Preparation of Ethyl 3-Piperidino-3-thioxopropionate (2). Ethyl malonylpiperidine (4.75 g, 23 mmol) was dissolved in toluene (100 mL) and treated with 5.1 g (23 mmol) of P_2S_5. The reaction mixture was stirred at room temperature until the amide had reacted completely (1 h). The solution was filtered, and the filtrate was dried and evaporated to give **2** (4 g, 76%) as an oil: NMR 1.28 (3 H, t), 1.70 (6 H, m), 3.60 (2 H m), 4.02 (2 H, s), 4.20 (2 H, q, overlapping a multiplet at 4.24 (2 H)).

Preparation of 3-(Carboethoxy)-2-thioxopiperidine (4). A solution of 3-(carboethoxy)-2-piperidone (3.0 g, 17.5 mmol) in toluene (100 mL) was treated with (3.9 g, 17.5 mmol) of P_2S_5. The mixture was stirred at room temperature until the starting material had been completely consumed. The toluene was then decanted. The insoluble precipitate was treated with cold 10% NaOH and extracted with ether. The ether and toluene solutions were combined and washed with aqueous NaOH, dried, and evaporated to give an oil. Crystallization from ethanol gave 1.2 g of **4** (36%): mp 113–114 °C; NMR 1.32 (3 H, t), 2.00 (2 H, m), 3.40 (2 H, m), 3.80 (1 H, t), 4.15 (2 H, q), 9.3 (1 H, br s).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.09; H, 7.06; N, 7.45.

Reduction of Compound 2. A. $NaBH_4$ at Basic pH. A solution of **2** (2.0 mmol) in THF was treated with methyl iodide (10.0 mmol) and stirred overnight. Partial precipitation of the salt occurred. The THF was evaporated, and the residue was washed with ether, dissolved in methanol, treated with sodium borohydride, and stirred for 2 h. The basic solution was poured into water, extracted with ether, dried, and evaporated to give an oil (26% yield) identified by NMR as **3** containing <10% of the fully reduced amine.

B. $NaBH_3CN$ at Acidic pH. A solution of 2.0 mmol of **2** in 10 mL of THF was treated with 10.0 mmol of methyl iodide. The solution was stirred overnight and the THF evaporated, leaving a yellow salt. The salt was dried in vacuo, dissolved in absolute ethanol (15 mL) and a trace of bromcresol green indicator was added. Sodium cyanoborohydride (22.0 mmol) was added, resulting in change of the indicator to dark blue. Ethanolic HCl was added dropwise over 1 h to maintain acidity as indicated by the yellow color of the indicator. At this point the solution was acidified to pH 1 and stirred overnight to hydrolyze any amine–borane adduct. The solution was diluted with water and extracted with ether, and the aqueous layer was cooled and carefully brought to pH 9 with cold 10% NaOH solution. Extraction with ether, drying, and evaporation gave a 53% yield of ethyl 3-piperidinopropionate as identified by the NMR spectrum: 1.23 (3 H, t), 1.50 (6 H, m), 2.40 (4 H, m), 2.60 (4 H, m), 4.20 (2 H, q).

Reduction of Compound 4 with $NaBH_4$. A solution of **4** (2.3 mmol) in THF was treated with methyl iodide. The salt precipitated and the THF was removed by evaporation. The dried salt was dissolved in methanol (15 mL) and treated cautiously with $NaBH_4$. After being stirred 2 h, the reaction mixture was separated into neutral and basic fractions by extraction. The neutral fraction contained only **5** (25%), identified by NMR comparison with an authentic sample. No significant basic product was obtained.

General Procedure for Vinylogous Thioamides 6a–6c. The 1-aryl-3-(dimethylamino)prop-2-enones used as starting materials were prepared from the appropriate acetophenone as described by Gupton.[8] The enaminone (15 mmol) in 100 mL of dry benzene was treated with P_2S_5 (15 mmol), and the solution was refluxed until disappearance of the starting material was complete. The dark benzene solution was decanted from the solid and the solid was washed with additional benzene. The benzene was washed with sodium bicarbonate, dried, and concentrated. The concentrated solution was passed through a silica gel column using 20% ether in benzene for elution. The intensely orange-brown band containing product was collected and concentrated, and the residue was crystallized from benzene–hexane. **6a**, 24%, mp 116–118 °C (lit.[12] mp 112–115 °C; **6b**, 32%, mp 130–140 °C dec; **6c**, 18%, mp 107 °C (lit.[12] mp 105–106 °C.

