# 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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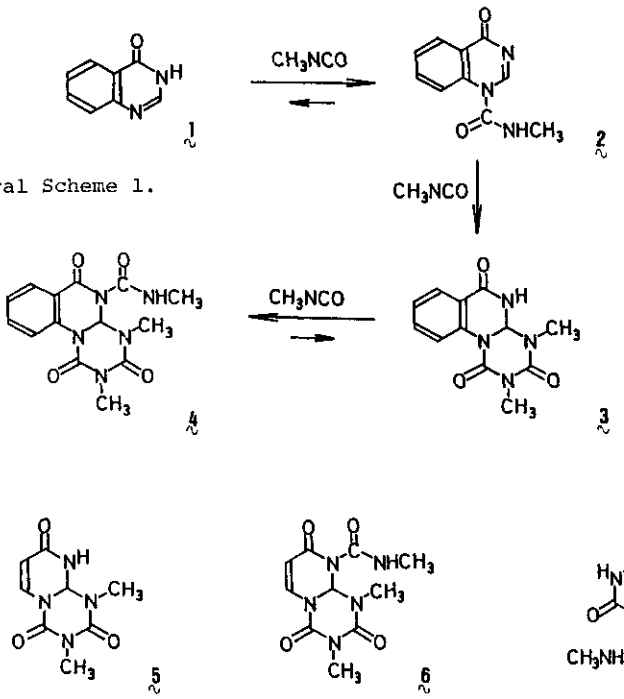
Abstract — Base-catalysed reactions of 4-pyrimidinone and 4-quinazolinone with methyl isocyanate gave the compounds with a pyrimido[1,2-a][1,3,5]triazine-2,4-dione ring system (3 and 5, respectively; 1:2-cyclic adducts). In contrast, some uracil derivatives afforded the 1-methylcarbamoyl compounds (7, 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, $^{1}$H-nmr, and $^{13}$C-nmr spectral data (Table 1).




General Scheme 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) 2 was mostly converted into 1 for a short time (less than 3 min, base-catalysed decomposition), (ii) 3 did not change at least for 20 h (no base-catalysed decomposition), (iii) 4 was mostly converted into 3 (base-catalysed decomposition), but not into 1. The same behavior was observed for 5. These results indicate that the reaction step from 2 to 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 (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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3. For example, A. Albert, Adv. Heterocyclic Chem., 32, 1(1982); R. Baker, "Organic Chemistry of Biological Compounds", Prentice-Hall(1971), Chap. 8.
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. m/e | IR(Nujol) $\nu_{CO}$ ($cm^{-1}$) | $^{13}$C-NMR $\delta_{CO}$ (ppm) | $^{1}$H-NMR δ (ppm) |
|---|---|---|---|---|---|---|
| 2 | 4[a)] | 194-196 | 203[g)] | 1740<br>1660 | 163.1[d)]<br>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<br>1690<br>1680 | 163.2[e)]<br>150.0<br>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<br>1720<br>1680<br>1650 | 164.1[d)]<br>152.1<br>151.9<br>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<br>1680 | 163.2[d)]<br>150.2<br>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<br>1710<br>1690 | 163.3[d)]<br>153.2<br>151.9<br>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 $CHCl_3$-hexane. b) Recryst. from acetonitrile.
c) Recryst. from AcOEt. d) $CDCl_3$/TMS. e) DMSO-$d_6$/TMS.
f) EI/MS(70 eV); $M^+$-value. g) EI/MS(20 eV); $M^+$-value.

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