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Pyrimidine Derivatives and Related Compounds. XLIII.[1] Studies on the Mechanism of the Ring Transformation of 6-Chloro-1,3-oxazine-2,4-diones to Barbituric Acids

Motoi Yogo,*,[a] Kosaku Hirota,*,[b] and Shigeo Senda[b]

Faculty of Pharmacy, Meijo University,[a] Tempaku-cho, Tempaku-ku, Nagoya 468, Japan and Gifu College of Pharmacy,[b] Mitahora-higashi, Gifu 502, Japan

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The mechanism of the ring transformation of 6-chloro-1,3-oxazine-2,4-diones (**1**) into barbituric acids (**2**) in the presence of primary aliphatic amines was studied. It has been elucidated that the mechanism involves initial attack on the 2-position of **1** by an amine and subsequent intramolecular cyclization of the ureide intermediate (**5**).

Keywords——ring transformation; barbituric acids; malonamoylureas; 6-chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione; 6-amino-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione; reduction of azido group

Previous studies[2] on the reaction of 6-chloro-1,3-oxazine-2,4-diones (**1**) with various amines showed that the use of such amines as methylamine or ethylamine caused a ring transformation of 1,3-oxazine to a pyrimidine ring system, giving barbituric acids (**2**) along with the open-chain ureas (**3**), while the use of secondary amines or aniline afforded the corresponding 6-substituted compounds. Further attempts to convert **3** into **2** were unsuccessful, which indicates that compound **3** is not an intermediate in the course of the conversion of **1** into **2**.

We have studied this ring transformation reaction in further detail to elucidate the mechanism and clarified that compounds **2** and **3** are both formed *via* the ureide intermediate (**5**).

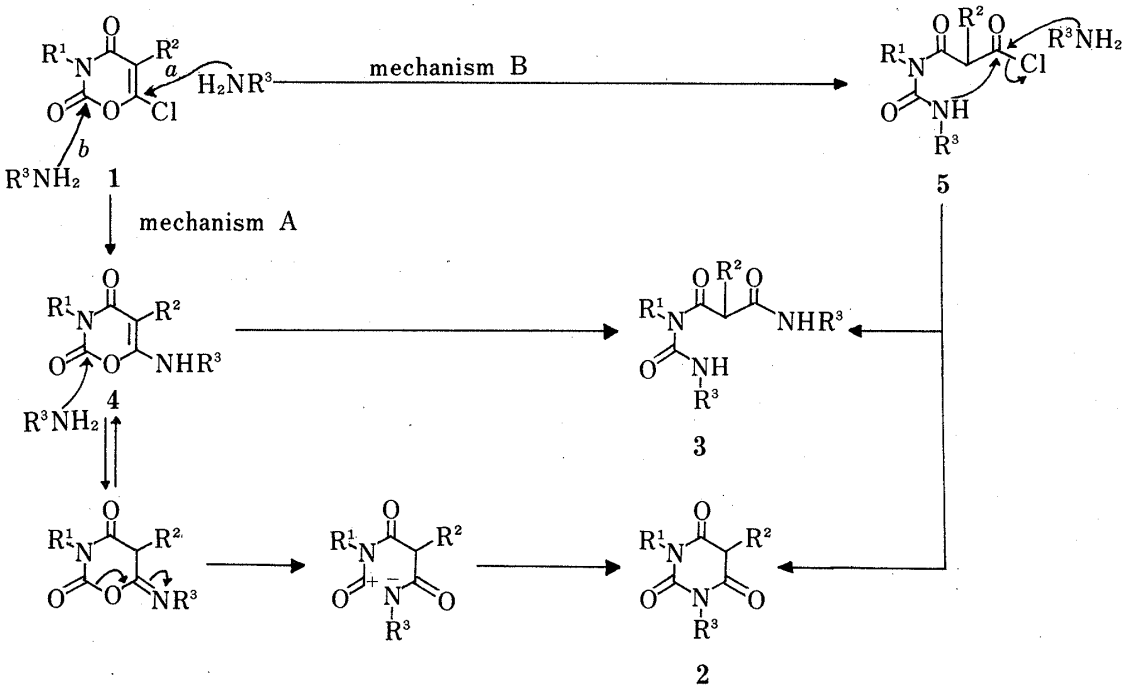
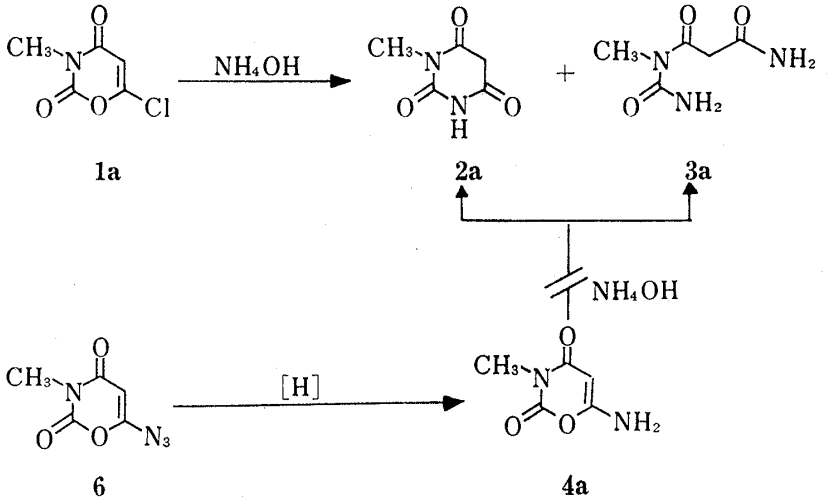


