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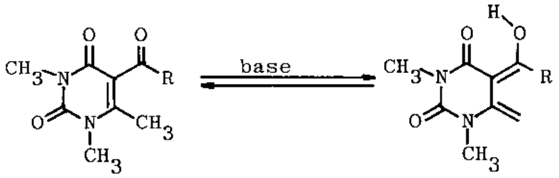
CYCLOADDITION REACTION OF A PYRIMIDINE-DIENOL

Shigeo Senda, Kosaku Hirota, Tetsuji Asao, and Isao Sugiyama
Gifu College of Pharmacy, Mitahora-Higashi, Gifu 502, Japan

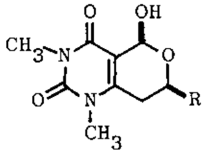
During studies directed toward the development of new synthetic routes to fused pyrimidines employing 6-methyluracils, we have found that 5-acyl-1,3,6-trimethyluracil (I) causes base-catalyzed isomerization to the dienol(II) which is a reactive and versatile heterocyclic diene in the Diels-Alder reaction.

Thus, treatment of 5-formyl-1,3-dimethyluracil(I) (R=H) with lithium diisopropylamide(LDA) afforded a dimer (III) (R=1,3,6-trimethyluracil-5-yl), which would be formed by the Diels-Alder reaction of the dienol(II) (R=H) and the aldehyde group of (I). The dimer was converted to a quinazoline (IV) (R^1=H, R^2=CO_2Me, R^3=Me) by refluxing in methanolic sodium hydroxide. 5-Acyl-1,3,6-trimethyluracil(I) (R=H,Me,OEt) reacted readily with dimethyl acetylenedicarboxylate in the presence of LDA yielding quinazolines (IV) (R^1=H, R^2=R^3=CO_2Me; R^1=Me, R^2=R^3=CO_2Me; R^1=OH, R^2=R^3=CO_2Me). Base-catalyzed cycloaddition of I (R=H, Me) with dimethyl maleate or dimethyl fumarate led to the formation of the 5,6,7,8-tetrahydroquinazoline (IV) (R^1=H, R^2=R^3=CO_2Me; R^1=Me, R^2=R^3=CO_2Me) with high stereoselectivity. In both the tetrahydroquinazolines, the relationship between the hydroxyl group at 5 position and the ester group at 6 position was determined to be cis. The adduct must be therefore formed by the Diels-Alder reaction of the (E)-dienol(II). Reaction of I (R=H) with other nucleophiles such as methyl vinyl ketone and N-phenylmaleimide afforded 7,8-dihydroquinazolines (IV) (R^1=R^3=H, R^2=COMe; R^1=H, R^2=CONHPh, R^3=CO_2H), respectively. Furthermore, the dienol (II) underwent cycloaddition reaction with aldehydes to yield pyrano[4,3-d]pyrimidines(III) (R=H, Et,Ph,$PhCH_2$,2-furfuryl), stereospecifically. Compound III (R=Ph) was epimerized to a 2:1 mixture with trifluoroacetic acid in DMSO and transformed to 1,3-dimethyl-6-(2-styryl)uracil(V) by refluxing in 10% HCl.

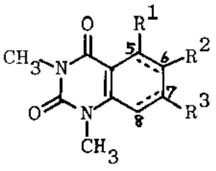


(I)

(II)



(III)



(IV)