Studies on Ketene and Its Derivatives. CIII[1]
Synthesis of Fused 4-Pyrimidones and Their Photoreactions.

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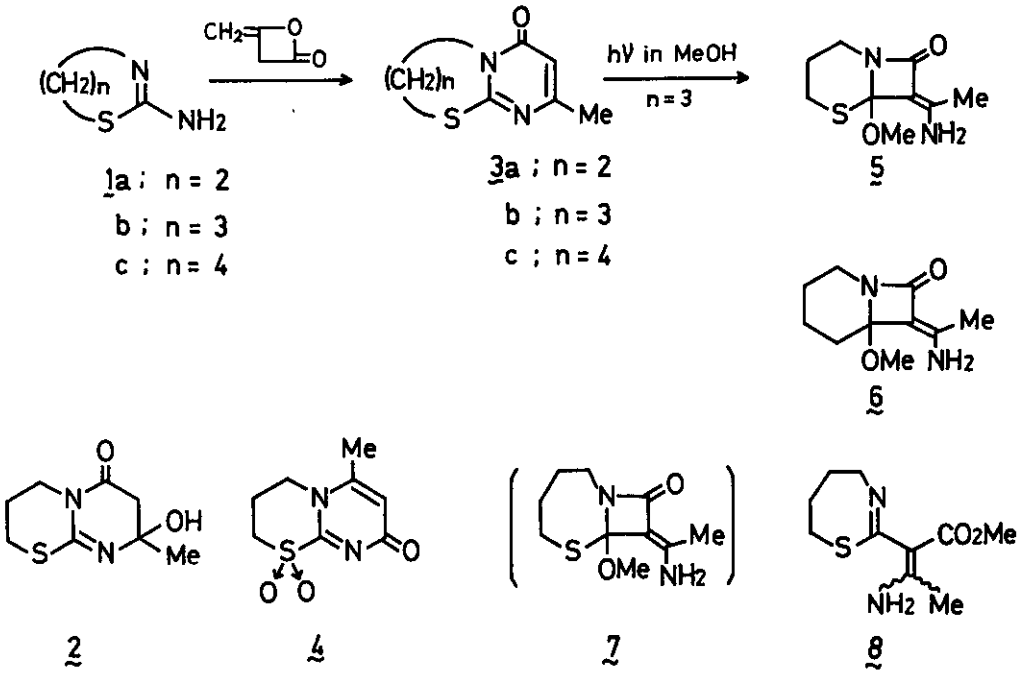
Abstract---- The reaction of diketene with 2-amino-2-thiazoline (1a), 2-amino-5,6-dihydro-4H-1,3-thiazine (1b) and 2-amino-4,5,6,7-tetrahydro-1,3-thiazepine (1c) gave rise to 7-methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-5-one (3a), 8-methyl-3,4-dihydro-2H,6H-pyrimido[2,1-b][1.3]thiazin-6-one (3b), and 9-methyl-2,3,4,5-tetrahydro-7H- pyrimido[2,1-b][1.3]thiazepin-7-one (3c), respectively. Photolysis of 3b in methanol gave 7-(1-aminoethylidene)-6-methoxy-8-oxo- 1-thia-5-azabicyclo[4.2.0]octane (5). However, similar photolysis of 3c did not afford the β-lactam (7), but methyl 3-amino-2-[4,5,6,7-tetrahydro-2-(1,3-thiazepinyl)]crotonate (8).

The reaction of diketene with primary amines is reported to give acetoacetamides, which further react with another molecule of diketene to afford either 1-substituted 3-acetyl-4-hydroxy-6-methyl-2-pyridones or N-substituted 2,6-dimethyl-4-pyrone-3-carboxamides.[2] However, the amines such as 2-aminopyridine or 2-aminobenzoxazole bearing cyclic amidine moiety react with diketene to give fused 4-pyrimidones.[3] Meanwhile, the novel photoreaction of 4-pyrimidones to give β-lactams has been reported by one of the present authors.[4]
In order to develop a new synthetic method of penam and cepham we have investigated the syntheses of fused 4-pyrimidones and their photoreactions, which are described in this communication.
When 2-amino-5,6-dihydro-4H-1,3-thiazine (1b)[5] was allowed to react with 1.2 molar equivalents of diketene in chloroform at 0 - 5° for 24 hr, 8-hydroxy-8-methyl-

3,4,7,8-tetrahydro-2H,6H-pyrimido[2,1-b][1.3]thiazin-6-one (2) was obtained in 80% yield. [compound (2)[6]: colorless prisms (ethyl acetate), mp 130 - 132° (dec.); ν max ($CHCl_3$) 3230, 1700, 1600 cm^{-1}; δ ($CDCl_3$) 1.43 (3H, s, $-CH_3$), 2.15 (2H, m, $-CH_2-C$), 2.75 (2H, s, $-COCH_2-$), 3.06 (2H, t, J = 6 Hz, $-S-CH_2-$), 3.90 (2H, t, J = 6 Hz, $N-CH_2-$), 4.05 (1H, b, OH)].