Chart 1

Two plausible mechanisms for the formation of **2** and **3** are shown in Chart 1. Mechanism A involves initial attack on the 6-position of **1** by an amine and formation of an intermediate (**4**). Further reaction of **4** with an additional molecule of the amine affords **3**, and ring cleavage and recyclization of the imino-tautomer of **4** gives **2**. Mechanism B involves initial attack on the 2-position of **1** by an amine and formation of an intermediate (**5**). Nucleophilic substitution of **5** with an additional molecule of the amine gives **3** and intramolecular recyclization of **5** yields **2**. In order to determine by which mechanism, A or B, compounds **2** and **3** are formed, the following experiments were carried out.

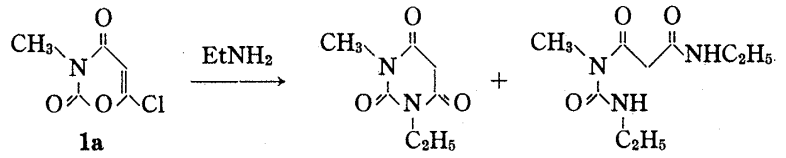
Treatment of 6-chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**1a**) with 5% aqueous solution of ammonia in tetrahydrofuran (THF) at 0—5°C afforded the expected 1-methylbarbituric acid (**2a**)[3] and 1-malonamoyl-1-methylurea (**3a**). If this reaction takes place in accordance with mechanism A, 6-amino-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**4a**) would be a key intermediate. Therefore, **4a** was prepared in order to examine its reactivity toward ammonia.



1a **2a** **3a** **6** **4a**

Chart 2

TABLE I. Effect of the Concentration of Ethylamine on the Yields of **2b** and **3b** in the Reaction of **1a** with Ethylamine

