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Synthesis of 4,5-Epiminotetrahydro-1,2-oxazine[1]

SADAO OIDA and EIJI OHKI

Central Research Laboratories, Sankyo Co., Ltd.[2]

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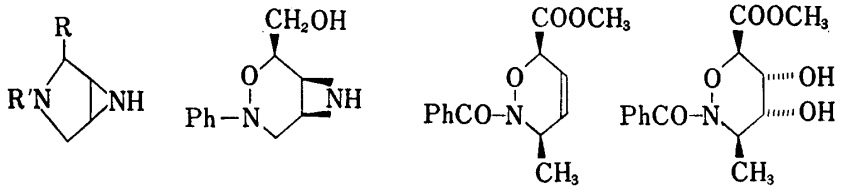
Osmium tetroxide oxidation of 2-phenyl-6-tetrahydropyranyloxymethyl-3,6-dihydro-1,2-oxazine (**5e**) afforded 2-phenyl-6β-tetrahydropyranyloxymethyltetrahydro-1,2-oxazine-4α,5α-diol (**8**), whose ditosylate (**10**) was converted into 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**2**) on successive treatment with sodium azide, lithium aluminum hydride, and acids. Conformation of **2** was discussed with reference to the nuclear magnetic resonance spectrum of **2**.

Recently, various explorations directed toward synthesis of mitomycins, the most important anticancer antibiotics, have made by many organic chemists centering around the Lederle researchers in U.S.A.[3] However, synthesis of 3,4-epiminopyrrolidine skeleton (**1**), one of the possible active principles of the antibiotics, still remains a problem to be solved for sythetic approach of the antibiotics. We wish to report herein a preparation of 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**2**) which would be convertible into some substituted 3,4-epiminopyrrolidine derivatives by hydrogenative fission of the N–O bond and



1 2 3 4

Chart 1

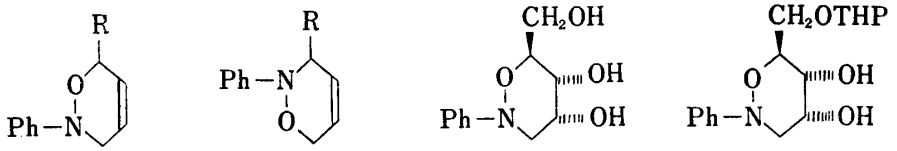
subsequent recyclization of the resulting aminoalcohol into a pyrrolidine ring. In 1963, Belleau and Au-Young[4] reported that hydroxylation of methyl 2-benzoyl-3β-methyl-3,6-dihydro-1,2-oxazine-6β-carboxylate (**3**) with osmium tetroxide was successfully effected under a high stereospecificity to give a *cis*-diol (**4**), suggesting the attack of the reagent from the less hindered side of **3**. In consideration of this observation, we examined an analogous oxidation reaction of 6-substituted 2-phenyl-3,6-dihydro-1,2-oxazine having no substituent in its 3-position, in order to provide an entry into stereospecific substitution at 4- and 5-positions of the oxazine molecule.

The starting materials were prepared in the following way. The Diels–Alder reaction of nitrosobenzene with an equivalent amount of 2,4-pentadienoic acid at a low temperature afforded 2-phenyl-3,6-dihydro-1,2-oxazine-6-carboxylic acid (**5a**), mp 113° (decomp.), in 86% yield. Similar treatment of nitrosobenzene with methyl 2,4-pentadienoate yielded the corresponding methyl ester (**5b**), mp 72—73°, which was identified with the sample obtained by

1) A part of this work was presented as a preliminary communication: S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1637 (1968).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
3) G.R. Allen, Jr., and M.J. Weiss, *J. Org. Chem.*, **30**, 2904 (1965); W. A. Remers, R.H. Roth, and M.J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965); *cf.* also their preceding papers.
4) B. Belleau and Y. Au-Young, *J. Am. Chem. Soc.*, **85** 64 (1963).

treatment of **5a** with diazomethane. Nuclear magnetic resonance (NMR) analysis of these adducts supported their structures (**5a** and **5b**) as shown in the experimental section and, in addition, Kresze and Firl's study[5] on the orientation of this Diels–Alder reaction also ruled out the predominance of the possible alternative formula (**6**). In order to avoid any intervension of the carboxylic function in the following hydroxylation reaction of the 4,5-double bond, the carboxyl group was reduced into a hydroxymethyl group; lithium aluminum hydride reduction of **5a** or **5b** gave 2-phenyl-3,6-dihydro-1,2-oxazine-6-methanol (**5c**), mp 58—59.5°, in a good yield without affecting the N–O bond. **5c** formed a syrupy acetate (**5d**) quantitatively.

Oxidation of **5d** with osmium tetroxide in the presence of pyridine and decomposition of the resulting adduct with sodium sulfite afforded a triol (**7**), mp 115.5—117°, in 41% yield. The other isomeric triol could not be detected in the reaction product. As it was found that the subsequent decomposition of the osmium tetroxide adduct with sodium sulfite unfavorably induced hydrolysis of the acetoxyl group in the side chain, alternative protection of the hydroxyl group of **5c** was made with a function stable to bases.



