

Japan Electron Optics Laboratory Co. JNM-RA-1 spectrum accumulator presuming Lorentzian line shapes.

Static experiments were performed by use of an inverted H-type mixing cell under nitrogen or argon.¹³ HMPA was distilled immediately before use from calcium hydride under reduced pressure. Me₂SO was thoroughly dried with molecular sieves before use. For HMPA-lithium reductions a volume of HMPA sufficient to form a 10⁻³ M solution of the ketone was placed in the two arms of the cell and deoxygenated by a stream of nitrogen for 0.5 h. The ketone was added to one arm of the cell and a pellet of freshly cut and cleaned lithium added to the other arm. The nitrogen purge was continued for a few minutes after the lithium solution had turned deep blue. At this point the solutions were mixed and drained into the fused silica cell for measurement. HMPA-(trimethylsilyl)sodium reductions were performed in a similar manner except that sodium methoxide was dissolved in a HMPA solution of hexamethyldisilane (Pierce Chemical Co.) in one arm of the cell. Flow experiments were performed as previously described for the Me₂SO-potassium *tert*-butoxide system using upflow through a Varian V-4549A cell with a dead space of ~0.05 mL. Flow rates could be adjusted by motor driven syringes so that ESR measurements could be made from 0.1 s to a few minutes after mixing.

Registry No.—1, 3947-97-5; 1⁻, 65405-28-9; 2, 24234-76-2; 2⁻, 65405-27-8; 7, 20420-52-4; 8, 64014-05-7.

References and Notes

- Aliphatic Semidiones. 34. This work was supported by grants from the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation.
- J. G. Concepcion and G. Vincow, *J. Phys. Chem.*, **80**, 857 (1976).
- G. A. Russell, R. L. Blankespoor, K. D. Trahanovsky, C. S. C. Chung, P. R. Whittle, J. Mattox, C. L. Myers, R. Penny, T. Ku, Y. Kosugi, and R. S. Givens, *J. Am. Chem. Soc.*, **97**, 1906 (1975).
- G. A. Russell and R. Blankespoor, *Tetrahedron Lett.*, 4573 (1971).
- H. Sakurai, A. Okada, H. Umino, and M. Kira, *J. Am. Chem. Soc.*, **95**, 955 (1973).
- P. B. Ayscough and R. Wilson, *J. Chem. Soc.*, 5412 (1963).
- Sakurai (ref 5) reports $a^H = 3.49$ (2), 2.38 (4), and 0.75 (4) G without detectable metal hyperfine splitting constants.
- D. H. Geske and A. L. Balch, *J. Phys. Chem.*, **68**, 3423 (1964); G. A. Russell and M. Young, *J. Am. Chem. Soc.*, **88**, 2007 (1966).
- A. Carrington and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 21 (1962).
- E. J. Smutny and J. D. Roberts, *J. Am. Chem. Soc.*, **77**, 3420 (1956).
- A. T. Blomquist and E. LaLancette, *J. Am. Chem. Soc.*, **83**, 1387 (1961).
- S. Skujins and G. A. Webb, *Chem. Commun.*, 598 (1968).
- G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964).
- Note Added in Proof.** Diphenylcyclobutene-1,2-semidione is also formed slowly when diphenylcyclopropanone is treated with potassium *tert*-butoxide in Me₂SO (experimental results with Dr. T. Morita). Under these conditions 2⁻ has a lifetime of hours. The reaction involves an example of carbonyl insertion, R₂C=O + CO + e⁻ → RC(O)=C(O⁻)R; see G. A. Russell, D. E. Lawson, and L. A. Ochrymowycz, *Tetrahedron*, **26**, 4697 (1970).

