identical with the "isatin" **3a** obtained by irradiation of enamide **2a** in the presence of *tert*-butylamine (see above).

Fremy's Salt Oxidation of "Isatins" 3 to Oxoaporphines 4. To a stirred solution of pure "isatins" **3** in pyridine–water (1:1) was added an excess of Fremy's salt[20] in 4% aqueous sodium carbonate. The amount of pyridine was increased if necessary for obtaining an homogeneous solution. Generally the reaction was over after 30–40 h. The mixture was then acidified (pH 5) with 10% HCl and extracted several times with Cl_2CH_2. The combined extracts were washed once with water, dried over anhydrous Na_2SO_4, and then evaporated to dryness. The yellow residue crystallized from EtOH to yield the corresponding oxoaporphines **4** in 65–85% yields.

The oxoaporphines[22] **4a** (oxoglaucine) and **4c** (lysicamine) thus obtained were found to be totally identical (IR, NMR, MS, melting point) with authentic samples of these compounds previously obtained by us.[4]

On the other hand crude, "isatin" **3c** obtained from irradiation of 360 mg of enamide **2c** in the presence of *tert*-butylamine by simple evaporation to dryness was submitted to Fremy's salt oxidation as above. The crude product obtained was purified by preparative TLC (silica gel plates, Cl_2CH_2 + 1% H_2O) to give 46 mg of lysicamine **4c**,[22] mp 210–211 °C (18% overall yield).

Fremy's Salt Oxidation of "Oxindoles" 5 to Oxoaporphines 4. To a stirred solution of crystalline **5a** (100 mg) in 10 mL of pyridine–water (1:1) was added an excess of Fremy's salt in the minimum amount of 4% aqueous sodium carbonate. After 48 h the reaction was quenched by addition of 10% HCl and the mixture was extracted with Cl_2CH_2. Evaporation of the solvent yielded crude oxoglaucine **4a**, which was purified by a short-column chromatography on neutral alumina (Woelm), activity IV, using Cl_2CH_2 + 1% EtOH as eluent. Oxoglaucine[22] **4a**, mp 225–226 °C (EtOH) was obtained in 70% yield.

On the other hand, crude **5b** obtained from irradiation of 20 mg of **2b** in the presence of triethyl amine by simple evaporation to dryness was submitted to Fremy's salt oxidation as above. After the usual workup, dicentrinone[22] **4b**, mp 300 °C dec, was obtained in 20% overall yield.

Under analogous conditions crude **5c** obtained from irradiation of 600 mg of enamide **2c** gave 114 mg (27.1% overall yield) of lysicamine[22] **4c**, mp 210–211 °C.

Hydrogen Peroxide Oxidation of "Isatin" 3a to Oxoglaucine 4a. A 50-mg sample of "isatin" **3a** was dissolved in 10 mL of hot dioxane and 6 mL of 10% NaOH. To this stirred yellow solution was added 6 mL of 3% hydrogen peroxide dropwise. The mixture was kept with stirring until an aliquot showed the disappearance of starting material (3 h). The solution was diluted with water and then extracted with Cl_2CH_2 several times. The combined extracts were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent yielded crude oxoglaucine **4a**, which crystallized from EtOH, mp 225–226 °C (43% yield).

Acknowledgment. We acknowledge the Comisiôn Asesora (Spain) for its financial support.

Registry No. 1a, 41823-67-0; **1b**, 80041-80-1; **1c**, 80041-81-2; **2a**, 80041-82-3; **2b**, 80041-83-4; **2c**, 80041-84-5; **3a**, 78178-94-6; **3c**, 64938-92-7; **4a**, 5574-24-3; **4b**, 16408-78-9; **4c**, 15444-20-9; **5a**, 80041-85-6; **5b**, 80041-86-7; **5c**, 80041-87-8; **6a**, 80041-88-9; oxalyl chloride, 79-37-8; dehydroglaucine, 22212-26-6.

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Unusual Reaction of *N*-Hydroxyphthalimido Ethers Leading to Oxygen–Nitrogen Heterocycles[1]

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Received November 14, 1980

Treatment of *N*-[(2,3-epoxypropyl)oxy]phthalimide (**1**) with alcohols under basic catalysis yields a new 3-[*o*-(carbomethoxy)phenyl]-5-(hydroxymethyl)-6*H*-1,4,2-dioxazine (**4a**) compound, whose structure was determined by X-ray crystallography. Similarly, the behavior of the higher [(epoxybutyl)oxy]phthalimide (**13**) and [(epoxypentyl)oxy]phthalimide (**18**) derivatives were investigated and compared to that of their *N*-[(3-halo-2-hydroxyalkyl)oxy]phthalimides. Formation of **4a**, *N*-[*o*-(carbomethoxy)benzoyl]-3-(hydroxymethyl)isoxazolidine (**15**), *N*-[*o*-(carbomethoxy)benzoyl]-4-hydroxy-1,2-oxazepine (**19**), and *N*-[*o*-(carbomethoxy)benzoyl]-3-(hydroxymethyl)-1,2-oxazine (**20**) from the corresponding epoxides **1**, **13**, and **18** is discussed in the light of Baldwin's rules.

During our studies relating to the synthesis of oximinopropanol derivatives[2] with β-adrenergic blocking activity[3] we considered hydroxyphthalimido ethers as possible synthons for the preparation of 3-(aminooxy)-2-hydroxypropanamine derivatives **7**.

Treatment of epoxy derivative **1**, readily available from *N*-hydroxyphthalimide and epibromohydrin, with an excess of *tert*-butylamine in MeOH failed to give the expected amino alcohol **3**. Instead, compound **4a** was formed in excellent yield in a few minutes. The ^1H NMR spectra of **4a** lacked a *tert*-butyl group but contained a methyl peak indicative of a methyl ester. The presence of an ester was further confirmed by a 1715-cm^{-1} absorption band in the IR spectrum. Additionally, the IR spectrum showed an OH function at 3400 cm^{-1}. The elemental analysis and mass spectral analysis of this material indicated a composition of $C_{12}H_{13}NO_5$, which could correspond to struc-

* G.L. and N.A., Institute de Pharmacologie; A.C., Laboratoire de Chimie Analytique.

