

SOME NOVEL REACTIONS OF 1,3-DIMETHYLURACILS II.¹
 STUDIES ON NEW STABLE PYRIMIDINE RING-OPENED COMPOUNDS.

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Abstract - The reaction of various 1,3-dialkyl-6-(N-substituted)amino-uracils(I) with dimethyl acetylenedicarboxylate(DMAD) in aprotic solvents gave new stable pyrimidine ring-opened compounds(II).

A large number of heterocycles from acetylenic esters have been synthesised.² We have recently reported photochemical cycloadditions of nucleic acid bases with dimethyl acetylenedicarboxylate(DMAD)³ and some novel addition reactions of benzoxazole derivatives with DMAD.⁴ We wish to report here a novel addition reaction of 1,3-dialkyl-6-(N-substituted)aminouracils(I) and DMAD. The reaction of 6-aminouracils with DMAD has been used in the synthesis of various pyrido(2,3-d)-pyrimidines.⁵ When 1,3-dimethyl-6-pyrrolidinouracil(Ia) was treated with DMAD at room temperature in dry aprotic solvents(THF, DMSO, DMF, CH₂Cl₂), N,N'-dimethyl-N-[3-methoxy-3-pyrrolidino-2-(3-carbomethoxypropynoyl)acryloyl]urea(IIa) was obtained in 80-81% yield. [mp 239°(dec), C₁₆H₂₁N₃O₆, m/e 351(M⁺), ¹H-nmr(CDCl₃) δ 1.75-2.28(4H, multiplet, -CH₂CH₂-) 2.98(3H, doublet, J=4Hz, -NHCH₃) 3.36-3.60(4H, multiplet, -CH₂NCH₂-), singlets each integrated for 3H at 3.36(NCH₃), 3.81(OCH₃) and 3.82(OCH₃), 8.10(1H, broad, NH), The ¹³C-nmr(CDCl₃) showed sixteen signals.]. The structural assignment of IIa based on the ¹H-nmr spectrum, ¹³C-nmr spectrum, mass spectrum and elemental analyses. This assignment is further confirmed by conversion of IIa into 1,3-dimethyl-5-(carbomethoxypropynoyl)-6-pyrrolidinouracil(III). [mp 257-261°, 20% yield, C₁₅H₁₇N₃O₅, m/e 319(M⁺), ¹H-nmr(CDCl₃) δ 2.0-2.4(4H, multiplet, -CH₂CH₂-), three singlets at 3.27(3H, NCH₃),

3.37(3H, NCH₃) and 3.89(3H, COOCH₃), 4.0-4.5(4H, multiplet, -CH₂NCH₂-). In the ¹³C-nmr(CDCl₃) spectrum, thirteen signals were observed.]. It is interesting to note that the compound VII⁶, structurally similar to IIa, is an unstable intermediate which readily cyclizes at room temperature to give a 5-substituted pyrimidine analogous to III. Compound IIa, however, was found to be stable at room temperature and it required heating(refluxing in DMF) for long time(overnight) to effect the cyclization to III but still in low yield(20%).