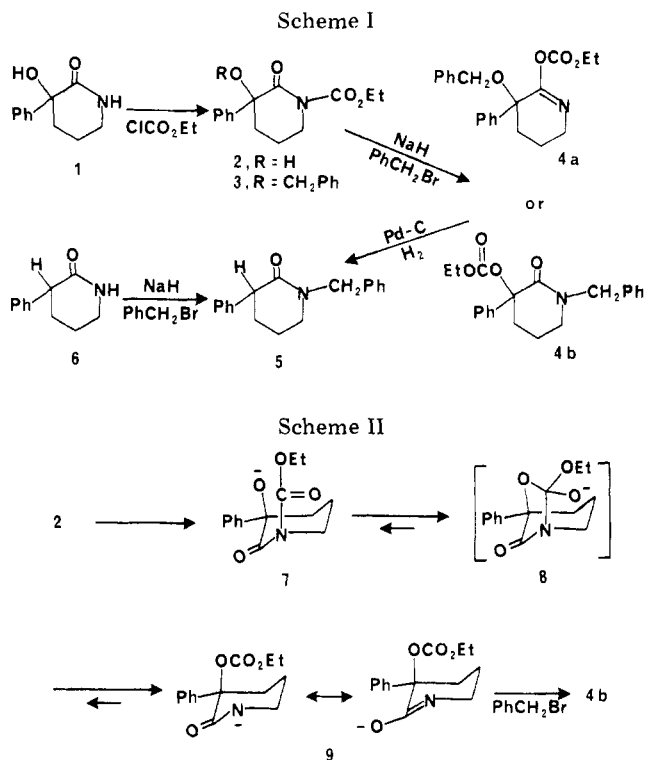
An Ethoxycarbonyl Migration from an Amide Nitrogen to Oxygen¹

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We wish to report what appears to be the first example of an ethoxycarbonyl group migration from an amide nitrogen to oxygen. Previous literature reports have shown that migration of the ethoxycarbonyl group can be a facile process. As early as 1906 it was shown by Blaise and Courtot² that an ethoxycarbonyl group could migrate more readily than a methyl group to a positive center. Subsequent reports have been very few in number but have included examples of alkoxy-carbonyl shifts to positive, neutral, and negative centers.³ The only studies that we have seen involving alkoxy-carbonyl migration between nitrogen and oxygen are those on the 2-aminophenols,^{3,4} *N*-ethoxycarbonylhydrastinine,⁵ and sub-

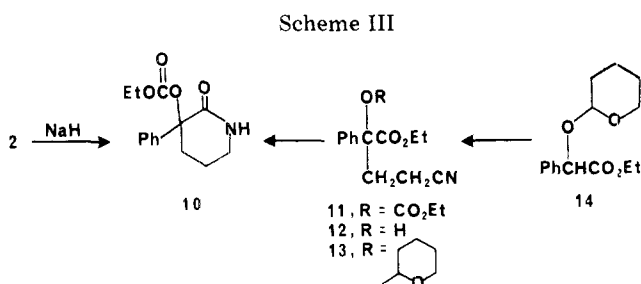


stituted isoquinolines,⁶ none of which involved an amide nitrogen.

Attempted O-benylation of 2, prepared from ClCO₂Et and 1 as shown in Scheme I, did not yield the expected product 3. The ¹H-NMR spectrum of the product was consistent with structure 3, but the IR spectrum contained carbonyl absorptions at 1750 (carbonate) and 1660 cm⁻¹ (lactam or lactim), suggesting a rearranged product such as 4a or 4b. The largest fragment in the mass spectrum was *m/e* 263 (*M*⁺ - 90). Hydrogenolysis of this product yielded a compound for which the IR spectrum indicated an N-substituted lactam (1640 cm⁻¹),⁷ and the ¹H-NMR spectrum showed loss of the ethoxycarbonyloxy group and the presence of two types of benzylic protons at δ 4.7 (singlet, 2 H) and 3.7 ppm (multiplet, 1 H). These observations were consistent with structure 5. Since amides undergo N-alkylation under basic conditions,⁸ an unambiguous synthesis of 5 (Scheme I) using 3-phenyl-2-piperidinone (6),⁹ PhCH₂Br, and NaH confirmed the structure assignment. The rearranged product was therefore formulated as structure 4b. The lack of a parent ion in the mass spectrum of 4b is consistent with a facile loss of the ethoxycarbonyloxy group via a McLafferty rearrangement, which is not possible in 4a.

