[Chem. Pharm. Bull. 17(10)1990—1999(1969)] UDC 547.867.1.07

Attempted Synthesis of 4,5-Epiminotetrahydro-1,2-oxazine

SADAO OIDA and EIJI OHKI

Central Research Laboratories, Sankyo Co., Ltd.[1]

(Received November 20, 1968)

Oxidation of 2-benzoyl-6-acetoxymethyl-3,6-dihydro-1,2-oxazine (**7**) with osmium tetroxide afforded a mixture of 4,5-*cis*-glycols which were separated and characterized as benzoyl derivatives (**8a** and **9a**). Similarly **7** was oxidized with potassium permanganate, yielding a 4α,5α-dihydroxyl derivative (**8b**) as the major product along with its 4β,5β-isomer (**9b**). On the other hand, treatment of **7** with pertrifluoroacetic acid gave a crystalline 4β,5β-epoxide (**12**) and a syrupy 4α,5α-epoxide (**13**) in a good yield. Further, **12** was treated with sodium azide in dimethylformamide to give a 5β-hydroxy-4α-azide (**14a**) and a 4β-hydroxy-5α-azide (**15a**). Conformational analysis of these synthesized compounds was carried out by nuclear magnetic resonance spectrometry. Attempted conversion of **8b** or **14a** into a 4,5-epimine was not successful.

In a previous paper,[2] we reported an oxidation of 2-phenyl--3,6-dihydro-1,2-oxazine 6-methanol (**1**) with osmium tetroxide to 4α,5α-dihydroxyl derivative (**2**) and a successive transformation of **2** into 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**3**), which would be an important intermediate for synthetic approach to 3,4-epiminopyrrolidine, one of the active principles of antitumor antibiotics, the mitomycins. However, the N-phenyl group of **1** is an undesirable substituent when it is to be converted into other substituents, because there is no simple method for its ultimate removal; in addition, the N-phenyl group of **1** also offers some limitation for the oxidizing reagents in the glycolation of its 3,4-double bond. Accordingly, we undertook a synthesis of 3,6-dihydro-1,2-oxazine whose nitrogen was blocked with easily-removable acyl function, and examined its conversion into corresponding 4,5-epiminotetrahydro-1,2-oxazine.

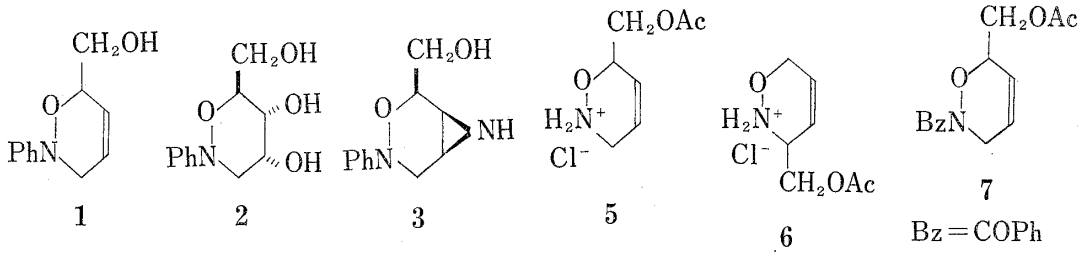


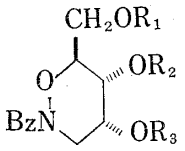
Chart 1

Lithium aluminum hydride reduction of methyl 2,4-pentadienoate and successive acetylation afforded 2,4-pentadienyl acetate (**4**), bp 65—67° (25 mmHg). The Diels–Alder reaction of **4** with 1-chloro-1-nitrosocyclohexane[3] at a low temperature for two weeks resulted in a formation of 6-acetoxymethyl-3,6-dihydro-1,2-oxazine hydrochloride (**5**), mp 144—146° (decomp.), in 71% yield. The nuclear magnetic resonance (NMR) spectrum of **5** exhibited a multiplet absorption centering at 4.02 ppm and the other multiplet at 5.21 ppm in a ratio of 2:1. The former would be due to two protons of the methylene bearing N-function and the latter to one proton of the methine bearing O-function, supporting the structure of **5**. In

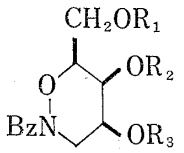
1) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
2) S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **17**, 939 (1969).
3) O. Wichterle and M. Hudlicky, *Collection Czech. Chem. Commun.*, **12**, 661 (1947).

addition, Kresze and Firl's study[4] on the orientation of this Diels–Alder reaction also ruled out the predominance of the possible alternative formula (**6**). Treatment of **5** with benzoyl chloride in pyridine gave a 2-benzoyl derivative (**7**), which served as a starting material for this study.

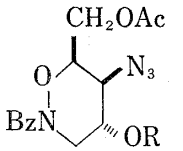
First, oxidation of **7** thus obtained with osmium tetroxide was examined as in the case of **1** to **2** described in the previous paper;[2] treatment of **7** with the reagent in ether and successive decomposition of the resulting adduct with sodium sulfite afforded a mixture of hydroxylated compounds, but in a low yield. The mixture could not be successfully separated into simple components; hence, it was benzoylated without further purification. Recrystallization and chromatographic purification of the benzoylated product yielded a benzoate (**8a**) of mp 189—190° and its isomer (**9a**) of mp 121.5—123°.



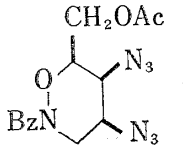
8a: $R_1=R_2=R_3=Bz$
b: $R_1=Ac$, $R_2=R_3=H$
c: $R_1=Ac$, $R_2=Ts$, $R_3=H$
d: $R_1=Ac$, $R_2=H$, $R_3=Ts$
e: $R_1=Ac$, $R_2=R_3=Ts$



