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Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

Reactions of Perfluoro(2,3-epoxy-2-methylpentane) with *o*-Phenylenediamine and Ethylenediamine

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Abstract—Perfluoro(2,3-epoxy-2-methylpentane) reacted with *o*-phenylenediamine and ethylenediamine via cleavage of the C–C bond to produce 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)-phenyl]propanamide and 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)ethyl]-propanamide, respectively. Presumably, these compounds are formed as a result of rearrangement of intermediate ketone generated by intramolecular haloform-type reaction. According to the NMR and X-ray diffraction data, 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)phenyl]propanamide in crystal exists as *Z* conformer with respect to the amide C–N bond.

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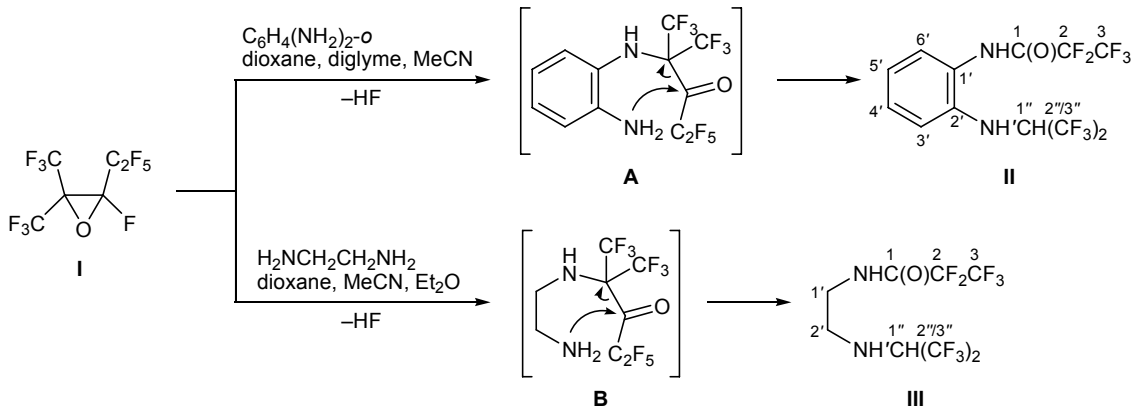
Perfluorinated olefin oxides are versatile synthons possessing a broad synthetic potential. They are capable of reacting with mono- and difunctional nucleophiles and electrophiles to afford various polyfunctional fluorine-containing compounds and heterocyclic systems which attract interest due to broad spectrum of their biological and other practically useful properties [1–11]. Reactions of mono- and disubstituted perfluorooxiranes with binucleophiles generally lead to the formation of heterocyclic compounds [1–3, 7–11]. Available data on reactions of trisubstituted perfluorooxiranes with binucleophiles are few in number.

We previously showed [12] that perfluoro(2,3-epoxy-2-methylpentane) (hexafluoropropylene dimer oxide, **I**) reacts with thiourea and urea in polar aprotic solvents to give unusual intramolecular haloform reaction products, 1-(2,2,3,3,3-pentafluoropropanoyl)-2-(2,2,2-trifluoro-1-trifluoromethylethyl)isothiourea and 1-(2,2,3,3,3-pentafluoropropanoyl)-3-(2,2,2-trifluoro-1-trifluoromethylethyl)urea, respectively. Heterocyclization of oxirane **I** to 2-amino-4-pentafluoroethyl-5,5-bis(trifluoromethyl)-4,5-dihydrooxazol-4-ol was observed in its reaction with urea in weakly polar dioxane [12].