Either an intermolecular or intramolecular mechanism can be envisioned for the conversion of 2 to 4b. However, it is unlikely that an intermolecular mechanism is operative since none of the O-benzylated product 3 was detected, even though PhCH₂Br was present before NaH addition. A mechanism which is consistent with previous studies on ethoxycarbonyl migrations from nitrogen to oxygen^{5,6} is suggested in Scheme II.

As depicted in Scheme II, it is likely that any equilibrium between 7 and 9 favors the delocalized amide anion 9. Alternatively, it is possible that the equilibrium favors anion 7 and that the PhCH₂Br simply reacts much faster with the amide anion 9, thus trapping a relatively small fraction of 9 as it is formed to yield 4b. In order to test this possibility, compound 2 was subjected to the conditions of rearrangement but without PhCH₂Br (Scheme III). In this case the only product formed was 10, and TLC showed no remaining starting material.



The structure assignment of **10** was confirmed by an alternate synthesis from ethyl 2-phenyl-2-(2-tetrahydropyranyloxy)acetate (**14**).¹⁰ As shown in Scheme III, compound **14** was cyanoethylated with $\text{CH}_2=\text{CHCN}$ and KO-*t*-Bu to afford **13**. Removal of the THP group with aqueous acid yielded **12**, and **12** was acylated using ClCO_2Et and NaH to give **11**. Hydrogenation of **11** over PtO_2 in acetic acid provided **10**.

These results suggest that any equilibrium between **7** and **9** lies overwhelmingly toward the side of **9**. The driving force for the rearrangement must therefore be formation of the delocalized amide anion **9**, which is more stable than anion **7**.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. The ¹H-NMR spectra were obtained on Varian Associates T60 and EM 360 spectrophotometers with 1% Me₄Si as the internal standard. Electron impact mass spectra were recorded using a Varian CH-5 spectrometer. Elemental analyses were performed on a Hewlett-Packard 185B CHN Analyser at the University of Kansas. *R_f* values were determined using Brinkmann precoated silica gel plates (Silica Gel 60 F-254, 5 × 10 cm, 0.25 mm layer).

1-Ethoxycarbonyl-3-hydroxy-3-phenyl-2-piperidinone (2). A solution of 4.0 g (0.021 mol) of 3-hydroxy-3-phenyl-2-piperidinone (**1**)¹⁰ and 5.7 g (0.052 mol) of ClCO_2Et in 350 mL of toluene was heated at reflux for 24 h and concentrated in vacuo, and the residue was crystallized from Et₂O-hexane to yield 4.2 g (76%) of **2**. Recrystallization from CHCl_3 -hexane yielded white needles: mp 66–67 °C; IR (CHCl_3) 3560 (OH), 1775 (C=O), and 1725 cm^{-1} (C=O); ¹H NMR (CDCl_3) δ 7.4 (s, 5 H, aromatic), 4.4 (q, 2 H, *J* = 7 Hz, ester CH₂), 4.1 (s, 1 H, OH), 3.8 (m, 2 H, CH₂N), 2.6–1.6 (m, 4 H, PhCCH₂CH₂), 1.4 (t, 3 H, *J* = 7 Hz, ester CH₃); MS (70 eV) *m/e* 263 (*M*⁺). Anal. Calcd for C₁₄H₁₇NO₄: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.09; H, 6.60; N, 5.51.