Anal. **6b**: Calcd for $C_{11}H_{12}N_3O_2S$: C, 55.9; H, 5.1. Found: C, 56.0; H, 5.1.

General Procedure for Methylation and Reduction of 6a–6c. A solution of **6** (0.15 mmol) in anhydrous THF (5 mL) was treated with 0.3 mL of methyl iodide and stirred at room temperature for 2 h. A yellow salt precipitated. The salt was separated by filtering or decantation and rinsed with ether. The salt was then dissolved in anhydrous methanol (5 mL) and treated very cautiously over 5 min with solid $NaBH_4$ (50 mg). Vigorous gas evolution occurs with each addition of sodium borohydride. After 0.5 h the reaction solution was poured into 2% HCl solution and extracted with ether. Basification and extraction with ether gave the amine, which was purified by distillation or crystallization. **8a**: 67% yield, bp ~ 100 °C (0.1 mm); NMR 2.15, 3.17 (overlapping s, 9 H), 2.84 (2 H, d), 5.58 (1 H, t), 7.31 (5 H, s). **8b**: 53% yield, mp 52–53 °C from hexane; NMR 2.15 (6 H, s), 2.20 (3 H, s), 2.80 (2 H, d), 5.70 (1 H, t), 7.45 (2 H, d), 8.24 (2 H, d). **8c**: 78% yield, bp ~ 125 °C (0.1 mm); NMR 2.14 (9 H, s), 2.90 (2 H, d), 3.74 (3 H, s), 5.56 (1 H, t), 6.88 (2 H, d), 7.20 (2 H, d).

Anal. **8a**: Calcd for $C_{12}H_{17}NS$: C, 69.5; H, 8.3. Found: C, 69.3; H, 8.3. **8b**: Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.1; H, 6.4. Found: C, 57.1; H, 6.4. **8c**: Calcd for $C_{13}H_{19}NSO$: C, 65.8; H, 8.1. Found: C, 65.7; H, 8.1.

Registry No. **1a**, 15563-45-8; **1a** methyl iodide, 78089-85-7; **1b**, 18732-58-6; **1b** methyl iodide, 73160-83-5; **1c**, 15563-40-3; **1c** methyl iodide, 61135-82-8; **1d**, 24815-46-1; **1d** methyl iodide, 78089-86-8; **1e**, 15563-35-6; **1e** methyl iodide, 78089-87-9; **1f**, 2628-58-2; **1f** methyl iodide, 57513-33-4; **1g**, 78089-88-0; **1g** methyl iodide, 78089-89-1; **1h**, 637-53-6; **1h** methyl iodide, 78089-90-4; **2**, 57005-87-5; **3**, 19524-67-5; **4**, 78089-91-5; **5**, 3335-05-5; (*E*)-**6a**, 65672-85-7; (*E*)-**6b**, 78089-92-6; (*E*)-**6c**, 22292-83-7; (*E*)-**7a**, 78089-93-7; (*E*)-**7b**, 78089-94-8; (*E*)-**7c**, 78089-95-9; (*E*)-**8a**, 78089-96-0; (*E*)-**8b**, 78089-97-1; (*E*)-**8c**, 78089-98-2; *N*-benzoylpyrrolidine, 3389-54-6; *N*-(phenylacetyl)pyrrolidine, 3389-53-5; *N*-benzoylpiperidine, 776-75-0; *N*-(phenylacetyl)-piperidine, 3626-62-8; *N*,*N*-dibutylbenzamide, 25033-65-2; *N*-methyl-*N*-phenylbenzamide, 1934-92-5; *N*-*sec*-butylbenzamide, 879-71-0; ethyl malonylpiperidine, 34492-46-1; 3-(carboethoxy)-2-piperidone, 3731-16-6; ethyl 3-piperidinopropionate, 19653-33-9; (*E*)-phenyl-3-(dimethylamino)prop-2-enone, 1131-80-2; (*E*)-1-(*p*-nitrophenyl)-3-(dimethylamino)prop-2-enone, 78089-99-3; (*E*)-1-(*p*-methoxyphenyl)-3-(dimethylamino)prop-2-enone, 78090-00-3; *N*-benzylpyrrolidine, 29897-82-3; *N*-(2-phenylethyl)pyrrolidine, 6908-75-4; *N*-benzylpiperidine, 2905-56-8; *N*-(2-phenylethyl)piperidine, 332-14-9; *N*,*N*-dibutylbenzylamine, 4383-27-1; *N*-methylaniline, 100-61-8; *N*-*sec*-butylbenzylamine, 46120-25-6; *N*-ethylaniline, 103-69-5; $NaBH_4$, 16940-66-2; $NaBH_3CN$, 25895-60-7.

