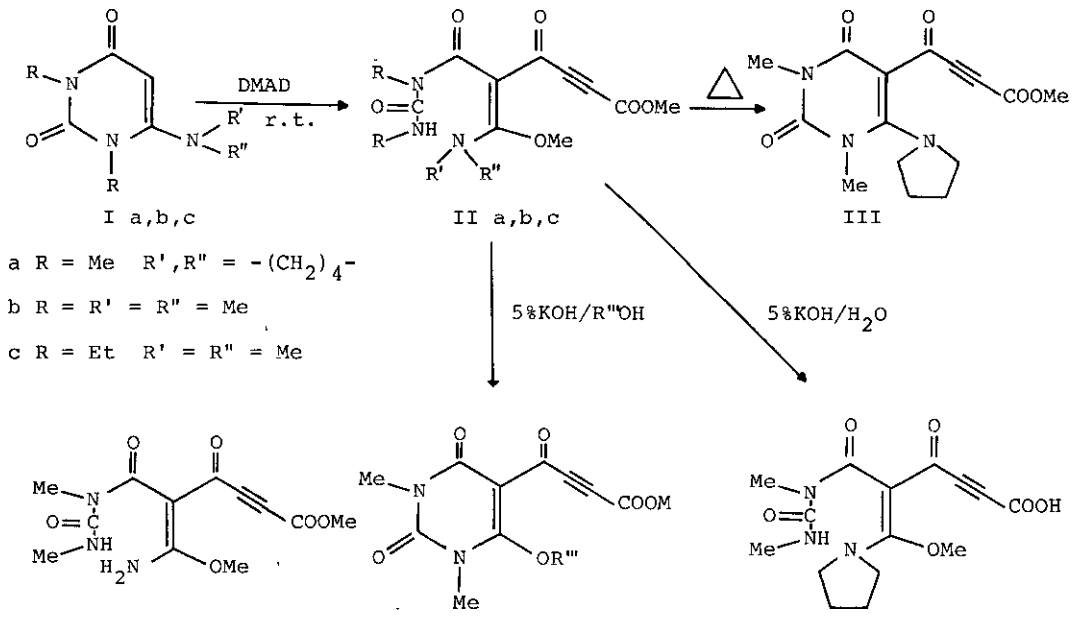
SOME NOVEL REACTIONS OF 1,3-DIMETHYLURACILS II.[1] STUDIES ON NEW STABLE PYRIMIDINE RING-OPEND COMPOUNDS.

Norio Kawahara*
Hokkaido College of Pharmacy, Katsuraoka-machi, Otaru-shi,
047-02, Japan
Tsuneo Itoh and Haruo Ogura
School of Pharmaceutical Sciences, Kitasato University,
Minato-ku, Tokyo, 108, Japan
and Kyoichi A. Watanabe
Sloan-Kettering Institute for Cancer Research, Rye, New York,
10580, U.S.A.

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, CH_2Cl_2), N,N'-dimethyl-N-[3-methoxy-3-pyrrolidino-2-(3-carbomethoxypropynoyl)acryloyl]urea(IIa) was obtained in 80-81% yield. [mp 239°(dec), $C_{16}H_{21}N_3O_6$, m/e 351(M^+), ^{1}H-nmr($CDCl_3$) δ 1.75-2.28(4H, multiplet, $-CH_2CH_2-$) 2.98(3H, doublet, J=4Hz, $-NHCH_3$) 3.36-3.60 (4H, multiplet, $-CH_2NCH_2-$), singlets each integrated for 3H at 3.36(NCH_3), 3.81 (OCH_3) and 3.82(OCH_3), 8.10(1H, broad, NH), The ^{13}C-nmr($CDCl_3$) showed sixteen signals.]. The structural assignment of IIa based on the ^{1}H-nmr spectrum, ^{13}C-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, $C_{15}H_{17}N_3O_5$, m/e 319(M^+), ^{1}H-nmr ($CDCl_3$) δ 2.0-2.4(4H, multiplet, $-CH_2CH_2-$), three singlets at 3.27(3H, NCH_3),

3.37(3H, NCH_3) and 3.89(3H, $COOCH_3$), 4.0-4.5(4H, multiplet, $-CH_2NCH_2-$), In the ^{13}C-nmr($CDCl_3$) spectrum, thirteen signals were observed.]. It is interesting to note that the compound VII[6], 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%).



I a,b,c

a R = Me R',R" = $-(CH_2)_4-$

b R = R' = R" = Me

c R = Et R' = R" = Me

II a,b,c

III

VII

V d M = K R''' = Me

e M = K R''' = Et

VI M = H R''' = Me

IV

Fig. 1

The addition reactions of 1,3-dimethyl-6-dimethylaminouracil(1b) 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), $C_{14}H_{19}N_3O_6$, m/e 325(M^+), ^1H-nmr($CDCl_3$) δ 2.92(3H, doublet, J=4Hz, $NHCH_3$), five singlets at 3.14(3H, NCH_3), 3.27(3H, NCH_3), 3.34(3H, NCH_3), 3.76(3H, OCH_3) and 3.85(3H, OCH_3), 9.26(1H, NH), The ^{13}C-nmr($CDCl_3$) showed fourteen signals.].