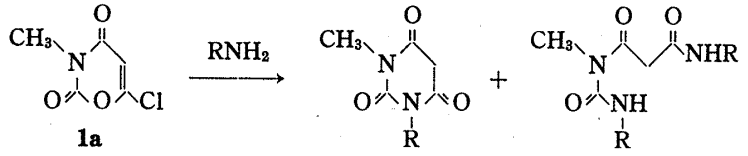


1a **2b** **3b**

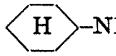
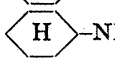
$EtNH_2$ Concentration in water (%)	$EtNH_2$ ml	Product ratio[a] **2b** : **3b**	Total yield[b] (%)
70	1.1	43 : 57	99
40	2	46 : 54	89
10	8	60 : 40	78
5	16	72 : 28	86
2.5	32	81 : 19	81
1	80	93 : 7	82

a) Product ratios were determined by ^{1}H-NMR analysis in $CDCl_3$ (from the absorption of methylene protons).
b) Yield of crude products.

TABLE II. Reaction of 6-Chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**1a**) with Amines

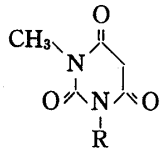


1a **2** **3**

Amines	R	Products Yields (%)[a] 2	3
40% CH_3NH_2	CH_3	45[b]	—
1% CH_3NH_2	CH_3	74	—
70% $C_2H_5NH_2$	C_2H_5	13[b]	58[b]
1% $C_2H_5NH_2$	C_2H_5	71	4
100% $C_3H_7NH_2$	C_3H_7	40	59
1% $C_3H_7NH_2$	C_3H_7	74	8
100% Iso $C_3H_7NH_2$	Iso C_3H_7	29	64
1% Iso $C_3H_7NH_2$	Iso C_3H_7	46	8
100% 		28	63
1% 		35	3
100% $C_6H_5CH_2NH_2$	$C_6H_5CH_2$	37	62
1% $C_6H_5CH_2NH_2$	$C_6H_5CH_2$	67	1

a) Yields of isolated products.
b) See lit.[2]

TABLE III. Barbituric Acids



Compound No.	R	mp (°C)	Recryst. solvt.	Formula	Analysis (%)[b] Calcd (Found) C	H	N
2c	C_3H_7	56—57	Ether–hexane	$C_8H_{12}N_2O_3$	52.16 (52.19	6.57 6.84	15.21 15.22)
2d	Iso C_3H_7	93—95	Hexane	$C_8H_{12}N_2O_3$	52.16 (51.86	6.57 6.74	15.21 15.16)
2e		92—93[a]	Ether	$C_{11}H_{16}N_2O_3$	58.91 (58.86	7.19 7.49	12.49 12.20)
2f	$C_6H_5CH_2$	109—110	Benzene–hexane	$C_{12}H_{12}N_2O_3$	62.06 (62.07	5.21 5.23	12.06 12.06)

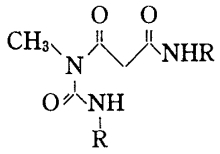
Compound No.	^{1}H-NMR ($CDCl_3$) δ ppm
2c	3.84 (2H, t, J=8 Hz, NCH_2), 3.66 (2H, s, C_5–H_2), 3.31 (3H, s, NCH_3), 1.64 (2H, sextet, J=8 Hz, CH_2), 0.95 (3H, t, J=8 Hz, CH_3)
2d	4.99 (1H, heptet, J=7 Hz, NCH), 3.60 (2H, s, C_5–H_2), 3.24 (3H, s, NCH_3), 1.43 (6H, d, J=7 Hz, $CH_3\times 2$)
2e	4.74—4.43 (1H, m, NCH), 3.61 (2H, s, C_5–H_2), 3.26 (3H, s, NCH_3), 2.44—1.12 (10H, m, C_5H_{10})
2f	7.53—7.24 (5H, m, C_6H_5), 5.06 (2H, s, NCH_2), 3.67 (2H, s, C_5–H_2), 3.29 (3H, s, NCH_3)

a) Lit.[4] mp 81—82°C.
b) In the mass spectra, all compounds showed the molecular ion peak.