(1) A preliminary communication of this work was presented at the 3rd IUPAC Symposium, Madison, WI, June 1980. This work forms part of a thesis for the degree of Doctorat ès-Sciences to be submitted by N.A. to the University Louis Pasteur, Strasbourg.
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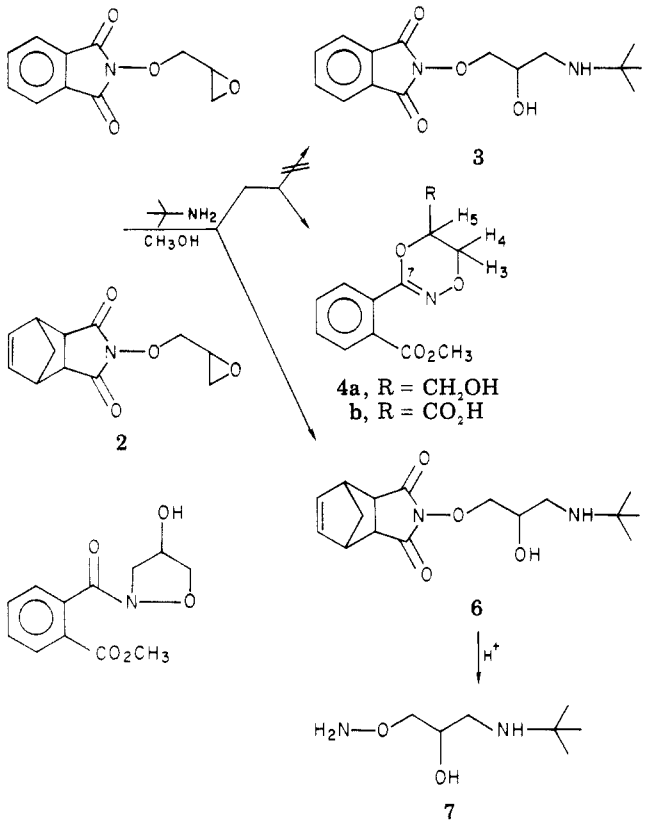
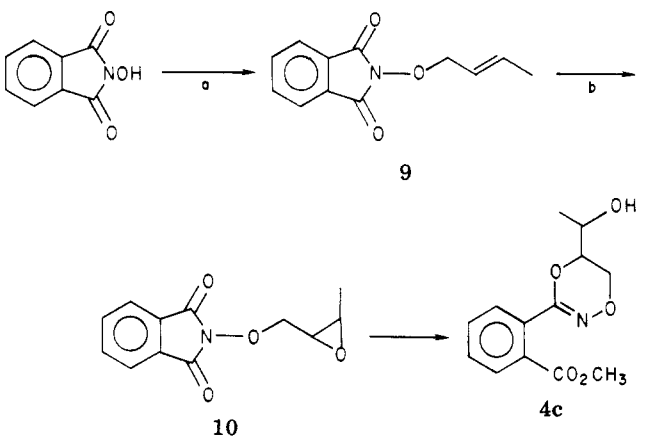
0022-3263/82/1947-0517$01.25/0

Scheme I



Scheme II



(a) NEt_3, DMF; (b) *m*-chloroperbenzoic acid, $CHCl_3$.

Scheme III

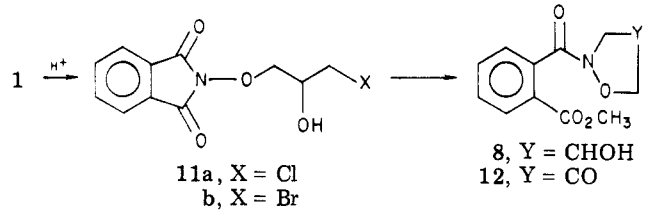
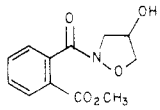
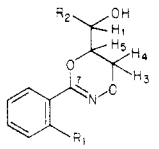


Table I. ^1H NMR Data for Compounds 4a,c,d and 8

compd no.[a]	structure and chemical shifts
	
8	δ_{CH_2} ~4.02 (m, 2 H), δ_{CH_2} ~4.26 (m, 2 H), δ_{CH_2} ~4.76 (m, 1 H)
	
4c (R_1 = CO_2CH_3, R_2 = CH_3)	δ_1 ~4.07 ($^3J_{1,CH_3}$ ≈ 6.5 Hz, $^3J_{1,5}$ ≈ 4 Hz), δ_{3or4} ~4.14 (1 H, $^2J_{3,4}$ ≈ 12.5 Hz, $^3J_{3,4,or5}$ ≈ 9 Hz), $\delta_{3,4,or5}$ ~4.35 (m, 2 H)
4d (R_1 = H, R_2 = H_2)	$\delta_{1,2}$ ~3.95 ($^2J_{1,2}$ ≈ 11.5 Hz, $^3J_{2,5}$ ≈ $^3J_{1,5}$ ≈ 5 Hz), δ_4 ~4.03, δ_3 ~4.26 ($^2J_{3,4}$ ≈ 11.5 Hz, $^3J_{3,5}$ ≈ 3 Hz, $^3J_{4,5}$ ≈ 6.5 Hz), δ_5 ~4.56 (m, 2 H), δ_{OH} ~2.06 (m, 1 H)
4a (R_1 = CO_2CH_3, R_2 = H_2)	$\delta_{1,2}$ ~3.86 ($^2J_{1,2}$ ≈ 12 Hz, $^3J_{2,5}$ ≈ $^3J_{1,5}$ ≈ 5 Hz), δ_4 ~4.06, δ_3 ~4.21 ($^2J_{3,4}$ ≈ 12 Hz, $^3J_{4,5}$ ≈ 6 Hz, $^3J_{3,5}$ ≈ 3 Hz, δ_5 ~4.52 (m, 1 H), δ_{OH} ~2.83 (t, J ≈ 6 Hz)

[a] All spectra were recorded at 250 MHz in $CDCl_3$. Values are in parts per million (δ).

tures **4a** or **8** (Scheme I). The mass spectrum of **4a** gave a parent peak at *m/e* 251 with major fragment ions at *m/e* 220, 163, and 149. The *m/e* fragment at 163 ($ArCO^+$) seemed to support[4] structure **8**, although phenyldioxazine derivatives can also give the same ion. The NMR spectrum of **4a**, when recorded at 250 MHz, revealed a hydroxyl group appearing as a triplet. Coupling constants measured on the AB portion were in agreement with the sequence HO–CH_2–CH–CH_2 (See Table I). It was anticipated that the C_7 carbon atom would appear as a doublet in the ^{13}C NMR due to coupling with H_5 (see Table II). However, it was observed as a complex multiplet because of additional coupling with H_3, H_4, and aromatic protons[5].

Attempted oxidation of **4a** to the corresponding aldehyde could not be achieved with a wide variety of reagents, Me_2SO–Ac_2O,[6] Me_2SO–TFAA,[7] Me_2SO–$Na_2Cr_2O_7$,[8] Me_2SO–$(COCl)_2$,[9] Me_2SO–DCC,[10] CrO_3–pyridine,[11] PCC–CH_2Cl_2,[12] PDC–CH_2Cl_2,[13] DMS–NCS,[14] and MnO_2,[15] and the Oppenauer and Kornblum methods.[16,17] Similar problems were reported during the oxidation of tetrahydrofurfuryl alcohol itself.[18] Oxidation of **4a** with pyridinium dichromate (PDC) in DMF[13] led to the acid **4b** with a 50% yield. The NMR spectrum showed an OH-exchangeable group at 11.5 ppm indicative of a CO_2H function. IR (KBr) confirmed this carboxylic function by a CO absorption at 1720 cm^{-1}. The formation of **4b** provided a basis for the assignment of a structure to **4a**. A

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(5) We thank a referee who suggested a possible distinction between **7** and **8** based on the existence of a 1,4-coupling for the C_7 in the ^{13}C NMR.

