

REACTIONS OF 4-PYRIMIDINONE DERIVATIVES WITH METHYL ISOCYANATE:
FORMATION OF PYRIMIDO[1,2-a][1,3,5]TRIAZINE-2,4-DIONE RING SYSTEM

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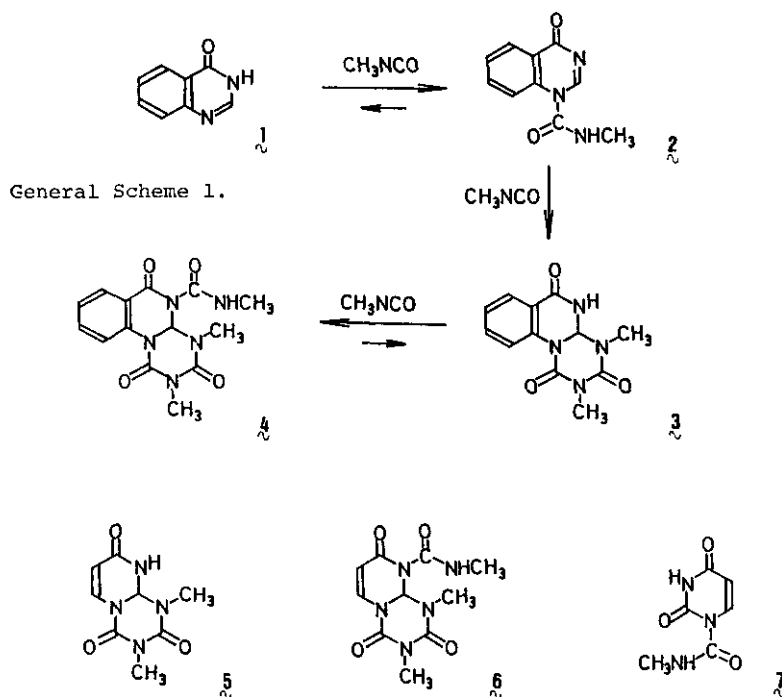
Abstract—Base-catalysed reactions of 4-pyrimidinone and 4-quinazolinone with methyl isocyanate gave the compounds with a pyrimido[1,2-a][1,3,5]triazine-2,4-dione ring system (**3** and **5**, respectively; 1:2-cyclic adducts). In contrast, some uracil derivatives afforded the 1-methylcarbamoyl compounds (**7**, 1:1-adducts).

Recently, we reported that the reactions of 4-pyridinone or 4-quinolinone with various alkyl isocyanates give condensed ring-1,3-dialkyl-1,3,5-triazine-2,4-dione derivatives (1:2-cyclic adducts).¹ The reaction proceeds via a stepwise addition of two alkyl isocyanates followed by an intramolecular Michael addition to the 4-pyridinone or 4-quinolinone skeleton; a new sequence from 4-pyridinones to form a six-membered ring.² In the course of studying general applicability of this cyclization, the reactions of diaza heterocyclic compounds such as 4-pyrimidinone and 4-quinazolinone with methyl isocyanate were investigated. It has been well known that substances having an annelated pyrimidine ring and/or triazine ring play a very important part in organic chemistry of biological compounds.³ We now communicate the easy formation-reaction of the ring system, pyrimido[1,2-a][1,3,5]triazine-2,4-dione.

To a solution of 4-quinazolinone (**1**) (1.00g, 0.68mmol) in DMF (23ml) containing 1,1,3,3-tetramethylguanidine (78mg, 0.68mmol) was added two equivalent of methyl isocyanate (0.80g, 14.0mmol) at room temperature under nitrogen atmosphere. The solution was stirred for 2 h. After evaporation of the solvent, the residue was chromatographed on silica gel (elution with chloroform [97]/ethanol [3]) to give 2,4-dimethyl-1,2,3,4,4a,5,6,11-octahydro-quinazolino[1,2-a][2,4,11]triazine-1,3,6-trione (**3**) (1:2-cyclic adduct; 32 % yield) as a main product and 5-methylcarbamoyl-2,4-dimethyl-1,2,3,4,4a,5,6,11-octahydroquinazolino[1,2-a][2,4,11]triazine-1,3,6-

trione (**4**) (1:3-adduct; 2% yield) and 1-methylcarbamoyl-4-oxo-1,4-dihydroquinazoline (**2**) (1:1-adduct; 14% yield) as by-products.⁴

Similarly, 4-pyrimidinone reacted with methyl isocyanate under similar conditions to afford 1,3-dimethyl-1,2,3,4,5,8,9,9a-octahydro-pyrimido[1,2-a][1,3,5]triazine-2,4,8-trione (**5**) (1:2-cyclic adduct; 19% yield) and 9-methylcarbamoyl-1,3-dimethyl-1,2,3,4,5,8,9,9a-octahydropyrimido[1,2-a][1,3,5]triazine-2,4,8-trione (**6**) (1:3-adduct; 25% yield).⁵ The structures of these products were determined on the basis of elemental analytical, mass spectral, and ir, ¹H-nmr, and ¹³C-nmr spectral data (Table 1).



It is reasonably understood that **4** was obtained by the further addition of methyl isocyanate to **3**, and **2** was isolated on the way of the formation of **3** (Scheme 1).¹ In order to get more mechanistic information, general reversibility of the reactions was tested under relatively higher base-concentrations: a small amount of each component compound of the Scheme 1 was stirred with a drop of 1,1,3,3-tetramethylguanidine in DMF or CHCl_3 (without methyl isocyanate), and the progress of the reaction was monitored by TLC, independently.