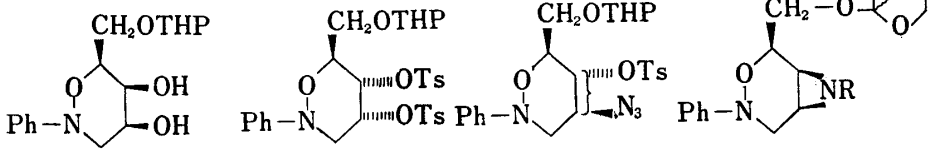
5a: R=COOH
5b: R=COOCH$_3$
5c: R=CH$_2$OH
5d: R=CH$_2$OCOCH$_3$
5e: R=CH$_2$OTHP

6: R=COOH or COOCH$_3$

7

8

THP=tetrahydropyranyl



9

10

11

12a and **12b**: R=H
13a and **13b**: R=COPh

Chart 2

First, benzylation of **5c** was attempted with benzyl chloride in the presence of sodium hydride in dimethyl sulfoxide, but without success, and only a colored complex mixture was obtained, which, presumably, had no original oxazine ring. On the other hand, treatment of **5c** with dihydropyran in the presence of acids afforded a tetrahydropyranyl derivative (**5e**) as a syrup of bp 180° (0.05 mmHg, bath temp.) in a quantitative yield. **5e** gave only one spot on thin-layer chromatogram and could not be separated into the possible epimers which would arise from the asymmetric center of the tetrahydropyranyl group.

Hydroxylation of **5e** with osmium tetroxide yielded a mixture of *cis*-diols, from which the major diol (**8**), mp 109—112°, in 66% yield, and the minor diol (**9**), mp 155—156°, in 1.6% yield, were separated. Hydrolysis of the major product (**8**) with aqueous acetic acid gave the above-described triol (**7**), while that of the minor (**9**) gave the other isomeric triol which could not be characterized due to the scarcity of the sample. This fact showed that **8** and **9** are isomeric in the configuration of the newly introduced hydroxyl groups and not

5) G. Kresze and J. Firl, *Tetrahedron Letters*, **1965**, 1163.

in the asymmetric center of the tetrahydropyranyl group. Furthermore, in consideration of the Belleau and Au-Young's study,[4] the structure of the predominant product (**8**) would be assigned as 2-phenyl-6β-tetrahydropyranyloxymethyl-4α,5α-dihydroxytetrahydro-1,2-oxazine, which indicates the attack of the reagent from the less hindered α-side of the 4,5-double bond of **5e**. Accordingly, the minor product (**9**) would be designated as the corresponding 4β,5β-dihydroxyl derivative as shown in the Chart. NMR analysis of **8** and **9** could make no direct contribution to their structural assignments. Presumably, this will be ascribed to an unseparable mixing of their eqimers which arose from the asymmetry of the protecting group.

Next, an attempt was made to transform the diol (**8**) into a 4,5-aminohydrine derivative which would be convertible to an aziridine. The most potential route to an aminohydrine involves initial protection of one hydroxyl group of **8**, tosylation of the remaining hydroxyl group, and subsequent substitution of the tosyl group with nitrogen function. Acetylation of **8** with one equivalent of acetic anhydride in pyridine afforded a mixture of monoacetate and diacetate, along with the unchanged **8**, and isolation of the monoacetate from the reaction mixture was not successful. Using one mole of the reagent, partial benzoylation yielded a syrupy monobenzoate, whose treatment with dilute hydrochloric acid gave a crystalline monobenzoyl triol, mp 189—191°. However, purification of the monobenzoate was wasteful and not of practical use. Benzoylation of **8** with excess of the reagent afforded a dibenzoate, mp 118—121°, quantitatively, whose partial hydrolysis was, however, hopeless, giving a mixture of **8** and the unchanged dibenzoate. Preliminary study also showed that tosylation of **8** at a low temperature gave a syrupy monotosylate predominantly, which formed a tosyloxyacetate by acetylation. The latter was, however, found to be inert to substitution reaction with sodium azide in dimethylformamide.[6]

Tosylation of **8** with excess of the reagent at room temperature gave a ditosylate (**10**), mp 141—144.5°, in 80% yield. Treatment of **10** with sodium azide in dimethylformamide gave a mixture of a syrupy azidotosylate (**11**), a diazide, and the unchanged **10** in a relative ratio of about 6:3:1 which was indicated by thin-layer chromatography. Chromatographic separation of these compounds on silicagel was not successful because of unstability of the products. Therefore, without further purification, reduction of the mixture with lithium aluminum hydride was carried out and gave a mixture of aziridines in 24.5% yield from **10**. Fractional recrystallization of the aziridine mixture yielded the major aziridine (**12a**), mp 136—137.5°, and the minor one (**12b**), mp 115—117°. The presence of an aziridine ring in these products (**12a** and **12b**) was indicated by their elementary analyses and their infrared spectra which exhibited no tosyloxy or azide absorption, but an N–H absorption. **12a** formed an N-benzoate (**13a**) of mp 111—111.5° and **12b** an N-benzoate (**13b**) of mp 118.5—120.5°, respectively. The infrared spectra of these benzoates exhibited a tertiary amide absorption at 1688 cm^{-1} for **13a** or at 1679 cm^{-1} for **13b** without any subsidiary absorption. The shifting of the amide absorption to a higher frequency was characteristic, suggesting the presence of an aziridine N–benzoate.[7] The NMR spectra of these aziridine derivatives could not be characterized well, but **12a** exhibited a multiplet absorption corresponding to the C–H protons of the aziridine ring at 2.25—2.75 ppm. Moreover, molecular ion peak in the mass spectrum of **12a** at 290 also gave an additional proof on its molecular formula.

