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Synthesis and CD spectral studies of some fused cholestenopyrimidines

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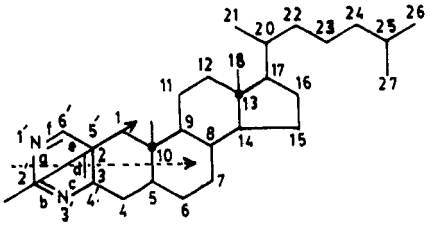
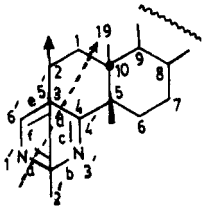
Abstract

Synthesis of unsubstituted 5α-cholesteno(3,2-d)- (5), (2,3-d)- (12), (3,4-d)- (15) and 5α- and 5β-cholest-3-eno(4,3-d)pyrimidines (21) and (21') has been achieved using hydroxymethylene derivatives of relevant cholestanones prepared from cholesterol(1). Their 2'-derivatives (5a - 5e), (12a), (15a - 15c), (21a - 21c) and (21'a,21'b) could also be prepared. Attempts to prepare cholest-1-eno(1,2-d)pyrimdine system through 5α-cholestan-1-one(28) failed. 5α-Cholest-6-eno(7,6-d)pyrimidine(33) was prepared by the reaction of cholestan-7-one with trisformylaminomethane. Three Cotton effects were observed between 350-200 nm in all these compounds in their CD spectra. They have been assigned to n $\rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions from long to short wave lengths. Quadrant rule has been applied for determining the sign of the first band CD, while helicity rule has been applied for the third band CD.

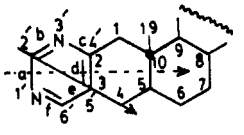
Present work describes the synthesis of six series of optically active cholestenopyrimidines (Fig.1), e.g. 5 and its 2'-derivatives (5a-5e), 12 and its



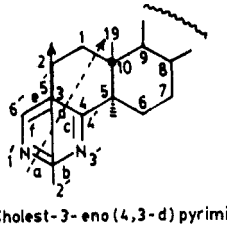
5α-Cholest-2-eno(3,2-d)pyrimidine 5



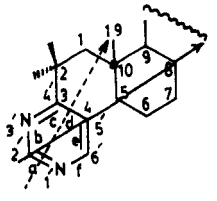
5β-Cholest-2-eno(4,3-d)pyrimidine 21'



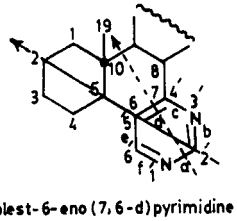
5α-Cholest-2-eno(2,3-d)pyrimidine 12



5α-Cholest-3-eno(4,3-d)pyrimidine 21



2,2-Dimethyl-5α-cholest-3-eno(3,4-d) pyrimidine 15



5α-Cholest-6-eno(7,6-d)pyrimidine 33

Fig.1. Nomenclature and Structure of the synthesized Cholestenopyrimidines

derivatives (12a), 15 and its 2'-derivatives (15a - 15c), 21 and 21' and their derivatives (21a - 21c, 21'a, 21'b) and 33. These compounds are rigid and therefore serve as good models for developing empirical rules correlating the CD sign with the stereochemistry of pyrimidine derivatives. In order to be able to frame these rules it was imperative to prepare these compounds having pyrimidine ring fused to different positions of chiral cholestane nucleus. Moreover, the schemes for the synthesis of these compounds had to be chosen in such a way that cholestenopyrimidines unsubstituted in pyrimidine ring could also be prepared as reference in each series for CD spectral studies.[1)]

Cholesterol (1) served as starting material for all the cholestenopyrimidines mentioned in the beginning. Compound 5 and its derivatives were synthesized according to the scheme shown in Fig.2.

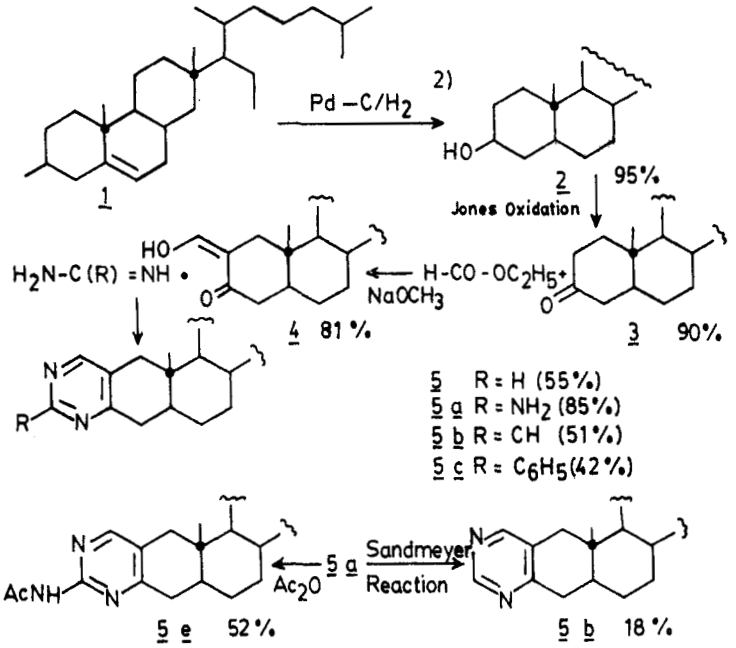


Fig.2. Synthesis of 5 and its 2'-Derivatives

Synthesis of 12 and its 2'-derivatives is shown in Fig.3 below.