Thus, 6-azido-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**6**)[2] was subjected to catalytic hydrogenation in THF in the presence of palladium on charcoal to give **4a** in 75% yield. Furthermore, **4a** was treated with 5% aqueous solution of ammonia under the same conditions as described above for the treatment of **1a**. However, compound **4a** was converted into neither **2a** nor **3a** and was recovered unchanged. From these results, it is obvious that the ring transformation does not take place in accordance with mechanism A, in which initial attack on the 6-position of **1** by an amine is involved.

On the other hand, it has already been reported that the reaction of **1a** with ethylamine gives a barbituric acid (**2b**) and a urea (**3b**). If the formation of **2b** and **3b** follows mechanism B, the product ratio of **2b** to **3b** would depend upon the concentration of the ethylamine solution used. Therefore, the reaction of **1a** with several concentrations of ethylamine solution was carried out. It was found that the less the concentration of ethylamine solution, the greater the yield of **2b** (as given in Table I), because intramolecular nucleophilic substitution occurred in preference to intermolecular substitution when dilute aqueous solution of ethylamine was used. These experimental results strongly support the view that the ring transformation proceeds according to mechanism B.

TABLE IV. Malonamoylureas



Compound No.	R	mp (°C)	Recryst. solvt.	Formula	Analysis (%)[a] Calcd (Found) C	H	N
3a	H	173—175 (dec.)	MeOH	$C_5H_9N_3O_3$	37.73 (37.84	5.70 5.77	26.41 26.22)
3c	C_3H_7	87—88	EtOAc	$C_{11}H_{21}N_3O_3$	54.30 (54.18	8.70 8.95	17.27 17.25)
3d	Iso C_3H_7	109—109.5	Hexane	$C_{11}H_{21}N_3O_3$	54.30 (54.12	8.70 8.73	17.27 17.28)
3e		111—112	EtOAc	$C_{17}H_{29}N_3O_3$	63.13 (62.89	9.04 9.04	12.99 13.02)
3f	$C_6H_5CH_2$	135—137	EtOAc	$C_{19}H_{21}N_3O_3$	67.24 (67.40	6.24 6.24	12.38 12.48)

Compound No.	^{1}H-NMR[b] δ ppm
3a	7.45 (2H, br s, NH_2), 7.04 (2H, br s, NH_2), 3.52 (2H, s, $COCH_2CO$), 3.10 (3H, s, NCH_3)
3c	8.96 (1H, br s, NH), 6.83 (1H, br s, NH), 3.91 (2H, s, $COCH_2CO$), 3.32 (3H, s, NCH_3), 3.23 (4H, t, J=7 Hz, $NCH_2\times2$), 1.59 (4H, sextet, J=7 Hz, $CH_2\times2$), 0.95 (6H, t, J=7 Hz, $CH_3\times2$)
3d	8.94 (1H, br s, NH), 6.92 (1H, br s, NH), 4.14 (1H, heptet, J=7 Hz, NCH), 4.04 (1H, heptet, J=7 Hz, NCH), 3.54 (2H, s, $COCH_2CO$), 3.30 (3H, s, NCH_3), 1.23 (6H, d, J=7 Hz, $CH_3\times2$), 1.21 (6H, d, J=7 Hz, $CH_3\times2$)
3e	8.92 (1H, br s, NH), 6.66 (1H, br s, NH), 4.12—3.40 (2H, m, NCH×2), 3.48 (2H, s, $COCH_2CO$), 3.29 (3H, s, NCH_3), 2.16—0.88 (20H, m, $C_5H_{10}\times2$)
3f	9.32 (1H, br s, NH), 7.33 (10H, s, $C_6H_5\times2$), 7.08 (1H, br s, NH), 4.49 (4H, d, J=6 Hz, $NCH_2\times2$), 3.53 (2H, s, $COCH_2CO$), 3.32 (3H, s, NCH_3)

a) In the mass spectra, all compounds showed the molecular ion peak.
b) The solvent was $CDCl_3$ except in the case of **3a** (DMSO-d_6).