Either of these aziridines (**12a** and **12b**) quantitatively afforded the same 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**2**), mp 180—183°, on treatment with dilute hydrochloric acid under removal of the tetrahydropyranyl group. This fact suggested that **12a** and **12b** were isomeric at the asymmetric center of the protecting group.

6) Presumably, this fact suggested that the partial tosylation of **8** fell in the equatorial hydroxyl group of 5-position and the resulting tosylate resisted the attack of nucleophile by its steric effect.

7) H.L. Spell, *Anal. Chem.*, **39**, 185 (1967).

The configurational assignment of 4β,5β-epimine to **2** should be valid as long as no anomalous epimerisation of the asymmetric centers took place in the various intermediates of this transformation; the ditosylate (**10**) of 4α,5α-diol (**8**) should, on nucleophilic attack of an azide ion, afford 4α-tosyloxy-5β-azide or 5α-tosyloxy-4β-azide (**11**). Either of these isomers (**11**), on treatment with lithium aluminum hydride, would be converted into the corresponding tosyloxyamine or the equivalent reaction complex, whose amino function further participates in a displacement reaction of the neighboring tosyloxy group, yielding the same anomeric mixture of 4β,5β-epiminotetrahydropyranyl derivatives (**12a** and **12b**). Acid hydrolysis of **12a** and **12b** gives the same **2**. On the other hand, the NMR spectrum[8] of **2** in deuteriodimethyl sulfoxide also afforded a satisfactory reflection of its structure as shown in Fig. 1. The assignments for chemical shifts are given in Table I.

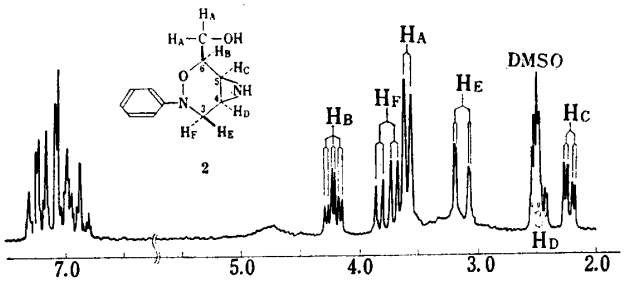


Fig. 1. The 100-MHz Spectrum of 2-Phenyl-4β,5β-epimino-6β-hydroxymethyltetrahydro-1,2-oxazine (**2**) in d_6-Dimethyl Sulfoxide

Table I. NMR Data of 2-Phenyl-4β,5β-epimino-6β-hydroxymethyltetrahydro-1,2-oxazine (**2**)

Proton	Chemical shift (δ ppm)	Coupling constant (cps)
H_A	3.59 (d)	
H_B	4.22 (dt)	$J_{AB}=5.8$
H_C	2.22 (dd)	$J_{BC}=2.6$
H_D	2.48 (ddd)	$J_{CD}=6.2$
H_E	3.13 (dd)	$J_{DE}=1.2$, $J_{DF}=5.8$
H_F	3.77 (dd)	$J_{EF}=12.2$
NH, OH	3.2 (br), 4.75 (br)	
Ph	7.06 (m)	

In order to evaluate more comprehensively the mutual distribution of substituents, all of the possible half-chair[9] conformations of *cis*- and *trans*-4,5-epiminotetrahydro-1,2-oxazine are illustrated in Chart (**A**—**D**), by Garbisch's model[10] which was successfully applied to the analysis of stereochemical reactions of cyclohexane ring. As seen from the Dreiding models, the relative distribution between the protons (H_E and H_F) at C-3 and the proton (H_D) at C-4 in **A** and **C** is different from that in **B** and **D**. In Forms **B** and **D**, the dihedral angle between H_D and H_E and the angle between Hd and Hf are approximately equal, predicting near coupling constants in J_{DE} and J_{DF}. On the other hand, the corresponding angles in Forms **A** and **C** are not equal, one of them deviating from 60° to rectangular. This predicts unequal coupling constants in H_{DE} and H_{DF}. The observed coupling constants, $J_{DE}=1.2$ cps and $J_{DF}=5.8$ cps, which are shown in Table I, should correspond to this relative location of these protons; and Form **A** or **C** most likely explains the coupling mode. On the other hand, Form **C** will be ruled out, if it is assumed that the massive side chain at C-6 has a *quasi*-equatorial configuration.