9a: $R_1=R_2=R_3=Bz$
b: $R_1=Ac$, $R_2=R_3=H$



10a: R=H
b: R=Ts



11

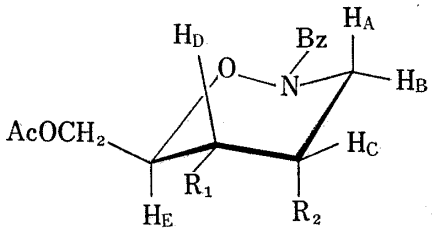
Chart 2

On the other hand, **7** was oxidized with potassium permanganate in the presence of magnesium sulfate and gave two kinds of glycols. The major glycol (**8b**), mp 120—122°, was converted into **8a** by deacetylation with ammonia and successive benzoylation, and also the minor one (**9b**), mp 131—134°, into **9a**. In consideration of the oxidation mode of the reagents used, these 4,5-dihydroxyl derivatives would be *cis*-glycols, and, furthermore, assuming that the reagent attacks the 4,5-double bond of **7** from the less-hindered side,[2,5] the major product (**8b**) would be designated as 2-benzoyl-4α,5α-dihydroxy-6β-acetoxymethyl-tetrahydro-1,2-oxazine and the minor one (**9b**) as its 4β,5β-dihydroxy isomer. The NMR analysis of **8b** also supported its stereochemistry as shown in Table I, No. 1. In fact, the absorption corresponding to the proton (H_C) of the methine at the 4-position could not be observed well. However, one proton of the neighboring methylene protons at the 3-position was detected as a doublet of doublets centering at 3.48 ppm and the other also as a doublet of doublets at 4.72 ppm. The former absorption in a higher field would be due to the axially-oriented H_A and the latter in a lower field to the equatorially-oriented H_B in consideration of the axial location of the nitrogen lone pair.[2,6] Accordingly, on the assumption of a chair conformation of tetrahydrooxazine ring with the location of the bulky side chain in an equatorial 6β-position, H_A would be assigned as 3β-proton and H_B as 3α-proton. The small coupling of H_A or H_B with the neighboring H_C, $J_{AC}=1.5$ and $J_{BC}=2.7$ cps, indicates that H_C is located in an equatorial position, 4β.

Following the procedure used in the conversion of **2** into **3**,[2] tosylation of 4α,5α-glycol (**8b**) with excess of the reagent was carried out. However, the infrared spectrum of the resulting syrupy product exhibited a hydroxyl absorption at 3450 cm^{-1} along with tosyloxyl absorptions at 1370 and 1177 cm^{-1}, indicating that it contained some not-fully tosylated material. The NMR spectrum of the reaction mixture suggested the predominance of a 5-monotosylate

4) G. Kresze and J. Firl, *Tetrahedron Letters*, **1965**, 1163.
5) B. Belleau and Y. Au-Young, *J. Am. Chem. Soc.*, **85**, 64 (1963).
6) F. Bohlman, D. Schumann, and H. Schulz, *Tetrahedron Letters*, **1965**, 173; F. Bohlman, D. Schumann, and C. Arndt, *ibid.*, **1965**, 2705.

Table I. NMR Data of 4α,5α-Substituted Derivatives



No.	Compound	R_1	R_2	Chemical shift (δ ppm)					Coupling constant (cps)				
				H_A	H_B	H_C	H_D	H_E	J_{AB}	J_{AC}	J_{BC}	J_{CD}	J_{DE}
1	**8b**	OH	OH	3.48 (dd)	4.72 (dd)	~4.2 (m)	~3.75 (m)	~4.2 (m)	14	1.5	2.7	—	—
2	**8c**	OTs	OH	3.44 (br.d)	4.47 (dd)	~4.2 (m)	4.58 (dd)	~4.2 (m)	13.5	1—2	3	2.5	9
3	**8d**	OH	OTs	3.33 (br.d)	4.66 (br.d)	5.25 (dt)	4.97 (dd)	4.25 (ddd)	14.5	1.8	3.3	3.3	9.2

The solvent was $CDCl_3$ containing a small amount of D_2O. The spectra of No. 1 and 2 were taken on a Varian A-60 spectrometer and that of No. 3 on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard.

(**8c**). As illustrated in Table I, No. 2, the doublet of doublets, J_{CD}=2.5 and J_{DE}=9 cps,[7] corresponding to the axial proton (H_B) at the 5-position appears in the lowest field around 4.58 ppm, indicating the presence of the tosyl group at the 5-position. Hence, it was found that the equatorial hydroxyl group of 4α,5α-glycol (**8b**) at the 5-position was predominantly tosylated.

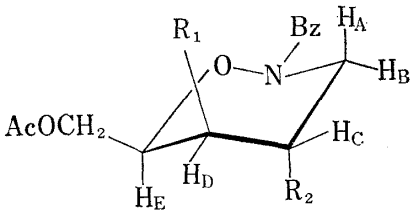
Without further purification, the tosylated product thus obtained was treated with sodium azide in dimethylformamide and gave a mixture of a monoazide (**10a**), mp 114.5—115°, and a diazide (**11**), mp 133—134.5°, along with an isomeric monotosylate (**8d**), mp 177—178°. These products were separated by silica gel chromatography and the yields of **10a**, **11**, and **8d** were 13.4, 4.1, and 6.3%, respectively. The infrared spectrum of **10a** indicated an azide absorption at 2120 cm^{-1} with a hydroxyl absorption at 3420 cm^{-1}, and its NMR data, as illustrated in Table II, No. 1, reflects the structure of a 5β-monoazide. The multiplet absorption centering at 3.64 ppm would correspond to the α-equatorial proton (H_B) attached to the carbon at the 5-position bearing the azide group, because its small half width (8 cps) indicates that the 5α-proton has an equatorial conformation. Formation of **10a** which was thus designated as a 4α-hydroxy-5β-azide derivative would originate from the 5-monotosylate (**8c**) and the latter α-tosyloxyl group would be attacked by an azide ion from the back. The structure of the diazide (**11**) was confirmed by elementary analysis and from its infrared spectrum with a strong azide absorption at 2120 cm^{-1}. Although there is no proof on the configuration of the azide groups, their β-configuration should be valid in consideration of this substitution mode. **11** would have originated from a possible 4α,5α-ditosyloxy derivative (**8e**).