1-Benzyl-3-ethoxycarbonyloxy-3-phenyl-2-piperidinone (4b). To a solution of 0.40 g (0.0015 mol) of **2** and 0.27 g (0.0016 mol) of PhCH₂Br in 10 mL of benzene and 0.5 mL of Me₂SO was added 0.038 g (0.0016 mol) of NaH. The mixture was stirred at 25 °C for 48 h and extracted, respectively, with 10 mL of H₂O, 15 mL of 5% NH₃, and 15 mL of saturated NaCl. The organic layer was dried (MgSO₄) and concentrated in vacuo to yield 0.50 g of a pale yellow oil. The oil was chromatographed in equal portions on 2 Brinkmann silica gel plates (20 × 20 cm, 2-mm layer) using 10% Et₂O in CHCl_3 as eluent. The major band (*R_f* 0.58) was isolated to yield 0.40 g (75%) of **4b** as a pale yellow oil: IR (liquid film) 1750 (carbonate) and 1660 cm^{-1} (lactam); ¹H NMR (CDCl_3) δ 7.3 (m, 5 H, aromatic), 4.8 (s, 2 H, PhCH₂), 4.2 (q, 2 H, *J* = 7 Hz, ester CH₂), 3.6–1.4 (m, 6 H, CH₂CH₂CH₂N), 1.3 (t, 3 H, *J* = 7 Hz, ester CH₃); MS (70 eV) *m/e* 263 (*M*⁺ - 90). Anal. Calcd for C₂₁H₂₃NO₄: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.60; N, 3.60.

1-Benzyl-3-phenyl-2-piperidinone (5). **Procedure A.** A mixture of 0.35 g (0.0010 mol) of **4b** and 0.2 g of 5% Pd-C (50% wet with H₂O) in 10 mL of absolute EtOH was hydrogenated at 1 atm for 17 h. The mixture was filtered and the filtrate was concentrated in vacuo to yield 0.24 g (71%) of **5** as a clear oil. TLC on silica (10% Et₂O in CHCl_3 elution) showed only one spot: *R_f* 0.54; IR (liquid film) 1640 cm^{-1} (N-substituted lactam); ¹H NMR (CDCl_3) δ 7.2 (d, 10 H, aromatic), 4.7 (s, 2 H, PhCH₂), 3.7 (m, 1 H, PhCH), 3.3 (m, 2 H, CH₂N), 2.4–1.6 (m, 4 H, PhCCH₂CH₂); MS (70 eV) *m/e* 265 (*M*⁺). Anal. Calcd for C₁₈H₁₉NO: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.27; H, 7.30; N, 5.08.

Procedure B. The general procedure was the same as that for the

preparation of **4b**, except that a mixture of 0.10 g (0.00057 mol) of 3-phenyl-2-piperidinone (**6**),⁹ 0.11 g (0.00063 mol) of PhCH₂Br, 0.015 g (0.00063 mol) of NaH, 5 mL of benzene, and 0.1 mL of Me₂SO was stirred at 25 °C for 12 h. After chromatography the major band (*R_f* 0.54) was isolated to yield 0.13 g (86%) of **5** as a clear oil. IR and ¹H-NMR spectra were identical to the product prepared in procedure A.

3-Ethoxycarbonyloxy-3-phenyl-2-piperidinone (10). **Procedure A.** A mixture of 0.10 g (0.00038 mol) of **2**, 0.0096 g (0.00040 mol) of NaH, 5 mL of benzene, and 0.1 mL of Me₂SO was stirred at 25 °C for 1 h and extracted with an equal volume of H₂O followed by 5 mL of saturated NaCl, and the organic layer was dried (MgSO₄). The solution was concentrated in vacuo to yield 0.10 g of an opaque oil. Addition of 2 mL of Et₂O and cooling yielded 0.07 g (70%) of **10** as a white solid which was recrystallized from CHCl_3 -Et₂O: mp 155–157 °C; IR (KBr) 3330 (NH), 1745 (carbonate), and 1640 cm^{-1} (lactam); ¹H NMR (CDCl_3) δ 7.4 (m, 5 H, aromatic), 6.7 (bs, 1 H, NH), 4.2 (q, 2 H, *J* = 7 Hz, ester CH₂), 3.8–1.5 (m, 6 H, CH₂CH₂CH₂N), 1.2 (t, 3 H, *J* = 7 Hz, ester CH₃); MS (70 eV) *m/e* 263 (*M*⁺). Anal. Calcd for C₁₄H₁₇NO₄: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.49; H, 6.53; N, 5.12.