In the present work we examined the reactions of perfluoro(2,3-epoxy-2-methylpentane) (**I**) with *o*-phenylenediamine and ethylenediamine in different solvents with a view to elucidate how the solvent nature affects the reaction direction and obtain new functionalized fluorinated organic compounds. Unlike the reaction with urea, oxirane **I** reacted with *o*-phenylenediamine (PDA) in dioxane via cleavage of the endocyclic C–C bond to give 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)-phenyl]propanamide (**II**). A probable mechanism of this reaction is shown in Scheme 1. Initially formed ketone **A** is stabilized by intramolecular haloform-type reaction involving attack by the amino group on the carbonyl carbon atom; as a result, amide **II** is formed instead of expected cyclization product. The ability of poly- and perfluoroalkyl isopropyl ketones to react with amines according to the haloform reaction pattern was demonstrated in [13, 14].

Apart from the IR and ^{1}H, ^{19}F, and ^{13}C NMR spectra and elemental analysis, the structure of propanamide **II** was determined by X-ray analysis. Compound **II** crystallized in a non-centrosymmetric space group. Several hierarchical levels may be distinguished in the crystal packing of **II**. The basic structural unit is a skewed stack of molecules oriented along the 0*a* axis. Molecules **II** within each stack are linked through intermolecular hydrogen bonds NH···O formed by

Scheme 1.

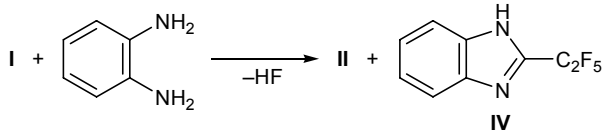


both NH groups with the carbonyl oxygen atoms in the neighboring molecules. This hydrogen bond is responsible for the rotation of the amide fragment $N^2C^{10}O^1$ through a dihedral angle of ~113° with respect to the benzene ring plane and *Z* conformation of that fragment (see figure). The CF_3 groups do not participate in specific intermolecular interactions, and they appear in staggered conformation. The benzene rings are packed along the [010] plane in a zigzag mode, so that the molecules are arranged head-to-tail and the packing becomes non-centrosymmetric. All stacks are assembled into layers separated by perfluoroalkyl tails. These layers may be regarded as the next hierarchical level.

The reaction of oxirane **I** with ethylenediamine in dioxane, diethyl ether, and acetonitrile led to the formation of 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)ethyl]propanamide (**III**) which was isolated as a colorless viscous liquid. Scheme 1 shows a probable mechanism of this reaction. Nucleophilic opening of the oxirane ring in **I** via intramolecular haloform-type reaction gives intermediate ketone **B** which undergoes rearrangement into amide **III**. The structure of **III** was determined on the basis of its IR, ^{1}H, ^{19}F, and ^{13}C NMR, and mass spectra and elemental composition.

Solvent nature was found to strongly affect the reaction direction and yield. When the reaction of **I** with PDA was carried out in dioxane, the reaction mixture contained (apart from compound **II** as the major product) a small amount of 2-pentafluoroethylbenzimidazole **IV** which was identified by ^{1}H and ^{19}F NMR; the spectral parameters of **IV** coincided with those reported in [9]. In going to more polar solvents (acetonitrile, diethylene glycol dimethyl ether), the yield of propanamide **II** decreased, and benzimidazole **IV** was formed as the major product (in diglyme; Scheme 2).

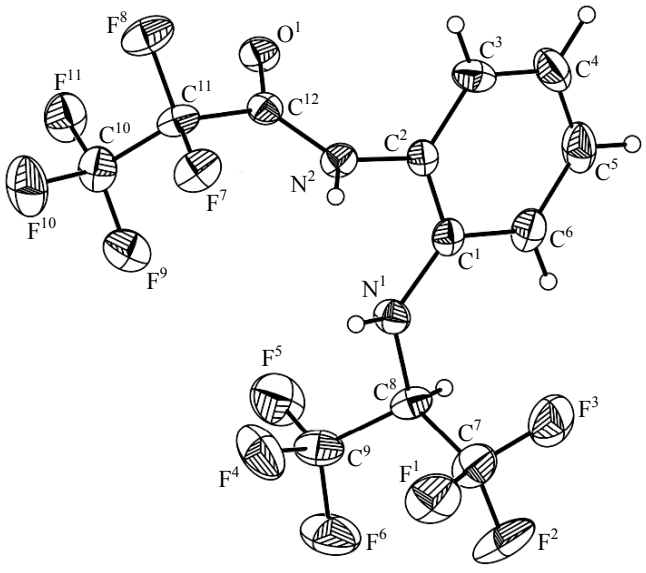
Scheme 2.