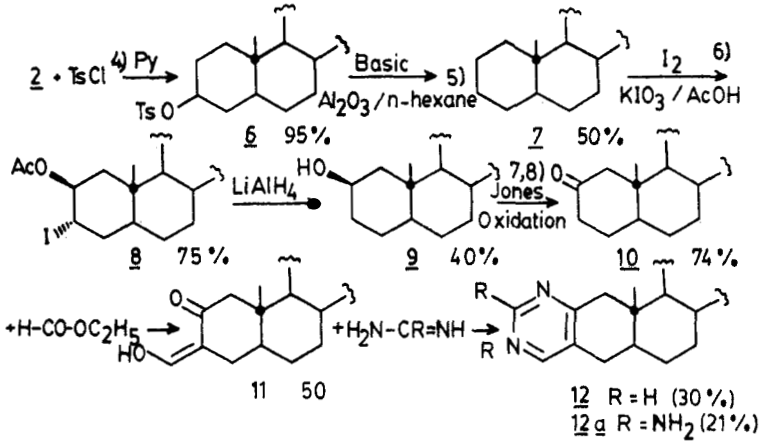


Fig.3. Synthesis of 12 and its 2'-Derivatives

Compound 15 and its 2'-derivatives could be synthesized through the steps given in Fig.4

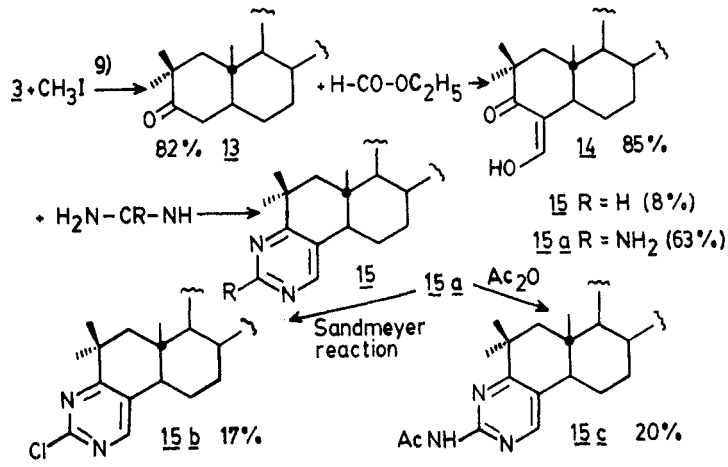


Fig.4. Synthesis of 15 and its 2'-Derivatives

Figures 5a and 5b show the synthetic steps used for the synthesis of 21', 21 and their 2'-derivatives. Compounds 21a and 21'c could not be obtained in pure state in spite of repeated medium pressure column chromatography.