Isotopic Labeling Studies of the Thermal Rearrangement of Phenyloxirane to Phenylethanal[1]

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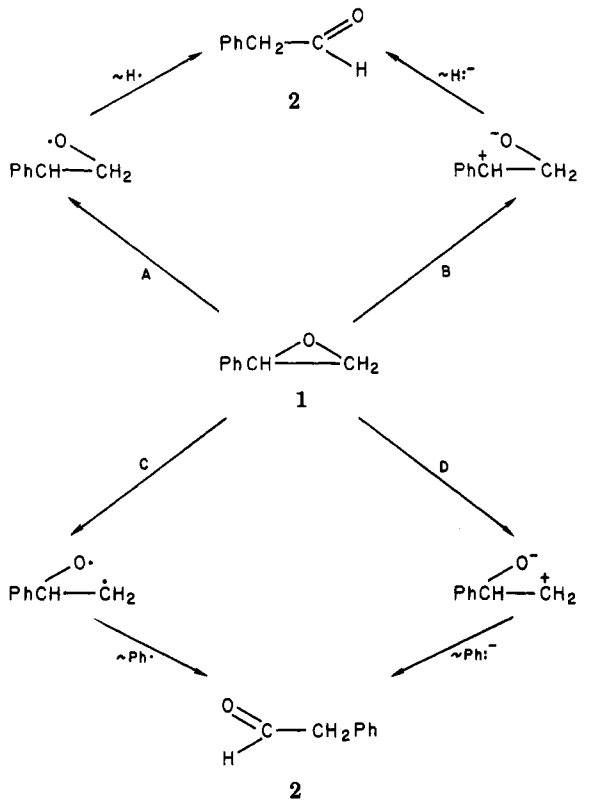
The thermal rearrangement of phenyloxirane (**1**) to phenylethanal (**2**) was reported by Watson and Young[2] to take place with first-order kinetics and without the production of acetophenone, which had been observed as an additional minor rearrangement product of photolysis of phenyloxirane[3] or of its reaction in the presence of sodium iodide, 1-iodopropane, and dimethyl sulfoxide.[4] The thermal rearrangement could be carried out neat or in solvents such as benzene, toluene, or xylene, either in sealed Pyrex-glass ampules or in a stainless-steel reaction vessel.[5,6] The yields in stainless-steel vessels decreased

(1) Generous support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
(2) Watson, J. M.; Young, B. L. *J. Org. Chem.* **1974**, *39*, 116–117.
(3) Gritter, R. J.; Sabatino, E. C. *J. Org. Chem.* **1964**, *29*, 1965.
(4) Bethell, D.; Kenner, G. W.; Powers, P. J. *J. Chem. Soc. D* **1968**, 227.

0022-3263/81/1946-3732$01.25/0

Scheme I



upon repeated reactions in the same vessel, but it was later reported that small amounts of alkaline earth sulfonates would prevent inhibition of the rearrangement in stainless-steel vessels.[7]

Watson and Young[2] suggested a mechanism for the rearrangement involving an opening of the C_1–O bond of the oxirane ring to produce an intermediate which is either a diradical (route A, Scheme I) or a switterion (route B, Scheme I), depending on whether the bond opening is homolytic or heterolytic, followed by a 1,2-shift of hydrogen, either as H· or H^-. They noted, however, that their kinetic data did not allow them to exclude the possibility of C_2–O bond cleavage followed by phenyl migration (routes C or D, Scheme I), although a C_1–O cleavage mechanism would be expected to be favored by the resonance stabilization of the benzylic radical or cation so produced.