II : **IV** = 88 : 12 (dioxane), 44 : 56 (MeCN), 25 : 75 (diglyme).

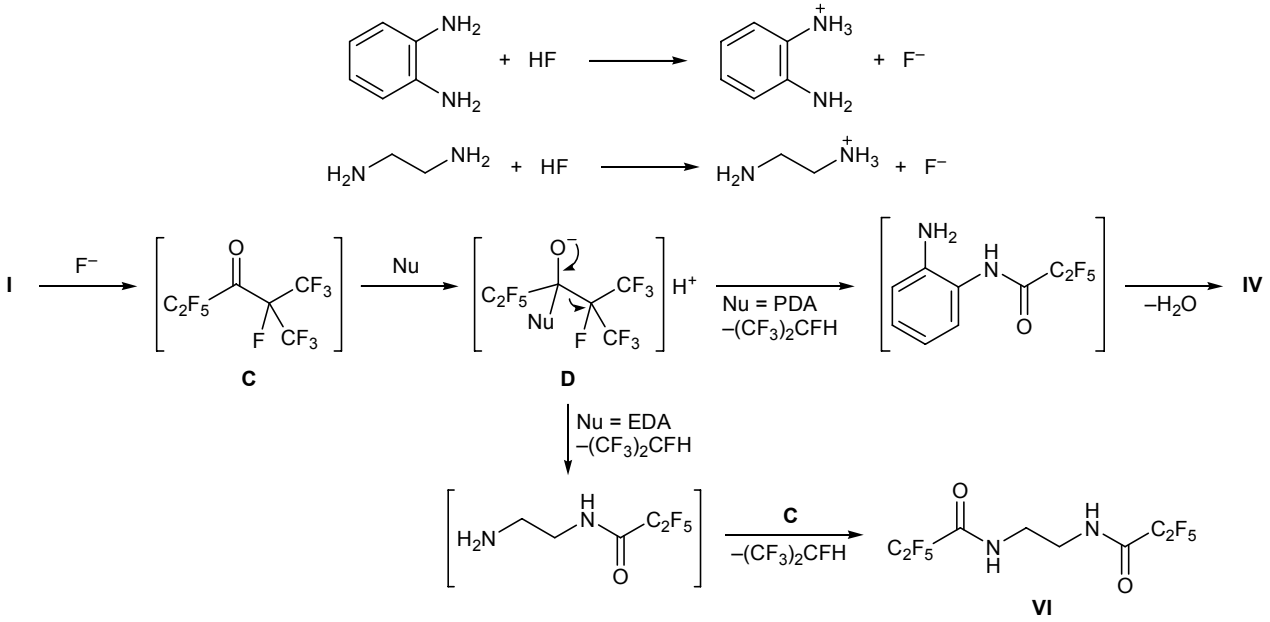
In the reaction mixture obtained from oxirane **I** and ethylenediamine we detected by IR and ^{19}F NMR spectroscopy a small amount of *N*,*N*′-ethylenebis-(2,2,3,3,3-pentafluoropropanamide) (**VI**). Its ^{19}F NMR spectrum coincided with that given in [7].

Compounds **IV** and **VI** may be formed as a result of concurrent isomerization of initial oxirane **I** by the



Molecular structure of 2,2,3,3,3-pentafluoro-*N*-[2-(2,2,2-trifluoro1-trifluoromethylethylamino)phenyl]propanamide (**II**) according to the X-ray diffraction data.

Scheme 3.



action of fluoride ion; generation of the latter in the reaction mixture is favored by increased solvent polarity. Haloform reaction of carbanionic intermediate **D** in the presence of *o*-phenylenediamine or ethylenediamine leads to benzimidazole **IV** or bis-amide **VI**, respectively (Scheme 3).

