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A New Class of Nitrosoureas. VIII.[1] Synthesis and Antitumor Activity of 3-Substituted 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-1-nitrosoureas

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A series of six 3-substituted 1-(2-chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-1-nitrosoureas (IVa—f) was prepared and tested for antitumor activities. Heating of cyclohexene oxide with various alkylamines followed by reaction with 2-chloroethyl isocyanate gave the corresponding ureas (IIIa—f), which were nitrosated with dinitrogen tetroxide to give the nitrosoureas (IVa—f). Decomposition of IVa and IV (IVd) d with aqueous sodium bicarbonate gave VIIa and VIIId, respectively, suggesting different modes activation. All the compounds obtained were remarkably active against leukemia L1210 and showed greater therapeutic ratios than the positive control: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU). Against Ehrlich ascites tumor, the nitrosoureas (IVa—c) having one β-hydroxyl group on a cyclohexyl moiety exhibited rather weak activities, but the compounds (IVd—f) having two kinds of β-hydroxyl groups showed strong activities and large therapeutic ratios. This seems to be due to the difference in activation mode between these types of nitrosoureas.

Keywords——chloroethyl nitrosourea; nitrosourea 3,3-disubstituted; *trans*-2-hydroxycyclohexyl derivative; antitumor activity; leukemia L1210; Ehrlich ascites carcinoma; 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea

In previous paper of this series,[2] we reported the synthesis and potent antitumor activity of various kinds of 3,3-disubstituted 1-(2-chloroethyl)-1-nitrosoureas which have a hydroxyl group on the β-position of their substituents. This new class of nitrosoureas having no proton at the N-3 position differs from known nitrosoureas in its activation mechanism. These compounds were activated by attack of the β-hydroxyl group on the carbonyl group to give cyclic carbamates and chloroethyl diazohydroxide without generation of isocyanates, and they exhibited remarkable antitumor activity. The study was extended to the synthesis of members of the new class of nitrosoureas corresponding to 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU). Described herein are the synthesis and the antitumor activity of 3-substituted 1-(2-chloroethyl)-3-(*trans*-2-hydroxycylohexyl)-1-nitrosoureas (IV). Some of these compounds exhibited more potent antitumor activity than CCNU.

Synthesis of Nitrosoureas and Discussion

The nitrosoureas (IVa—f) analogous to CCNU were prepared *via* the sequence outlined in Chart 1.

Heating of cyclohexene oxide (I) with primary amines in a sealed tube at 150°C for 20 h gave *N*-substituted *trans*-2-hydroxycyclohexylamines (II). The crude products (II), some of which could be isolated as crystals, were allowed to react with 2-chloroethyl isocyanate and the resulting urea derivatives (IIIa—f) were purified by chromatography. However, the ureas thus obtained were found to be extremely unstable, and they readily changed to the oxazoline derivatives (V) even when stored in a refrigerator for a few days. Therefore, the ureas (III) should be treated quickly at low temperature and nitrosated as soon as possible. Thus, in a typical procedure, a mixture of I and *n*-butylamine was heated at 150°C for 20 h, and then concentrated. Reaction of the residue with 2-chloroethyl isocyanate in tetrahydrofuran (THF) at 5°C gave the urea (IIIb) which was purified by silica gel chromatography. IIIb was

