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X-Ray Structure Determination and NMR Characterization of Some Fused Heterocycles with a 1,3,5-Triazine-2,4(1*H*,3*H*)-dione Ring. Reaction of 2-Amino-4(3*H*)-pyrimidinone with Chloroformyl Isocyanate

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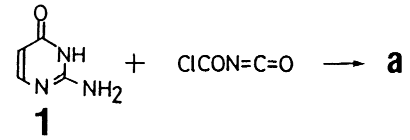
Synopsis. The reaction product **a** of 2-amino-4(3*H*)-pyrimidinone with chloroformyl isocyanate was methylated and the two resulting products were determined as **4** (for the major product) and **5** (for the minor one) by X-ray crystal structure analyses. In a DMSO solution of **a**, the **2a** tautomer was shown to be predominant by ^{13}C NMR analysis.

The reactions and reactivities of heterocyclic compounds have been extensively studied in view of synthetic, mechanistic, and biological interest.[1,2] We have reported on the formation of fused 1,3,5-triazine-2,4(1*H*,3*H*)-diones by a reaction of 4(1*H*)-pyridinone with alkyl isocyanates.[3,4]

Recently, Kamal et al.[5] communicated the reaction of 2-aminopyrimidine with chloroformyl isocyanate (CFI)[6] to give 2*H*-pyrimido[1,2-*a*][1,3,5]triazine-2,4-(3*H*)-dione. As an extension of our synthetic studies using 4-pyridinone families,[3] we carried out a reaction of 2-amino-4(3*H*)-pyrimidinone (**1**) with CFI in acetonitrile under heterogeneous conditions. Here, we describe the structures of the reaction product and the dialkylated derivatives which have been determined by means of X-ray and ^{13}C NMR analyses.



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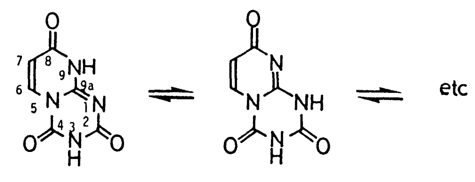
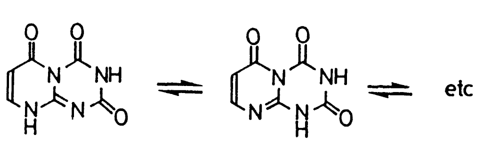


2a **2b**

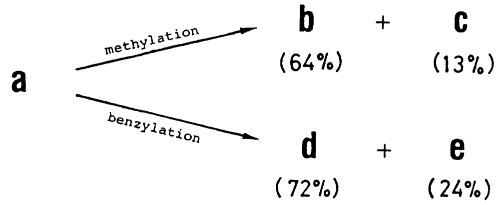


3a **3b**

Experimental

Materials. 2-Amino-4(3*H*)-pyrimidinone (mp 273—275 °C; 4.0 g; 36 mmol), which was synthesized by following the literature method,[7] was suspended in acetonitrile and triethylamine (4.0 g; 40 mmol). An acetonitrile solution (10 ml) of chloroformyl isocyanate (3.2 ml; 40 mmol) was added dropwise with cooling to the above solution under nitrogen atmosphere. The mixture was stirred overnight at room temperature. After removal of the solvent, water (40 ml) was added. The precipitated product was collected, washed twice with water (20 ml), and dried in vacuo (5.9 g; 91% yield, **a**); mp 279—281 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=12.38 (1H, br, NH), 11.88 (1H, br, NH), 8.16 (1H, d, J=8.1 Hz, =CH-N), 6.05 (1H, d, J=8.1 Hz, =CH-CO); ^{13}C NMR (DMSO-d_6) δ=162.47 (C7), 152.55 and 151.24 (C2, C4), 146.35 (C8a), 134.25 (C5), 108.32 (C6); IR (Nujol) 1770, 1710, 1650 (CO) cm^{-1}; MS (70 eV) *m/z* 180 (M$^+$); pK_{a_1}=5.47±0.01, pK_{a_2}=9.71±0.03 (20 °C, H_2O); Anal. ($C_6H_4N_4O_3$) C, H, N.