The yield of compounds **II** and **III** also depended on the isolation procedure. Treatment of the reaction mixture with water reduced the yield owing to partial acid hydrolysis. The best yield of propanamide **II** was obtained in dioxane, and of propanamide **III**, in diethyl ether provided that the isolation procedure excluded treatment with water.

Thus we have shown that the reactions of perfluorinated oxirane **I** with *o*-phenylenediamine and ethylenediamine involve cleavage of the oxirane C–C bond and yield propanamides **II** and **III**, respectively, as a result of regioselective nucleophilic attack on the disubstituted oxirane carbon atom and subsequent intramolecular haloform-type reaction. The described reactions may be regarded as a method for the preparation of new perfluorinated propanamide derivatives which attract interest as potential complexing agents and biologically active substances.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance-500 spectrometer at 500.1, 125.7, and 470.5 MHz, respectively, using tetramethylsilane (^{1}H, ^{13}C) and C_6F_6 as internal standards and DMSO-d_6 as solvent; the ^{19}F chemical shifts are given relative to $CFCl_3$ and are positive in stronger field. Signals in the ^{1}H and ^{13}C NMR spectra were assigned using two-dimensional heteronuclear ^{1}H–^{13}C HSQC and HMBC techniques. The mass spectra were obtained on a Fisons MD 800 GC–MS system (HP-5 quartz capillary column, 25 m × 0.25 mm, film thickness 0.25 μm; carrier gas helium; electron impact, 70 eV). The IR spectra were measured in the range 400–4000 cm^{-1} on a Perkin Elmer Spectrum One FT-IR spectrometer equipped with a diffuse reflectance (DR) or attenuated total reflectance (ATR) accessory (for solid samples). The elemental compositions were determined on a Perkin Elmer PE 2400 analyzer.

Oxirane **I** was synthesized according to the procedure described in [15]. The solvents used were purified and dried according to standard procedures.

The X-ray diffraction data for compound **II** were acquired on an Xcalibur 3 automatic four-circle diffractometer equipped with a CCD detector [115(2) K, λMo$K_α$, graphite monochromator, ω-scanning with a step of 1°], following standard procedure. No correction for absorption was introduced, and anomalous scattering was not evaluated. Orthohombic crystals, space group $Pna2_1$; unit cell parameters: a = 8.3579(8), b = 11.0885(14), c = 16.1577(16) Å; V = 1497.4(3) $Å^3$; Z = 4; μ = 0.209 mm^{-1}. Total of 3399 reflection intensities were measured in the range $3.05 < \theta < 26.38°$; 1519 reflections were independent (R_{int} = 0.0280);

completeness 95.7% for θ = 26.00°. The structure was solved and refined using SHELX software [16]. The refinement against F^2 was performed by the full-matrix least-squares procedure in anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms attached to carbons were placed into positions calculated on the basis of geometry considerations and were included in the refinement procedure in isotropic approximation with dependent thermal parameters according to the *riding* model. The NH hydrogen atoms were localized by the direct method, and their positions were refined independently. The final divergence factors were R_1 = 0.0265, wR_2 = 0.0302 for reflections with $I > 2\sigma(I)$ and R_1 = 0.0500, wR_2 = 0.0313 for all reflections; goodness of fit S = 1.011; Δρ = 0.196/–0.160 $\bar{e}$ Å^{-3}. The set of crystallographic data for compound **II** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 924237) and is available at *www.ccdc.cam.ac.uk/data_request/cif*.