The infrared spectrum of **8d** here separated indicated tosyloxy absorptions at 1178 and 1358 cm^{-1} with a hydroxyl absorption at 3530 cm^{-1}. NMR analysis of **8d**, as shown in Table I, No. 3, suggested the structure of a 4α-monotosylate, because an absorption corresponding to the equatorial proton (H_C) at the 4-position appears as a multiplet shifted to a lower field around 5.32 ppm with small coupling with the neighboring protons, J_{AC}=1.8, J_{BC}=3.3, and J_{CD}=3.3 cps. Survival of the tosyloxy group in **8d** without any effect on the azide ion during this substitution reaction is still beyond rational interpretation. Thus, it was found that

7) These coupling constants in the NMR spectrum of 8c indicate that H_D is oriented axially and H_C equatorially giving further support to the structure of the *cis*-4,5-substituents of this series.

tosylation of the *cis*-glycol (**8b**) and successive treatment with sodium azide did not offer a hopeful access to the synthesis of 4,5-epimine because we had failed to obtain the desired intermediate, an azidotosylate (**10b** or an alternate formula) which might be converted into 4,5-epimine on reduction with lithium aluminum hydride in similar to the case of **2** to **3**.[2] Furthermore, any approach from **10a** was also abandoned because of its low yield.

Table II. NMR Data of 4α,5β-Substituted Derivatives



No.	Compound	R_1	R_2	Chemical shift (δ ppm)					Coupling constant (cps)					
				H_A	H_B	H_C	H_D	H_E	J_{AB}	J_{AC}	J_{BC}	J_{CD}	J_{DE}	J_{BO}
1	**10a**	N_3	OH	3.75 (dd)	4.55 (ddd)	4.14 (m)	3.64 (m)	4.40 (dt)	14.5	1.8	2.7	~5	1.8	1
2	**14d**	OMs	N_3	3.86 (dd)	4.63 (ddd)	4.45 (m)	4.83 (m)	4.48 (m)	14.4	2.2	2.3	3.7	1.5	1.2

The spectrum of No.1 was determined in $CDCl_3$ containing a small amount of D_2O and that of No. 2 in acetone-d_6 on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard.

Next, we turned to the examination of 4,5-epoxy derivatives, which would be transformed into a compound suitable for aziridine formation. An entry into the 4,5-epoxide should be provided through epoxidation of the double bond in **7**. It was initially observed that the 4,5 double bond was inert to the action of perbenzoic acid, peracetic acid, and anhydrous peracetic acid. However, rapid and hopeful epoxidation of **7** was found to be effected with more powerful pertrifluoroacetic acid in the presence of disodium hydrogenphosphate. Following the Emmons method,[8] treatment of **7** with pertrifluoroacetic acid afforded a crystalline epoxide (**12**), mp 80.5—81.5°, and a syrupy isomer (**13**), in a good yield. **12** and **13** revealed the same spot on thin-layer chromatogram and they also could not be separated by silica gel column chromatography. **12** was obtained in a pure state by recrystallization, in 40% yield, while **13** could not be purified.

Treatment of the syrupy crude epoxide (**13**) thereby obtained with sodium azide in dimethylformamide afforded the afore-mentioned 4α-hydroxy-5β-azido derivative (**10a**), mp 114—115°, as a main product.[9] This fact indicates that the syrupy epoxide (**13**) has a 4α,5α-configuration in consideration of the *trans*-opening mode of its epoxide ring. Subsequently, the isomeric crystalline epoxide (**12**) would be designated as a 4β,5β-epoxide, whose structure was further verified by its NMR analysis as will be mentioned later. Analogous treatment of **12** with sodium azide gave two kinds of azidoalcohols which were isomeric with **10a**, the major product (**14a**), mp 108—111°, and the minor one (**15a**), mp 143.5—144.5°. **14a** formed a syrupy acetate (**14b**), tosylate (**14c**), mp 123.5—124.5°, and a mesylate (**14d**), mp 97—98°, while **15a** formed an acetate (**15b**), mp 104.5—105.5°, and a mesylate (**15c**), mp 141.5—142.5°. As the original epoxide has a 4β,5β-configuration, the introduced azide group in **14a** (or **15a**) has an α-configuration and **14a** (or **15a**) would be assigned as 5β-hydroxy-4α-azide or 4β-hydroxy-5α-azide.

8) W.D. Emmons and G.B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955), and its preceding papers.
9) As a minor product of this reaction, powder of mp 128.5—130.5° was isolated as shown in the experimental part. The infrared spectrum showed the presence of hydroxyl and azide groups, indicating that this product would be an isomeric 4β-azido-5α-hydroxyl derivative.

The final structural assignment of **14a** as 2-benzoyl-6β-acetoxymethyl-4α-azido-5β-hydroxy-tetrahydro-1,2-oxazine and that of **15a** as its 4β-hydroxy-5α-azido isomer was made from their NMR analysis. As illustrated in Table III, NMR spectra of **15a** (No. 1), its acetate (**15a**, No. 2), and its mesylate (**15c**, No. 3) exhibited an analogous pattern. As seen from the NMR data of the azido-acetate (**15b**) (Table III, No. 2), a multiplet absorption corresponding to the axial proton (H_C) at the 4-position with J_{AC}=10, J_{BC}=5.5, and J_{CD}=9 cps appears in the lowest field centering at 5.12 ppm, indicating the presence of the acetyl group at the 4-position. Thus, the spectrum of **15b** reflects the structure of 4β-acetoxy-5α-azide.

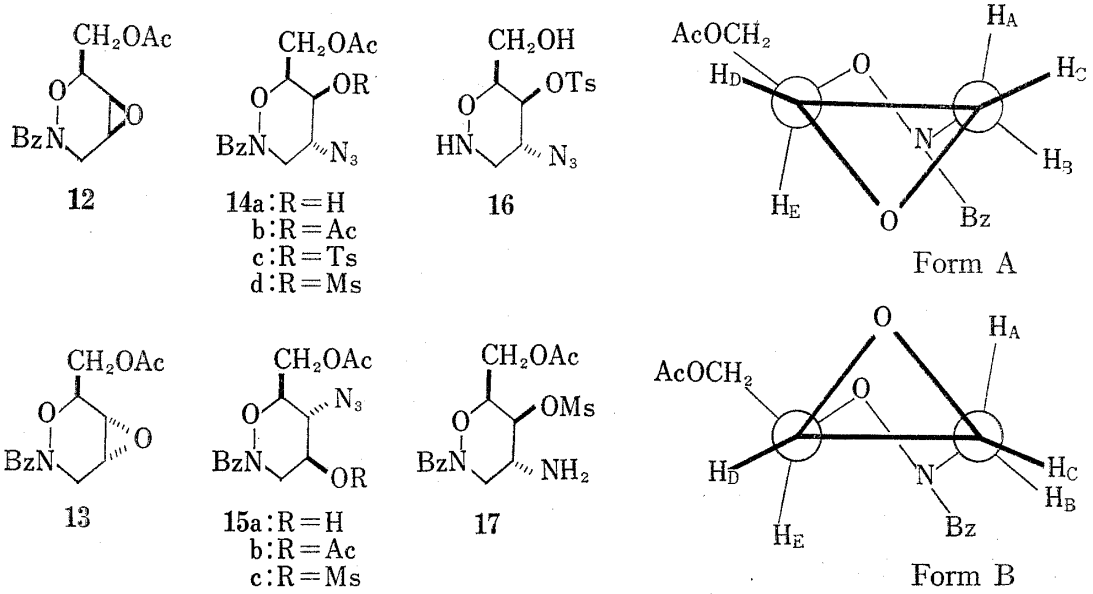
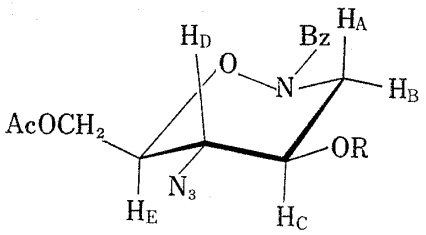


