The Chemistry of *i*-Steroids

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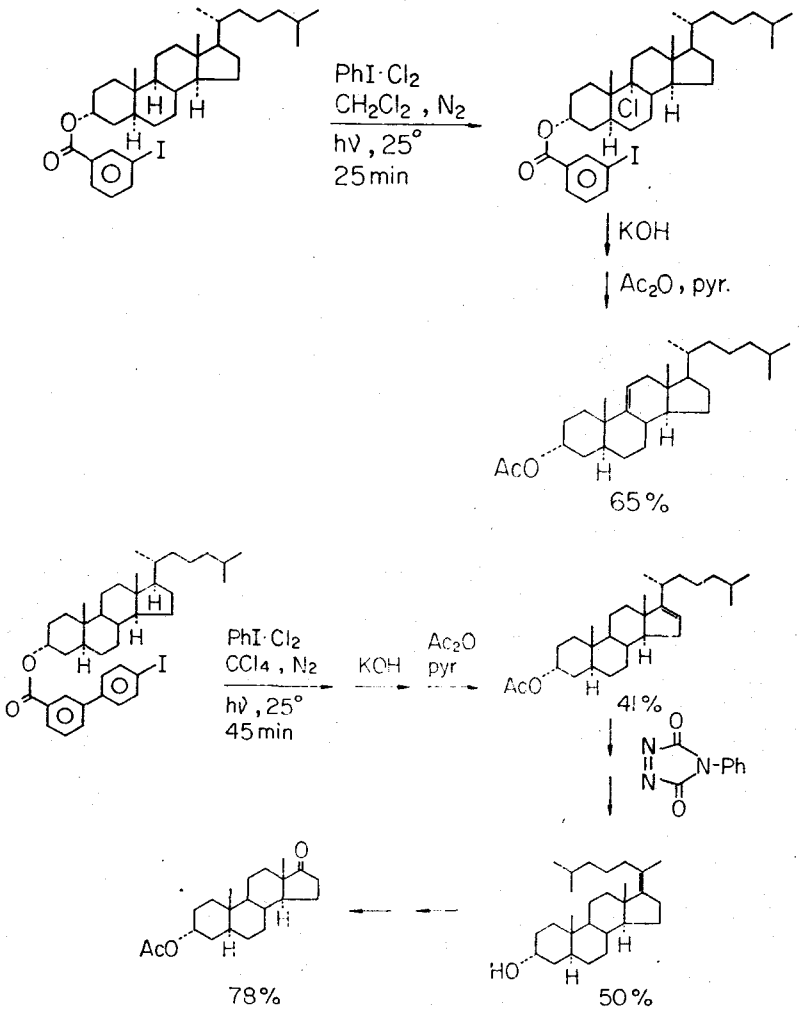
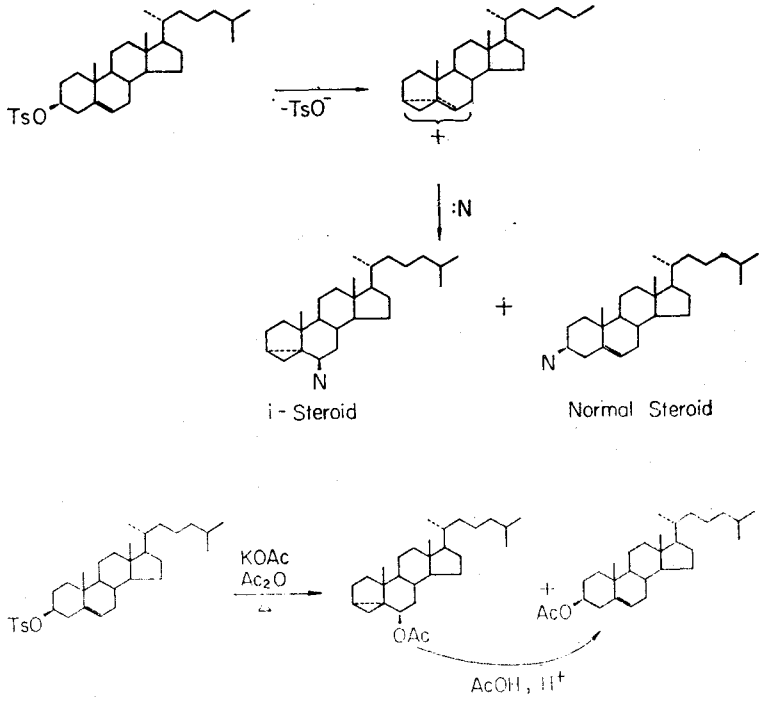
Remote functionalization method repesents one of the most facinating developments in organic chemistry in recent year. The reactions perfor med by Breslow[1](Fig. 1 and 2) are more widely applicable compared to the well-known Barton reactions[2] and it is possible to select the precise positions to be functionalzed by adjusting the length of the bridge joining the unactivated and activating sides of the substrate molecule. Two examples here invole the functionalization of