Isotopic labeling suggests itself as a simple and direct way of determining whether the phenylethanal is formed by the shift of hydrogen or phenyl or, possibly, both. This paper describes experiments in which phenyloxirane molecules labeled with ^2H and ^{13}C were prepared and subjected to the rearrangement reaction.

Results and Discussion

Previous to the work with isotopically labeled material, experiments aimed at optimizing the yield of the rearrangement reaction in glass apparatus were performed, and considerable difficulty was encountered in obtaining consistently good yields. Variations in procedure that were found to have little or no effect on the yield were (1) pretreatment of the glass reaction ampules with base, (2) pretreatment of the glass ampules with acid, (3) use of thiophene-free benzene as solvent, and (4) degassing and sealing the glass ampules at different pressures. Addition of crushed Pyrex glass did increase the rate of rearrangement, which indicated a surface effect of some sort on the rearrangement reaction. A "seasoning" effect was noted; better yields of rearrangement product were often obtained when thermolyses were carried out in ampules that had been used previously. This also was indicative of the influence of the surface of the glass on the reaction, but the exact nature of the effect is not understood, since it did not appear to be related to adsorbed acid or base. The fact that the rate of rearrangement was independent of the air pressure above the sample suggested that an ionic mechanism is more plausible for the rearrangement than a radical process, since a higher concentration of oxygen would be expected to inhibit the latter type of mechanism.

Experiments with Deuterium-Labeled Phenyloxirane. By reference to Scheme I it may be seen that if the β-hydrogens of phenyloxirane (1) are replaced by deuterium atoms, as in 2-phenyl[3,3-$^2H_2$]oxirane, rearrangement by paths A or B will produce phenylethanal (2) in which one deuterium is in the β-position and one in the α-position. If rearrangement occurs by paths C or D, both deuterium atoms will be in the α-position of the phenylethanal. Proton NMR analysis of the rearrangement product should distinguish between these two possibilities.

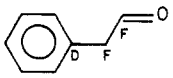
2-Phenyl[3,3-$^2H_2$]oxirane was synthesized and subjected to thermolysis in benzene solution at 275 °C for 3 h. The phenylethanal in the reaction mixture was converted to the 2,4-dinitrophenylhydrazone derivative in order to put the rearrangement product in a form which was stable to purification and analytical procedures. The chemical shifts of the protons in the α- and β-positions to the aromatic ring were well-separated, of course, at δ 3.73 and 7.58, respectively. The ^1H NMR analysis of the products from two runs showed integration values of 1.00 and 0.94 H at δ 3.73 and 0.00 and of 0.06 H at δ 7.58. The small signal at δ 7.58 in one run was probably due to an impurity or possibly to some hydrogen–deuterium exchange during the preparation of the 2,4-dinitrophenylhydrazone. Thus, these experiments with deuterium-labeled phenyloxirane strongly suggested that the rearrangement occurs by a hydrogen shift, as in path A and/or B.

Experiments with ^{13}C-Labeled Phenyloxirane. To reinforce the evidence obtained from deuterium labeling, phenyloxirane labeled with ^{13}C in the β-position with respect to the aromatic ring was synthesized. On reference to Scheme I again, it may be seen that if 2-phenyl[3-^{13}C]oxirane rearranged by a hydrogen shift (paths A or B), phenylethanal with ^{13}C remaining in the β-position to the ring would result, whereas a phenyl shift (path C or D) would put the ^{13}C in the α-position with respect to the ring.

