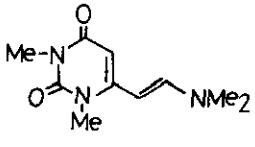
CYCLOADDITION REACTION OF 6-VINYLURACIL AND ITS APPLICATION TO A NEW SYNTHESIS OF QUINAZOLINES

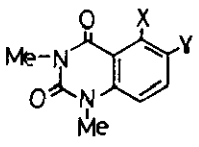
Shigeo Senda, Kosaku Hirota, Tetsuji Asao, and Yasuhiro Toyota
Gifu College of Pharmacy, Mitahora-Higashi, Gifu 502, Japan

We describ here that 6-(2-dimethylaminovinyl)-1,3-dimethyluracil(I) is a reactive and versatile heterocyclic diene in the Diels-Alder reactions accessible for the synthesis of biologically interesting quinazoline 5 and/or 6-carboxylic acids.

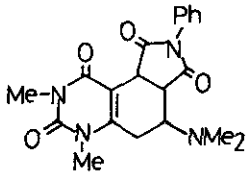
Reaction of I with dimethyl acetylenedicarboxylate in acetonitrile at room temperature gave dimethyl 1,3-dimethylquinazoline-2,4(1H,3H)-dione 6,7-dicaboxylate (IIa, X=Y=CO_2Me) in 19% yield. Compound IIa was also obtained in 71% or 36% yield by treatment of I with dimethyl maleate or dimethyl fumarate in refluxing benzene. Similar treatment of I with N-phenylmaleimide gave a 1:1 aduct(III), quantitatively. Alkaline hydrolysis of III afforded the 6,7-dihydroquinazoline(IVa, X=CO_2H; Y=CONHPh), which was hydrolyzed to the dicarboxylic acid(IVb, X=Y=CO_2H) by refluxing in hydrochloric acid. Treatment of I with maleic anhydride in refluxing methanol led to the formation of the quinazoline 6-carboxylate(IIb, X=H; Y=CO_2Me) in 16% yield involving a cycloaddition reaction, elimination of dimethylamine, addition of methanol and decarboxylation. When the cycloaddition was carried out in refluxing benzene, the 6,7-dihydroquinazoline(IVc, X=$CONMe_2$; Y=CO_2H) was obtained quantitatively. Acidic hydrolysis of IVc gave IVb. The 6,7-dihydroquinazoline(IV) was readily converted into quinazoline carboxylic acid. Thus, pyrolysis of IVb in nitrobenzene at 210° gave the quinazoline 5-carboxylic acid(IIc, X=CO_2H; Y=H), quantitatively. On the other hand, treatment of IVb or IVc with bromine in acetic acid afforded the quinazoline 6-carboxylic acid(IId, X=H; Y=CO_2H) in good yield.



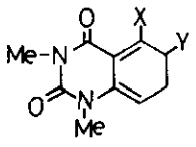
I



II



III



IV