The results were (i) $\mathbf{2}$ was mostly converted into $\mathbf{1}$ for a short time (less than 3 min, base-catalysed decomposition), (ii) $\mathbf{3}$ did not change at least for 20 h (no base-catalysed decomposition), (iii) $\mathbf{4}$ was mostly converted into $\mathbf{3}$ (base-catalysed decomposition), but not into $\mathbf{1}$. The same behavior was observed for $\mathbf{5}$. These results indicate that the reaction step from $\mathbf{2}$ to $\mathbf{3}$ is generally irreversible under such basic conditions. This is in contrast with the fact that in the case of 1:2-cyclic adduct of 4-quinolinone, the corresponding step has generally reversible nature,⁶ and must reflect certain effects of the nitrogen atom on the ring-closing and ring-opening steps. It is the important observation that the cyclization occurs only in one way at the C-2 (not at the C-6) position of the 4-pyrimidinone ring. The selectivity may be caused by electron deficiency at the C-2 position which results from electronegative nitrogen atom adjacent to the reaction center. As reported by Oine et al.,⁷ electron deficiency at the C-2 position of the 4-quinazolinone accelerates such a ring-closing step.⁸

Under the similar conditions, uracil (1.00g, 8.9mmol) was stirred for 2 h with methyl isocyanate (2.62g, 45.9mmol) in DMF (20ml) containing 1,1,3,3-tetramethylguanidine (1.03g, 0.90mmol) at room temperature under nitrogen atmosphere. In this case, only the 1:1-adduct ($\mathbf{7}$) was obtained in a 33% yield (mp 173°C, dec).⁹ Both 5-fluorouracil and 5-bromouracil bearing electron-withdrawing groups, and further 3-methyluracil where an acidic proton is protected by a methyl group, gave the corresponding 1:1-adducts in 46% (mp 171°C, dec),¹⁰ 41% (mp 197.5°C, dec), and 63% yields (mp 133-134.5°C), respectively. Further studies of these reactions are now in progress.

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4. Recovered 4-quinazolinone, 52% yield.

5. Recovered 4-pyrimidinone, 45% yield. In this case, the corresponding 1:1-adduct could not be isolated.
6. The starting material, 4-quinolinone, was observed after a short time under the same basic conditions as the case of (ii).
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8. The more fundamental step is the ring-closing one from the 1:2-acyclic adduct (not isolated in this case,¹) not shown in the general scheme 1, chain-form) to the 1:2-cyclic adduct (ring-form).
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Table 1. Physical Data of Some Pyrimido[1,2-a][1,3,5]triazine-2,4-dione and Its Related Derivatives

Compound	Yield (%)	mp (°C)	M.S. IR(Nujol) m/e ν_{CO} (cm ⁻¹)	¹³ C-NMR δ_{CO} (ppm)	¹ H-NMR δ (ppm)
2	4 ^{a)}	194-196	203 ^{g)} 1740 1660	163.1 ^{d)} 152.3	9.64(1H, brd, NH) ^{d)} , 9.15(1H, s, CH), 8.39-7.47(4H, m, ArH), 3.07(3H, d, J=4.5 Hz, CH ₃)
3	21 ^{b)}	271-274	260 1740 1690 1680	163.2 ^{e)} 150.0 149.8	9.31(1H, brd, NH) ^{e)} , 7.96-7.37(4H, m, ArH), 6.31(1H, d, J=1 Hz, CH), 3.12(3H, s, CH ₃), 3.07(3H, s, CH ₃)
4	1 ^{a)}	267-274	317 ^{g)} 1730 1720 1680 1650	164.1 ^{d)} 152.1 151.9 150.0	8.52(1H, brd, NH) ^{e)} , 8.03-7.43(4H, m, ArH), 6.67(1H, s, CH), 3.11(3H, s, CH ₃), 3.03(3H, s, CH ₃), 2.70(3H, d, J=4.9 Hz, CH ₃)
5	8 ^{c)}	198-199	210 1740 1680	163.2 ^{d)} 150.2 147.3	8.66(1H, brd, NH) ^{e)} , 7.61(1H, d, J=7.8 Hz, =CH), 6.04(1H, brd, CH), 5.42(1H, dd, J=7.8 and 1.3 Hz, =CH), 3.08(3H, s, CH ₃), 2.98(3H, s, CH ₃)
6	18 ^{a)}	148(dec)	267 ^{g)} 1740 1710 1690	163.3 ^{d)} 153.2 151.9 150.4	8.96(1H, brd, NH) ^{d)} , 7.42(1H, dd, J=8.0 and 0.7 Hz, =CH), 7.23(1H, d, J=0.7 Hz, CH), 5.33(1H, d, J=8.0 Hz, =CH), 3.17(3H, s, CH ₃), 2.93(3H, d, J=4.6 Hz, CH ₃), 2.85(3H, s, CH ₃)

a) Recryst. from CHCl₃-hexane. b) Recryst. from acetonitrile.
 c) Recryst. from AcOEt. d) CDCl₃/TMS. e) DMSO-d₆/TMS.
 f) EI/MS(70 eV); M⁺-value. g) EI/MS(20 eV); M⁺-value.

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