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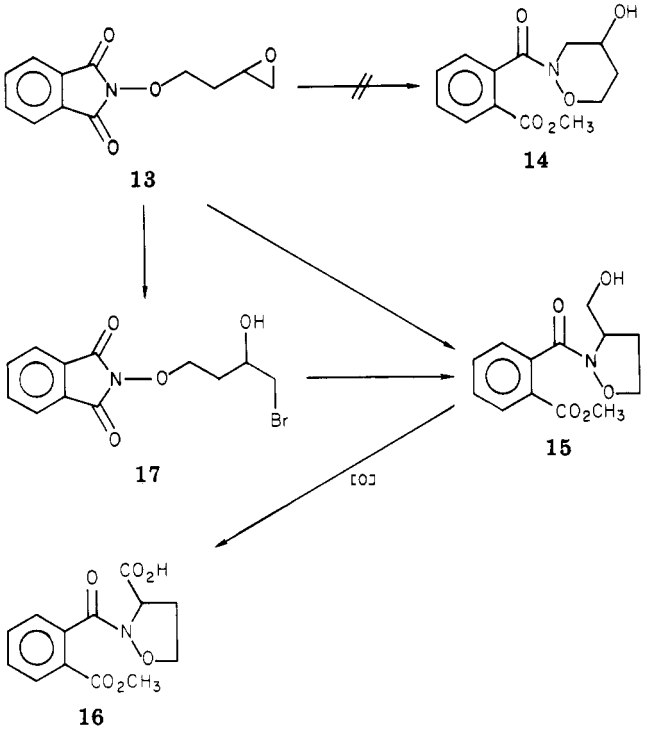
Table II. ^{13}C NMR Data for Compounds 4a,c,d and 8

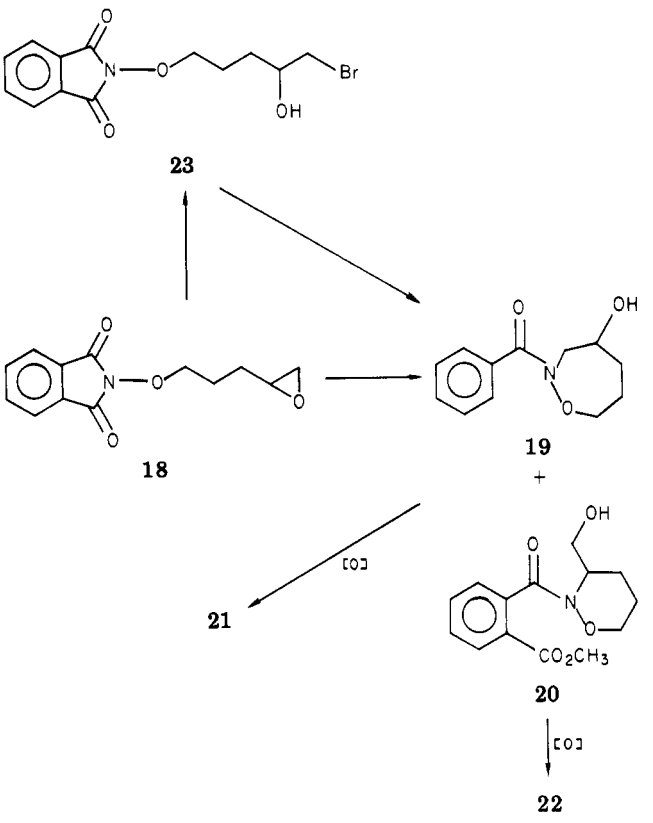
compd	shift, δ							
	CH_3 (ester)	CH_2N	CH_2O	COH	CH	C=N	CON	CO (ester)
8[a]	52.7	53.8	77.0	72.7			137.3	166.8
4c[b]	52.4		66.7	78.2	63.4	156.5		167.5
4d[c]			61.4	64.9	74.3	154.8		
4a[d]	52.5		61.1	64.3	75.0	156.4		167.6

[a] Spectrum recorded at 90 MHz with CD_2Cl_2 as the solvent. [b] Assignments of peaks are in agreement with the shifts observed in the spectrum of the *C*-methyl-substituted compound. [c] Spectrum recorded at 90 MHz with $CDCl_3$ as the solvent. [d] Spectrum recorded at 250 MHz with $CDCl_3$ as the solvent.

Scheme IV



Scheme V



definite proof was obtained by an X-ray determination (see Experimental Section).

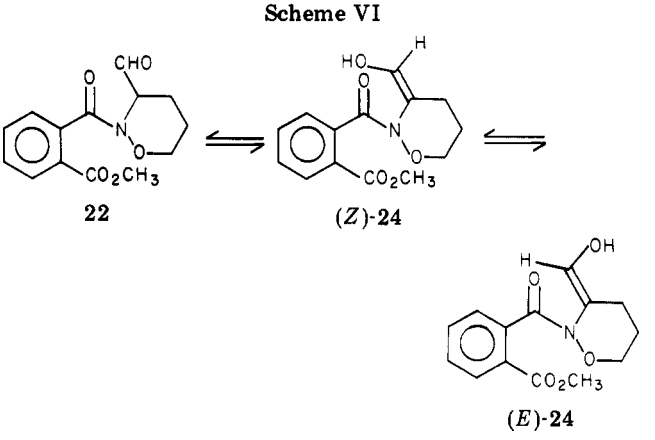
The potential interest of these heterocycles led us to examine this cyclization further to examine the generality and effect of structural changes. When compound **10** (Scheme II) was treated under conditions similar to those for **1**, the dioxazine **4c** was obtained (see Table I). This observation is in better accordance with the formation of **4a** from **1**, since a methyl group on the epoxide function might have prevented the formation of a 1,4,2-dioxazine ring. From the value of the **4c** coupling constant $^3J_{1,5}$ = 4 Hz (θ = 45°), it was concluded that **4c** had the erythro configuration.

The isoxazolidine **8** was obtained from the halohydrins **11a** and **11b** by treatment with an amine equivalent (Scheme III). The IR spectrum of **8** showed a CO absorption for ester at 1710 cm^{-1}, a CO absorption at 1630 cm^{-1} attributable to a hydroxamate function, and a OH band at 3400 cm^{-1}. Oxidation of **8** with PDC in refluxing CH_2Cl_2[13] gave **12** as shown by the appearance of a 4 H singlet (NCH_2 and OCH_2) in the NMR spectrum at 4.15 ppm. Results obtained with the epoxide derivative **13** are summarized in Scheme IV.