IIc [mp 270°(dec), $C_{16}H_{23}N_3O_6$, m/e 353(M^+), ^{1}H-nmr(DMSO-d_6) δ 1.05(6H, multiplet, 2×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×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-opend 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 ^{1}H and ^{13}C-nmr spectra of IIa,b,c showed that R' and R" is non-equivalent. It can be interpreted that II

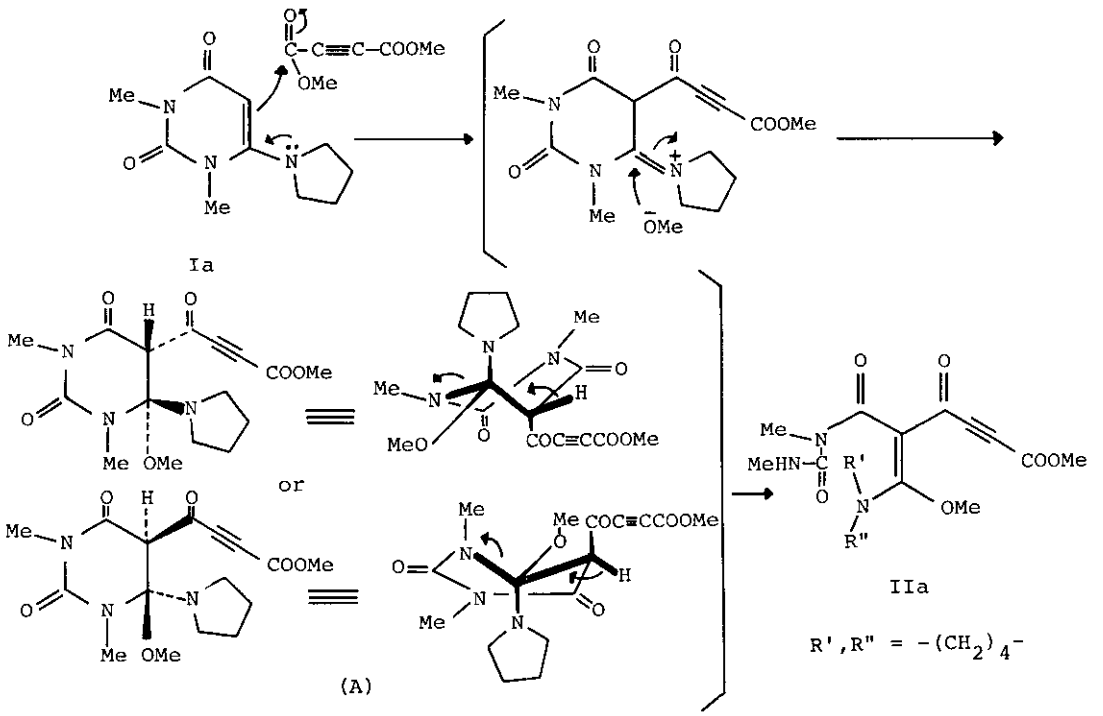


Fig. 2

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/H_2O 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, $C_{15}H_{19}N_3O_6$, m/e 319(M^+-H_2O), ^{1}H-nmr(DMSO-d_6) δ 1.85(4H, multiplet, $-CH_2CH_2-$), 2.75(3H, doublet, J=4Hz, NCH_3, When D_2O was added, the signal converted to singlet.), 3.11(3H, s, NCH_3), 3.55(3H, s, OCH_3), 3.38(4H, multiplet, CH_2NCH_2), 8.62(1H, broad, NH), In the ^{13}C-nmr(DMSO-d_6) 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°, $C_{11}H_9N_2O_6K$, ^{1}H-nmr(D_2O) δ 2.81(3H, s, NCH_3), 3.28(3H, s, NCH_3), 3.65(3H, OCH_3), In the ^{13}C-nmr(D_2O, dioxane is internal reference) spectrum, eleven signals were observed.]; Ve [mp > 300°, $C_{12}H_{11}N_2O_6K$, ^{1}H-nmr(D_2O) δ 1.21(3H, triplet, J=11Hz, $-CCH_3$), 2.72(3H, s, NCH_3), 3.26(3H, s, NCH_3), 4.19(2H, quartet, J=11Hz, OCH_2C), In the ^{13}C-nmr(D_2O) 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°, $C_{11}H_{10}N_2O_6$, m/e 266(M^+), ^{1}H-nmr(D_2O) δ 2.77(3H, s, NCH_3), 3.26(3H, s, NCH_3), 3.69(3H, s, OCH_3), In the ^{13}C-nmr(DMSO-d_6) spectrum, eleven signals were observed.].

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