2-Phenyl[3-^{13}C]oxirane, in which the ^{13}C enrichment was 24.5%, was subjected to thermolysis in benzene solution at 275 °C for 12 h. Two identical runs were made, and analysis of both crude reaction mixtures by cross-correlation ^1H NMR indicated >95% conversion to phenylethanal, which was isolated by preparative gas chromatography. A sample from the first run was analyzed by ^{13}C NMR. The relevant chemical shifts and integration areas of the phenylethanal-^{13}C and of ordinary phenylethanal are given in Table I. Although it was not found to be possible to calculate the exact proportion of ^{13}C in the α- and β-positions from the ^{13}C NMR data, it is obvious that the integration area of the β-carbon (peak F) is much larger, compared to the peaks for D and E, in the phe-

(5) Watson, J. M., private communication. We thank Dr. Watson for suggesting this study and for helpful discussions during the course of the work.
(6) Watson, J. M. U.S. Patent 3 860 614, 1975; *Chem. Abstr.* **1974**, *81*, 169301.
(7) Watson, J. M. U.S. Patent 3 927 110, 1975; *Chem. Abstr.* **1975**, *83*, 147301.

Table I. ^{13}C NMR Data for Phenylethanal and Phenylethanal-^{13}C from Rearrangement of 2-Phenyl[3-^{13}C]oxirane



ABC

chemical shift, δ	assignment[a]	area of peak[c] unlabeled[c]	area of peak[c] labeled[d]
50.46	E	1519.94	93.12
132.67	D	430.29	60.76
198.09	F	750.79	2482.58

[a] Peaks assigned to carbons A-C were obscured by the [^{2}H]benzene solvent. [b] Arbitrary instrumental units. [c] Ordinary phenylethanal. [d] Phenylethanal-^{13}C produced by rearrangement from 2-phenyl[3-^{13}C]oxirane.

nylethanal produced from the labeled phenyloxirane than in the ordinary (unlabeled) phenylethanal. Thus, the ^{13}C NMR data was in agreement with the ^2H data, indicating that hydrogen rather than phenyl shifted.

Samples of the rearrangement product from both runs were analyzed by mass spectroscopy to give data from which a more quantitative estimate of the position of the label could be made by using the method of Biemann.[8] The calculations were applied to the relative abundance of the ions at m/e 91 ($^{12}C_7H_7^+$) and 92 ($^{12}C_6{}^{13}CH_7^+$), the unlabeled and labeled tropylium ions, which include the α- but not the β-carbon atoms from phenylethanal.[9] By comparison of the relative abundance of the ions at m/e 91 and 92 with the values of m/e 120 ($^{12}C_8H_8O^+$) and 121 ($^{13}C^{12}C_7H_8O^+$), the unlabeled and labeled molecular ions, it was shown (within an experimental error of <2%) that all of the ^{13}C enrichment in the phenylethanal produced by rearrangement of 2-phenyl[3-^{13}C]oxirane remained in the position β to the ring, the result expected from a hydrogen shift according to route A or B of Scheme I.

Experimental Section

Qualitative gas chromatography was carried out with a Varian Model 2440 instrument equipped with a linear temperature programmer and using a 15 m × 3.2 mm column packed with 30% SE-30 on Chromosorb P. A Varian Model A-700 chromatograph equipped with a 3 m × 3.4 mm column packed with 30% SE-30 on Chromosorb P was used for preparative work. Qualitative ^1H NMR spectra were obtained by using either a Varian A-60 or a Perkin-Elmer R-12 spectrometer. Quantitative spectra were obtained by a cross-correlation technique using a Varian A-60 spectrometer interfaced with a Nicolet 1080 computer. Qualitative and quantitative ^{13}C NMR analyses were performed on a Bruker WH-90 instrument. Mass spectra were obtained by using a Bell and Howell Model 21-491 spectrometer interfaced with a Finnigan/INCOS data system. The quantitative data used were the average of at least 50 scans.

2-Phenyl[3-^{13}C]oxirane. The Grignard reagent prepared from benzyl chloride was carbonated by a standard procedure in which $Ba^{13}CO_3$ (Monsanto Chemical Co., Mound Lab., AEC, containing 92.2 mol % ^{13}C and 7.8 mol % ^{12}C) was utilized. The resulting 2-phenyl[1-^{13}C]acetic acid was treated with LAH to yield 2-phenyl[1-^{13}C]ethanol, which was dehydrated by distillation at atmospheric pressure from potassium hydroxide pellets to yield 2-phenyl[1-^{13}C]ethene. Oxidation of this crude product with m-chloroperbenzoic acid in dichloromethane gave 2-phenyl[3-^{13}C]oxirane, bp 100–108 °C (25 mm). The enrichment of ^{13}C in the product was calculated to be 24.5%.[10]