8) The NMR spectra were teken on a Varian HA-100 with tetramethylsilane as an internal standard.
9) In this discussion, the possible boat conformations are left out bacause of their higher strain.
10) E.W. Garbisch, S.M. Schildkraut, and D.M. Patterson, *J. Am. Chem. Soc.*, **87**, 2932 (1965); D.J. Pasto and F.M. Klein, *J. Org. Chem.*, 33, 1468 (1968).

Thus, the NMR spectrum of **2** reflects Form **C**, also supporting the above prediction on the structure of **2**.

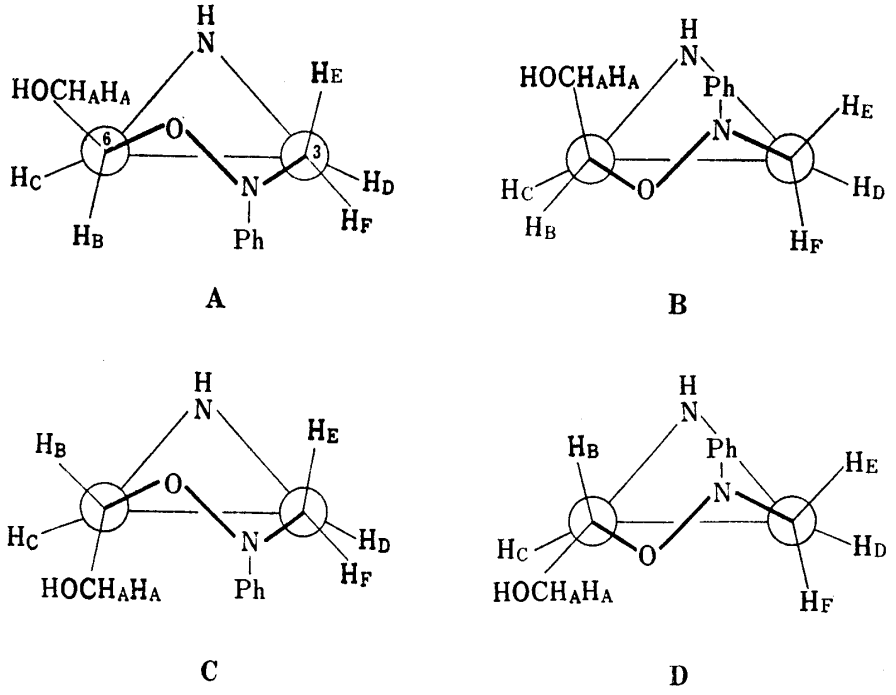


Chart 3

Moreover, the different chemical shifts of H_E and H_F suggest that the N-phenyl group has an equatorial configuration and the resulting axial location of the nitrogen lone-pair affects signals of H_E at the *trans* position to shift to a higher field than those of H_F at the gauch position.[11]

Finally, we wish to mention additional experiments directed towards the formation of 4,5-epiminoöxazine. At the outset, a preliminary attempt was made on halogenation of 4,5-double bond in 2-phenyl-3,6-dihydro-1,2-oxazine-6-carboxylic acid (**5a**), expecting that the neighboring carboxyl group would take part in the addition reaction to yield some halogeno-γ-lactone or the like. However, treatment of **5a** with bromine in acetic acid or iodine–potassium iodide in water did not give any expected product, but an inseparable complex mixture. Furthermore, in order to gain access to the minor *cis*-diol (**9**), alternative method of hydroxylation of **5e** was examined. However, attempts to apply hydroxylation of **5e** with the iodine-silver acetate-wet acetic acid reagent[12] gave disappointing results. In addition, the most direct potential route to aziridine formation should involve treatment of **5e** with azidoformate[13] or with dichlorourethan,[14] followed by treatment with bases. Several applications of these procedures to **5e** were also hopeless. Moreover, hydrogenation of the crude azidotosylate (**11**) over Adams catalyst, followed by treatment with dilute alkali or treatment of **11** with 80% hydrazine hydrate and Raney Ni yielded the same epimeric mixture of aziridines (**12a** and **12b**) obtained by treatment of **11** with lithium aluminum hydride. Each aziridine component was isolated from these reaction products and identified, but the yield was quite low.

The aziridine derivative (**2**) thereby obtained was found to show no activity against leukemia L-1210.

11) F. Bohlman, D. Schumann, and H. Schulz, *Tetrahedron Letters*, **1965**, 173; F. Bohlman, D. Schumann, and C. Arndt, *ibid.*, **1965**, 2705.
12) R.B. Woodward and G.V. Brutcher, *J. Am. Chem. Soc.*, **80**, 209 (1958).
13) A.C. Oehlschlager, P. Tilman, and L.H. Zalkow, *Chem. Commun.*, 596 (1965).
14) T.A. Foglia and D. Swern, *J. Org. Chem.*, **31**, 3625 (1966).

Experimental

Melting points are not corrected. Infrared spectra were determined on a Perkin-Elmer Model 221 or a Perkin-Elmer Infracord (Model 137), NMR spectra usually on a Varian A-60 spectrometer, and mass spectra[15] on a Hitachi RMU-6D mass spectrometer. The removal of solvent *in vacuo* was accomplished by a rotating flash evaporator at 20—30 mm and usually at 35—50°. Plates for thin-layer chromatography were prepared with Silicagel G (E. Merck AG) and visualization of spots was effected by spraying iodine or by spraying conc. H_2SO_4, followed by heating.