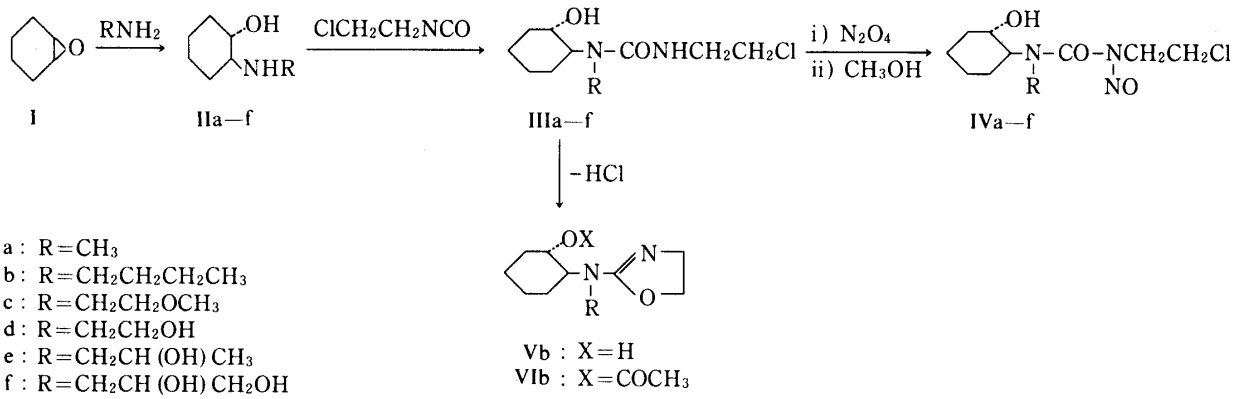


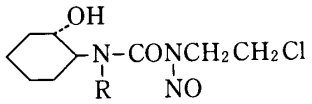
Chart 1

obtained as an oil and showed infrared spectrum (IR) signals at 3330 (br, NH, OH), 1620 (CO) and 1520 (NHCO) cm^{-1}, and nuclear magnetic resonace (NMR) signals at δ 0.9—2.1 (m, ring protons and $CH_2CH_2CH_3$), 4.80 (1H, d, t, J=8.4 Hz), and 6.47 (b, NH). The signal at around δ 4.80 was observed in all the ureas (IIIa—f) and, therefore, this was assigned to the ring proton α to the hydroxyl group. The mass spectrum of IIIb exhibited characteristic peaks at m/e 240 (M^+—36 (HCl)), 233, 235 (M^+—43 ($CH_2CH_2CH_3$)), and 99 (M^+—177 ($N(C_4H_9)CONHCH_2CH_2Cl$). The structure of IIIb was thus determined to be 3-*n*-butyl-1-(2-chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)urea. When IIIb was allowed to stand at room temperature for 6 d, it changed almost completely to Vb, which was separated by chromatography. Vb was a strongly hydroscopic powder, and showed IR signals at 3430 (OH) and 1680 (C=N) cm^{-1}, and mass peaks at m/e 240 (M^+), 179 (M^+—61 (H_2O, $CH_2CH_2CH_3$)), and 99 (M^+—141 ($N(C_4H_9)$–C(=N)–O–)). Acetylation of Vb gave the acetate (VIb), which showed IR signals at 1730 (CO), 1670 (C=N) and 1230 (–O–) cm^{-1}, and mass peaks at m/e 282 (M^+) and 212 (M^+—70 (–C(=N)–O–)). Thus, Vb was determined to be 2-(*n*-butyl-(*trans*-2-hydroxycyclohexyl)amino)oxazoline. The nitrosation of the ureas thus obtained was carried out by the use of dinitrogen tetroxide as described in our previous paper.[2b] Two equivalents of dinitrogen tetroxide was introduced into a mixture of the urea (IIIa) and anhydrous sodium acetate in ethyl acetate, and then methanol was added to decompose the nitrous ester of the hydroxyl group. After purification by chromatography, the nitrosourea (IVa) was obtained in 73% yield, mp 69—70°C. It showed the IR signal due to the nitrosoureido group at 1670 cm^{-1}, the NMR signal due to NCH_3 at δ 3.01, and mass peaks at m/e 233, 235 (M^+—30 (NO)), and 156 (M^+—107 ($N(NO)$-CH_2CH_2Cl)). Thus, IVa was determined to be 1-(2-chloroethyl)-3-methyl-3-(*trans*-2-hydroxycyclohexyl)-1-nitrosourea. The yields and the physical data for the nitrosoureas (IVa—f) are listed in Table I.

In the previous paper[2] we demonstrated that 3,3-disubstituted nitrosoureas having a β-hydroxyl group on their substitutents are activated by attack of the hydroxyl group on the carbonyl group to give the oxazolidinones and chloroethyl diazohydroxide without generation of isocyanates. The nitrosoureas prepared in the present study were expected to be activated in a similar manner.

