REACTION OF 2,3,6-TRIMETHYLPYRIMIDIN-4-ONE AND DIMETHYL ACETYLENEDICARBOXYLATE[1]

Takao Yamazaki*, Junko Tanii, Yoshiro Hirai, and Katsuhide Matoba
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan

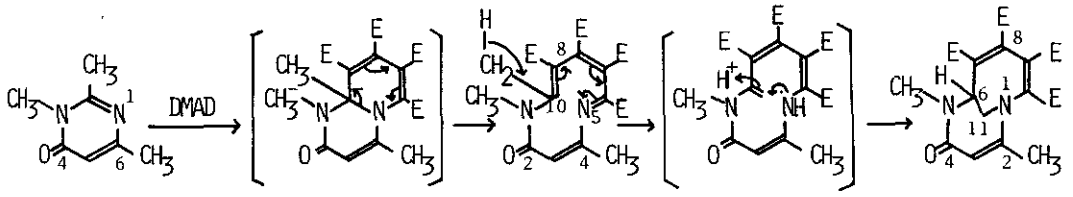
Abstract — Treatment of 2.3.6-trimethylpyrimidin-4-one with dimethyl acetylenedicarboxylate(DMAD) gave tetramethyl 2,5-dimethyl-4-oxo-1,5-diazabicyclo[4.4.1]undecane-2,7,9-triene-7,8,9,10-tetracarboxylate(II) and tetramethyl 1,4,10-trimethyl-2-oxo-1,5-diazacyclodecane-3,5,7,9-tetraene-6,7,8,9-tetra-carboxylate(III) in 36.2 and 27.9% yields, respectively. The reduction products with sodium borohydride and the catalytic-reduction products of II or III are also discussed.

We have studied systematically the photochemical reactions[2] and the reactions with sodium amide or hydrazine of pyrimidin-4-one.[3] Now, we are going to report the reaction of 2,3,6-trimethylpyrimidin-4-one(I) with dimethyl acetylenedicarboxylate (DMAD). An optimal condition to obtain the adduct was to heat a mixture of I and an excess of DMAD on an oil bath at 50°C overnight. The crude products were directly fractionated through a silica gel column. Two isomeric products were successively eluted with 20% AcOEt in benzene, whose empirical formula were determined to be $C_{19}H_{22}N_2O_9$, corresponded to 1:2 adduct of I and DMAD, from the mass spectra and the elemental analyses. First eluted product, 36.2% yield, mp 197-199°C(brown prisms), exhibited in the ^1H NMR spectrum two singlets(each 3H) at 2.24(C_2-Me) and 3.42 ppm(N-Me), a double-doublet(1H) at 2.51 ppm(C_{11}-H) and a multiplet(2H) between 3.3-3.6 ppm(C_6- and C_{11}-H). In the ^{13}C NMR spectrum, the signals of a triplet and a doublet due to the C_{11} and C_6 appeared at 30.59 and

44.10 ppm, respectively. From the above physical and spectral data, the first eluted product may be tetramethyl 2,5-dimethyl-4-oxo-1,5-diazabicyclo[4.4.1]undecane-2,7,9-triene-7,8,9,10-tetracarboxylate(II). The down-field shift of one proton of C_{11}-protons in the ^1H NMR spectrum would be explained in terms of the anisotropy effect induced by the C_2-double bond.

Second eluted product, 27.9% yield, mp 142-144°C(yellow-green prisms), exhibited in the ^1H NMR spectrum a doublet(3H, J=1 Hz, allyl coupling), two singlets(each 3H), and a doublet(1H, J=1 Hz, allyl coupling) signals at 2.09, 2.38, 2.92, and 5.99 ppm due to the C_4-, C_{10}-, N-methyl protons, and C_3-proton, respectively, and in the UV spectrum absorption maxima at λ380(ε:4400), 285(sh., 6100), and 247 nm(16800). cf; II: λ_{max}312(ε: 18500) and 224 nm(16800). From the above physical and spectral data, the structure of the second eluted product was suggested to be tetramethyl 1,4,10-trimethyl-2-oxo-1,5-diazacyclodecane-3,5,7,9-tetraene-6,7,8,9-tetracarboxylate(III). Compound III was converted into II by heating at 160°C for 13 h.

The mechanism for the formation of these 1:2 adducts is proposed as shown in Chart 1.