2-Phenyl-3,6-dihydro-1,2-oxazine-6-carboxylic Acid (5a)——A solution of 3.02 g of pentadienoic acid and 3.23 g of nitrosobenzene in 30 ml of $CHCl_3$ was kept at 5° for 24 hr. The solvent was removed *in vacuo* at room temperature[16] and the resulting brown residue crystallized on standing. This residue was washed with a small amount of cold ether and 5.43 g (86%) of **5a** was obtained as pale yellow crystals, mp 113° (decomp.). Analytical sample was obtained by recrystallization from benzene as plates, mp 114° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3050, 2650 (broad, COOH), 1713, 1730 (COOH). NMR ($CDCl_3$) δ ppm: 3.85 (2H, doublet, $J=3$ cps, $-\underline{N}-C\underline{H}_2-$), 5.02 (1H, multiplet, $-C\underline{H}-O-$), 6.15 (2H, doublet, $J=1$ cps, $-C\underline{H}=C\underline{H}-$), 7.30 (5H, complex absorption, aromatic), 11.42 (1H, singlet, $-COO\underline{H}$). *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.61; H, 5.49; N, 6.69.

Methyl-2-phenyl-3,6-dihydro-1,2-oxazine-6-carboxylate (5b)——A solution of 39.5 g of methyl pentadienoate and 39.0 g of nitrosobenzene in 400 ml of $CHCl_3$ was allowed to stand at 5° for 24 hr. After the solvent was removed *in vacuo*, the resulting crystalline residue was recrystallized from MeOH to 47.0 (61%) of **5b** as prisms, mp 72—73°. IR ν_{max}^{Nujol} cm^{-1}: 1759 ($-COOCH_3$). NMR ($CDCl_3$) δ ppm: 3.77 (3H, singlet, $-COOC\underline{H}_3$), 3.82 (2H, multiplet, $-\underline{N}-C\underline{H}_2-$), 5.02 (1H, multiplet, $-C\underline{H}-O-$), 6.12 (2H, multiplet, $-C\underline{H}=C\underline{H}-$), 7.3 (5H, complex absorption, aromatic). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.63; H, 6.00; N, 6.33.

Treatment of the carboxylic acid (**5a**) with CH_2N_2 afforded **5b**, mp 72—73°, which was identified with the sample obtained as above.

2-Phenyl-3,6-dihydro-1,2-oxazine-6-methanol (5c) and Its Acetate (5d)——To a suspension of 4.5 g of $LiAlH_4$ in 100 ml of dry ether was added slowly a solution of 10.0 g of **5a** in 250 ml of dry ether. During addition, the reaction mixture was cooled in an ice bath and stirred vigorously. Then, the mixture was allowed to stand at room temperature for 1 hr and the excess $LiAlH_4$ was decomposed by careful addition of EtOAc. After addition of a saturated solution of NH_4Cl the resulting precipitate was filtered off. The organic layer was separated and the auqeous layer was extracted with ether. The combined organic layer and extracts was dried and evaporated *in vacuo* to leave a crystalline mass, which was recrystallized from benzene-hexane to 6.6 g (71%) of **5c** as prisms, mp 58—59.5°. IR ν_{max}^{Nujol} cm^{-1}: 3280 (–OH). NMR ($CDCl_3$) δ ppm: 2.63 (1H, broad singlet, –OH), 3.85 (4H, multiplet, $-N-C\underline{H}_2-$ and $-O-C\underline{H}_2-$), 4.64 (1H, multiplet, $-C\underline{H}-O-$), 5.98 (2H, multiplet, $-C\underline{H}=C\underline{H}-$), 7.25 (5H, multiplet, aromatic). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.20; H, 6.80; N, 7.29.

To a suspension of 3.54 g of $LiAlH_4$ in 50 ml of dry ether was added dropwise a solution of 16.5 g of the ester (**5b**) in 150 ml of dry ether, with cooling and stirring. By the same work-up as above, 12.0 g (83%) of **5c**, mp 57—59°, was obtained.

A solution of 955 mg of **5c** and 600 mg of Ac_2O in 5 ml of pyridine was stood at room temperature for 6 hr. The reaction mixture was poured into ice-water and extracted twice with ether. The extract was dried and the solvent was removed *in vacuo*. The acetate (**5d**) was obtained as a syrup (1.185 g). IR $\nu_{max}^{liq.}$ cm^{-1}: 1748 (ester). NMR ($CDCl_3$) δ ppm: 2.12 (3H, singlet, $C\underline{H}_3COO-$), 3.83 (2H, multiplet, $-\underline{N}-C\underline{H}_2-$), 4.35 (2H, multiplet, $-C\underline{H}_2-O-$), 4.75 (1H, multiplet, $-C\underline{H}-O-$), 6.00 (2H, multiplet, $-C\underline{H}=C\underline{H}-$), 7.20 (5H, complex absorption, aromatic).