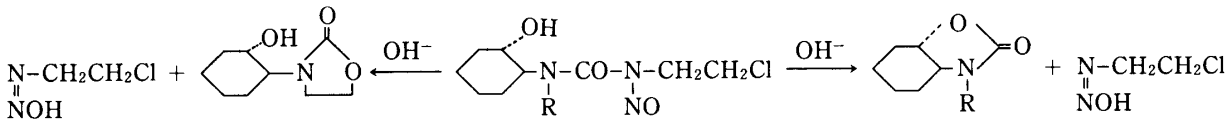
In fact, the *N*-methyl derivative (IVa) readily decomposed in sodium bicarbonate solution to give VIIa, mp 52—53°C, in quantitative yield. VIIa showed an IR signal at 1740 (CO) cm^{-1}, NMR signals at δ 1.2—2.0 (m, ring protons) and 2.65 (s, NCH_3), and a mass peak at m/e 155 (M^+). Thus, VIIa was determined to be *trans*-3-methyl-perhydrobenzoxazol-2-one, as

TABLE I. Yields and Physical Data for 3-Substituted 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-1-nitrosoureas



Compound No.	R	Form	Yield (%)	IR (cm^{-1})	NMR (in d_6-DMSO)	Mass peaks (*m/e*)
IVa	CH_3	69—70°C(dec.)	73	3460(OH)[a] 1670(CO)	1.0—2.1(8H, m)[c] 3.01(3H,s, NCH_3)	233, 235(M^+-30)[f] 156(M^+-107)[g]
IVb	$CH_2CH_2CH_2CH_3$	Yellow oil	69	3450(OH)[b] 1680(CO)	0.91—2.1(15H, m)[d]	275, 277(M^+-30)[f] 198(M^+-107)[g]
IVc	$CH_2CH_2OCH_3$	Yellow oil	72	3430(OH)[b] 1690(CO)	1.09—1.98(8H, m)[c] 3.24(3H,s, OCH_3)	277, 279(M^+-30)[f] 200(M^+-107)[g]
IVd	CH_2CH_2OH	Yellow oil	68	3380(OH)[b] 1680(CO)	1.18—1.97(8H, m)[c]	263, 265(M^+-30)[f] 185(M^+-107)[g]
IVe	CH_2CHCH_3 (OH)	Yellow oil	65	3400(OH)[b] 1680(CO)	1.0—2.0(11H, m)[e]	277, 279(M^+-30)[f] 200(M^+-107)[g]
IVf	CH_2CHCH_2OH (OH)	Yellow oil	55	3370(OH)[b] 1690(CO)	1.25—2.0(8H, m)[c]	293, 295(M^+-30)[f] 216(M^+-107)[g]

a) Measured in Nujol mull.
b) Measured as a liquid film.
c) Signals due to cyclohexyl ring protons.
d) Signals due to cyclohexyl ring protons and $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_3$.
e) Signals due to cyclohexyl ring protons and $>CH\text{-}C\underline{H}_3$.
f) Peaks of (M^+-30 (NO)).
g) Peaks of (M^+-107 $N(NO)CH_2CH_2Cl$)).



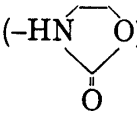
VIIId IVa : R=CH_3 IVd : R=CH_2CH_2OH VIIa : R=CH_3