When **13** was dissolved in MeOH containing a catalytic amount of amine, a quantitative yield of compound was readily formed. **14** or **15** were both possible structures for this compound. The 250-MHz NMR spectrum did not allow us to distinguish between the sequence NCH_2–CH(OH)–CH_2 and N–CH–CH_2OH. Treatment of **15** with the same reagents as those used for the attempted oxidation of **4a** into the corresponding aldehyde also proved unsuccessful. However, the acid **16** could be obtained by using PDC in DMF,[13] as indicated by its IR, NMR, and mass spectra. When the epibromohydrin **17**, prepared from the epoxide **13**, was treated with 1 equiv of amine in MeOH, the same compound, **15**, was obtained.

When the epoxide **18** was used, it gave a 1:1 mixture of **19** and **20** (Scheme V) which could be separated by silica

Scheme VI

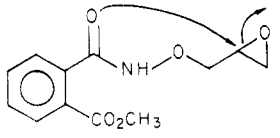


gel column chromatography.

As expected, the oxidation of **19** and **20** gave ketone and aldehyde derivatives **21** and **22**, respectively. Treatment of **23** prepared from **18** with 1 equiv of amine in MeOH led to **19** and **20** in the same 1:1 ratio. The aldehyde **22** (Scheme VI) exists in $CDCl_3$ solution as a 1:3 mixture of aldehyde and enols. The enol appears in the NMR spectrum as a doublet centered at 5.60 ppm (J = 6 Hz). Addition of D_2O to the solution results in a rapid exchange of the 5.55-ppm signal. The IR spectrum showed absorptions at 3440 cm^{-1}, thus confirming the presence of the enolic form **24**. The 40-cm^{-1} bathochromic shift of the **24** amide bond with respect to that for **20** confirms the existence of the presence of hydrogen bonding with the hydroxylic proton.

Discussion

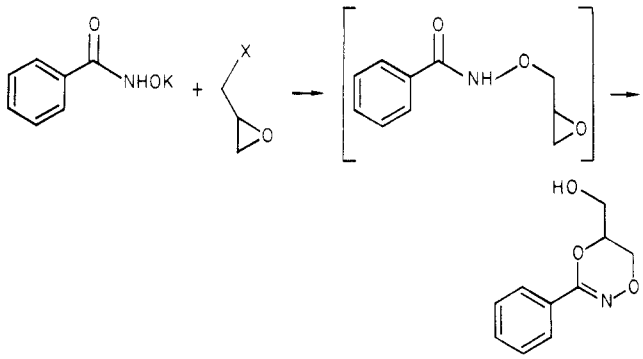
The reactions described are the first example of the opening of a phthalimido ether derivative by MeOH in the presence of an amine. When phthalimido ethers bearing an epoxide ring in the side chain were used, only a catalytic amount of base was required. Halohydrin derivatives, however, took up 1 equiv of amine. The fact that *tert*-butylamine was not incorporated cannot be accounted for by its bulkiness since ethylamine and methylamine gave the same results. It became evident that the initial step was the breakage of the CO–N bond, which is weakened by both the conjugation with the aromatic nucleus and the presence of the adjacent oxygen atom. This was confirmed by treatment of *N*-(2,3-epoxypropyl)phthalimide under the same conditions which gave rise to the opening of the epoxide ring. Norbornene ether **2** reacted as expected to give the aminohydroxypropanamine derivative **6** which was subsequently converted to **7** (Scheme I). This demonstrated the utility of norbornene ethers rather than phthalimido ethers when ring-opening reactions are to be avoided. The use of Amberlite (OH^- form) as a basic catalyst proved to be particularly suitable for the study of such a reaction, as under these conditions the reaction was slower and could be monitored by TLC. Furthermore, the simple removal of the resin by filtration allowed the isolation of the intermediate **25** in a pure form. When various amines (*tert*-butylamine isopropylamine, tetramethylguanidine) were employed, **25** was always contaminated by the final product **4a**.



25

The intermediate **25** was fully characterized by IR and NMR spectra. This *O*-alkyl benzohydroxamate derivative could then be made to collapse by intramolecular attack of the epoxide either by nitrogen or oxygen. Baldwin's rules[19] gave a rationale for the opening of epoxide derivatives which proceed by an exo-type mechanism. In the case of **25**, a preferential 4-exo attack by nitrogen could be predicted. In fact, we observed a 6-exo ring opening by oxygen on the more hindered side of the epoxide although an oxygen atom is presumably a less potent nucleophile than nitrogen. The oxygen attack seemed unlikely in as much as the reaction was carried out in alcohol and in the absence of Ag^+ ions, known to favor O-alkylation.[20] Nevertheless, 6-endo ring openings have been

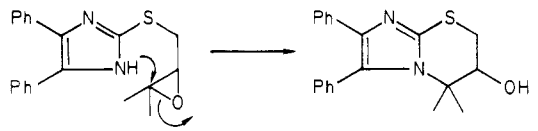
Scheme VII[a]



4d

[a] X = Cl, Br.

reported in the literature. Thus Alper et al.[21] described the synthesis of a tetrahydropyrimido[1,2-*a*]benzimidazole arising by a nucleophilic attack of nitrogen on an epoxide ring, disfavored by Baldwin's rules. Similarly, the 5,5-dimethyl-6-hydroxy-2,3-diphenyl-7*H*-imidazo[2,1-*b*][1,3]-thiazine was obtained by a 6-endo reaction, in spite of the presence of a *gem*-dimethyl-substituted epoxide.[22]



Additional examples of reactions which do not obey Baldwin's rules can be found in the literature.[23-25]

Furthermore, it was shown that changes in experimental conditions modified the manner of opening.[26,27] The formation of **8** from the bromohydrin derivative **11** obeyed a 5-exo(tet) process; in fact, under our experimental conditions we have shown that the reaction proceeded through the intermediacy of **25** which afforded **8** by an unfavored 5-endo process. Bromohydrin **17** was converted to epoxide **13** before its transformation into **15** by a favored 5-exo process. The epoxide **18** or the bromohydrin derivative **23** gave a 1:1 mixture of **19** and **20** by an unfavored 7-endo and a favored 6-exo process, respectively. The formation of **19** (45% yield) was surprising since the opening of the epoxide obeyed a 7-endo process which was not discussed by Baldwin. To the best of our knowledge, such 7-endo ring opening has not been reported in the literature. Johnson et al.[28] reported the formation of N-benzoylisoxazolidine and 3-phenyl-5*H*-1,4,2-dioxazine from 1,3-dibromopropane and 1,2-dibromoethane, respectively, by reaction with potassium benzohydroxamate. We have shown that potassium benzohydroxamate in $MeOH/H_2O$ reacted with epichlorohydrin or epibromohydrin to give the methylenehydroxydioxazine **4d** probably through the intermediacy of an epoxide not isolated under the reaction conditions used (Scheme VII).

