyl ($\nu_{max.}$ 1730 cm.$^{-1}$) and the hydroxy ($\nu_{max.}$ 3300 cm.$^{-1}$) groups. The $^1$H n.m.r. spectrum showed important quartets at $\tau$5.7 and 6.45 which are assigned to the 5$\alpha$-H in the 3$\alpha$-hydroxy- and the 3$\beta$-hydroxy-compounds respectively. The protons at C(1) gave two overlapping AB quartets centred at $\tau$7.43 and 7.53, the lower-field quartet being assigned to the 3$\alpha$-hydroxy-compound. The hydroxy group proton gave a broad multiplet (exchanged in $D_2O$) at $\tau$6.8. Further confirmation of the structures (5; R=H) was provided by their conversion with EtOH/HCl to the acetal ketone (5; R=Et) and by their cleavage with $Pb(OAc)_4$ to the carboxylic acid (11, R=H). The acetal ketone (5; R=Et) crystallised as a single epimer and is assigned the 3$\alpha$-ethoxy-configuration on the basis of the $^1$H n.m.r. spectrum which showed a single AB quartet centred at $\tau$7.43 (1-2H). The methylene protons of the ethoxy group gave two overlapping quartets owing to their diastereotopicity. Final proof of the identity of the carboxylic acid (11; R=H) was afforded by its reaction with diazomethane to give the methyl ester (11; R=Me) and by its conversion to the lactone (12) ($\nu_{max.}$ 1785 cm.$^{-1}$) through hydrolysis and subsequent treatment with toluene-p-sulphonic acid in benzene.

The very different product distribution observed in the two Grignard reactions may be attributed to the different stabilities of the initially formed adducts (13; R=H) and (13;R=MeO). Possibly,electron release from the MeO-group in (13; R=MeO) is important in facilitating its breakdown to the carbonyl compound which would react further in the expected manner.

The reaction of the dihydropyran (2; $R^1$=H, $R^1$=$C_8H_{17}$) with monoperphthalic acid may proceed as indicated in Scheme 2. Stabilisation of the intermediate (15) by the 3-phenyl group may be of importance particularly since nucleophilic attack at C(3) in (14) by phthalate or perphthalate ion (Scheme 1) would not be stereoelectronically favoured assuming mainly $\alpha$-epoxidation occurs. The low solubility of phthalic acid in ether may also be of some importance in this and one other reaction.[7]

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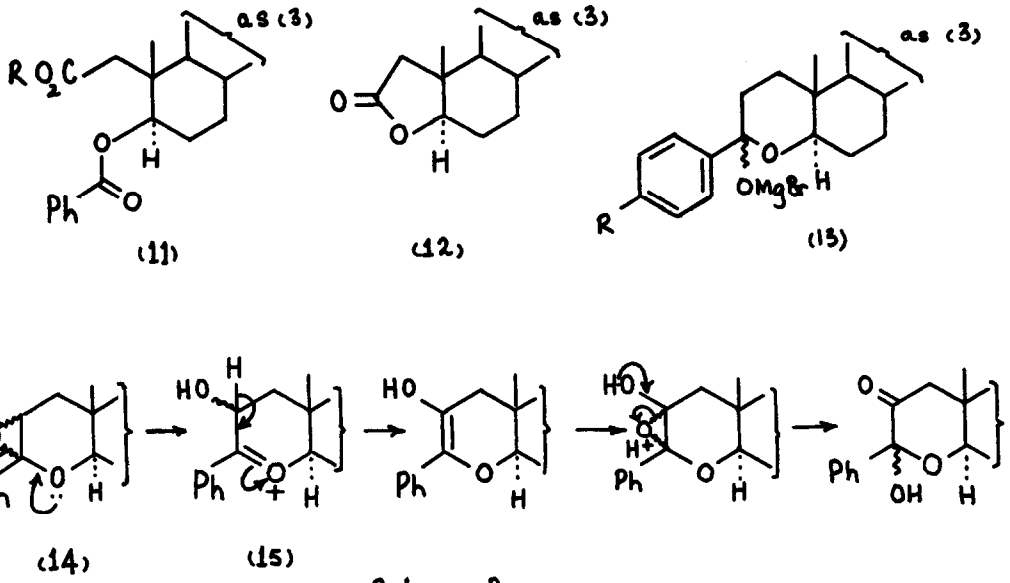


Scheme 2

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