Procedure B. A mixture of 1.5 g (0.0049 mol) of the nitrile **11** and 0.15 g of PtO₂ in 35 mL of glacial acetic acid was hydrogenated on a Parr shaker at 45 psi for 10 h and filtered, and the filtrate was made basic with 35% NaOH. This solution was extracted with CHCl_3 (3 × 35 mL), the extracts were dried (MgSO₄), and the solvent was removed in vacuo. The residual oil was triturated with Et₂O and cooled to yield a white solid. Fractional recrystallization from CHCl_3 -hexane yielded 0.20 g (21%) of **1** as the first crop and 0.30 g (23%) of **10** as the second crop. Compound **10** was recrystallized from CHCl_3 -Et₂O: mp 156.5–157.5 °C; IR and ¹H NMR spectra were identical to that for the product in procedure A.

Ethyl 4-Cyano-2-ethoxycarbonyloxy-2-phenylbutyrate (11). A solution of 3.0 g (0.013 mol) of **12** and 0.31 g (0.013 mol) of NaH in 40 mL of benzene and 1 mL of Me₂SO was heated briefly to reflux and cooled to 50 °C, and 1.4 g (0.013 mol) of ClCO_2Et was added. After heating at reflux an additional 1.5 h, the mixture was cooled to 25 °C and stirred overnight. The solution was extracted with 50 mL of H₂O followed by 50 mL of saturated NaCl, dried (MgSO₄), and concentrated in vacuo. The residue was distilled to yield 2.8 g (71%) of **11** as a clear oil: bp 150 °C (0.3 mm); IR (liquid film) 1795 (carbonate) and 1750 cm^{-1} (ester); ¹H NMR (CDCl_3) δ 7.4 (m, 5 H, aromatic), 4.2 (m, 4 H, carbonate and ester CH₂), 3.3–2.3 (m, 2 H, PhCCH₂), 2.0 (t, 2 H, CH₂CN), 1.25 (m, 6 H, carbonate and ester CH₃). Anal. Calcd for C₁₆H₁₉NO₅: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.95; H, 6.30; N, 4.40.

Ethyl 4-Cyano-2-hydroxy-2-phenylbutyrate (12). A solution of 15 g (0.047 mol) of **13** in 250 mL of absolute EtOH and 50 mL of 20% HCl was heated at reflux for 1 h, reduced in vacuo to half volume, made basic with 3 N NaOH, and extracted with Et₂O (3 × 100 mL). The extracts were dried (MgSO₄) and concentrated in vacuo. Distillation of the residual oil gave 5.8 g (53%) of **12** as a clear oil: bp 123 °C (0.018 mm); IR (liquid film) 3410 (OH) and 1730 cm^{-1} (C=O); ¹H-NMR (CDCl_3) δ 7.3 (m, 5 H, aromatic), 4.2 (q, 2 H, *J* = 7 Hz, ester CH₂), 3.9 (bs, 1 H, OH), 1.4 (m, 4 H, CH₂CH₂CN), 1.2 (t, 3 H, *J* = 7 Hz, ester CH₃). Anal. Calcd for C₁₃H₁₅NO₃: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.43; N, 5.66.

Ethyl 4-Cyano-2-phenyl-2-(2-tetrahydropyranyloxy)butyrate (13). To a stirred solution of 100 g (0.380 mol) of **14**¹⁰ in 80 mL of *t*-BuOH was added 14.2 g (0.130 mol) of KO-*t*-Bu. A solution of 100 g (1.89 mol) of acrylonitrile in 70 mL of *t*-BuOH was added dropwise over 45 min and stirring was continued for 1 h. The reaction mixture was poured into 200 mL of cold 2% HCl and filtered, the filtrate was passed through a bed of alumina on a Buchner funnel, and the solvent was removed in vacuo. The residual oil was placed on a high vacuum rotary evaporator to remove (CH₃)₃COCH₂CH₂CN, bp 40 °C (0.2 mm). The residue crystallized upon standing to provide 85.0 g (71%) of **13**. Recrystallization from CH₃OH-H₂O yielded white plates: mp 94–95 °C; IR (KBr) 2225 (CN) and 1725 cm^{-1} (C=O); ¹H NMR (CDCl_3) δ 7.4 (s, 5 H, aromatic), 4.7 (bs, 1 H, OCHRO), 4.4–3.9 (q, 2 H, *J* = 7 Hz, ester CH₂), 3.9–3.3 (m, 2 H, OCH₂), 2.9–2.2 (m, 4 H, CH₂CH₂CN), 2.2–1.4 (m, 6 H, CH₂CH₂CH₂), 1.4–1.0 (t, *J* = 7 Hz, ester CH₃). Anal. Calcd for C₁₈H₂₃NO₄: C, 68.13; H, 7.30; N, 4.14. Found: C, 68.44; H, 7.40; N, 4.14.