2-Phenyl-4α,5α-dihydroxytetrahydro-1,2-oxazine-6β-methanol (7)——To a solution of 916 mg of **5d** and 0.4 ml of pyridine in 20 ml of dry ether was added a solution of 1.00 g of OsO_4 in 20 ml of dry ether over a period of 15 min with cooling and stirring. The mixture was stirred for further 30 min with cooling. The resulting brown precipitate was collected by filtration and washed with ether. The precipitate was placed in a mixture of 25 ml of EtOH and 40 ml of H_2O, 10 g of Na_2SO_3 was added, and the mixture was refluxed with stirring for 3 hr. The solid was collected and washed with 20 ml of EtOH. The combined filtrate and washings was concentrated to 30 ml under a reduced pressure and extracted with several portions of EtOAc. The combined extract was dried over anhyd. Na_2SO_4 and the solvent was removed *in vacuo* to leave 648 mg of crude crystals of **7**, mp 50—80°, whose NMR spectrum showed the presence of adhesive contamination of AcOEt. The crude product was recrystallized twice from EtOAc to afford 363 mg (41%) of **7** as needles, mp 115.5—117°. By rapid heating, the needles melted at 94—96°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (broad, –OH). *Anal.* Calcd for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.38; H, 6.67; N, 6.34.

15) Authors are grateful to Dr. S. Nozoe, Tokyo University, for measurement of the mass spectra.
16) When the residue was heated on a water bath, it decomposed explosively.

2-Phenyl-6-tetrahydropyranyloxymethyl-3,6-dihydro-1,2-oxazine (5e)——A mixture of 955 mg of **5c**, 924 mg of dihydropyran, 3 mg of *p*-TsOH, and 5 ml of dry $CHCl_3$ was refluxed for 2 hr. The solvent and excess dihydropyran were removed *in vacuo* and left 1.45 g of a red syrup which was shown to be homogeneous by thin-layer chromatography. Analytical sample was obtained by rectification as a pale yellow syrup, bp 180° (0.05 mm Hg, bath temp.). NMR ($CDCl_3$) δ ppm: 1.3—2.3 (6H, complex absorption) 3.25—4.25 (6H, complex absorption, $-CH_2-N-$ and $-CH_2-O-$), 4.72 (2H, complex absorption, $-O-CH-O-$, $=CH-C-O-$), 5.97 (2H, 5.97 (2H, $-CH=CH-$), 7.20 (5H, complex absorption, aromatic).

2-Phenyl-6β-tetrahydropyranyloxymethyltetrahydro-1,2-oxazine-4α,5α-(8) and -4β,5β-diol (9)——To an ice-cold solution of 3.34 g of a crude tetrahydropyranyl ether (**5e**), prepared from 2.25 g of **5c** and 1.8 ml of pyridine in 60 ml of dry ether, was added a solution of 3.0 g of OsO_4 in 50 ml of dry ether during 30 min, and the mixture was stirred with cooling for 1 hr. The resulting brown precipitate was collected and washed with dry ether. The product was added to a mixture of 75 ml of EtOH, 120 ml of H_2O, and 30 g of Na_2SO_3, and the mixture was refluxed with stirring for 3 hr. The solid was collected by filtration and washed with 50 ml of EtOH. The combined filtrate and washings was concentrated to 100 ml under a reduced pressure, and extracted with three 50 ml portions of $CHCl_3$. The combined extract was dried over anhyd. Na_2SO_4 and the solvent was removed *in vacuo* to afford 2.82 g of a crystalline residue, which was recrystallized from benzene–hexane (1:1) to 2.40 g of 4α,5α-diol (**8**) as an amorphous powder, mp 108—110.5°. The yield from **5c** was 66%. The analytical sample was obtained by recrystallization from benzene–hexane as needles, mp 109—112°, IR ν_{max}^{Nujol} cm^{-1}: 3380, 3230. *Anal.* Calcd. for $C_{16}H_{23}O_5N$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.08; H, 7.38; N, 4.77.

A mixture of 79 mg of the diol (**8**), 1 ml of AcOH, and 1 ml of H_2O was allowed to stand at room temperature for 12 hr. The solution was basified with $NaHCO_3$ solution, extracted with three 10 ml portions of AcOEt, and the extract was dried over anhyd. Na_2SO_4. Removal of the solvent from the extract and recrystallization of the residue from AcOEt gave 25 mg of the triol (**7**), mp 115—117,° which was identified with the sample described earlier by comparison of mp and infrared spectra.

The combined mother liquor from the recrystallization of **8** was concentrated and allowed to stand for a long time, giving 254 mg of crystals, mp 116—140°, which were recrystallized twice from MeOH to 57 mg of the isomer (**9**) as colorless plates, mp 155—156°. IR ν_{max}^{Nujol} cm^{-1}: 3540, 3430. *Anal.* Calcd. for $C_{16}H_{23}O_5N$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.95; H, 7.54; N, 4.56.