Chart 2

TABLE II. Anititumor Activities of Nitrosoureas

Compd. No.	Anti-L1210 activity[a] ILS$_{30}$[c] (mg/kg/d×5)	OD[d]	ILS$_{max}$ (%)	Therapeutic[e] ratio	Anti-Ehrlich activity[b] MED[f] (mg/kg/d×5)	MTD[g]	Therapeutic[h] ratio
CCNU	4.9	25	>757.1[i]	5.1	12.5	50	4
IVa	2.0	25	>757.1[i]	12.5	6.25	25	4
IVb	5.0	50	>757.1[i]	10.0	25	50	2
IVc	2.0	25	>757.1[i]	12.5	3.12	25	8
IVd	0.5	12.5	>757.1[i]	25.0	0.78	25	32
IVe	1.0	12.5	>757.1[i]	12.5	0.78	25	32
IVf	0.4	12.5	>114.3	31.3	0.195	25	128

a) Anti-leukemic activity on L1210 in mice; leukemic cells (10^5) were inoculated *i.p.* into male BDF_1 mice and *i.p.* administration was begun 24 h after the inoculation and perfomed once daily for 5 d.
b) Growth-inhibitory effect on Ehrlich ascites tumor cells in mice; the ascites cells (10^6) were inoculated *i.p.* into female ICR mice and *i.p.* administration was begun 24 h after the inoculation and performed once daily for 5 d.
c) Daily dose providing 30% increase in life-span over the control. ILS (%)=(T/C-1)×100.
d) Optimal dose : the daily dose providing the maximum increase in life-span.
e) Therapeutic ratio=OD/ILS$_{30}$.
f) Minimum effective dose : the minimum dose which shows 100% inhibition of the growth of the tumor.
g) Maximum tolerated dose : the maximum dose which shows 100% inhibition of the growth of the tumor without causing the death of mice.
h) Therapeutic ratio=MTD/MED.
i) All treated mice survived for more than sixty days.

expected. However, in the case of IVd, two β-hydroxyl groups can possibly participate in the activation mechanism. IVd quickly decomposed in sodium bicarbonate solution to give VIIId, mp 114°C, as the sole product in quantitative yield. VIIId showed IR signals at 3360 (OH) and 1730 (CO) cm^{-1}, NMR signals at δ 1.26—2.0 (m, cyclohexyl ring protons) and 4.26 (2H, t, J=8 Hz, $NCH_2C\underline{H}_2O$), and mass peaks at m/e 185 (M^+) and 98 (base peak, M^+—87 ()). The NMR signal at δ 4.26 due to $C\underline{H}_2O$ could be assigned to the oxazolidinone ring protons, because the s gnals due to CH_2O in 3-(2-hydroxyethyl)-oxazolidin-2-one have been reported to appear at δ 4.24 (in the ring) and 3.64 (in the 2-hydroxyethyl group).[2a] Thus, VIIId was determined to be 3-(*trans*-2-hydroxycyclohexyl)-oxazolidin-2-one. The difference between the activation mechanisms of these compounds may influence the antitumor activity.

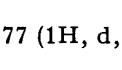
Antitumor Activities of the Nitrosoureas (IVa—f) and Discussion

The nitrosoureas (IVa—f) were tested for antitumor activities against leukemia L1210 and Ehrlich ascites carcinoma by the methods described in the previous paper.[2a] The results are listed in Table II together with comparative data for CCNU.

All the nitrosoureas prepared in the present study were remarkably active against leukemia L1210 and showed greater therapeutic ratios than CCNU. Sixty-day survivors with leukemia L1210 were found at the optimal dose for many of the nitrosoureas (IVa—e). On the other hand, the nitrosoureas (IVa—c) having one β-hydroxyl group on the cyclohexyl moiety exhibited rather weak activities against Ehrlich ascites carcinoma. The compounds (IVd—f), having two kinds of β-hydroxyl groups, however, showed strong activities and large therapeutic ratios against Ehrlich ascites tumor. This seems to be due to the difference in activation mode between the former (IVa—c) and the latter (IVd—f) (see Chart 2). Among these nitrosoureas, IVd had excellent activities against both leukemia L1210 and Ehrlich ascites carcinoma as compared with CCNU. Further work on the synthesis and antitumor activity of this new class of nitrosoureas is in progress.

Experimental

IR spectra were recorded with a Hitachi IR-215 spectrometer, and NMR spectra with a JEOL PMX-60 spectrometer using tetramethylsilane (TMS) as an internal standard in d_6-dimethylsulfoxide (DMSO). Column chromatography was carried out on Merck Silica gel 60. Thin-layer chromatography (TLC) was performed on Merck TLC plates (Silica gel 60 F_{254}) and 30% sulfuric acid was used as the spray reagent.