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In conclusion, this work describes an efficient intramolecular ring opening of phthalimido ether epoxides into the isoxazolidine 8 and 1,4,2-dioxazine **4a**. Hydrolysis[29] of these heterocycles yields 4-hydroxyisoxazolidine, 3-(hydroxymethyl)isoxazolidine, 3-(hydroxymethyl)-1,2-oxazine, and 4-hydroxy-1,2-oxazepine, compounds which are difficult to prepare[30] and have not previously been reported. The mechanism by which these heterocycles were obtained did not necessarily follow Baldwin's rules, which are to be applied with caution when functionalized heterocycles are involved. The biological activity of these heterocycles is currently under investigation.

Experimental Section

Melting points were determined on a Koffler hot bench. IR spectra were determined in $CHCl_3$ on a Beckman IR-33 spectrometer. Analyses were performed by the Service central de microanalyses du CNRS. Mass spectra were recorded on a LKB 2009.

Routine NMR spectra were recorded on either a Perkin-Elmer R24-B or on a multispin Bruker WH-90 at 90 MHz or at 250 MHz on a Cameca 250.

Chemical shifts in the ^1H NMR spectra were measured relative to internal Me_4Si. Chemical shifts in the ^{13}C NMR spectra were measured relative to the central peak of the solvent, either CD_2Cl_2 or $CDCl_3$.

***N*-[(2,3-Epoxypropyl)oxy]phthalimide (1).** Epibromohydrin (1.06 g, 7 mmol) was added dropwise to a stirred solution of *N*-hydroxyphthalimide (1 g, 6 mmol) and triethylamide (1.7 mL, 12 mmol) in anhydrous DMF (5 mL). After 12 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The epoxy derivative 1 obtained (0.8 g) was purified by silica gel column chromatography with $CHCl_3$/EtOAc (8:2) as the eluent; 0.46 g (35% yield). Recrystallization from absolute EtOH gave white crystals: mp 150–152 °C; IR 1730, 1790 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 2.5–2.9 (m, 2 H, CH_2 oxirane), 3.3–3.65 (m, 1 H, methine proton), 3.9–4.6 (m, 2 H, CH_2O). Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.38. Found: C, 60.26; H, 4.08; N, 6.44.

***N*-[(2,3-Epoxypropyl)oxy]norbornene-2,3-dicarboximide (2).** Epibromohydrin (0.23 mL, 2.8 mmol) was added dropwise to a stirred solution of *N*-hydroxy-5-norbornene-2,3-dicarboximide (0.5 g, 2.8 mmol) and triethylamine (0.78 mL, 5.6 mmol) in anhydrous DMF (2 mL). After 18 h the reaction mixture was diluted with water and extracted with $CHCl_3$. After the usual workup, 0.6 g (91% yield) of practically pure **2** was obtained. It was recrystallized from cyclohexane: mp 95–97 °C; IR 1720, 1780 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 1.4–1.9 (dd, 2 H, CH_2), 2.5–2.9 (m, 2 H, oxirane protons), 3.1–3.5 (m, 5 H), 3.7–4.4 (m, 2 H, CH_2O), 6.1 (s, large, 2 H, CH=CH). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.23; H, 5.60; N, 5.99.

3-[*o*-(Carbomethoxy)phenyl]-5-(hydroxymethyl)-6*H*-1,4,2-dioxazine (4a). Three drops of *tert*-$BuNH_2$ were added with stirring to a solution of **1** (1 g, 45 mmol) in MeOH (10 mL). After 1 h, the solvent was removed under vacuum, and the crystalline residue (1.1 g, 100%) was recrystallized from benzene to give **4a**: mp 95–97 °C; IR 3500 (OH), 1715 (ester), 1610 cm^{-1} (C=N, weak). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.36; H, 5.21; N, 5.57. Found: C, 57.43; H, 5.24; N, 5.54.

X-ray Analysis. The compound crystallized in the triclinic system with a = 7.638 (1), b = 9.151 (1), c = 9.624 (1) Å and α = 84.68 (1), β = 70.35 (1), γ = 68.04 (1)°; space group $P\bar{1}$ with a calculated density of 1.42 g/cm^3. Intensity data were collected on a fully automated Nonius CAD-4 diffractometer by using graphite-monochromated Cu K radiation (1.541 78 Å) and a ω–θ scan (ω/θ = 1). Of the 1991 unique reflections with θ < 65° measured in this fashion, 1731 were observed after correction for Lorentz–polarization effects. The structure was solved by direct methods[31] and electron density synthesis. Besides the expected aromatic ring, a second six-membered ring appeared from Fourier maps. Careful selection of atoms finally yielded the correct structure which is a dioxazine derivative. Block-diagonal-matrix least-squares refinements of nonhydrogen atoms given by anisotropic temperature factors converged to a residual value of 0.093. Further refinements after introduction of the hydrogens in theoretical positions or in positions revealed on difference Fourier maps (140 expected H), and affected by isotropic temperature factors, led to the current minimum residual of 0.079. Additional data are given as supplementary material.

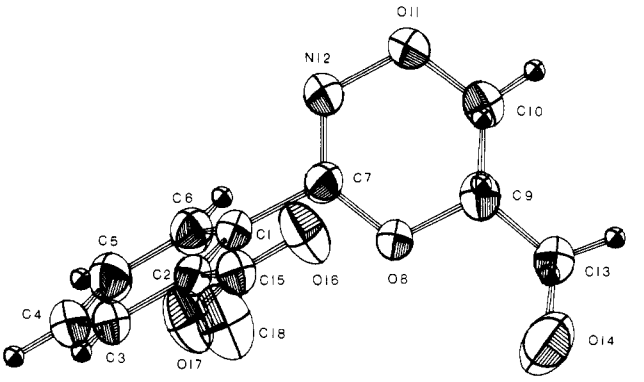

Figure 1. Computer drawing of the calculated conformation of **4a**, with ellipsoids of thermal motion.

Figure 1 is a computer-generated perspective drawing of the final X-ray model.[32] The nonplanar dioxazine ring is shown as a mean plane of atoms [O(7), O(8), N(12), and O(11) with O(9) and C(10), respectively, below (–0.268 (4) Å) and above (0.374 (5) Å)]. Individual bond distances and angles generally agree well with accepted values. The crystalline cohesion is ensured by an hydrogen bond between N(12) and O(14) at 1 + x,y,z and by van der Waals contacts.