Chart 3

TABLE III. NMR Data of 4β,5α-Substituted Derivatives



No.	Compound	R	Chemical shift (δ ppm)					Coupling constant (cps)				
			H_A	H_B	H_C	H_D	H_E	J_{AB}	J_{AC}	J_{BC}	J_{CD}	J_{DE}
1	**15a**	H	4.20 (dd)	4.78 (dd)		3.4—4.2 (m)		12.5	10	4.5	—	—
2	**15b**	Ac	3.18 (dd)	4.86 (dd)	5.12 (ddd)	3.75 (m)		12.4	10	5.5	9	—
3	**15d**	Ms	3.39 (dd)	5.00 (dd)	4.79 (ddd)	3.75 (m)		12.5	9.8	5.6	9	—

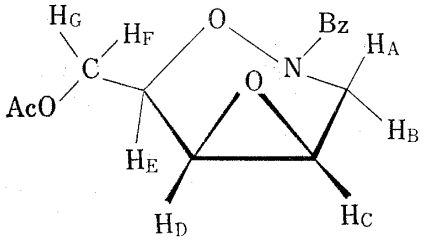
The spectrum of No. 1 was determined in $CDCl_3$ containing a small amount of D_2O, on a Varian A-60 spectrometer.
The spectra of No. 2 and 3 were taken in $CDCl_3$ on a Varian HA-100 spectrometer.

On the other hand, the structural assignment of 5β-hydroxy-4α-azide for the isomer (**14a**) was also supported by NMR analysis of its mesylate (**14d**) (Table II, No. 2). Contrasting with the spectrum of **15b**, a multiplet absorption due to the equatorial proton (H_D) at the 5-posi-

tion with small coupling constants, J_{ED}=1.5, J_{CD}=3.7, and J_{BD}=1.2 cps, was observed in the lowest field centering at 4.83 ppm, indicating that the mesylated hydroxyl group is located at the 5-position. Thus, the assignment of **14b** as 4α-azido-5β-mesyloxy derivative most likely explains its NMR data.

This structural assignment of **14a** and **15a** supported that the original oxide ring in **12** is β-oriented and its ring opening reaction is effected far in favor of formation of **14a** having diaxial substituents. In addition, the structural assignment of 2-benzoyl-6β-acetoxymethyl-4β,5β-epoxytetrahydro-1,2-oxazine for the epoxide (**12**) was independently verified by NMR analysis with its spin-decoupling study as illustrated in Table IV. The pattern of the spectrum was found to be quite similar to that of 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**1**) reported in a previous paper.[2] Following the same evaluation as described in the case of **1**, the NMR data of **12** reflect the Dreiding model of the 4β,5β-epoxide which was prepared on the assumption of a bulky side chain located in a quasi-equatorial orientation; as shown in the Chart by Garbisch's projection[2,10] the dihedral angle between H_A and H_C is almost equal to the angle between H_B and H_C in the case of the α-epoxide (see Form A), while these angles are not equal in the case of the β-epoxide (see Form B). Consequently, in the former case, a near-coupling constant between J_{AC} and J_{BC} would be predicated, and it would not be so in the latter case. As seen from Table IV, the observed corresponding coupling constants, J_{AC}=0.8and J_{BC}=4.0 cps, were different, pointing to the latter case (β-epoxide).

Table IV. NMR Data of 4β,5β-Epoxide (12)



H_A	3.97 (ddd)	J_{AB}=13.8, J_{AC}=0.8 J_{AC}=0.7
H_B	4.44 (dd)	J_{BC}=4.0,
H_C	3.54 (ddd)	J_{CD}=4.1
H_D	3.27 (ddd)	J_{DE}=1.3
H_E	*ca.* 4.32 (ddd)	J_{EF}=3.1, J_{EG}=8.2
H_F	*ca.* 4.25 (dd)	J_{FG}=12.0
H_G	*ca.* 4.08 (dd)	

The spectra were determined in $CDCl_3$ on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard.

The conversion of the azido-alcohol tosylate or mesylate (**14c** or **14d**), having diaxial 4,5-substituents, into 4α,5α-epimine would be presumed possible by reduction of the azide group and successive displacement of the neighboring sulfonyloxy group with the resulting amine. Following the method for the preparation of **1**,[2] treatment of azidotosylate (**14c**) with lithium aluminum hydride in ether was attempted, but without success, giving a complex mixture in a low yield, which could not be separated into any simple material. On the other hand, refluxing of **14d** with 80% hydrazine hydrate and Raney nickel in ethanol also gave a disappointing result and the only product isolated from the reaction mixture was benzoyl hydrazide, mp 111—112.5°. Formation of benzoyl hydrazide suggests that fascile fisssion of the N-benzoyl bond in

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).