In this reaction, therefore, the use of low concentration solution of amines would provide barbituric acids of the ring transformation products in much better yields.

Thus, the reaction of **1a** with a high concentration and a 1% aqueous solution of amines was carried out. As shown in Table II, barbituric acids (**2**) were obtained in good yields when 1% aqueous solution of amines such as *n*-alkylamines and benzylamine was used. However, the use of isopropylamine and cyclohexylamine reduced the yields of barbituric acids (**2d** and **2e**), probably due to steric hindrance.

Thus, it is anticipated that the reaction of **1** with dilute aqueous solution of amines provides a convenient method for preparing asymmetric 1,3-disubstituted barbituric acids.

Experimental

All melting points are uncorrected. Column chromatography was run using Silica-gel (Wakogel C-200). Centrifugal thin layer chromatography (CTLC) was carried out on a Harrison centrifugal thin layer chromatotron Model 7924 with Kieselgel 60 GF_{254} (Merck) of 2 mm layer thickness. The flow rate was 4 ml/min. Mass spectra (MS) were recorded on a Hitachi M-52 spectrometer and infrared (IR) spectra were obtained on a JASCO IRA-1 spectrophotometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance spectrometer with tetramethylsilane as an internal standard. Chemical shifts were quoted in parts per million (s=singlet, d=doublet, t=triplet, m=multiplet, br s=broad singlet).

1-Methylbarbituric Acid (2a) and 1-Malonamoyl-1-methylurea (3a)——A 5% NH_4OH solution (16 ml) was added to a stirred solution of **1a** (600 mg, 3.7 mmol) in THF (10 ml) dropwise at 0—5°C, and the mixture was stirred for 15 min. AcOH (1 ml) was added to the reaction mixture and the solvent was evaporated off *in vacuo*. The residue was chromatographed on a column with $CHCl_3$–MeOH (2: 1). From the earlier fractions, **3a** (110 mg, 27%) was isolated (Table IV).

Compound **2a** was isolated from the later fractions with the same solvent and recrystallized from EtOH to give colorless plates (170 mg, 32%), mp 133—135°C (lit.[3] mp 132°C). Compound **2a** was identical with an authentic sample.[3]

6-Amino-3-methyl-2*H*-1,3,-oxazine-2,4(3*H*)-dione (4a)——A mixture of **6** (2000 mg, 11.9 mmol) and THF (50 ml) was hydrogenated in the presence of 5% Pd-C (200 mg). Usual treatment of the reaction mixture and subsequent recrystallization from MeOH gave colorless needles (1270 mg, 75%), mp 176—177°C (dec.). *Anal.* Calcd for $C_5H_6N_2O_3$: C, 42.25; H, 4.26; N, 19.71. Found: C, 42.33; H, 4.24; N, 19.46. MS *m/e*: 142 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3330, 3140 (NH_2). ^{1}H-NMR (DMSO-d_6) δ: 7.54 (2H, br s, NH_2), 4.66 (1H, s, C_5–H), 3.08 (3H, s, CH_3).

Reaction of 1a with Primary Amines——(Table I): A solution of **1a** (600 mg, 3.7 mmol) in THF (10 ml) was treated with an aqueous solution of ethylamine as described for the preparation of **2a** and **3a**. THF was evaporated off *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$. After removal of $CHCl_3$, the residue was dried *in vacuo* and dissolved in $CDCl_3$ for ^{1}H-NMR analysis.

(Tables II, III and IV): A solution of **1a** (600 mg, 3.7 mmol) in THF (10 ml) was treated with an amine (15 mmol) as described above. When methylamine was used, only 1,3-dimethylbarbituric acid was obtained on recrystallization of the residue. In other cases, the residue was subjected to CTLC. Elution with $CHCl_3$ gave barbituric acids (**2b—f**) and further elution with ethyl acetate afforded malonamoylureas (**3b—f**).

References and Notes

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