3-[*o*-(Carbomethoxy)phenyl]-5-carboxy-6*H*-1,4,2-dioxazine (4b). The alcohol **4a** (2.0 g, 8 mmol) was added to a solution of pyridinium dichromate (12 g, 32 mmol) in 24 mL of DMF. After being stirred at ambient temperature for 9 h, the solution was poured into 100 mL of water and extracted with $CHCl_3$ (3 × 50 mL). The organic phase was washed with 1 N K_2CO_3. The aqueous phase was acidified with 1 N HCl and extracted with $CHCl_3$. Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution gave 1.06 g (50%) of acid: mp 163–164 °C (benzene); IR (KBr) 1720 cm^{-1} (CO_2H); NMR (Me_2SO-d_6) δ 3.85 (s, 3 H, OCH_3), 4.2–4.5 (m, 2 H, CH_2), 4.85–5.1 (m, 1 H, CH), 7.3–7.9 (m, 4 H, Ar). Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.27. Found: C, 54.47; H, 4.28; N, 5.39.

3-[*o*-(Carbomethoxy)phenyl]-5-(1-hydroxyethyl)-1,4,2-dioxazine (4c). Compound **4c** was prepared from **10** as described for the preparation of **4a**: 0.7 g (100%); IR 3500 (OH), 1720 (ester), 1615 cm^{-1} (C=N).

3-Phenyl-5-(hydroxymethyl)-6*H*-1,4,2-dioxazine (4d). A solution of potassium benzohydroxamate (8 g, 46 mmol), epibromohydrin (6.5 g, 4 mL), and anhydrous K_2CO_3 (12.5 g) in MeOH (32 mL) and H_2O (24 mL) was stirred at 45–50 °C for 8 h.

Methanol was then removed at reduced pressure, water was added, and the mixture was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried, and the $CHCl_3$ was evaporated. The crude product (3.6 g) was chromatographed on a silica gel column with EtOAc/hexane (2:8) as the eluent to give methyl benzoate (2.2 g, 36% yield) and then with EtOAc/hexane (5:5) to give the dioxazine **4d**. Purification of **4d** was achieved by recrystallization from benzene: 0.8 g (9% yield); mp 69–71 °C; IR 3400 (OH), 1600 cm^{-1} (C=N). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.24. Found: C, 62.16; H, 5.77; N, 7.34.

***N*-[(3-*tert*-Butyl-2-hydroxypropyl)oxy]-5-norbornene-2,3-dicarboximide (6).** A solution of *N*-[(2,3-epoxypropyl)-

(29) Amlaiky, N.; Leclerc, G., *Synthesis*, in press.
(30) See, for example, the preparation of hexahydro-1,2-oxazepines by rearrangement of piperidine *N*-oxide: Quin, L. D.; Shelburne, F. A. *J. Org. Chem.* **1965**, *30*, 3135.
(31) Germain, G.; Main, P.; Woolfson, M. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274.
(32) Johnson, C. K. Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN, 1965.

oxy]-5-norbornene-2,3-dicarboximide (2; 6.3 g, 26 mmol) and *tert*-butylamine (8.5 mL, 78 mmol) in EtOH (80 mL) was heated at 50 °C for 4 h. The solvent was evaporated to give a yellow oil which was induced to crystallize by scratching: 7 g (87% yield); mp 200–201 °C (hydrochloride salt); IR 1720, 1780 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 1.53 (s, large, 11 H, *tert*-butyl and CH_2N protons) 3.3 (s, large, 6 H), 4.15 (d, 2 H, CH_2O), 4.3–4.6 (s, 1 H, OH). Anal. Calcd for $C_{16}H_{25}N_2O_4Cl$: C, 55.72; H, 7.30; N, 8.12. Found: C, 55.74; H, 7.22; N, 828.

3-(Aminooxy)-*N*-*tert*-butyl-2-hydroxypropanamine (7). A solution of **6** (0.65 g, 2 mmol) and hydrazine hydrate (0.1 g, 2 mmol) in 95% EtOH (3 mL) was heated under reflux for 20 min. The solvent was evaporated, and the crude mixture was (0.7 g) chromatographed on a silica gel column with EtOAc as the eluent to give the *N*-amino-5-norbornene-2,3-dicarboximide (0.33 g, 88% yield) and then with EtOAc/MeOH/$NHEt_2$ (8:1.5:0.5) to give the oxy amine **7**: 0.27 g (80% yield); mp 150–151 °C (oxalate salt). Anal. Calcd for $C_9H_{20}N_2O_6{\cdot}H_2O$: C, 40.0; H, 8.20; N, 10.36. Found: C, 40.35; H, 8.63; N, 11.05.

***N*-[*o*-(Carbomethoxy)benzoyl]-4-hydroxyisoxazolidine (8).** A solution of *N*-[(3-bromo-2-hydroxypropyl)oxy]phthalimide (0.5 g, 1.6 mmol) and *tert*-butylamine (0.13 g, 1.8 mmol) in MeOH (4 mL) was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and the residue was taken up to 10% aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined $CHCl_3$ solutions were dried over $MgSO_4$ and evaporated (0.5 g, ~100% yield). Recrystallization from benzene gave pure **8**: mp 112–114 °C; IR 3500 (OH), 1710 (ester), 1640 cm^{-1} (CO–N–O). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.36; H, 5.21; N, 5.57. Found: C, 57.22; H, 5.17; N, 5.67.

***N*-(2-Butenoxy)phthalimide (9).** A stirred solution of *N*-hydroxyphthalimide (5 g, 30.6 mmol), 1-chloro-2-butene (3 mL, 30.6 mmol), and triethylamine (8.5 mL, 60 mmol) in anhydrous DMF was heated to 70 °C for 3 h. Water was added, and the mixture was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water and brine, dried, and evaporated to give **9**, 5.9 g (88% yield). The product was recrystallized from cyclohexane: mp 115–116 °C; IR 1730, 1790 cm^{-1} (CO–N–CO), 1675 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.5–1.8 (m, 3 H, CH_3), 4.4–4.8 (m, 2 H, CH_2O), 5.6–6.0 (m, 2 H, CH=CH). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.44. Found: C, 66.29; H, 5.08; N, 6.29.

***N*-(2,3-Epoxy-3-methylbutoxy)phthalimide (10).** A solution of *N*-(2-butenoxy)phthalimide (**9**; 4.2 g, 19.3 mmol) and *m*-chloroperbenzoic acid (4.3 g, 25 mmol) in $CHCl_3$ (20 mL) was heated under reflux for 4 h. The $CHCl_3$ solution was washed successively with 10% aqueous Na_2SO_3, 10% aqueous $NaHCO_3$, and H_2O and then dried over $MgSO_4$. The crude product obtained (5.4 g) after evaporation of the solvent was chromatographed on a silica gel column with EtOAc/hexane (6:4) as the eluent to give **10** (3.9 g, 86% yield) which was recrystallized from cyclohexane: mp 93–94 °C; IR 1730, 1790 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 1.3 (d, 3 H, CH_3), 2.6–3.3 (m, 2 H, oxirane protons), 4.1–4.4 (m, 2 H, CH_2O). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.79; H, 4.75; N, 6.0. Found: C, 61.60; H, 4.73; N, 6.1.