Registry No.—**1**, 65379-06-8; **2**, 65379-07-9; **4b**, 65379-08-0; **5**, 65379-09-1; **6**, 51551-56-5; **10**, 65379-01-3; **11**, 65379-02-4; **12**, 65379-03-5; **13**, 65379-04-6; **14**, 65379-05-7; ClCO_2Et , 541-41-3; PhCH₂Br, 100-39-0.

References and Notes

- (1) This work was supported by NIH Training Grant GM 1341 and Research Grant NS 12429.
- (2) E. E. Blaise and A. Courtot, *Bull. Soc. Chim. Fr.*, **35**, 360, 589 (1906).
- (3) R. M. Acheson *Acc. Chem. Res.*, **4**, 177 (1971).
- (4) L. H. Amundsen and C. Ambrosio, *J. Org. Chem.*, **36**, 3130 (1971).
- (5) M. D. Rozwadowska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **24**, 685 (1976); *Chem. Abstr.*, **86**, 121221g (1977).
- (6) M. D. Rozwadowska, *Can. J. Chem.*, **55**, 164 (1977).
- (7) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962, p 47.
- (8) B. C. Challis and J. A. Challis in "The Chemistry of Amides", J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 748.
- (9) E. E. Smisson and P. J. Wirth, *J. Org. Chem.*, **40**, 1576 (1975).
- (10) J. Ayres, Ph.D. Dissertation, University of Kansas, Lawrence, Kans. 1970.

Communications

Conversion of Epoxides to Olefins with Trifluoroacetyl Iodide and Sodium Iodide¹

Summary: Trifluoroacetyl iodide has been found to react with epoxides in the presence of excess sodium iodide to produce the related olefins in high yield; the reaction stereospecifically generates olefins of the same geometry as the epoxides.

Sir: Several methods of deoxygenating epoxides to produce olefins have been reported. Nonstereospecific procedures include treatment of epoxides with chromous salts² or with zinc-copper couple.³ Stereospecificity is obtained using reagents such as triphenylphosphine selenide,⁴ potassium selenocyanate-methanol,⁵ hexamethyldisilane-KOMe,⁶ and lithium diphenylphosphide.⁷ We recently described the conversions of epoxides to *vic*-dihalides with triphenylphosphine dihalides;⁸ the dihalides were then reduced to olefins with, for example, zinc. The diastereomer content of the *vic*-dihalide was found to be quite solvent dependent; deviation from the predominant backside displacement of C-O by bromide with increasing solvent polarity was ascribed to internal participation by the bromine which had performed the initial displacement (Scheme I). To the extent that such bridging occurred, the diastereomer of opposite configuration was formed, and the olefin ultimately generated was of the same geometry as that of the initial epoxide.

We wished to construct a product from an epoxide that might react exclusively via an onium ion to convert that epoxide to the olefin of the same geometry. Neighboring iodine is, of course, more proficient in interacting with an adjacent carbonium ion than is bromine. However, triphenylphosphine diiodide could not be made to react with aliphatic epoxides.