Preparation of 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-3-methylurea (IIIa)——A mixture of 2 g of cyclohexene oxide (I) and 30 ml of 30% methanolic methylamine solution was heated in a sealed tube at 150°C for 22 h, then concentrated. The crude product (2.5 g, oil, IR $\nu_{max}^{liq.}$ cm^{-1} 3300, 1650) was dissolved in 30 ml of THF, and 3 g of 2-chloroethyl isocyanate was added to the solution under cooling. The mixture was stirred at room temperature for 30 min, then the separated powder was collected, washed with THF and dried. IIIa was obtained in 85% yield. mp 148—150°C. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3260, 1590, 1530. NMR (in d_6-DMSO) δ: 1.0—2.1 (8H, m, ring protons), 2.96 (3H, s, NCH_3), 4.77 (1H, d, t, J=9 Hz, ) 6.40 (1H, br, NH). MS m/e: 234, 236 (M^+), 216, 218 (M^+-18 (H_2O)), 99 (M^+-135 ($N(CH_3)CONHCH_2CH_2Cl$)). *Anal.* Calcd for $C_{10}H_{19}N_2ClO_2$: C, 51.16; H, 8.15; N, 11.93; Cl, 15.10. Found: C, 51.16; H, 8.28; N, 11.94; Cl, 15.37.

Preparation of 3-*n*-Butyl-1-(2-chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)urea (IIIb)——A mixture of I (2 g), *n*-butylamine (8 g) and ethanol (10 ml) was heated at 150°C for 22 h, then concentrated. The crude product (3 g, mp 35—37°C, IR ν_{max}^{Nujol} cm^{-1} 3300, 1600) was dissolved in 30 ml of THF, and 2.6 g of 2-chloroethyl isocyanate was added to the solution under cooling. After being stirred at room temperature for 30 min, the mixture was concentrated *in vacuo* below 20°C. The residue was chromatographed on silica gel (solvent: ethyl acetate–methanol=12: 1) to give IIIb in 75% yield as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3330 (br), 1620, 1520. NMR (in d_6-DMSO) δ: 0.9—2.1 (15H, m, ring protons, $CH_2CH_2CH_3$), 4.80 (1H, d, t, J=8.4 Hz,

), 6.47 (1H, br, NH). MS *m/e*: M$^+$, not detected (Calcd for $C_{13}H_{25}N_2ClO_2$: 276, 278), 240 (M$^+$−36 (HCl)), 233, 235 (M$^+$−43 ($CH_2CH_2CH_3$)), 99 (M$^+$−177 (N(C_4H_9)CONHCH$_2$CH$_2$Cl)).

Preparation of 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-3-(2-methoxyethyl)urea (IIIc)——A mixture of I (2 g), 2-methoxyethylamine (10 g) and ethanol (10 ml) was heated at 150°C for 20 h, then concentrated. The crude product (3.4 g, mp 38—40°C, IR ν_{max}^{Nujol} cm^{-1} 3390, 3140, 1660) was treated with 2-chloroethyl isocyanate (2.6 g) in THF and the mixture was worked up as described for the preparation of IIIb to give the urea (IIIc) in 73% yield as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3340 (br), 1620, 1530. NMR (d_6-DMSO) δ: 1.1—2.1 (8H, ring protons), 3.42 (3H, s, OCH_3), 4.86 (1H, d, t, J=9 Hz, ), 6.45 (1H, br, NH). MS *m/e*: M$^+$, not detected (Calcd for $C_{12}H_{23}N_2ClO_3$: 278, 280), 242 (M$^+$−36 (HCl)), 233, 235 (M$^+$−45 (CH_2OCH_3)), 99 (M$^+$−179 (N($CH_2CH_2OCH_3$)CONHCH$_2$CH$_2$Cl)).