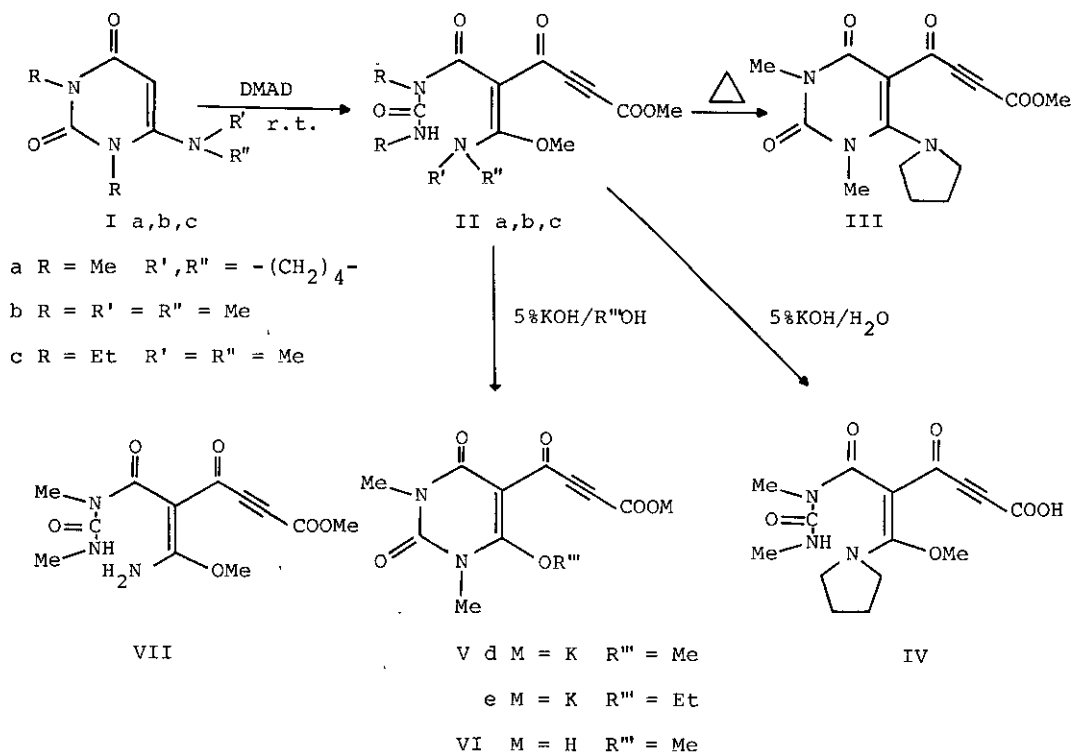


Fig. 1

The addition reactions of 1,3-dimethyl-6-dimethylaminouracil(Ib) and 1,3-diethyl-6-dimethylaminouracil(Ic) with DMAD under similar conditions were studied. The ring-opened products(IIb and IIc) were also obtained in 40-43% yield. IIb [mp 240° (dec), C₁₄H₁₉N₃O₆, m/e 325(M⁺), ¹H-nmr(CDCl₃) δ 2.92(3H, doublet, J=4Hz, NHCH₃), five singlets at 3.14(3H, NCH₃), 3.27(3H, NCH₃), 3.34(3H, NCH₃), 3.76(3H, OCH₃) and 3.85(3H, OCH₃), 9.26(1H, NH), The ¹³C-nmr(CDCl₃) showed fourteen signals.].

IIc [mp 270°(dec), $C_{16}H_{23}N_3O_6$, m/e 353(M^+), 1H -nmr(DMSO- d_6) δ 1.05(6H, multiplet, $2 \times C-CH_3$), four singlets at 2.97(3H, NCH_3), 3.10(3H, NCH_3), 3.55(3H, OCH_3) and 3.67(3H, OCH_3), 3.84(4H, multiplet, $2 \times N-CH_2-C$), 8.67(1H, NH), The ^{13}C -nmr(DMSO- d_6) showed sixteen signals.]. But we could not obtain a stable ring-opened compound by treatment of 6-(N-substituted)aminouracils(I, $R' = H, Me$; $R'' = H$) with DMAD in same conditions described above. Thus, it may be concluded that 1,3-dimethyl (or diethyl)-6-(N-substituted)aminouracils(Ia,b,c) give the stable pyrimidine ring-opened products by treatment with DMAD in aprotic solvents at room temperature, whereas 1,3-dialkyl-6-aminouracils(I, $R' = R'' = H$) do not. On the basis of the molecular model examination, the formation of II can be formulated as shown in Fig.2. It may be assumed that after the nucleophilic addition of I to DMAD, when the C_5-H bond keeps an anti-coplanar relationship with the N_1-C_6 bond in an intermediate(A), the pyrimidine ring breaks to give II. The 1H and ^{13}C -nmr spectra of IIa,b,c showed that R' and R'' is non-equivalent. It can be interpreted that II