14d by this reaction is feasible in agreement with the fact that treatment of **14c** with bases afforded 4α-azido-5β-tosyloxytetrahydro-1,2-oxazine-6β-methanol, (**16**) mp 137.5—138.5°. Hydrogenation of the azidomesylate (**14d**) over palladized charcoal in methanol gave a syrupy aminomesylate (**17**) which was characterized as its N-benzoyl derivative, mp 153.5—155°. However, treatment of the aminomesylate (**17**) with triethylamine was not successful, also giving an unidentified complex mixture. Further, preliminary attempt on the fission of N–O bond in the trerahydro-1,2-oxazine ring of **14c** or **14d** by treatment with zinc in acetic acid[11] or by hydrogenation over the Adams catalyst gave a disappointing result.

Finally, we would like to mention that, as seen from discussions described above, conformational analysis of these tetrahydro-1,2-oxazine derivatives is approximately possible by NMR spectrometry in the way similar to that of cyclohexane derivatives.

Experimental

Melting points are not corrected. Infrared spectra were determined on a Perkin–Elmer Model 221 or a Perkin–Elmer Infracord, and NMR spectra on a Varian A–60 or HA–100 spectrometer. The removal of solvent *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50°. Plates for thin-layer chromatography were prepared with silica gel (E. Merck AG) and visualization of spots was effected by spraying iodine or spraying conc. H_2SO_4, followed by heating.

2,4-Pentadienyl Acetate (**4**)——To a stirred suspension of 17.0 g of $LiAlH_4$ in 170 ml of dry ether, 70.0 g of methyl 2,4-pentadienoate was added dropwise at −25° to −30° over a period of 2 hr. The resulting mixture was further stirred at 0° for 2 hr and excess of the reagent was decomposed by careful addition of 20 ml of AcOEt with cooling. After careful addition of 300 ml of 20% dil. H_2SO_4, the aqueous layer was separated and extracted twice with ether. The combined ether layer and extract was washed with dil. $NaHCO_3$ solution, and dried over anhyd. Na_2SO_4. After removal of the solvent, the residue was fractionally distilled, yielding 31.5 g (60%) of 2,4-pentadienol, bp 65—68° (25 mmHg) (reported[12] bp 70—72.5° (30 mmHg)).

To an ice-cold solution of pentadienol thereby obtained in 60 ml of pyridine, 65 g of Ac_2O was added dropwise and the mixture was allowed to stand at room temperature for 5 hr. The product was poured into 200 ml of ice-water, and extracted with 200 ml of ether. The extract was washed with dil. HCl with cooling and dried over anhyd. Na_2SO_4. The residue obtained by removal of the solvent was fractionally distilled, giving 39.7 g (85%) of 2,4-pentadienyl acetate, bp 64—67° (24 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1748, 1230. NMR ($CDCl_3$) δ ppm: 2.05 (3H, singlet, $C\underline{H}_3COO$-), 4.61 (2H, doublet, J=5.5 cps, =CH–$C\underline{H}_2$–O–), 5.0—6.6 (5H, complex absorption, =C$\underline{H}$–).

6-Acetoxymethyl-3,6-dihydro-1,2-oxazine Hydrochloride (**5**) **and Its 2-Benzoate** (**7**)——A solution of 57.7 g (0.458 mole) of 2,4-pentadienyl acetate (**4**) and 67.5 g (0.458 mole) of 1-chloro-1-nitrosocyclohexane in 80 ml of EtOH and 160 ml of ether was kept at 5° for 4 days. The resulting colorless precipitate was collected and washed with a small amount of ether, yielding 26.9 g of **5**, mp 139—142° (decomp.), as leaflets.

To the residual reaction solution was further added 40 g of 1-chloro-1-nitrosocyclohexane and the mixture was kept at 5° for 15 days. Thus, additional crop of **5** (36.3 g), mp 140—143°, was obtained. Total yield, 71%. Analytical samples were prepared by recrystallization from EtOH as leaflets, mp 144—146° (decomp.), which decomposed on long-standing at room temperature. IR ν_{max}^{Nujol}: 1744 cm^{-1}. NMR (D_2O) δ ppm: 2.14 (3H, singlet, $C\underline{H}_3COO$–), 4.02 (2H, multiplet, –$\overset{1+}{N}$H–$C\underline{H}_2$–), 4.42 (2H, doublet, J=4.5 cps, –$C\underline{H}_2$–O–), 5.21 (1H, multiplet, –C$\underline{H}$–O–), 6.12 (2H, multiplet, –C$\underline{H}$=C$\underline{H}$–). *Anal.* Calcd. for $C_7H_{12}O_3NCl$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.27; H, 6.25; N, 7.33.

To an ice-cooled solution of 19.35 g (0.100 mole) of **5** in 100 ml of pyridine was added dropwise 20 g (0.142 mole) of benzoyl chloride with stirring. Working up in the usual manner, 17.82 g (68%) of **7**, mp 73—74°, was obtained as prisms (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1745 (ester), 1628 (amide). NMR ($CDCl_3$) δ ppm: 1.87 (3H, singlet, $C\underline{H}_3COO$–), 4.07 (2H, doublet, J=5 cps, –$C\underline{H}_2$–O–), 4.42 (2H, multiplet, –$\overset{|}{N}$–$C\underline{H}_2$–), 4.70 (1H, multiplet, –C$\underline{H}$–O–), 5.91 (2H, multiplet, –C$\underline{H}$=C$\underline{H}$–), 7.3—7.9 (5H, multiplet, phenyl). *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.18; H, 5.76; N, 5.47.

2-Benzoyl-6β-benzoyloxymethyl-4α,5α-dibenzoyloxy-(**8a**) **and -4β,5β-dibenzoyloxytetrahydro-1,2-oxazine** (**9a**) (**Osmium Tetroxide Oxidation of 7**)——To an ice-cold solution of 1.03 g of **7** and 0.4 ml of pyridine in

11) Differing from the case of 3,6-dihydro-1,2-oxazine with unblocked nitrogen, the N-benzoyl derivative (**7**) was found to be inert to treatment with zinc in acetic acid. *cf.* O. Wichterle and S. Svastal, *Collection Czech. Chem. Commun.*, **16**, 33 (1951).

12) A.D. Mebane, *J. Am. Chem. Soc.*, 74, 5227 (1952).

