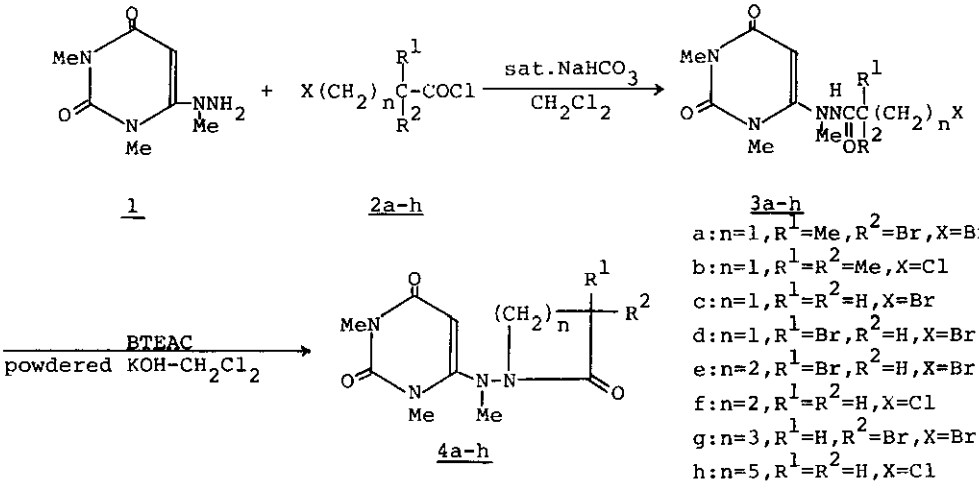
SYNTHESIS OF NEW URACILES HAVING N-AMINO-β-, γ -, AND δ-LACTAMS

Tadashi Okawara, Toshifumi Shono, Tetsuo Yamasaki, and
Mitsuru Furukawa

Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-hon-machi, Kumamoto 862, Japan

Abstract ——— The reaction of 1,3-dimethyl-6-methylhydrazinouracil **1** with various haloacyl halides **2** afforded N-haloacylhydrazinouraciles **3**, which were converted into the corresponding lactams **4** by treatment with KOH in the presence of BTEAC.

A preceding paper reported the preparation of N-substituted amino-β-, γ-, and δ-lactams,[1] which induced high differentiation of Friend leukemia cell with extremely weak cytotoxicity.[2] Such a differentiation-inducing activity required the existence of the aromatic ring in the amino moiety and of bromine at the α-position on the lactam ring. In an attempt to obtain compounds with increased inducing differentiation ability, we synthesized new β-, γ-, and δ-lactams bearing uracil moiety, which possesses structural similarity to a



1 2a-h

3a-h
a:n=1,R1=Me,R2=Br,X=Br
b:n=1,R1=R2=Me,X=Cl
c:n=1,R1=R2=H,X=Br
d:n=1,R1=Br,R2=H,X=Br
e:n=2,R1=Br,R2=H,X=Br
f:n=2,R1=R2=H,X=Cl
g:n=3,R1=H,R2=Br,X=Br
h:n=5,R1=R2=H,X=Cl

4a-h

DNA base.

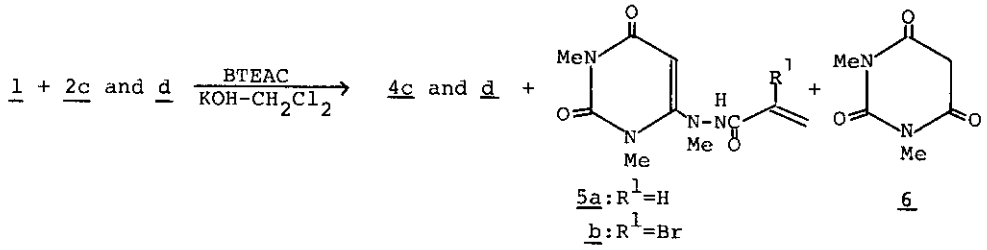
1,3-Dimethyl-6-(1-methylhydrazino)uracil **1**,[3] readily available from 6-chloro-1,3-dimethyluracil, was allowed to react with various haloacyl halides **2** in sat. aq.$NaHCO_3$-CH_2Cl_2 to afford N-haloacylhydrazinouraciles **3**. Compounds **3** were converted into N-[[N-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)]-N-methylamino]-β-, γ-, and δ-lactams **4** in 65-80% yield by stirring with powdered KOH in CH_2Cl_2 in the presence of benzyltriethylammonium chloride (BTEAC). The results are summarized in Tables 1 and 3.