2-Phenyl-6β-tetrahydropyranyloxymethyl-4α,5α-tosyloxytetrahydro-1,2-oxazine (10)——To an ice-cooled solution of 8.00 g of **8** in 60 ml of pyridine was added 19.0 g of *p*-TsCl in small portions. After standing at room temperature for 20 hr, the reaction mixture was poured into ice-water and extracted twice with $CHCl_3$. The extract was dried and evaporated to leave 15.94 g of a pale yellow syrup, which crystallized on trituration with MeOH. Thus, 12.8 g (80%) of the crude ditosylate (**10**), mp 135—139°, was obtained. Analytical sample was obtained by recrystallization from MeOH as prisms, mp 141—144.5°, whose mp was not always sharp or constant. IR ν_{max}^{Nujol} cm^{-1}: 1375, 1178 ($-SO_3-$). NMR ($CDCl_3$) δ ppm: 1.6 (6H, broad), 2.45 (6H, singlet), 3.15—5.35 (10H, complex absorption), 6.7—7.95 (13H, complex absorption, aromatic). *Anal.* Calcd. for $C_{30}H_{35}O_9NS_2$: C, 58.33; H, 5.71; N, 2.27. Found: C, 58.09; H, 5.68; N, 2.32.

2-Phenyl-6β-tetrahydropyranyloxymethyl-4β,5β-epiminotetrahydro-1,2-oxazine (12a and 12b)——A mixture of 11.2 g (0.0182 mole) of **10**, 3.54 g (0.0545 mole) of NaN_3, and 110 ml of dimethylformamide was kept at 130—140° with stirring for 2 hr, the cooled mixture was diluted with *ca.* 150 ml of H_2O, and extracted twice with ether. The extract was dried and evaporated *in vacuo* to dryness, leaving 7.81 g of a yellow syrup. The thin-layer chromatography of this product indicated three components, azidotosylate (**11**), diazide, and the unchanged ditosylate (**10**), in a relative ratio of *ca.* 6:3:1. Attempted separation of these components by means of silicagel chromatography was not successful and only a small amount of diazide was obtained as an oil, whose infrared spectrum exhibited no tosyl absorption but azide absorption at 2120 cm^{-1}, and other components were converted into an unidentifiable mixture. Therefore, without any purification, the crude product of **11** containing the diazide and **10** was used for the following reaction. (i) To a suspension of 2.47 g of $LiAlH_4$ in 100 ml of dry ether was added a solution of 7.44 g of crude **11** over a period of 30 min with ice-cooling and stirring. After completion of the addition, the reaction mixture was stirred under cooling for 2 hr and further at room temperature for 2 hr. The excess $LiAlH_4$ was cautiously decomposed by addition of H_2O, the mixture was stirred for 1.5 hr, filtered, and the solid was washed several times with ether. The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave 4.40 g of a yellow syrup, which crystallized on digestion with a small amount of ether. The crystals were collected and washed with cold ether, giving 1.22 g (24.3% from **10**) of needles, mp 114—124° which revealed one spot on thin-layer chromatogram. Fractional recrystallization of this product from ether–acetone gave two kinds of crystals, the major product (**12a**) melted at 136—137.5° and the minor one (**12b**) at 115—117°. IR ν_{max}^{Nujol} cm^{-1}: (for **12a**); 3250 (NH), 1600, 1493, 754, 690 (aromatic); (for **12b**); 3230 (NH), 1600, 1493, 756, 695 (aromatic). NMR ($CDCl_3$) (for **12a**) δ ppm: 0.80 (1H, broad singlet, $-NH$), 1.3—2.1 (6H, multiplet, methylene protons), 2.25—2.75 (2H, CH of aziridine) 3.2—4.2 (6H, multiplet, $-N-CH_2-$ and $-O-CH_2-$), 4.4—4.85 (2H, multiplet, $-O-CH-$), 6.9—7.5 (5H, complex absorption, aromatic). *Anal.* Calcd. for $C_{16}H_{22}O_3N_2$: C, 66.18; H, 7.64; N, 9.65. Found (for **12a**): C, 65.74; H, 7.50; N, 9.61. Found (for

12b): C, 65.74; H, 7.40; N, 9.67. The mass spectrum of **12a** exhibited a molecular ion peak at 290. (ii) The crude product of **11** (2.29 g) was dissolved in 50 ml of MeOH and 1.5 g of PtO_2 (Adams catalyst) was added. A slow stream of H_2 was passed while the mixture was stirred for 2.5 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave 1.91 g of a colored syrup, to which 0.1N NaOH solution was added. The mixture was extracted several times with ether. The extract was dried and evaporated *in vacuo* to dryness, giving 1.29 g of a yellow syrup, which was chromatographed over 15 g of silicagel. The $CHCl_3$–MeOH (1%) eluate (100 ml) was evaporated to afford 190 mg of unchanged **10**, mp 123—140°. The next eluate (100 ml) of the same solvent was evaporated to afford 340 mg of a crystalline residue, which was recrystallized from ether to give 148 mg of a mixture of **12a** and **12b** as needles, mp 119—127°, in a yield of 8.8% from **10**. Further recrystallization from ether gave 108 mg of **12a**, mp 129—133°, and 6 mg of **12b**, mp 115—117°. These products were identified with the respective samples obtained as above dy infrared spectrometry. (iii) A mixture of 359 mg of crude **11**, 1.5 ml of 80% hydrazine hydrate, 20 mg of Raney Ni (W-2), and 15 ml of EtOH was gently refluxed for 2.5 hr. After filtration, the solvent was evaporated *in vacuo* and the residue was dissolved again in ether. The solution was washed with 0.1N NaOH solution and dried over anhyd. Na_2SO_4. Removal of the solvent *in vacuo* left 252 mg of a yellow syrup, which afforded 26 mg (9.8% from **10**) of **12a**, mp 130—133.5°, on digestion with a small amount of ether. The mother liquor was chromatographed over 6 g of silicagel. The $CHCl_3$–MeOH (1%) eluate gave 38 mg of a crystalline residue, which was recrystallized from ether to give 17 mg (6.4% from **10**) of **12b** as needles, mp 114.5—116°.