Preparation of 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-3-(2-hydroxyethyl)urea (IIId)——A mixture of I (2 g), ethanolamine (2.5 g) and ethanol (10 ml) was heated at 150°C for 24 h, then concentrated. The residue was dissolved in 50 ml of ethyl acetate–THF (5: 1) solution, and 4.2 g of 2-chloroethyl isocyanate was added to the solution under cooling. The mixture was stirred at room temperature for 30 min, then the insoluble material ($HOCH_2CH_2NHCONHCH_2CH_2Cl$) was filtered off. The filtrate was concentrated *in vacuo* below 20°C. The residue was chromatographed to give IIId in 61% yield as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (br), 1610, 1520. NMR (in d_6-DMSO) δ: 1.0—2.1 (8H, m, ring protons), 4.78 (1H, d, t, J=9 Hz, ), MS *m/e*: 264, 266 (M$^+$, Calcd for $C_{11}H_{21}N_2ClO_3$), 197 (M$^+$−67 (HCl, CH_2OH)), 99 (M$^+$−165 (N(CH_2CH_2OH)-CONHCH$_2$CH$_2$Cl)).

Preparation of 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-3-(2-hydroxy-*n*-propyl)urea (IIIe)——The urea IIIe was obtained by the reaction of I with 2-hydroxy-*n*-propylamine followed by treatment with 2-chloroethyl isocyanate in 70% yield as an oil in the same manner as described for the preparation of IIId. IR $\nu_{max}^{liq.}$ cm^{-1}: 3290 (br), 1665, 1505. NMR (in d_6-DMSO) δ: 1.0—2.1 (11H, m, ring protons, —CHCH_3), 4.79 (1H, d, t, J=8 Hz, ), 6.45 (1H, br, NH). MS *m/e*: 278, 280 (M$^+$, Calcd for $C_{12}H_{23}N_2ClO_3$), 211 (M$^+$−67 (H_2O, CH_2Cl)), 99 (M$^+$−179 (N($CH_2CHOH\cdot CH_3$)CONHCH$_2$CH$_2$Cl)).

Preparation of 1-(2-Chloroethyl)-3-(2,3-dihydroxy-*n*-propyl)-3-(*trans*-2-hydroxycyclohexyl)urea (IIIf)——The urea IIIf was obtained by the reaction of I with 2,3-dihydroxy-*n*-propylamine followed by treatment with 2-chloroethyl isocyanate in 60% yield as an oil in the same manner as described for the preparation of IIId. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (br), 1670, 1505. NMR (in d_6-DMSO) δ: 1.0—2.1 (8H, m, ring protons), 4.79 (1H, d, t, J=8 Hz, ). MS *m/e*: M$^+$, not detected (Calcd for $C_{12}H_{23}N_2ClO_4$: 294, 296), 241 (M$^+$−53 (H_2O, Cl)), 227 (M$^+$−67 (HCl, CH_2OH)), 197 (M$^+$−97 (HCl, CH(OH)CH_2OH)).

Formation of the Oxazoline Derivative (Vb) from the grea (IIIb)——The urea IIIb (1.4 g) was allowed to stand at room temperature for 6 d. The resultant oil, which gave only a single spot on TLC (Rf=0.08, Rf=0.7 for IIIb (ethyl acetate–methanol=12: 1)) was purified by silica gel chromatography (chloroform–ethyl acetate–methanol=2: 1: 1) to give 1.0 g (83%) of 2-(*n*-butyl-(*trans*-2-hydroxycyclohexyl)amino) oxazoline (Vb) as a hygroscopic powder. IR $\nu_{max}^{liq.}$ cm^{-1}: 3430, 1680. NMR (in $CDCl_3$) δ: 0.96—2.07 (15H, m, ring protons, $CH_2CH_2CH_3$), 4.85 (1H, d, t, J=7.9 Hz, ). MS *m/e*: 240 (M$^+$, Calcd for $C_{13}H_{24}N_2O_2$), 179 (M$^+$−61 (H_2O, $CH_2CH_2CH_3$)), 99 (M$^+$−141 (N(C_4H_9)- )).