***N*-[(3-Chloro-2-hydroxypropyl)oxy]phthalimide (11a).** HCl (10 drops) added with stirring to a solution of **1** (0.8 g, 36 mmol) in $CHCl_3$ (10 mL). After 1 h water was added, and the organic phase was separated, dried over $MgSO_4$, and evaporated to dryness. Recrystallization from benzene gave *N*-[(3-chloro-2-hydroxypropyl)oxy]phthalimide: 0.9 g (~100% yield); mp 111–113 °C; IR 1730, 1790 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 3.5–3.8 (m, 2 H, CH_2Cl), 4.1 (m, 1 H, CH), 4.1–4.4 (m, 2 H, CH_2O). Anal. Calcd for $C_{11}H_{10}NO_4Cl$: C, 51.67; H, 3.94; N, 5.47. Found: C, 51.80; H, 3.84; N, 5.56. *N*-[(3-Bromo-2-hydroxypropyl)oxy]phthalimide (**11b**) was similarly prepared: mp 85–86 °C; ^1H NMR ($CDCl_3$) δ 3.3–3.6 (m, 2 H, CHBr), 4.2–4.5 (m, 2 H, CH_2O). Anal. Calcd for $C_{11}H_{10}NO_4Br$: C, 44.02; H, 3.35; N, 4.66. Found: C, 44.16; H, 3.20; N, 4.6.

***N*-[*o*-(Carbomethoxy)benzoyl]-4-oxoisoxazolidine (12).** Ketone **12** was prepared by the addition of **8** (0.5 g, 2 mmol) in one portion to a solution of pyridinium dichromate (3 g, 7.9 mmol) in CH_2Cl_2 (6 mL) at room temperature. The solution was refluxed for 15 h, cooled, diluted with diethyl ether, filtered on Celite, dried over $MgSO_4$, and concentrated under reduced pressure to give the ketone: 225 mg (45% yield); mp 126–127 °C (CCl_4); IR 1775 (ester), 1715 cm^{-1} (CO, ketone), 1665 cm^{-1} (CO–N); ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H, CH_3), 4.15 (s, 4 H, NCH_2, OCH_2). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.61. Found: C, 57.9; H, 4.52; N, 5.7.

***N*-[(3,4-Epoxybutyl)oxy]phthalimide (13).** A solution of *N*-(3-butenoxy)phthalimide (10 g, 46 mmol) prepared by the method of Grochowski and Jurczak[33] and *m*-chloroperbenzoic acid (10.32 g, 60 mmol) in CH_2Cl_2 (250 mL) was heated under reflux for 4 h. The CH_2Cl_2 solution was washed successively with 10% aqueous Na_2SO_3, 10% aqueous $NaHCO_3$, and H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to leave **13**: 10.9 g (98% yield); mp 74–75 °C; IR 1730, 1790 cm^{-1} (CO–N–CO); ^1H NMR ($CDCl_3$) δ 1.95–2.2 (m, 2 H, CH_2CH), 2.65–3.0 (m, 2 H, CH_2O), 3.15–3.4 (m, 1 H, CHO). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.0. Found: C, 61.84; H, 4.70; N, 6.14.

***N*-[*o*-(Carbomethoxy)benzoyl]-3-(hydroxymethyl)isoxazolidine (15).** Compound **15** was prepared from **13** via **14** as described for the preparation of **4a**: 1.6 g (~100% yield); IR 3400 (OH), 1720 (ester), 1630 cm^{-1} (CON).

***N*-[*o*-(Carbomethoxy)benzoyl]-3-carboxyisoxazolidine (16).** Compound **16** was prepared from alcohol **15** according to the method of Corey and Schmidt:[13] 100 mg (36% yield); IR 1730 (ester), 1730 (acid), 1650 cm^{-1} (CON); ^1H NMR ($CDCl_3$) δ 2.3–3.2 (m, 4 H, CH_2CH_2), 3.85 (s, 3 H, CH_3), 3.7–5.3 (m, 1 H, CH).

***N*-[(4-Bromo-3-hydroxybutyl)oxy]phthalimide (17).** Compound **17** was prepared from **13** as described for the preparation of **11b**; mp 89–90 °C. Anal. Calcd for $C_{12}H_{12}NO_4Br$: C, 45.88; H, 3.85; N, 4.45. Found: C, 46.01; H, 3.84; N, 4.64.

***N*-(4,5-Epoxypentyloxy)phthalimide (18).** This was prepared from 1-bromo-4-pentene and *N*-hydroxyphthalimide, followed by epoxidation (87% overall yield) as described for **13**; mp 114–115 °C.

***N*-[*o*-(Carbomethoxy)benzoyl]-4-hydroxy-1,2-oxazepine (19) and *N*-[*o*-(Carbomethoxy)benzoyl]-3-(hydroxymethyl)-1,2-oxazine (20).** Compounds **19** and **20** were prepared from **18** as described for the preparation of **4a**. Separation was carried out by silica gel column chromatography with ethyl acetate as the eluent. For **19**: 900 mg (45% yield); mp 133–134 °C. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.13; N, 5.01. Found: C, 60.18; H, 6.12; N, 5.15. For **20**: 900 mg (45% yield); oil.

***N*-[*o*-(Carbomethoxy)benzoyl]-4-oxo-1,2-oxazepine (21).** The alcohol **19** (0.86 g, 3.1 mmol) was oxidized with chromium trioxide and pyridine in methylene chloride according to the procedure of Ratcliffe and Rodehorst.[11] The crude product was recrystallized from benzene, giving pure **21**: 0.7 g (80% yield); mp 148–149 °C; IR 1730 (ester), 1670 (CO, ketone), 1670 cm^{-1} (CO–N). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.7; H, 5.48; N, 5.01.

***N*-[*o*-(Carbomethoxy)benzoyl]-3-formyl-1,2-oxazine (22).** This was prepared as for **21**: 500 mg (60% yield); IR 3440 (OH), 1735 (ester), 1695 (aldehyde), 1690 cm^{-1} (CO–N); ^1H NMR ($CDCl_3$) δ 2.0–2.9 (m, 4 H, CH_2CH_2), 3.7–4.3 (m, 5 H, OCH_2, OCH_3), 5.6 (d, J = 6 Hz), 9.55 (s). The integration value of the signals at 9.55–5.6 ppm corresponds to a single H.

***N*-[(5-Bromo-4-hydroxypentyl)oxy]phthalimide (23).** Compound **23** was prepared from **18** as described for the preparation of **11b**: ~100% yield; mp 68–69 °C.