Methylation of **a** was performed in DMF by excess methyl iodide in the presence of potassium carbonate. After the usual workup by medium-pressure column chromatography (silica gel), two kinds of dimethyl derivatives, **b** (mp 253—256 °C, 64% yield) and **c** (mp 218—219 °C, 13% yield) were obtained. Similarly, after benzylation of **a** by excess benzyl bromide, **d** (mp 122—123 °C, 72% yield) and **e** (mp 253—255 °C, 24% yield) were obtained(: for ^{13}C NMR data, see Table 2).



X-Ray Analysis. Colorless crystals of **b** and **c** were obtained by recrystallizations from ethanol and **d** from acetonitrile. Crystal data and analytical conditions are summarized in Table 1.[4a] Three dimensional intensity data were collected on a Rigaku AFC-5FOS automated four-circle diffractometer at room temperature. Mo$K\alpha$ (λ 0.710679 Å) radiation with a graphite crystal monochromator in the incident beam was used. Unit cell constants were determined by a least-squares fit of 15—25 reflections in the range of $15° < 2\theta < 35°$ for all cases. Intensity data were reduced to structure factors without any absorption corrections. Structures were reduced by MULTAN direct methods, refined by block-diagonal least-squares methods. Non-hydrogen atoms were assigned with anisotropic temperature factors. Hydrogen atoms were found from difference Fourier calculations and refined with isotropic thermal parameters. In the case of **c**, hydrogens were not included in the computation. The function minimized was $\sum\omega\,(|F_o|-|F_c|)^2$ with the same equation as described before.[4a]

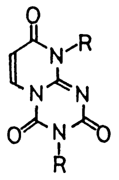
Computations were carried out on a FACOM S3500 superminicomputer at Material Analysis Center, ISIR, Osaka Univ. or an ACOS-850 computer at Crystallographic Research Center, IPR, Osaka Univ.[8] In the former case, RASA and ANCHOR software were employed for structure analyses and a 3-dimensional graphic display, respectively.[9] From the results, it was determined that the structure of **b** is

Table 1. Crystal and Experimental Data for **b**, **c**, **d**

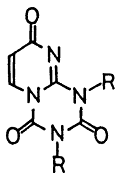
Compound	**4** (**b**)	**5** (**c**)	**8** (**d**)
Formula	$C_8H_8N_4O_3$	$C_8H_8N_4O_3$	$C_{20}H_{16}N_4O_3$
Molecular weight	208.18	208.18	360.24
Crystal system	triclinic	tetragonal	orthorhombic
Space group	$P\bar{1}$	$P\bar{4}2bc$	$Fdd2$
a/Å	10.1187(7)	17.228(5)	39.083(9)
b/Å	10.4462(13)	17.228(5)	16.794(4)
c/Å	4.3015(10)	6.4446(25)	10.714(3)
a/deg	89.181(15)		
b/deg	95.687(11)		
c/deg	106.220(8)		
V/Å^3	434.39(12)	1912.78(14)	7031.82(26)
Z	2	8	16
D_c/g cm^{-3}	1.5922	1.4463	1.3620
μ(Mo $K\alpha$), cm^{-1}	1.232	1.356	1.022
Crystal size/mm^3	0.4X0.3X0.2	0.2X0.08X0.1	0.4X0.3X0.15
Scan method	θ-2θ	θ-2θ	θ-2θ
Scan range $\Delta(2\theta)$/deg	1.4+0.5tanθ	1.40+0.7tanθ	1.20+0.6tanθ
Scan speed in 2θ/deg min^{-1}	4	4	12
$2\theta_{max}$/deg	55	55	60
Background/s	2X5.0	2X5.0	2X5.0
Refl. measd	2270	1549	2845
Refl. independ.	2003	1366	2640
Direct method	MULTAN84	MULTAN84	MULTAN(78),84
Refl. used[a]	1694	800	1568
Final R	0.048	0.083	0.046
Final R_w	0.040	0.076	0.041

a) $F_o > \sigma(F_o)$.

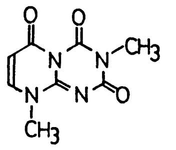
4, that of **c** is **5**, and that of **d** is **8**. Tables of the final atomic positional and thermal parameters, and anisotropic thermal parameters of the non-hydrogen atoms, F_o and F_c, and figures of bond lengths for **b**, **c**, **d** are deposited as Document No. 8794 at the Office of the Editor of Bull. Chem. Soc. Jpn.