Table 1. N-[[N-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroprimidin-6-yl)]-N-methylamino]-β-, γ-, and δ-lactams **4**

	Mp(°C)	Yield(%)	Irν_{max}(KBr) cm^{-1}	M^+(m/z)
4a	142.5-143.5	74	1780, 1660, 1650	330, 332
4b	138-139	65	1760, 1650, 1640	266
4c	170.5-171.5	5	1760, 1650, 1640	238
4e	191.5-192.5	80	1700, 1655, 1640	330, 332
4f	177.5-178.5	65	1690, 1650, 1640	252
4g	135-136	78	1690, 1670, 1645	265[a]

a) M^+-HBr

In the cases of **2c** and **2d**, the β-elimination occurred preferentially to afford α, β-unsaturated hydrazide **5** (30-43% yield) and 1,3-dimethylbarbituric acid (**6**, 10-15%), in addition to the β-lactams **4c** and **4d** (0-5%). The structures of **4a-d** and **5a-b** were confirmed by the spectral data. Compound **6** was identified by comparison of the ir spectrum with that of an authentic sample.[4]



Alkaline hydrolysis of **5** was considered to produce **6**. Indeed, upon standing for 7 days at room temperature in sat. $NaHCO_3$-CH_2Cl_2, **5a** and **b** gave **6** and the corresponding N-acylhydrazine. Unfortunately, cyclization of **3h** to ε-lactam **4h**

failed under various conditions.

The differentiation-inducing activity of these new compounds for Friend leukemia cells is currently being investigated.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded as KBr pellet on a JASCO IRA-1 grating infrared spectrometer. ^{1}H-Nmr spectra were determined with a Hitachi R-600 spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL-01 SG mass spectrometer.

β, γ, and δ-Haloacyl halides (2)

These compounds were prepared from the corresponding carboxylic acids.[5]

General Procedure for N-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)-N-mehtyl-N'-ω-haloacylhydrazine (3)

To a vigorously stirred solution of 1,3-dimethyl-6-methylhydrazinouracil **1** (1.84 g, 10 mmol) in CH_2Cl_2 (30 ml)-sat.aq.$NaHCO_3$ (15 ml) was gradually added haloacyl halide **2** (10 mmol) under cooling with ice-water. The reaction mixture was stirred for 1 h at room temperature. The CH_2Cl_2 layer was separated, washed with water (15 mlx3), dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The residue was recrystallized from EtOH. The results are shown in Table 2. Satisfactory elemental analyses were not obtained because these compounds decomposed to 1,3-dimethylbarbituric acid during recrystallization.

General Procedure for β-Lactams 4a-d

To a solution of **3a-d** (5 mmol) in CH_2Cl_2 (20 ml) was added powdered KOH (0.56 g, 10 mmol) and BTEAC (20 mg), and the mixture was stirred for 3 h at room temperature. The CH_2Cl_2 layer was separated, washed with water (15 mlx3), dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was recrystallized from CH_2Cl_2-n-hexane or EtOH. The results are summarized in Tables 1 and 3.

General Procedure for γ- and δ-Lactam 4e-h

To a vigorously stirred solution of **1** (0.92 g, 5 mmol) in CH_2Cl_2 (30 ml)-5% aq. NaOH (4 ml) was added dropwise **2e-h** (5 mmol) at room temperature. After the addition was over, 5% NaOH (8 ml) and BTEAC (20 mg) were added to the reaction mixture, which was stirred for 3 h at room temperature. The CH_2Cl_2 layer was separated, washed with water (15 mlx3), dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was recrystallized from CH_2Cl_2-n-hexane or EtOH. The results are shown in Tables 1 and 3.

Table 2. N-(1,3-Dimethyl-2,4-dioxopyrimidine-6-yl)-N-methyl-N'-haloacyl-hydrazine 3

	Mp(°C)	Yield(%)	^{1}H-Nmr (δ) (solvent)
3a	166-167	80	(DMSO-d_6)1.97(3H,s,Me),2.97(3H,s,Me),3.15(3H,s,Me), 3.27(3H,s,Me),4.18(1H,d,CHH,J=10Hz),4.33(1H,d,CHH, J=10Hz),5.37((1H,s,uracil(H-5)),10.55(1H,s,NH)
3b	125-130 (dec.)	76	unstable
3c*		46	(DMSO-d_6)2.71(2H,t,CH_2,J=6Hz),3.00(3H,s,Me),3.24 (3H,s,Me),3.37(3H,s,Me),3.89(2H,dd,CH_2,J=6Hz),5.31 (1H,s,uracil(H-5)),9.01(1H,s,NH)
3d	154-156	88	(DMSO-d_6)2.94(3H,s,Me),3.15(3H,s,Me),3.25(3H,s,Me), 3.99(2H,dd,CH_2,J=7 and 9Hz),4.56(1H,dd,CH,J=7 and 9Hz),5.41(1H,s,uracil(5-H)),9.25(1H,s,NH)
3g	139-140	87	($CDCl_3$)2.16(6H,m,CH x3),3.00(3H,s,Me),3.26(3H,s,Me) 3.39((5H,m,Me and CH_2),4.32(1H,m,CH),5.36(1H,s, uracil(5-H)),9.25(1H,s,NH)
3h*		88	($CDCl_3$)1.65(8H,m,CH_2x4),2.28(2H,t,CH_2,J=6Hz),2.99 (3H,s,Me),3.26(3H,s,Me),3.34(3H,s,Me),3.57(2H,t, (CH_2,J=6Hz),5.26(1H,s,uracil(5-H)),8.59(1H,s,NH)