2,3-Epoxypropyl *o*-(Carbomethoxy)benzohydroxamate (25). Epoxide **1** (100 mg) suspended in MeOH (3 mL) was treated with Amberlite (OH^- form, approximately 100 mg) for a few minutes and filtered. Formation of an intermediate during the reaction was monitored by TLC. After evaporation of the MeOH, the NMR and IR spectra were recorded: IR 3240 (NH), 1720 (ester), 1670 cm^{-1} (CONH); ^1H NMR ($CDCl_3$) δ 2.5–2.9 (m, 2 H, CH_2 oxirane), 3.1–3.5 (m, 1 H, methine proton), 3.85 (s, 3 H, OCH_3), 3.9–4.5 (m, 2 H, CH_2O).

Acknowledgment. We express our gratitude to Drs. J. P. Kintzinger, A. Solladié, and E. Krempp for helpful discussions of the NMR data. We thank Dr. J. D. Ehrhardt for the mass spectra.

Registry No. **1**, 80041-90-3; **2**, 80041-91-4; **4a**, 80041-92-5; **4b**, 80041-93-6; **4c**, 80041-94-7; **4d**, 80041-95-8; **6**, 80041-96-9; **6**·HCl,

(33) Grochowski, E.; Jurczak, J. *Synthesis* **1976**, 682.

80041-97-0; **7**, 67435-25-0; **7** oxalate, 80041-98-1; **8**, 80041-99-2; **9**, 38945-22-1; **10**, 80042-00-8; **11a**, 80042-01-9; **11b**, 80042-02-0; **12**, 80042-03-1; **13**, 80042-04-2; **15**, 80042-05-3; **16**, 80042-06-4; **17**, 80042-07-5; **18**, 80042-08-6; **19**, 80042-09-7; **20**, 80042-10-0; **21**, 80042-11-1; **22**, 80042-12-2; **23**, 80042-13-3; (*E*)-**24**, 80042-15-5; (*Z*)-**24**, 80042-16-6; **25**, 80042-14-4; epibromohydrin, 3132-64-7; *N*-hydroxyphthalimide, 524-38-9; *N*-hydroxy-5-norborene-2,3-dicarboximide, 21715-90-2; *tert*-butyl amine, 75-64-9; potassium benzohydroxamate, 32685-16-8; *N*-amino-5-norbornene-2,3-dicarboximide, 4180-86-3; 1-chloro-2-butene, 591-97-9; *N*-(3-butenoxy)phthalimide, 80042-17-7; 1-bromo-4-pentene, 1119-51-3.

Supplementary Material Available: Tables III–VI containing fractional coordinates, anisotropic thermal parameters, bond lengths and bond angles for **4a** (4 pages). Ordering information is given on any current masthead page.

Acyl Nitrene Cyclizations in Antibiotics. Synthesis of 6″-Aminogentamicin C_2†

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Received June 23, 1981

The insertion reaction of an acyl nitrene has been used to functionalize the branched-chain sugar moiety, garosamine, of the antibiotic gentamicin C_2. Contrary to expectations based on intermolecular reactions in simple systems, insertion into the branched-chain methyl group was found to be competitive with insertion into the neighboring methylene group. A new approach is described for the preparation of azidocarbonates from hindered alcohols. The first example of the insertion of an acyl nitrene into a carbamate is described.

As part of a program directed toward the modification of aminocyclitol antibiotics[1,2] it was considered desirable to develop a method to functionalize the branched-chain methyl group of the garosamine moiety of gentamicin C_2 (**1**, Chart I). Our previous success in functionalizing the 4-α-methyl group of 3-β-lanostenol via nitrene insertion reactions[3] led us to explore the chemistry of the 4-oxycarbonyl nitrene species **2** with the ultimate intention of introducing an extra amino group into the gentamicin molecule.

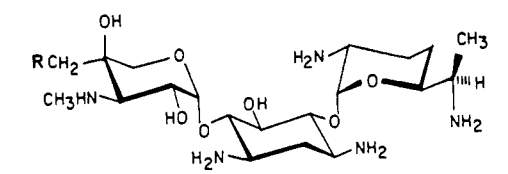
A number of competing reaction pathways were possible in principle, including insertion into the C–H bonds at C-2 and C-5 as well as the desired insertion into the *C*-methyl group.

Two factors suggested that unwelcome insertion into C-5 might predominate over insertion into the *C*-methyl group. First was the greater reactivity of secondary compared to primary hydrogen toward nitrenes. This preference has been shown to be approximately tenfold in the thermolytic reactions of ethyl azidoformate with 2-methylbutane.[4] Second, it has been amply demonstrated in intermolecular reactions that ether oxygens promote insertion of nitrenes into the C–H bonds α to the oxygen atom. This has been explained in terms of a hydrogen extraction–recombination process involving radicals or the intermediacy of an O–N ylide intermediate, **3**.[5] A priori the ring oxygen of **2** is suitably disposed to influence the course of reaction of the generated nitrene, possibly involving the ylide intermediate **3**.

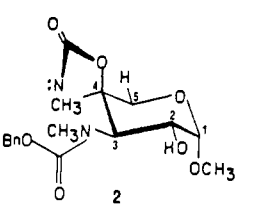
However, we[3] and others[6] have shown that in *intra*molecular reactions of this type, conformational factors are of primary importance. Our prediction that, in the present case, insertion into the methyl group would be competitive with insertion at C-5 has been realized.

Preliminary studies were conducted on methyl β-garosaminide obtained from gentamicin by methanolysis and synthesized recently in these laboratories.[7] Methyl 3-*N*-(benzyloxycarbonyl)-β-garosaminide **4** was benzoylated in pyridine to give **5** in high yield. The lack of reactivity

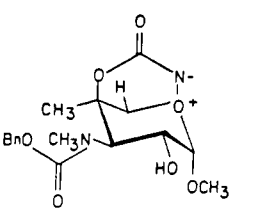
Chart I



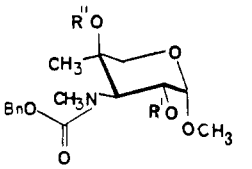
1 R = H
28 R = NH_2



2



3



4	R′ = H	R″ = H
5	R′ = COC_6H_5	R″ = H
6	R′ = H	R″ = $CONHNH_2$
7	R′ = COC_6H_5	R″ = $CONHSO_2Tol$
8	R′ = COC_6H_5	R″ = $CONCH_3SO_2Tol$
9	R′ = H	R″ = CON_3

of the tertiary hydroxyl group in this molecule is well established[8] and precluded the preparation of an azidocarbonate by standard methods. In our hands neither

† This work was presented at the International Carbohydrate Conference in Sydney, Australia, July 1980.

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0022-3263/82/1947-0523$01.25/0