20 ml of dry ether was added a solution of 1.00 g of OsO_4 in 20 ml of dry ether with stirring over a period of 20 min, and then the miuture was stirred with cooling for 1.5 hr. The precipitate thereby formed was collected, whased with ether, and added to a mixture of 25 ml of EtOH and 40 ml of H_2O. After addition of 10 g of Na_2SO_3, the mixture was refluxed for 2.5 hr with stirring. The solid was collected and washed with 15 ml of EtOH. The combined filtrate and washings was concentrated under a reduced pressure to *ca.* 30 ml and extracted with three 20 ml portions of EtOAc. After dyring over anhyd. Na_2SO_4, the extract was evaporated *in vacuo* to leave 134 mg of a yellow syrup, which was dissolved in 2 ml of pyridine and excess of benzoyl chloride was added. After standing for 10 hr at room temperature, the mixture was poured into ice–water and extracted with benzene. The extract was washed successively with dil. HCl, dil. $NaHCO_3$ solution, and H_2O, and dried over anhyd. Na_2SO_4. The viscous residue (0.3 g) obtained by removal of the solvent partly crystallized on standing. The crystals collected were washed with cold ether to afford 35 mg (1.6%) of crude **8a** as powder of mp 185—188°. Recrystallization from benzene–EtOH gave **8a** as powder, mp 189—190°. IR ν_{max}^{Nujol} cm^{-1}: 1724 (ester), 1633 (amide). *Anal.* Calcd. for $C_{33}H_{27}O_8N$: C, 70.08; H, 4.81; N, 2.48. Found: C, 69.94; H, 5.00; N, 2.67.

The non–crystallized product left after removal of **8a** was chromatographed over 7 g of silica gel. Removal of the solvent from fractions eluted with benzene gave 150 mg of a crystalline mass, which was recrystallized from EtOH to 73 mg (3.3%) of **9a** as prisms of mp 121.5—123°. IR ν_{max}^{Nujol} cm^{-1}: 1734 (ester), 1656 (amide). *Anal.* Calcd. for $C_{33}H_{27}O_8N$: C, 70.08; H, 4.81; N, 2.48. Found: C, 70.26; H, 5.04; N, 2.54.

2-Benzoyl-6β-acetoxymethyl-4α,5α-dihydroxy (8b), and 4β,5β-dihydroxytetrahydro-1,2-oxazine (9b) (Potassium Permanganate Oxidation of 7)——To an ice–cooled and stirred mixture of 1.986 g of **7**, 3.0 g of magnesium sulfate and 50 ml of acetone was added dropwise a solution of 1.613 g of potasssium permanganate in 35 ml of H_2O over a period of 3 hr. Then, the reaction mixture was left at room temperature for 30 min. The solid was filtered and washed several times with acetone. The combined filtrate and washings was concentrated at room temperature under a reduced pressure to *ca.* 30 ml and extracted successively with three 15 ml portions of $CHCl_3$ and three 15 ml portions of EtOAc. The combined extract was dried over anhyd. Na_2SO_4 and the solvent was evaporated *in vacuo*, leaving 1.704 g of a yellow syrup, which partly crystallized on standing. The crystals were collected and recrystallized from ether–EtOAc to yield 815 mg (36%) of **8b** as leaflets, mp 120—122°. IR ν_{max}^{Nujol} cm^{-1}: 3470, 3390 (OH), 1749 (ester), 1625 (amide). *Anal.* Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.69; H, 5.84; N, 4.70.

The mother liquor of the recrystallization of **8b** and the uncrystallized reaction product left were combined and evaporated to dryness *in vacuo* and the residue was chromatographed over 15 g of silica gel. Removal of the solvent from fractions eluted with 1% MeOH–$CHCl_3$ (*ca.* 200 ml) gave 350 mg of a crystalline mass which was recrystallized from ether–EtOAc to 196 mg of a mixture of **8b** and **9b**, melting at 100—110°. This mixture was fractionally recrystallized again from ether–EtOAc, giving 63 mg of **9b** as needles, mp 131—134°, along with 41 mg of **8b**, mp 120.5—122°. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3290 (OH), 1743 (ester), 1630 amide). *Anal.* Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.70; H, 5.84; N, 4.79.

Conversion of 8b into 8a and 9b into 9a——A solution of 100 mg of **8b** in 3 ml of NH_3–saturated MeOH was allowed to stand at room temperature for 3 hr. The solvent was removed *in vacuo* at room temperature, the residue was dissolved in 3 ml of pyridine, and 300 mg of benzoyl chloride was added. The reaction mixture was left overnight at room temperature and poured into ice–water, extracted with 10 ml of benzene, which was washed successively with dil. HCl, $NaHCO_3$ solution, and H_2O. After drying, the solvent was evaporated *in vacuo* to dryness and the residue was recrystallized from EtOH, giving 121 mg (62% from **8b**) of **8a** as prisms, mp 121.5—123°, which was identical with the sample obtained above by comparison of melting points and infrared spectra.

9b (13 mg) was also converted into **9a** (15 mg) of mp 188—189.5° by the same procedure as described above. Comparison of infrared spectra showed that the product was identical with the corresponding sample described before.

2-Benzoyl-6β-acetoxymethyl-4α-hydroxy-5α-tosyloxy- (8c), -4α-tosyloxy-5α-hydroxy- (8d), -4α-hydroxy-5β-azido- (10a), and -4β,5β-diazidotetrahydro-1,2-oxazine (11) (Tosylation of 8b, followed by Treatment with Sodium Azide)——A solution of 476 mg (0.00124 mole) of **8b** and 623 mg (0.00327 mole) of TsCl in 10 ml of pyridine was allowed to stand overnight at room temperature. The mixture was poured into ice water and extracted with 30 ml of benzene. The extract was washed with cold dil. HCl and dried over anhyd. Na_2SO_4. The solvent was removed *in vacuo* to leave 726 mg of a syrup whose infrared absorption at 3450 cm^{-1} showed the presence of a hydroxyl group and those at 1370 and 1177 cm^{-1} showed that of a tosyl group. Thin–layer chromatography of the reaction product showed it was homogeneous without any unchanged material (**8b**). As already discussed, this reaction product mainly contained **8c** from NMR spectrometric data.