Acetylation of Vb with acetic anhydride and pyridine gave the acetate (VIb) in 90% yield as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1730, 1670, 1230. MS *m/e*: 282 (M$^+$, Calcd for $C_{15}H_{26}N_2O_3$), 212 (M$^+$−70 (- ), 152 (M$^+$−130 (-  , CH_3COOH)).

General Procedure for the Preparation of 3-Substituted 1-(2-Chloroethyl)-3-(*trans*-2-hydroxycyclohexyl)-1-nitrosoureas (IVa—f)——The urea (0.01 mol) was dissolved in 50 ml of ethyl acetate and then anhydrous sodium acetate (0.02 mol) was added. Dinitrogen tetroxide (0.025 mol) was introduced into the mixture at −5°C during 10 min under stirring. After 10 min, 5 ml of methanol was added to the mixture and the whole was stirred at the same temperature for 10 min. Anhydrous sodium acetate (0.02 mol) and 10 ml of water were then added at −5°C. The whole was stirred vigorously for 10 min and the pH of the mixture

was confirmed to be about 5. After filtration, the organic layer was collected, dried, filtered, and concentrated. The residue was purified by silica gel chromatography (solvent: ethyl acetate–benzene–methanol). The nitrosoureas (IVb—f) thus obtained were unstable yellow oils except for IVa (mp 69—70°C (dec.)), and the yields and physical properties are listed in Table I.

Decomposition of the Nitrosoureas (IVa, d) in Sodium Bicarbonate Solution——The nitrosourea IVa (230 mg) was dissolved in 10 ml of 10% sodium bicarbonate solution and the mixture was stirred at room temperature for 3 h, then concentrated *in vacuo*. The residue was extracted with tetrahydrofuran and the organic layer was dried, and concentrated. The residual colorless oil, which gave only a single spot on TLC, was purified by chromatography on a short column of silica gel (chloroform–methanol=10: 1) to give 150 mg (97%) of *trans*-3-methylperhydrobenzoxazol-2-one (VIIa) as colorless crystals. mp 52—53°C, IR ν_{max}^{Nujol} cm^{-1}: 1740, 1010. NMR (in d_6-DMSO) δ: 1.20—2.0 (8H, m, ring protons), 2.65 (3H, s, NCH_3). MS *m/e*: 155 (M^+). *Anal.* Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.60; H, 8.46; N, 8.99.

3-(Trans-2-hydroxycyclohexyl)-oxazolidin-2-one (VIIId) was similarly obtained from IVd in 95% yield as colorless crystals. mp 114°C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1730, 1090, 1025. NMR (in d_6-DMSO) δ: 1.26—2.0 (8H, m, ring protons), 4.26 (2H, t, $J=8$ Hz, $=NCH_2CH_2O-$). MS *m/e*: 185 (M^+), 98 (base peak, M^+-87 (HN(C=O)O)). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.38; H, 8.11; N, 7.57. Found: C, 58.35; H, 8.09, N, 7.61.

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References

1) Part VII: T. Morikawa, K. Tsujihara, M. Takeda, and Y. Arai, *Chem. Pharm. Bull.*, **30**, 4365 (1982).
2) *a*) Part I: K. Tsujihara, M. Ozeki, T. Morikawa, and Y. Arai, *Chem. Pharm. Bull.*, **29**, 2509 (1981); *b*) Part II: K. Tsujihara, M. Ozeki, T. Morikawa, N. Taga, M. Miyazaki, M. Kawamori, and Y. Arai, *ibid.*, **29**, 3262 (1981); *c*) Part III: T. Morikawa, M. Ozeki, N. Umino, M. Kawamori, Y. Arai, and K. Tsujihara, *ibid.*, **30**, 534 (1982); *d*) Part IV: K. Tsujihara, M. Ozeki, T. Morikawa, M. Kawamori, Y. Akaike, and Y. Arai, *J. Med. Chem.*, **25**, 441 (1982); *e*) Part VI: T. Morikawa, M. Takeda, Y. Arai, and K. Tsujihara, *Chem. Pharm. Bull.*, **30**, 2386 (1982).