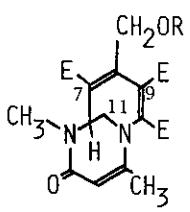
I III II

E=COOCH$_3$ Chart 1

Next, these products were reduced in two ways. One was the reduction with sodium borohydride(SBH) and the other was catalytic reduction using PtO_2 as a catalyst. The structure of the product obtained in the reduction of II with SBH(2.5 mol. eq.) in ethanol was suggested from the following data to be monohydroxymethyl compound and from the structural consideration(methoxycarbonyl groups at the C_7- and C_9-positions are vinylogous urethane moieties) and the steric reason(methoxycarbonyl group at the C_{10} position may be sterically hindered) to be trimethyl 8-hydroxymethyl-4-oxo-1,5-diazabicyclo[4.4.1]undecane-2,7,9-triene-7,9,10-tricarboxylate (IVa). The conversion yield was 88.1%. NMR($CDCl_3$), ppm: 3.61, 3.73 and 3.82(each 3H, s, OMe), 3.7-3.9(2H, m, -CH_2-OH). Mass, m/z 394(M^+). IVa-acetate(IVb): mp 143-145°C. NMR($CDCl_3$), ppm: 3.61, 3.70 and 3.83(each 3H, s, OMe), 4.18 and 4.23 (each 1H, d, J=12.1 Hz, -CH_2-OAc). Mass, m/z 436(M^+). The elemental analysis of IVb

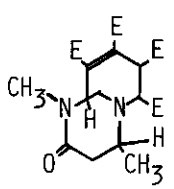
satisfied the formula of $C_{20}H_{24}N_2O_9$. The catalytic reduction of II gave tetrahydro compound, whose structure was revealed to be tetramethyl 2,5-dimethyl-4-oxo-1,5-diazabicyclo[4.4.1]undecan-7-ene-7,8,9,10-tetracarboxylate(V) from the following UV and NMR data. V: mp 171-173°C. UV(MeOH),λ_{max}301 nm(ε: 310). NMR($CDCl_3$), ppm: 1.15(3H, d, J=7 Hz, C_2-Me), 3.29(1H, d, J=5 Hz, C_9-H), 4.41(1H, d, J=5 Hz, C_{10}-H). The elemental analysis of V satisfied the formula of $C_{19}H_{26}N_2O_9$.

When III was reduced with SBH under the similar conditions to those used in II, 3-[3,4,5,6-tetra(methoxycarbonyl)-2-methyl-1,2-dihydropyridin-1-yl]crotonylmethylamide(VI) was obtained in 72.0% yield. VI: a viscous oil. IR($CHCl_3$): ν_{max} 3450 cm^{-1}. UV(MeOH), λ_{max}283 and 250 nm. ^1H NMR($CDCl_3$), ppm: 1.25(3H, d, J=6 Hz, C_2-Me), 2.79(3H, d, J=5 Hz, >N-Me, this signal turned to a singlet one by D_2O treatment for long time), 4.71(1H, q, J=6 Hz, C_2-H), 6.06(1H, br s, >NH, this signal disappeared by D_2O treatment for long time). Finally the catalytic-reduction product obtained from III in 87.8% yield was suggested to be tetramethyl 1,4,10-trimethyl-2-oxo-1,5-diazacyclodecane-3,8-diene-6,7,8,9-tetracarboxylate(VII). VII: mp 168-170°C. IR(KBr): ν_{max}3400 cm^{-1}. UV(MeOH),λ_{max}334(ε: 1300), 288(5600), 228(5200). NMR($CDCl_3$), ppm: 1.46(3H, d, J=6 Hz, C_{10}-Me), 3.53(1H, m, C_{10}-H), 3.64(1H, d, J=8 Hz, C_7-H), 4.31(1H, d, J=8 Hz, C_6-H).

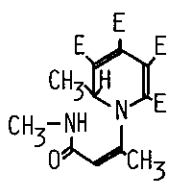


IV

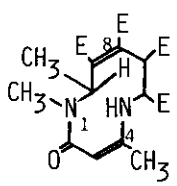
a: R=H
b: R=Ac



V



VI



VII

E=$COOCH_3$

Chart 2

The results mentioned above are interesting although a lot of studies have been reported on the reactions of DMAD with nitrogen-containing heterocycles.[4]

ACKNOWLEDGEMENTS

The authors thank Prof. T. Momose and Dr. O. Muraoka, Faculty of Pharmaceutical Sciences, Kinki University, for the measurements of NMR spectra.

REFERENCES AND NOTES

1) A part of this work was presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 1985.

2) Y. Hirai, H. Kenmei, and T. Yamazaki, Heterocycles, 1982, 17, 337.

3) Y. Hirai, H. Egawa, S. Yamada, and T. Yamazaki, Heterocycles, 1983, 20, 1243.

4) R. M. Acheson and N. F. Elmore, Advances in Heterocyclic Chem., 1978, 23, 263.

Received, 8th August, 1985