2-Phenyl[3,3-$^2H_2$]oxirane was prepared from phenylacetic acid and lithium aluminum deuteride (98% enriched), followed by dehydration and oxidation as in the preparation of 2-phenyl[3-^{13}C]oxirane:[11] ^1H NMR ($CDCl_3$) δ 3.73 (s, 1 H), 7.23 (s, 5 H). For 2-phenyloxirane: ^1H NMR ($CDCl_3$) δ 2.73 (dd, J = 5.5, 2.5 Hz, 1 H), 3.07 (dd, J = 5.5, 4.0 Hz, 1 H), 3.79 (dd, J = 2.5, 4.0 Hz, 1 H), 7.25 (s, 5 H).

The **2,4-dinitrophenylhydrazone of phenylethanal** was prepared,[12] and its ^1H NMR spectrum was determined. Owing to the low solubility of the derivative in $CDCl_3$, a time-averaging cross-correlation technique was required to give a satisfactory spectrum: δ 3.73 (d, J = 6.0 Hz, 2 H), 7.27 (s, 5 H), 7.58 (t, J = 6.0 Hz, 1 H), 7.92 (d, J = 9.9 Hz, 1 H), 8.30 (dd, J = 9.9, 2.3 Hz, 1 H), 9.05 (d, J = 2.3 Hz, 1 H), 11.04 (br s, 1 H).

Thermolysis of 2-Phenyl[3,3-$^2H_2$]oxirane. Two seasoned ampules (7.6 cm × 1.0 cm o.d., heavy-wall Pyrex glass) were prewashed with benzene, and each was charged with 0.6 mL of a 1:8 (v/v) solution of 2-phenyl[3,3-$^2H_2$]oxirane in benzene. The ampules were purged with dry air to remove any water vapor, cooled in liquid nitrogen, degassed, and sealed at <3 mm pressure. The two sealed tubes were placed in a stainless-steel high-pressure reaction vessel (10 cm × 2.2 cm o.d.) along with a few milliliters of benzene. This vessel was heated in a silicone oil bath to 275 ± 2 °C for 3 h. After the tubes cooled, the reaction mixtures from both tubes were combined and stirred with 2% sulfuric acid (ca. 70 mL) for 2 h to convert any surviving phenyloxirane to the corresponding glycol. The organic layer was separated, washed with water and saturated NaCl solution, and dried over $MgSO_4$. After evaporation of the benzene solvent, the 2,4-dinitrophenylhydrazone of the phenylethanal was prepared as before and recrystallized from aqueous ethanol.

The ^1H NMR ($CDCl_3$) spectra obtained by the time-averaged cross-correlation technique on samples from two separate experiments were as follows: sample no. 1, δ 3.73 (s, 0.94 H), 7.58 (s, 0.06 H); sample no. 2, δ 3.73 (s, 1.00 H).

Thermolysis of 2-Phenyl[3-^{13}C]oxirane. 2-Phenyl[3-^{13}C]-oxirane (100 mg, 0.83 mmol, 24.5% ^{13}C enriched) was dissolved in benzene (800 mg) and the solution was dried over 4-Å molecular sieves. The solution was placed in a seasoned ampule (7.6 cm × 1.0 cm o.d., heavy-wall Pyrex glass) with a small amount (ca. half of the volume of the solution) of crushed Pyrex glass. The ampule was degassed, sealed as described above, and placed in the stainless-steel reaction vessel with external benzene, where it was heated at 275 ± 2 °C for 12 h. Cross-correlation ^1H NMR analysis of the crude product mixture indicated >95% conversion of phenyloxirane to phenylethanal. The product was purified by preparative GC and analyzed by ^{13}C NMR. The ^{13}C NMR data are presented in Table I.