C-11 of steroid(Fig. 1), which is of the central importance in corticosteroid synthesis, and the removal of alkyl side chain(Fig. 2), which points to the synthesis of sex hormones.

Breslow's reactions were designed to reach unactivated tertiary hydrogens by using 3α-steroidal derivatives. Inspection of molecular models indicates that one should have the functionalizing group approaching from the β-side to achieve direct functionalization of the alkyl side chain on ring D. It would be interesting to see whether β-side activaing groups can indeed attack hydrogens on the same side.

i-Steroids are formed in the solvolysis reactions of cholesteryl tosylate[3] and the mechanism of their formation was discussed by Winstein[4] as one of the first examples of neighboring group participation. (Fig. 3) They were used in limited cases in synthetic applications, particularly when it is necessary to protect 3β-hydroxy-Δ^5 functionality common in representative sterols.[5] Its easy preparation and the facile conversion back to 3β-hydroxy-Δ^5 series (Fig. 4) suggest i-steroidal compounds as ideal candidates for



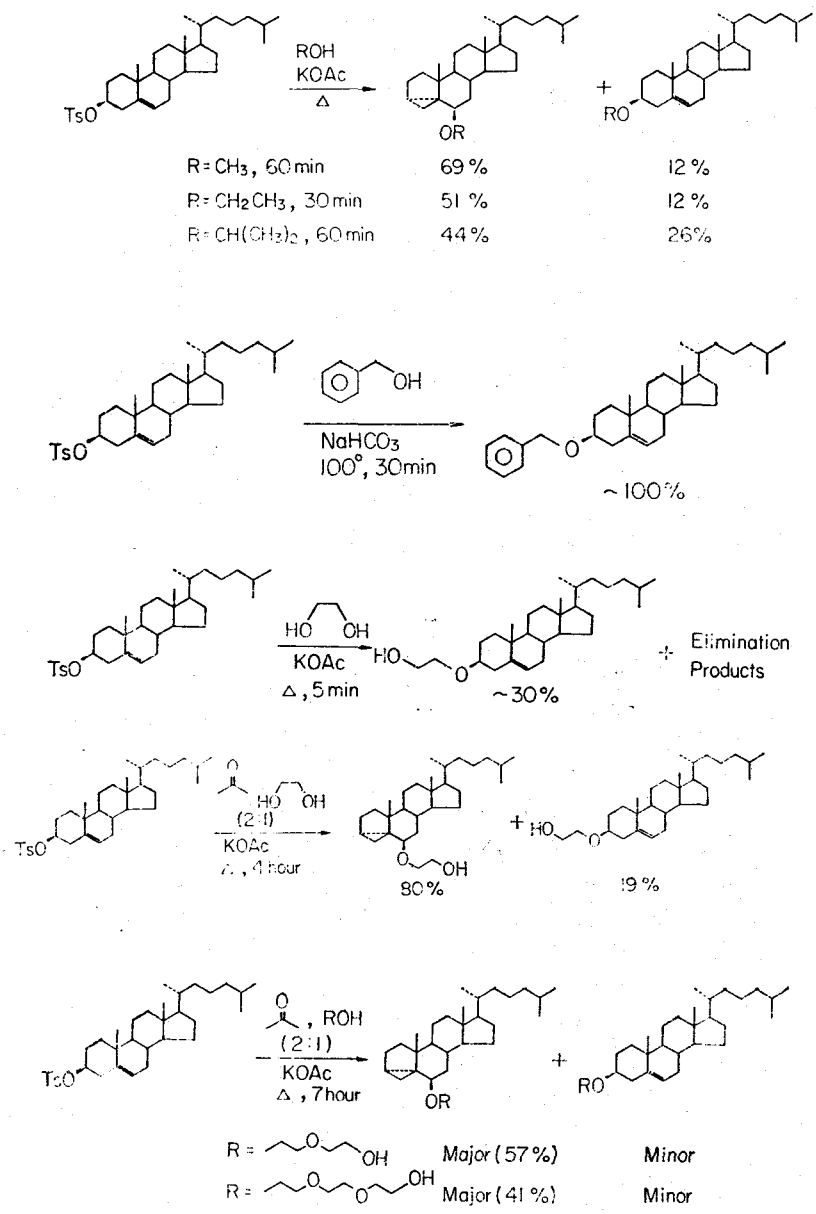
remote functionalization on the β-side. This report concerns the synthesis and the study of the physica lproperties of a number of i-steroids which are suitable for future functionalization experiments.