When this reaction was carried out at reflux, compound (2) and 8-methyl-3,4-dihydro-2H,6H-pyrimido[2,1-b][1.3]thiazin-6-one (3b) of mp 122 - 123° (lit.[7] 119.5 - 121°), together with a small amount of 6-methyl-3,4-dihydro-2H,8H-pyrimido[2,1-b][1.3]thiazin-8-one 1,1-dioxide (4), were obtained in 50 and 30% yields, respectively. [compound (4): colorless prisms (ethyl acetate), mp 100°, ν max (KBr) 1645, 1595 cm^{-1}; δ (CF_3COOH) 2.40 (2H, m, $-C-CH_2-C-$), 2.54 (3H, s, $-CH_3$), 3.47 (2H, t, J = 6 Hz, $-S-CH_2-$), 4.32 (2H, t, J = 6Hz, $-N-CH_2-$), 6.55 (1H, s, ring proton)].



Scheme I

Furthermore, the use of 2.5 molar equivalents of diketene in benzene gave rise to compound (3b) in 70% yield. Compound (2), on heating in benzene for 6 hr, was transformed into 3b, but a yield was low (20%).

Similarly, reaction of 2-amino-2-thiazoline (1a)[8] with 2.5 molar equivalents of diketene in benzene at reflux for 2.5 hr gave 7-methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-5-one (3a) of mp 124 - 125° (lit.[9] mp 127 -128°) in 95% yield.

Reaction of hydrobromide of 2-amino-4,5,6,7-tetrahydro-1,3-thiazepine (1c)[10] with excess diketene in water in the presence of triethylamine with ice cooling gave 9-methyl-2,3,4,5-tetrahydro-7H-pyrimido[2,1-b][1.3]thiazepin-7-one (3c) in 14% yield. [compound (3c): colorless prisms (ether), mp 73 - 74°; νmax ($CHCl_3$) 1672; δ ($CDCl_3$) 1.7 - 2.2 (4H, m, -C-C$\underline{H}_2$C$\underline{H}_2$-C), 2.20 (3H, s, -C$\underline{H}_3$), 2.95 - 3.20 (2H, m, -S-C$\underline{H}_2$-), 4.35 - 4.60 (2H, m, -N-C$\underline{H}_2$-), 6.17 (1H, s, ring proton)].

Photolysis of 3a in methanol resulted in the recovery of the starting material. However, irradiation of 3b in methanol with mercury lamp (3000 Å) gave the product (5) as colorless prisms (ethyl acetate) of mp 175 - 177° in 66% yield. The NMR spectrum (DMSO-d_6) showed signals at δ 2.00 (3H, s), 3.23 (3H,s) and 5.87 (2H, b), representing a methyl group, a methoxy group and an amino group, respectively. In the IR spectrum, the streching bands of carbonyl group and C=C double bond were observed at 1710 and 1690 cm^{-1}, respectively. The IR spectrum also exhibited the absorbtion band of primary amine at 3430 and 3360 cm^{-1}. Furthermore, the UV spectrum (MeOH) showed λmax at 271 nm (ε 2.19×10^4). These spectral data are resemble to those of 7-(1-aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]-octane (6) reported in a previous paper.[4] Therefore, compound (5) was assigned the β-lactam structure, 7-(1-aminoethylidene)-6-methoxy-8-oxo-1-thia-5-aza-bicyclo[4.2.0]octane.

Irradiation of 3c in a similar fashion gave an oil, whose IR spectrum showed the presence of 8-(1-aminoethylidene)-7-methoxy-9-oxo-1-thia-6-azabicyclo[5.2.0]-nonane (7) [νmax ($CHCl_3$) 3480, 3300, 1715 cm^{-1}] besides the starting (3c) (1670 cm^{-1}).

Purification of this oil by silica gel column chromatography gave a 13% yield of methyl 3-amino-2-[4,5,6,7-tetrahydro-2-(1,3-thiazepinyl)]crotonate (8), which would be formed by the acidic rearrangement of 7 in a column.[11]

[compound (8): colorless plates (ether), mp 68 - 70°; ν max ($CHCl_3$) 3520, 3340, 2950, 1665, 1610 cm^{-1}; δ ($CDCl_3$) 1.60 - 2.2 (4H, m, -C-C$\underline{H}_2$C$\underline{H}_2$-C-), 1.99 (3H, s, -C$\underline{H}_3$), 2.92 (2H, t, J = 6 Hz, -S-C$\underline{H}_2$-), 3.70 (3H, s, -OC$\underline{H}_3$), 3.89 (2H, t, J = 6

Hz, N-CH_2-), 7.9 - 8.8 (2H, b, NH_2); MS m/e, 288 (M^+)].

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