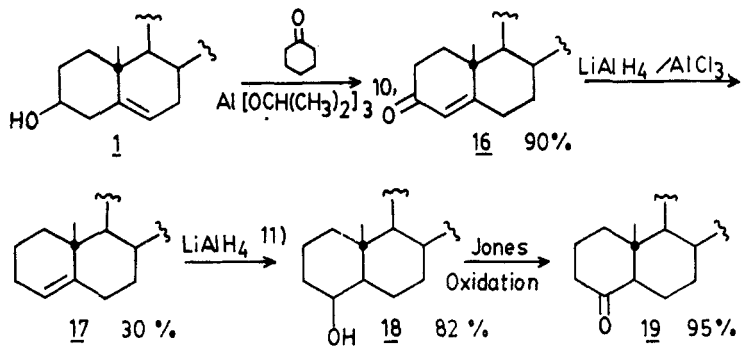


Fig.5a Initial Steps in the Synthesis of 21' and 21

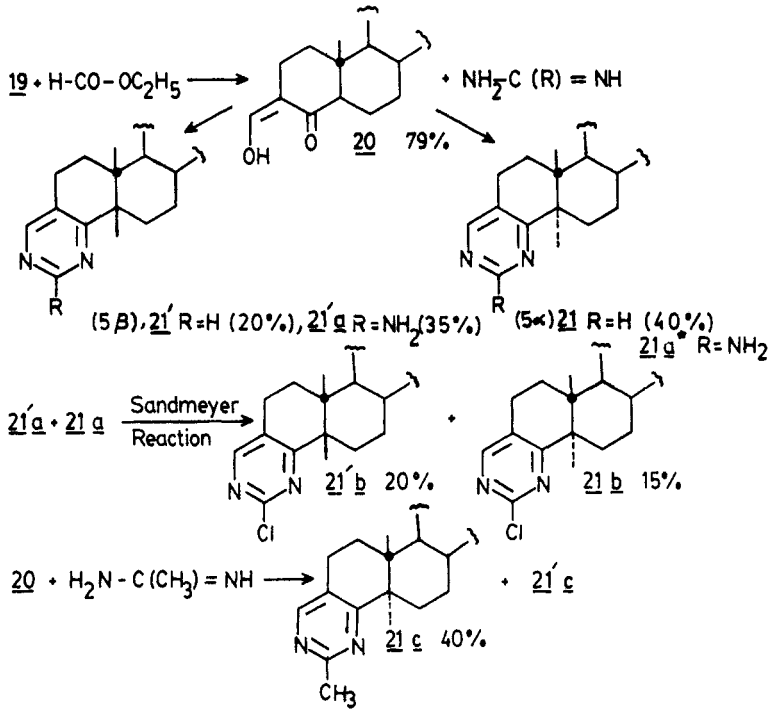


Fig.5b Synthesis of 21', 21 and their 2'-Derivatives

According to the plan, following attempts were made to synthesize 5α-cholestan (1,2-d)pyrimidine system which were unsuccessful(Fig.6)

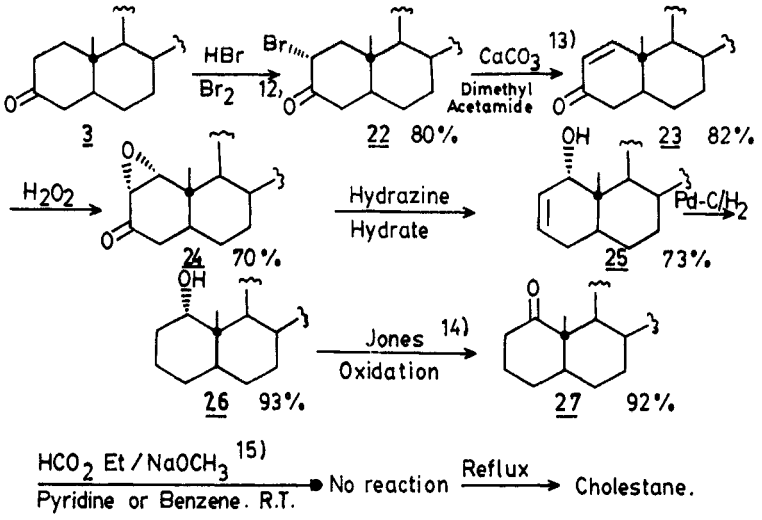


Fig.6 Synthesis of 5α-cholestan-1-one

The synthesis of unsubstituted 33 only could be achieved by the method shown in Fig.7. Compound 32 refused to react with $HCO_2Et/NaOEt$ and therefore 2'-derivatives of 33 could not be prepared.

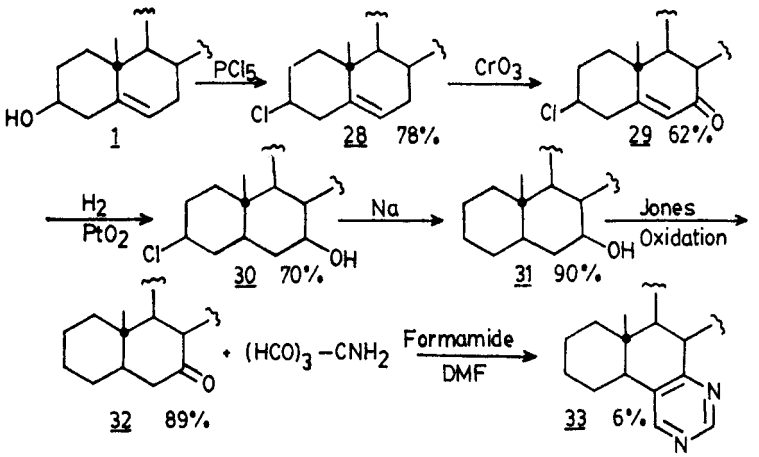


Fig.7 Synthesis of 33

Confirmation of the structure of the synthesized compounds was done with the help of IR, ^1H and ^{13}C NMR and mass spectral studies. ^{13}C NMR measurements were specially important for determining the configuration at C-5 in 5 - and 5 -cholest-3-eno(4,3-d)pyrimidine series.

The CD spectra of cholesteno-pyrimidines exhibit three Cotton effects between 320 and 220 nm. Quadrant rule is applied for assigning the Cotton effect of the first band CD and molecules are viewed along the continuous arrows. (Fig.1) Helicity rule explains the Cotton effect of the third band CD and molecules are viewed along the broken arrows. Series 5 shows first band positive and second band negative. In 12 series first and third bands are negative. In 15 series first band is negative and third band is positive which shows boat conformation of ring A. In 21 series both bands are positive and in 21' series both are negative as expected.

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