The tosylated mixture thus obtained was dissolved in 10 ml of dimethylformamide and 500 mg of NaN_3 was added. After heated at 130° for 6 hr with stirring, the reaction mixture was diluted with 20 ml of H_2O and extracted with two 20 ml portoins of $CHCl_3$. After drying, the extract was evaporated *in vacuo* to leave 560 mg of a red syrup which was chromatographed over 5 g of silica gel. The benzene–ether (4:1, v/v) eluate (30 ml) gave 44 mg of a crystalline mass which was recrystallized from EtOH, affording 23 mg

(4.1% from **8b**) of a diazide (**11**) as prisms, mp 133—134.5°. IR ν_{max}^{Nujol} cm^{-1}: 2120 (azide), 1739 (ester), 1650 (amide). *Anal.* Calcd. for $C_{14}H_{15}O_4N_7$: C, 48.69; H, 4.38; N, 28.40. Found: C, 48.69; H, 4.66; N, 28.20.

The next benzene–ether (4:1, v/v) eluates (30 ml×3) gave 320 mg of a syrup which crystallized on standing. Recrystallization from benzene afforded 70 mg (13.4% from **8b**) of a monoazide (**10a**) as fine needles, mp 114.5—115°. IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 2120 (azide), 1749 (ester), 1629 (amide). *Anal.* Calcd. for $C_{14}H_{16}O_5N_4$: C, 52.49; H, 5.04; N, 17.49. Found: C, 52.79; H, 5.23; N, 17.20.

The final benzene–ether (1:1, v/v) eluates (30 ml×4) gave 80 mg of a crystalline residue which was recrystallized from EtOH, yielding 46 mg (6.3% from **8b**) of a monotosylate (**8d**) as needles, mp 177—178°. IR ν_{max}^{Nujol} cm^{-1}: 3530 (OH), 1734 (ester), 1676 (amide), 1178, 1358 (sulfonate). *Anal.* Calcd. for $C_{21}H_{23}O_8NS$: C, 56.21; H, 5.16; N, 3.12. Found: C, 56.39; H, 5.30; N, 3.20.

2-Benzoyl-6β-acetoxymethyl-4β,5β-(12) and -4α,5α-epoxytetrahydro-1,2-oxazine (13) (Epoxidation of 7 with Pertrifluoroacetic Acid)——To an ice–cooled suspension of 0.35 ml of 90% H_2O_2 in 2.5 ml of ethylene dichloride was added 2.0 ml of trifluoroacetic anhydride over a 5-min period. The resulting solution was added dropwise during 15 min to a stirred and ice–cold solution of 1.66 g of **7** in 8 ml of ethylene dichloride containing 6.3 g of suspended disodium hydrogen phosphate. The mixture was stirred for 1.5 hr and then 20 ml of H_2O was added. The organic phase was collected and the aqueous phase was extracted twice with $CHCl_3$. The combined organic phase and extract was dried and evaporated *in vacuo*, leaving 1.886 g of a pale yellow syrup, which was dissolved in 4 ml of ether containing a small amount of EtOH and kept at 0° for 2 days. The resulting crystals (1.037 g, 59%), mp 74.5—77°, were collected. The analytical value of this product was satisfactory for $C_{14}H_{15}O_5N$ (Calcd.: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.65; H, 5.63; N, 5.12) and the product revealed one spot on thin–layer chromatogram. However, its NMR spectrum exhibited two kinds of acetyl absorption at 1.88 ppm and 1.99 ppm, indicating that the product was a mixture of epoxides (**12** and **13**) in a relative ratio of 4:1 which was also evaluated from absorption intensities of the acetyl group. Recrystallization of the mixed epoxides from 2 ml of EtOH gave 667 mg of pure **12** as plates, mp 80.5—81.5°. Concentration of the mother liquor gave further crop (43 mg) of **12**, mp 79—80.5°. Total yield was 710 mg (40% from **5**). IR ν_{max}^{Nujol} cm^{-1}: 1741 (ester), 1632 (amide). *Anal.* Calcd. for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.03; H, 5.51; N, 4.99.

The isomeric 4α,5α-epoxide (**13**) was obtained as a crude product (305 mg) by evaporation of the mother liquor left after recrystallization of **12**, but could not be obtained in a crystalline form.

2-Benzoyl-6β-acetoxymethyl-4a-hydroxy-5β-azidotetrahydro-1,2-oxazine (10a) (Treatment of 13 with NaN_3)——The crude syrupy 4α,5α-epoxide (**13**) (135 mg) obtained above was dissolved in 1.8 ml of dimethylformamide and 160 mg of NaN_3, 30 mg of NH_4Cl and 0.25 ml of H_2O were added. The mixture was warmed on a steam bath for 5 hr and, then, was diluted with H_2O. Extraction with $CHCl_3$ and evaporation of the extract gave 145 mg of a syrup which was chromatographed over 5 g of silica gel. Evaporation of the solvent from fractions eluted with 1% (v/v) MeOH–$CHCl_3$ (50 ml) gave 25 mg of a crystalline mass which was recrystallized from benzene to give 12 mg of powder, mp 129.5—130.5°. IR ν_{max}^{Nujol} cm^{-1}: 3430 (OH), 2110 (N_3), 1745 (ester), 1633 (amide). *Anal.* Calcd. for $C_{14}H_{16}O_5N_4$: C, 52.49; H, 5.04; N, 17.49. Found: C, 52.45; H, 5.20; N, 17.66.

Further elution with the same solvent mixture (100 ml) followed by evaporation of the solvent gave 65 mg of a crystalline mass which was recrystallized from benzene–hexane to give 30 mg of **10a** as fine needles of mp 114—115.° Identification of the samples was carried out by mixed mp and infrared spectrometry.

2-Benzoyl-6β-acetoxymethyl-4α-azido-5β-hydroxy- (14a) and -4β-hydroxy-5α-azidotetrahydro-1,2-oxazine (15a), and Their O-Acyl Derivatives——A mixture of 5.50 g of **12**, 6.45 g of NaN_3, 1.17 g of NH_4Cl, 70 ml of dimethylformamide, and 10 ml of H_2O was heated on a steam bath for 4 hr and concentrated to 40 ml under a reduced pressure. The concentrate was poured into 40 ml of ice–water and extracted with two 50 ml portions of $CHCl_3$. The extract was dried and evaporated *in vacuo*, leaving 6.5 g of a thick syrup. A small amount of the product was chromatographed on silica gel and two crystalline azido–alcohols, the major, mp 108—111°, and the minor, mp 143.5—144.5°, was separated. Then, the crude syrup was dissolved in 6 ml of benzene and, after a small amount of crystals of the major azido–alcohol was added, was allowed to stand for 2 days in a refrigerator. Colorless powder that slowly deposited was collected and washed with cold benzene, yielding 2.112 g (33%) of crude **14a**, mp 104.5—107°.