It was found that trifluoroacetic anhydride (1 equiv) and sodium iodide (1 equiv) reacted exothermically with (*Z*)-7,8-epoxy-2-methyloctadecane⁹ (in 1:1 CH₃CN-THF) to produce a β -iodotrifluoroacetate [NMR (CCl₄) δ 4.06 (m, CHI), 4.72 (m, CHO₂CCF₃)] which on exposure to sodium iodide (3 equiv) in the same solvent system for 24 h spontaneously generated iodine, sodium trifluoroacetate, and the corresponding *Z* olefin in 90% yield. Similarly, the corresponding *E* epoxide upon treatment with trifluoroacetyl iodide (generated in situ) and excess sodium iodide produced the *E* olefin, again in 90% yield. In the absence of more definitive data, it is presumed that the yellow-orange solution of anhydride and sodium iodide contains trifluoroacetyl iodide; the epoxides are stable in solutions containing trifluoroacetic anhydride alone. Identification of the gross structure of the olefins was made by comparison with authentic samples;⁸ analysis of geometry was accomplished by epoxidation with *m*-chloroperbenzoic acid, and examination of the re-

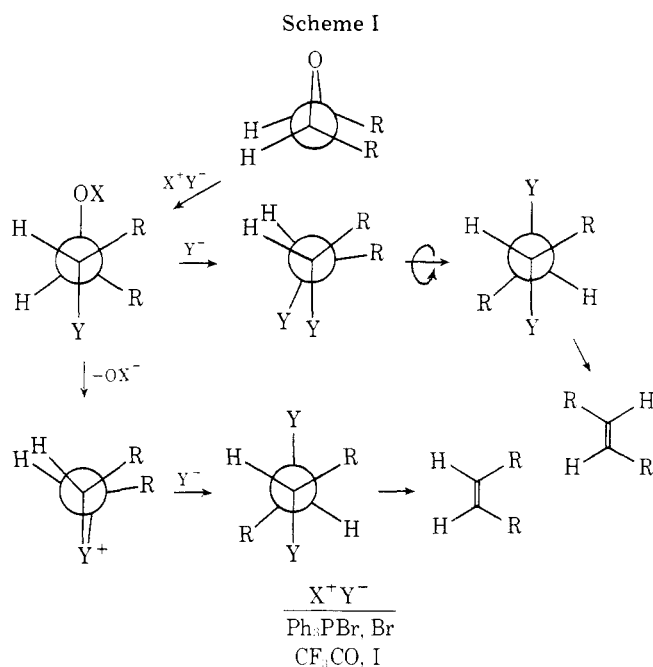


Table I. Reactions of Epoxides with Trifluoroacetyl Iodide

Reactant	Geom-etry	Product	Geom-etry	% yield
1,2-Epoxycyclohexane		Cyclohexene		77 ^a
1,2-Epoxydecane		1-Decene		91 ^b
5,6-Epoxydecane	93% <i>Z</i>	5-Decene	93% <i>Z</i>	95 ^b
5,6-Epoxydecane	94% <i>E</i>	5-Decene	95.5% <i>E</i>	95 ^b
7,9-Epoxy-2-methyloctadecane	97.5% <i>Z</i>	2-Methyl-7-octadecene	97.7% <i>Z</i>	90 ^a
7,8-Epoxy-2-methyloctadecane	97.5% <i>E</i>	2-Methyl-7-octadecene	>97% <i>E</i>	90 ^a

^a Estimated by GLC. ^b Distilled yield; checked by GLC.

sulting epoxides by capillary gas chromatography (DEGS, 4 mm × 46 m, 170 °C, helium carrier at 4 mL/min). Retention times were 10.2 (*trans*-epoxide) and 10.8 min (*cis*-epoxide); the initially employed *cis*-epoxide (97.5% *cis*) provided 97.7% *cis*-olefin, and the *trans*-epoxide (97.5% *trans*) provided >98% *trans*-olefin. The conversions of several epoxides to olefins with trifluoroacetyl iodide generated in situ from trifluoroacetic anhydride and NaI are given in Table I. It is apparent that the reaction proceeds in high yield and is stereospecific for the epoxides of 1,2-dialkylethenes.

The transformations involved bear comparison with the