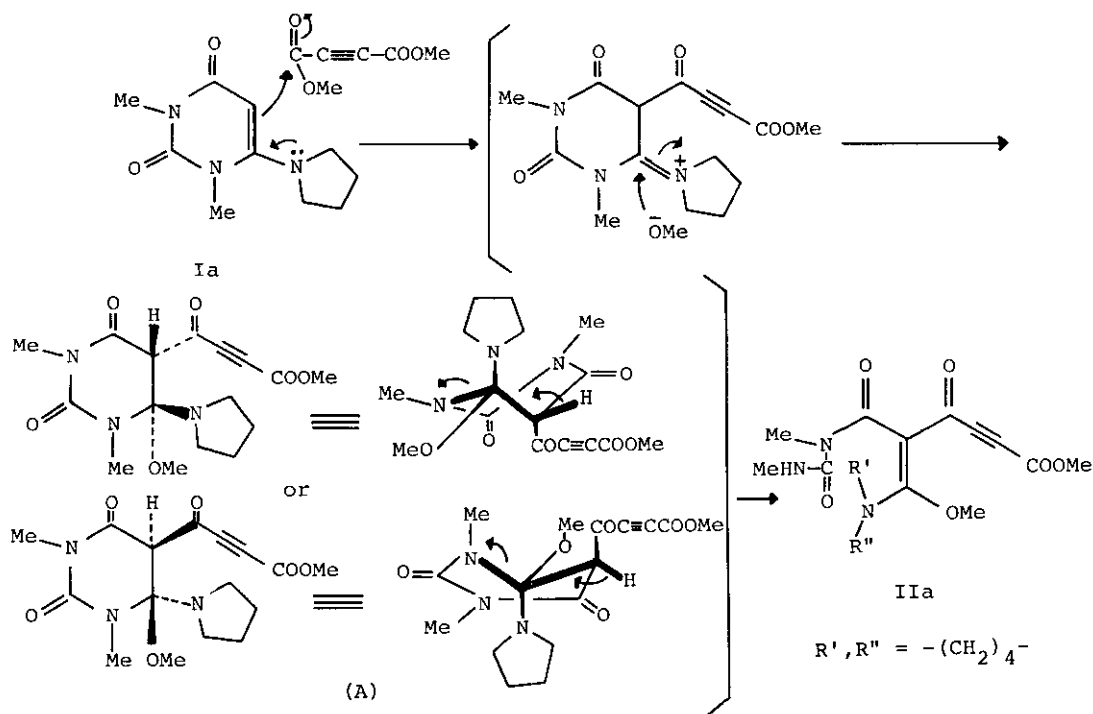


Fig. 2

has a certain rigid spatial structure and this sterical requirement may be closely related to the cyclization rate of II to the propynoyl derivative(III). The reason why IIa resists to the cyclization compared to the 6-amino compound(VII) is not obvious, but it may be chiefly attributed to the steric hindrance caused by the close proximity of $-NR'(R'')$ and C_2 -carbonyl group. The ring-opened compound(IIa) was treated in 5%KOH/H₂O at room temperature for 2 hr. After acidified, a crystalline compound(IV) was obtained as the only isolable product from the mixture by ion exchange chromatography(Amberlite XAD-2). [mp 224-228°(dec), in 55% yield, C₁₅H₁₉N₃O₆, m/e 319(M⁺-H₂O), ¹H-nmr(DMSO-d₆) δ 1.85(4H, multiplet, -CH₂CH₂-), 2.75(3H, doublet, J=4Hz, NCH₃, When D₂O was added, the signal converted to singlet.), 3.11(3H, s, NCH₃), 3.55(3H, s, OCH₃), 3.38(4H, multiplet, CH₂NCH₂), 8.62(1H, broad, NH), In the ¹³C-nmr(DMSO-d₆) spectrum, fifteen signals were observed.]. Furthermore, IIa and IIb were treated in 5%KOH/R''OH(R'' = Me, Et) at room temperature and crystalline compounds(Vd and Ve) were obtained from the reaction mixture in 43% and 53% yields, respectively. Vd [mp > 300°, C₁₁H₉N₂O₆K, ¹H-nmr(D₂O) δ 2.81(3H, s, NCH₃), 3.28(3H, s, NCH₃), 3.65(3H, OCH₃), In the ¹³C-nmr(D₂O, dioxane is internal reference) spectrum, eleven signals were observed.]; Ve [mp > 300°, C₁₂H₁₁N₂O₆K, ¹H-nmr(D₂O) δ 1.21(3H, triplet, J=11Hz, -CCH₃), 2.72(3H, s, NCH₃), 3.26(3H, s, NCH₃), 4.19(2H, quartet, J=11Hz, OCH₂C), In the ¹³C-nmr(D₂O) spectrum, twelve signals were observed.]. This assignment is confirmed by the fact that the product Ve possesses an OEt group in the molecule, when EtOH(R'' = Et) is used as the solvent. 1,3-Dimethyl-5-(3-carboxypropynoyl)-6-methoxyuracil(VI) was prepared by treatment of Vd in an aqueous solution of hydrochloric acid. [mp > 300°, C₁₁H₁₀N₂O₆, m/e 266(M⁺), ¹H-nmr(D₂O) δ 2.77(3H, s, NCH₃), 3.26(3H, s, NCH₃), 3.69(3H, s, OCH₃), In the ¹³C-nmr(DMSO-d₆) spectrum, eleven signals were observed.].

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