Recrystallization from benzene gave pure **14a** as powder, mp 108—111°. IR ν_{max}^{Nujol} cm^{-1}: 3360 (OH), 2120 (N_3), 1741 (ester), 1652 (amide). *Anal.* Calcd. for $C_{14}H_{16}O_5N_4$: C, 52.49; H, 5.04; N, 17.49. Found: C, 52.43; H, 5.14; N, 17.34.

Acetylation of **14a** with Ac_2O in the presence of a trace of *p*-TsOH afforded a syrupy acetate (**14b**) which was not further purified. IR $\nu_{max}^{liq.}$ cm^{-1}: 2120 (N_3), 1751 (ester), 1660 (amide).

Treatment of **14a** with TsCl in pyridine gave a tosylate (**14c**), mp 123.5—124.5°, as prisms (from MeOH) in 84% yield. IR ν_{max}^{Nujol} cm^{-1}: 2100 (N_3), 1745 (ester), 1645 (amide), 1383, 1183 (tosyl). *Anal.* Calcd. for $C_{21}H_{22}O_7N_4S$: C, 53.16; H, 4.67; N, 11.81. Found: C, 52.93; H, 4.77; N, 11.68.

Treatment of **14a** with MsCl in pyridine gave a mesylate (**14d**), mp 97—98°, as powder (from EtOH–ether) in 86% yield. IR ν_{max}^{Nujol} cm^{-1}: 2100 (N_3), 1745, 1645. *Anal.* Calcd. for $C_{15}H_{18}O_7N_4S$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.28; H, 4.57; N, 14.08.

The mother liquor of crystallization of **14a** was further allowed to stand in a refrigerator, giving 607 mg (9.5%) of the minor isomer (**15a**) as plates of mp 138—132°. Analytical sample was obtained by recrystallization from benzene as prisms, double mp 131—132°/143.5—144.5°. IR ν_{max}^{Nujol} cm^{-1}: 3440 (OH), 2130 (N_3), 1742 (ester), 1641 (amide). *Anal.* Calcd. for $C_{14}H_{16}O_5N_4$: C, 52.49; H, 5.04; N, 17.49. Found: C, 52.60; H, 5.21; N, 17.28.

15a formed an acetate (**15b**) as needles (from ether), mp 104.5—105.5°. IR ν_{max}^{Nujol} cm^{-1}: 2110, 1750, 1740, 1659. *Anal.* Calcd. for $C_{16}H_{18}O_6N_4$: C, 53.03; H, 5.01; N, 15.46. Found: C, 52.75; H, 5.17; N, 15.47.

15a formed a mesylate (**15c**) as fine needles (from benzene–$CHCl_3$), mp 141.5—142.5°, in 80% yield. *Anal.* Calcd. for $C_{15}H_{18}O_7N_4S$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.02; H, 4.54; N, 14.19.

Attempted Lithium Aluminum Hydride Reduction of 14c——To an ice-cooled and stirred suspension of 300 mg of $LiAlH_4$ in 25 ml of dry ether was added dropwise a solution of 506 mg of **14c** in 10 ml of dry ether over a 10-min period. After the addition was completed, the mixture was stirred for 1 hr under ice-cooling. The excess $LiAlH_4$ was decomposed with EtOAc, 5 ml of H_2O was added, and the precipitate was filtered off. The etheral layer was separated and the aqueous phase was extracted with two 20 ml portions of $CHCl_3$. The combined organic layer was dried and evaporated to leave 110 mg of an oily product. Its thin-layer chromatography showed that the product was a complex mixture.

Treatment of 14c with Hydrazine Hydrate and Raney Ni——A mixture of 220 mg of **14c**, 1 ml of 80% hydrazine hydrate, 20 mg of Raney Ni (W-2), and 10 ml of EtOH was refluxed for 2.5 hr. The mixture was concentrated *in vacuo*, poured into cold Na_2CO_3 solution, and extracted with two 10ml portions of $CHCl_3$. The dried extract was evaporated *in vacuo* to give 43 mg of a crystalline residue which was recrystallized from MeOH–ether, giving 10 mg of benzoyl hydrazide, mp 111—112.5°. IR ν_{max}^{Nujol} cm^{-1}: 3310, 3220, 1662, 1620, 1570.

4α-Azido-5β-tosyloxytetrahydro-1,2-oxazine-6β-methanol (**16**)——A solution of 300 mg of **14c** and 20 mg of NaOH in 5 ml of MeOH was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was crystallized from EtOH, giving 166 mg of **16** as needles, mp 137—138°. Analytical sample, mp 137.5—138.5°, was obtained as fine leaflets by further recrystallization from EtOH. IR ν_{max}^{Nujol} cm^{-1}: 3280, 3230, 2100, 1360, 1177. *Anal.* Calcd. for $C_{12}H_{16}O_5N_4S$: C, 43.90; H, 4.91; N, 17.07. Found: C, 44.08; H, 4.99; N, 16.93.

2-Benzoyl-6β-acetoxymethyl-4α-amino-5β-mesyloxytetrahydro-1,2-oxazine (**17**)——A mixture of 308 mg of **14d**, 30 mg of 10% Pd–C, and 6 ml of MeOH was stirred and H_2 gas was slowly passed through for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*, leaving 272 mg of **17** as a colorless syrup. This product was dissolved in 2 ml of pyridine and 300 mg of benzoyl chloride was added. The mixture was allowed to stand at room temperature overnight. Working up in the usual manner, 354 mg of a red syrup was obtained. The syrup partly crystallized on standing and recrystallization from EtOH containing a small amount of $CHCl_3$ yielded 128 mg (43% from **14c**) of an N-benzoylated derivative of **17** as fine needles, mp 153.5—155°. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1740, 1660, 1640, 1545, 1380, 1171. *Anal.* Calcd. for $C_{22}H_{24}O_8N_2S$: C, 55.46; H, 5.08; N, 5.88. Found: C, 55.58; H, 5.20; N, 5.72.

Acknowledgement We are indebted to Dr. G. Sunagawa, Director, and Dr. I. Iwai, Assistant Director, of our laboratories for their encouragement and also to Mr. Y. Ohashi for his technical assistance.