4 (R = CH_3-)
8 (R=$C_6H_5CH_2$-)



5 (R = CH_3-)
9 (R=$C_6H_5CH_2$-)



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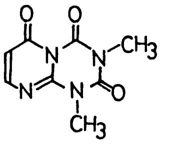

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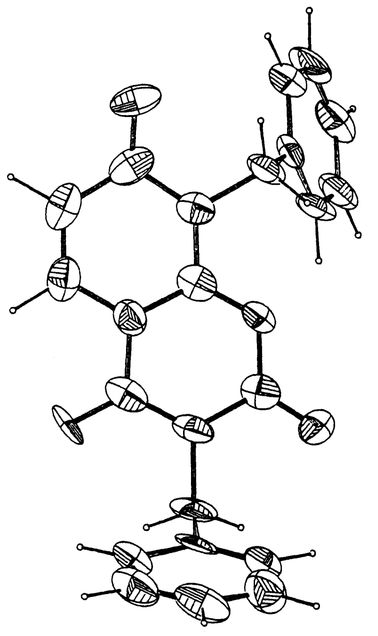

Fig. 1. ORTEP view of **d**. The non-hydrogen atoms were drawn at the 50% probability level and the hydrogen atoms at an arbitrary diameter.

Results and Discussion

By using elemental analysis, mass, ^{1}H, and ^{13}C NMR spectroscopic data of **a**, we could not identify one of four possible structures among **2a**, **2b**, **3a**, and **3b**. Since it was difficult to obtain a single crystal, **a** was converted into dimethyl (**b**,**c**) and dibenzyl derivatives (**d**, **e**). By X-ray crystal analyses, the structures of **b**, **c**, and **d** were confirmed to be **4**, **5**, and **8** (Fig. 1), respectively. Neither abnormal bond lengths nor bond angles were found in these structures.[4a)] These results suggest that the reaction of 2-amino-4(3*H*)-pyrimidinone with CFI gives 2*H*-pyrimido[1,2-*a*][1,3,5]triazine-2,4,8(3*H*,9*H*)-trione in high yield.

^{13}C NMR data of alkyl-substituted derivatives of **2a** or **2b** are summarized in Table 2. There exist clear

Table 2. ^{13}C NMR Data (δ, ppm from TMS)$^{a)}$

Compd	*N*-Subst$^{b)}$ of **2a** or **2b**	Solvent$^{c)}$)	C8	C4, C2	C9a	C6	C7
4(b)	3,9-Me$_2$ (**2a**)	C	159.29	152.60, 150.32	146.99	132.74	107.95
5(c)	1,3-Me$_2$ (**2b**)	C	168.05	147.82, 146.54	144.67	132.83	112.40
8(d)	3,9-Bz$_2$ (**2a**)	C	159.25	152.13, 150.00	146.87	132.86	108.01
9(e)	1,3-Bz$_2$ (**2b**)	C	167.90	147.76, 146.18	144.52	132.93	112.72
10	9-Bz$^{d)}$ (**2a**)	D	159.77	153.11, 151.87	146.72	134.01	106.28
11	1-Bz$^{d)}$ (**2b**)	D	167.92	148.08, 148.02	144.47	133.74	110.53
12	3-Bz$^{d)}$ (**2a**/**2b**)	D	161.30	152.43, 150.66	147.13	135.00	108.32
2	None (**2a**/**2b**)	D	162.47	152.55, 151.24	146.35	134.25	108.32

a) Bruker AM360 (90 MHz). b) Bz: $C_6H_5CH_2$-. c) C: $CDCl_3$, D: DMSO-d_6. d) Ref. 2a.

differences in ^{13}C NMR chemical shifts. We can classify them into two types of derivatives: compounds with an alkyl substituent at the N-9 position and those at the N-1 position. For example, compared with N-1 substitutions (**5**, **9**, **11**), N-9 substitutions (**4**, **8**, **10**) show upfield-shifts in C8 (ca. 8 ppm), C7 (ca. 4 ppm), and downfield-shifts in C2, C4 (ca. 4 ppm), C9a (ca. 2 ppm): on the other hand, there are no clear differences in the ^{1}H NMR chemical shifts (C6-H, C7-H) between the two classes.

The ^{13}C NMR data of the parent compound (**2**) and the monobenzyl derivative at N-3 position (**12**)$^{2a)}$ resemble each other. Furthermore, both compounds show a very similar ^{13}C NMR pattern to the former (N-9) substitution class. These observations indicate that the tautomer structure **2a** is much more favorable than **2b** in a DMSO solution.

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