Solvolyses in simple alcohols:

i-Ethers were major products in methanol, ethanol, and 2-propanol (Fig. 5). Bulkier alcohols produced lower yiely of i-ethers, possibly due to the steric hindrance and the smaller dielectric constant. In benzyl alchol, no i-ether was formed, but a high yield of normal benzyl ether was obtained (Fig. 6).

Solvolyses in diols:

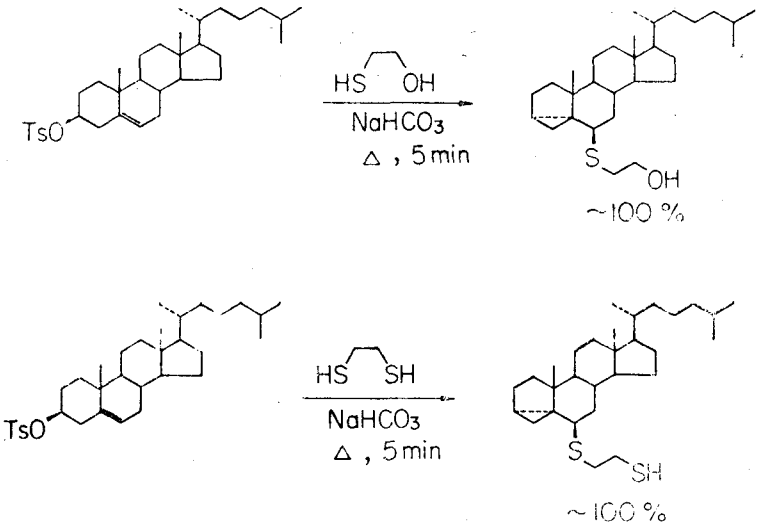
Brief reflux of cholesteryl tosylate suspension in ethylene glycol produced normal ether and



elimination products. (Fig. 7) In acetone-ethylene glycol (2:1) mixture, however, *i*-ether was obtained as the major product accompanied by a small amount of normal ether. (Fig. 8) The completion of the reaction required longer reaction time but no elimination products were noticed. With equivalent of ethylene glycol in acetone, no reaction occurred. Diethylene glycol and triethylene glycol behaved in the same way. (Fig. 9)

Solvolyses in thiols:

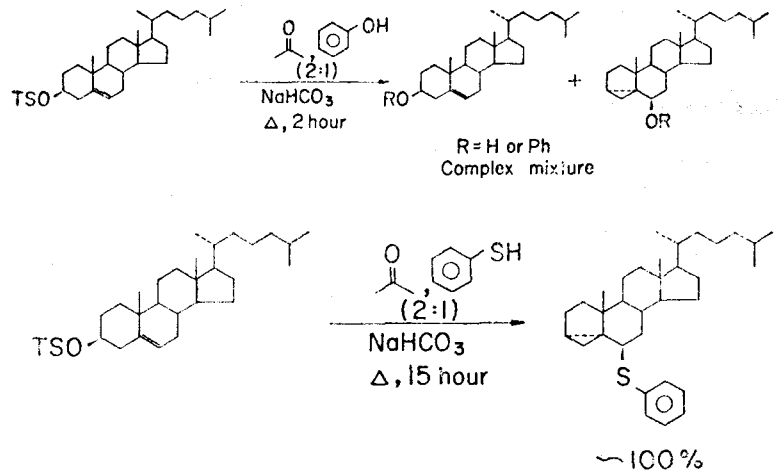
Reaction in mercaptoethanol quickly yielded a single product in almost quantitative yield. (Fig. 10) The structure was identified as the *i*-thioether from the nmr data. It indicates that i-steroid derivatives are formed exclusively in the presence of good nucleophiles like thiols. As



expected, *i*-thioether was obtained in high yield in ethanedithiol solvolysis. (Fig. 11)

Solvolyses in phenols:

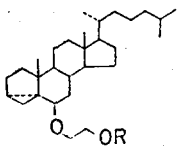
Reaction in acetone-phenol (2:1) gave rise to a complex reaction mixture which contain normal phenyl ether, cholesterol, and *i*-cholesterol. (Fig. 12) On the other hand, solvolysis in acetone-thiophenol (2:1) produced a single product, which was assigned to be *i*-thiophenoxy



derivative. (Fig. 13)

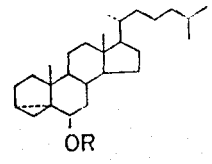
Nuclear magnetic resonance study:

Various *i*-etheres of simple alcohols showed identical chemical shifts for H-18 as well as H-19. (Fig. 14) In various aromatic esters of ethylene glycol i-ether H-18 appears to experience noticeable shielding effect compared to those in the parent ethylene glycol *i*-ether and its succinate. (Fig. 15) This clearly indicates that there is at least partial solution state contribution from the conformation in which the aromatic groups are on top of C-18 and possibly C-20. Interestingly, no such shielding effect on



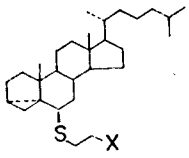
Chemical Shifts from TMS(Hz)

	(H-19)	(H-18)
R=H	59	42
R=Benzoyl	60	40
R=m-Iodobenzoyl	60	38
R=p-Benzoylbenzoyl	60	39
R=m-Benzoylbenzoyl	58	37
R=3,5-Dinitrobenzoyl	60	37
R=Succinyl	58	42



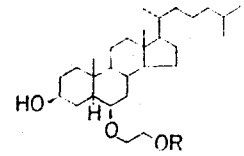
Chemical Shifts from TMS(Hz)

	(H-19)	(H-18)
R=H	61	42
R=CH_3	61	42
R=CH_2CH_3	61	42
R=$CH(CH_3)_2$	61	42



Chemical Shifts from TMS(Hz)

	(H-19)	(H-18)
X=OH	61	43
X=OBenzoyl	62	43
X=SH	61	45
X=S-p-Benzoylbenzoyl	62	44
X=S- 	67	45



Chemical Shifts from TMS(Hz)

	(H-19)	(H-18)
R=H	57	40
R=m-Iodobenzoyl	56	34

H-18 was observed in sulfur analogs (Fig. 16). It implies that with i-thioethers the conformation is less favorable for remote functionalization. of the side chain. With normal 6β ether of ethylene glycol, the shielding effect of the aromatic ester group was found to be more pronounced than in the cases of *i*-ethers. (Fig. 17)

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References

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