2-Phenyl-6β-tetrahydropyranyloxymethyl-4β,5β-(N-benzoyl)epiminotetrahydro-1,2-oxazine (13a and 13b)——A solution of 50 mg of **12a** and 70 mg of benzoyl chloride in 0.5 ml of pyridine was stood at room temperature for 2 hr. The mixture was poured into ice–water and extracted with ether. The extract was washed with $NaHCO_3$ solution and dried. Removal of the solvent *in vacuo* left a crystalline mass which was recrystallized from hexane containing a small amount of ether to afford 34 mg (50%) of **13a** as needles, mp 111—111.5°. Benzoylation of 20 mg of **12b** by the same procedure gave 13 mg of **13b**, mp 118.5—120.5° (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: (for **13a**) 1679 (amide); (for **13b**) 1688 (amide). *Anal.* Calcd. for $C_{23}H_{26}O_4N_2$: C, 70.03; H, 6.64; N, 7.10. Found (for **13a**): C, 69.52; H, 6.45; N, 7.04. Found (for **13b**): C, 69.85; H, 6.63; N, 7.06.

2-Phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**2**)——A mixture of 100 mg of **12a** and 2 ml of 1N HCl was stood at room temperature for 2 hr. The solution was basified with dil. NaOH solution with cooling and extracted twice with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to give 84 mg of a crystalline residue, which was recrystallized from EtOH–ether, giving 59 mg (83%) of **2** as fine leaflets, mp 180—183°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 3250 (shoulder) (NH and OH). *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.42; H, 7.07; N, 13.42. The mass spectrum of **2** showed a molecular ion peak at 206.

By the same precedure as above, 17 mg of **12b** gave 9 mg of **2**, mp 179—182.5°, which was identical with the sample obtained earlier by mixed mp and infrared spectrometry.

Attempted Partial Benzoylation of 8——To a solution 154 mg of **8** in 0.5 ml of pyridine was added a solution of 70 mg of benzoyl chloride in 0.5 ml of pyridine with stirring and cooling, and the mixture was stood for 3 hr at room temperature. The thin-layer chromatography of the reaction mixture showed the existence of monobenzoate of **8**, along with unchanged **8** and a small amount of dibenzoate. The mixture was poured into ice–water and extracted with ether. The extract was washed successively, with H_2O, dil. HCl, dil. $NaHCO_3$ solution, and H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent *in vacuo* left 184 mg of a colorless syrup which was chromatographed over 6 g of alumina. The benzene–ether (1:1 v/v) eluate was evaporated to give 125 mg of monobenzoate of 8 as a syrup. The monobenzoate was treated with 2 ml of 1N HCl in 2 ml of EtOH at room temperature for 1 hr. After neutralization with dil. Na_2CO_3 solution, the reaction mixture was diluted with H_2O, and extracted with AcOEt. The extract was dried and evaporated to give a crystalline mass which was recrystallized from EtOH–AcOEt to a triol monobenozate as prisms, mp 189—191°. *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.49; H, 5.84; N, 4.25.

Attempted Partial Hydrolysis of the Dibenzoate of 8——A mixture of 200 mg of **8**, 400 mg of benzoyl chloride, and 2 ml of pyridine was stood for 3 hr at room temperature. The reaction mixture was poured into ice–water and extracted with ether. The extract was washed with dil. K_2CO_3 solution and dried. Evaporation of the solvent *in vacuo* left a yellow syrup (322 mg) which was chromatographed over 6 g of alumina. The benzene–ether eluate was evaporated and the residue was recrystallized from EtOH to give a dibenzoate of **8** as needles, mp 118—123°. IR ν_{max}^{Nujol} cm^{-1}: 1725 (ester). *Anal.* Calcd. for $C_{30}H_{31}O_7N$: C, 69.62; H, 6.04; N, 2.71. Found: C, 69.54; H, 6.07; N, 2.60.

The dibenzoate thereby obtained was dissolved in dioxan and an equivalent amount of aqueous dil. NaOH solution was added. The mixture was heated on a water bath for 4 hr. Thin-layer chromatography of the reaction product did not show the presence of monobenzoate, but the presence of **8**, along with the unchanged dibenzoate.

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