A second 100-mg sample of 2-phenyl[3-^{13}C]oxirane was thermolyzed exactly as described above, and the product was isolated as before. Mass spectra of the phenylethanal produced in both runs were obtained, and the spectral data were treated by the method of Biemann[8] to calculate the enrichment of ^{13}C in the carbons α and β to the benzene ring. Comparison of the m/e 120 and 121 peaks gave values of 24.5% and 24.2%, respectively, for the phenylethanal molecular ion from the two runs, confirming that no isotope was lost in the rearrangement. Similar calculations based on the m/e 91 and 92 peaks gave values of 0.58% and 0.29% ^{13}C enrichment, respectively, for the tropilium ion, which includles all of the carbon atoms except that in β-CHO group.[9]

Registry No. 1, 96-09-3; **2**, 122-78-1; **2** 2,4-dinitrophenyl-

(8) Biemann, K. "Mass Spectrometry, Organic Chemical Applications"; McGraw-Hill: New York, 1962; Chapter 5.

(9) Similar calculations were used to locate the position of ^{13}C in the product from the automerization of n-propylbenzene-α-^{13}C. Cf.: Roberts, R. M.; Gibson, T. L. *J. Am. Chem. Soc.* **1971**, *93*, 7340–7341.

(10) The signals of m/e 119, 120, and 121 in the mass spectrum of phenyloxirane did not give consistent ratios of relative abundance, so the isotopic enrichment of 2-phenyl[3-^{13}C]oxirane could not be determined directly from its mass spectrum. For this reason, an analysis was done on the phenylacetic acid precursor by using the method of Biemann,[8] and it was assumed that there was no loss of rearrangement of isotope in the last two steps of the synthesis of 2-phenyl[3-^{13}C]oxirane. The validity of this assumption was confirmed by the mass spectrometric analysis of the phenylethanol produced by rearrangement (vide infra).

(11) This synthesis was performed by George Odom.

(12) Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. "Modern Experimental Organic Chemistry", 3rd ed.; Saunders: Philadelphia, 1979; p 298.

hydrazone, 2074-04-6; 2-phenyl[1-^{13}C]acetic acid, 57825-33-9; 2-phenyl[1-^{13}C]ethanol, 35462-98-7; 2-phenyl[1-^{13}C]ethene, 61415-37-0; 2-phenyl[3-^{13}C]oxirane, 78064-69-4; 2-phenyl[3,3-$^{2}H_2$]oxirane, 66255-92-3; phenylethanal-^{13}C, 78064-70-7.

Novel Condensation of 2,3-Epoxybutanal with 2-Aminopyridine and 2-Aminopyrazine. Synthesis and Stability of 3-(1-Hydroxyethyl)imidazo[1,2-*a*]azines

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In this study, we report a novel condensation of 2,3-epoxybutanal with 2-aminopyridine and 2-aminopyrazine. This unprecedented mode of reaction of an α,β-epoxy carbonyl compound is applied to synthesis of 3-(1-hydroxyethyl)imidazo[1,2-*a*]azines, which are not readily accessible by functionalization of the parent heterocycles due to their facile decomposition to the latter. The X-ray structure of a derived ketone is also reported as a characterization of the geometry of the imidazo[1,2-*a*]pyrazine ring system. The NMR signal and coupling constant assignments for the ring system are corrected.

Base-catalyzed hydrogen–deuterium exchange of imidazo[1,2-*a*]azines **1a,b** occurs at positions 3 (faster) and 5 (slower).[1a,b] This result suggests that kinetic deprotonation should afford anions **2a,b** which might be functionalized with aldehydes or ketones (Scheme I). Thermal reactions of methyl analogues of **1a** with acetaldehyde have been reported to result in inefficient condensation to give analogues of **4a**.[2] Condensation of **2a** with cyclohexanone gave a low yield of the 3-(1-hydroxycyclohexyl) analogue of **4a**.[3] These results suggest that 3-(1-hydroxyalkyl)-imidazo[1,2-*a*]azines **4** may be unstable with respect to **1** and **2**.

We investigated the condensation of **5a,b** with a mixture of cis and trans epoxy aldehyde **6** with the intent of developing a regioselective synthesis of compounds **4**, using the mechanistic hypothesis of Scheme II.