*This compound decomposed to **6** and N-acylhydrazine during recrystallization.

Table 3. N[[N-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)]-N-methylamino]-β-, γ-, and δ-lactams (**4**)

	^{1}H-Nmr (δ) (solvent)	Analysis(%) Calcd.(Found) C	H	N
4a	(DMSO-d_6)1.94(3H,s,Me),3.04(3H,s,Me), 3.34(3H,s,Me), 3.43(3H,s,Me),3.71(1H,s,CHH),3.73(1H,s,CHH),5.42 (1H,s,uracil(H-5))	39.90 (39.71)	4.57 (4.46)	16.92 (16.44)
4b	(DMSO-d_6)1.33(6H,s,Mex2),3.00(3H,s,Me),3.19(2H,s, CH_2),3.34(3H,s,Me),3.41(3H,s,Me),5.39(1H,s, uracil(H-5))	54.12 (54.09)	6.81 (6.81)	21.04 (20.99)
4c	(DMSO-d_6)2.85(2H,t,CH_2,J=6Hz),3.02(3H,s,Me),3.34 (3H,s,Me),3.40(5H,m,Me and CH_2),5.41(1H,s, uracil(5-H))	50.41 (50.34)	5.92 (5.74)	23.52 (23.59)
4e	($CDCl_3$)2.52(2H,m,CH_2),2.98(3H,s,Me),3.33(8H,s,Mex2 and CH_2)4.37(1H,dd,CH,J=3 and 6Hz),5.45(1H,s, uracil(5-H))	39.90 (40.01)	4.57 (4.44)	16.67 (16.67)
4f	($CDCl_3$)2.31(4H,m,CH x2),2.97(3H,s,Me),3.25-3.52(8H, m,Mex2 and CH_2),5.39(1H,s,uracil(5-H))	52.37 (52.46)	6.39 (6.19)	22.21 (22.18)
4g*	($CDCl_3$)2.32(4H,m,CH_2x2),2.99(3H,s,Me),3.34(8H,m, Mex2, and CH_2),4.63(1H,s,CH),5.37(1H,s,uracil(5-H))	42.46 (42.81)	5.48 (5.34)	15.24 (15.20)

*contained 0.5 EtOH

N-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)-N-methyl-N'-acrylolyhydrazine derivatives (5a,b)

5a:mp 125-126°C. ^{1}H-Nmr($CDCl_3$)δ:3.08(3H,s,Me),3.30(3H,s,Me),3.39(3H,s,Me), 5.32(1H,s,uracil(5-H)),5.90(1H,m,CH),6.35(2H,m,CH_2),9.02(1H,br,NH). Irν_{max}^{KBr}cm^{-1}:3316(NH),1680,1647(C=O).

5b:mp 153-154°C. ^{1}H-Nmr($CDCl_3$)δ:3.09(3H,s,Me),3.30(3H,s,Me),3.38(3H,s,Me), 5.39(1H,s,uracil(5-H)),6.22(1H,d,HHC=,J=4.9Hz),7.11(1H,d,HHC=,J=4.0Hz), 8.94(1H,br,NH). Irν_{max}^{KBr}cm^{-1}:3212(NH),1688,1647(C=O).

REFERENCES

1. T. Okawara, R. Kato, and M. Furukawa, Chem. Pharm. Bull., 1984, **32**, 2426.

2. H. Morioka, M. Takezawa, H. Shibai, T. Okawara, and M. Furukawa, Agri. Biol. Chem., 1986, **50**, 1757.

3. H. Biltz and H. Wittek, Chem. Ber., 1921, **54**, 1035.

4. T. Okawara, T. Matsuda, and M. Furukawa, Chem. Pharm. Bull., 1982, **30**, 1225.

Received, 7th March, 1988