Reaction of **5b** with 1 equiv of **6** in ether–CH_2Cl_2 resulted in vigorously exothermic reaction giving a multitude of products including a trace of the desired **4b**. In spite of the negative result, we were encouraged by the report of Posner and Rogers that adsorption of nucleophiles, including amines, on activity I alumina catalyzed their reaction with epoxides.[4]

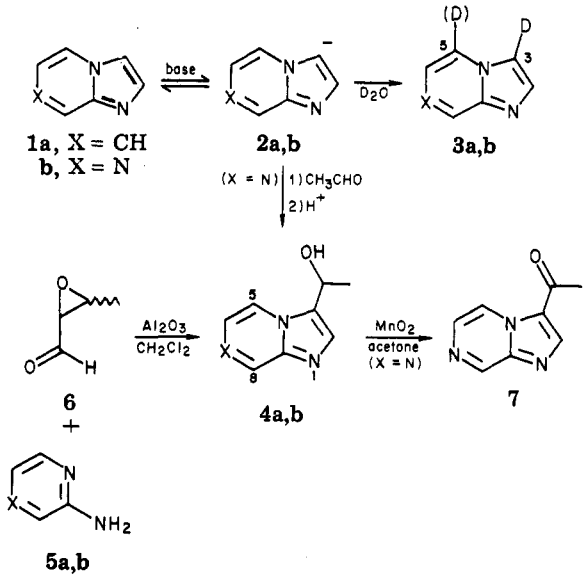
A suspension of **5b** adsorbed on alumina in CH_2Cl_2 reacted with 1 equiv of aldehyde **6** at room temperature to give a 26% yield of **4b**, after extraction of the alumina with methanol–CH_2Cl_2 and sublimation of the extracted products. When the alumina was extracted with hot methanol, a mixture of **4b** and imidazo[1,2-*a*]pyrazine was isolated.

Comparable reaction of **5a** with **6** gave **4a** in 53% yield. Attempted sublimation of **4a** gave a mixture of **4a** and imidazo[1,2-*a*]pyridine. These results confirm the instability of alcohols **4** with respect to **1**.

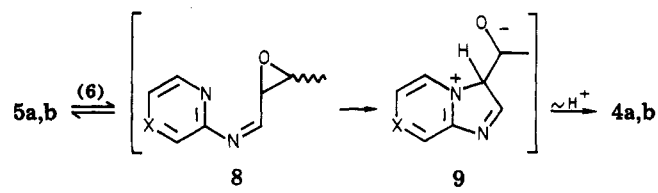
Oxidation of **4b** with excess MnO_2 in acetone for 6 days at room temperature gave ketone **7** in 81% yield. The structure of **7** was confirmed by its infrared and NMR spectra and unambiguously by single-crystal X-ray analysis (see Experimental Section).

The NMR of **7** shows a characteristic H_5 signal at δ 9.40, indicative of strong deshielding by the 3-acetyl function. From present NMR data and data on other substituted imidazo[1,2-*a*]pyrazines (W. C. Lumma, Jr., unpublished),

Scheme I



Scheme II



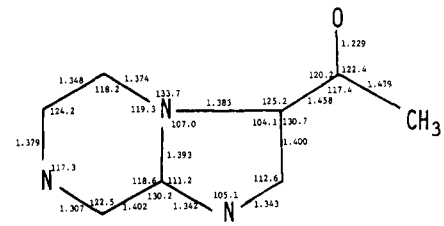


Figure 1. Bond distances (Å) and bond angles (deg) for **7**. The estimated standard deviations are 0.007 Å and 0.4°, respectively.

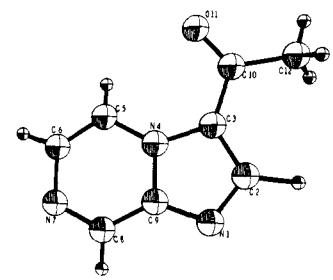


Figure 2. Drawing of **7** viewed perpendicular to the molecular plane.

(1) (a) Pyridines: Paudler, W. W.; Helmick, L. S. *J. Chem. Soc., Chem. Comm.* **1967**, 377. (b) Pyrazines: DePompei, M. F.; Paudler, W. W. *J. Heterocycl. Chem.* **1975**, *12*, 861.
(2) Hand, E. S.; Paudler, W. W.; Zachow, S. *J. Org. Chem.* **1977**, *42*, 3377.
(3) Paudler, W. W.; Shin, H. G. *J. Org. Chem.* **1968**, *33*, 1638.
(4) Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208.

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