2,2,3,3,3-Pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)phenyl]propanamide (II). *a*. A glass ampule was charged with 1.1 g (10.2 mmol) of *o*-phenylenediamine and 20 ml of dioxane, the mixture was cooled with dry ice, 1.62 g (5.1 mmol) of oxirane **I** was added, and the ampule was sealed, allowed to warm up to room temperature, and heated for 5 h on a water bath at ~80°C with intermittent shaking. The ampule was then cooled and opened, the mixture was filtered, and the filtrate was evaporated on a Petri dish to obtain 2.4 g of a light brown solid which contained (according to the ^{19}F NMR data), propanamide **II** and benzimidazole **IV** at a ratio of 88:12. The product was extracted with methylene chloride, the extract was evaporated, and the solid residue, 1.7 g, was purified by column chromatography on silica gel using methylene chloride–hexane (3:1) as eluent, followed by recrystallization from hexane. Yield of **II** 1.32 g (64%), colorless crystals, mp 85–86°C. IR spectrum (DR), ν, cm^{-1}: 3391 (NH), 3208, 2923 (C–H), 1701 (C=O), 1610 (C=C$_{arom}$), 1527 (amide II). ^{1}H NMR spectrum, δ, ppm: 5.51 d (1H, H′, ^3J = 11.3 Hz), 5.92 d.sept (1H, 1″-H, ^3J = 11.3, $^3J_{HF}$ = 7.0 Hz), 6.94 t.d (1H, 5′-H, J = 7.6, 1.2 Hz), 7.20 d (1H, 3′-H, J = 7.2 Hz), 7.23 d.d (1H, 6′-H, J = 7.9, J = 1.5 Hz), 7.28 d.d.d (1H, 4′-H, J = 8.2, 7.3, 1.2 Hz), 10.89 s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 56.16 sept (C$^{1″}$, $^2J_{CF}$ = 30.5 Hz), 106.82 t.q (C^2, $^1J_{CF}$ = 266.4, $^2J_{CF}$ = 38.1 Hz), 115.43 s (C$^{3′}$), 117.81 q.t (C^3, $^1J_{CF}$ = 286.8, $^2J_{CF}$ = 35.1 Hz), 120.24 s (C$^{5′}$), 122.56 s (C$^{1′}$), 123.75 q (C$^{2″}$, C$^{3″}$, $^1J_{CF}$ = 285.1 Hz), 127.85 s (C$^{6′}$), 128.51 s (C$^{4′}$), 139.74 s (C$^{2′}$), 156.27 t (C^1, $^2J_{CF}$ = 25.6 Hz). ^{19}F NMR spectrum, δ$_F$, ppm: 71.80 d (6F, 2″-F, 3″-F, $^3J_{HF}$ = 7.0 Hz), 82.80 s (3F, 3-F), 121.99 s (2F, 2-F). Found, %: C 35.75; H 1.45; F 51.45; N 6.97. $C_{12}H_7F_{11}N_2O$. Calculated, %: C 35.64; H 1.73; F 51.73; N 6.93.

The ^{19}F NMR spectrum of **IV** coincided with that given in [9].

b. As described above in *a*, from 3.65 g (11.56 mmol) of **I** and 2.49 g (23 mmol) of *o*-phenylenediamine in 30 ml of acetonitrile we obtained 4.8 g of a light brown solid which contained compounds **II** and **IV** at a ratio of 44:56 (^{19}F NMR). The product was extracted with methylene chloride, the extract was evaporated, and the residue, 3.02 g, was treated as described above in *a*. We thus isolated 1.4 g (30%) of compound **II**.

The undissolved material remaining after extraction with methylene chloride was purified by column chromatography on silica gel using chloroform–methanol (10:0.5) as eluent, followed by recrystallization from aqueous methanol. Yield of **IV** 0.98 g (36%).

c. A glass ampule was charged with 3.3 g (30.6 mmol) of *o*-phenylenediamine and 35 ml of dioxane, the mixture was cooled with dry ice, 4.9 g (15.5 mmol) of compound **I** was added, and the ampule was sealed, allowed to warm up to room temperature, and heated for 3 h on a water bath at ~80°C with intermittent shaking. The ampule was then cooled and opened, the mixture was poured into ice water, and the precipitate was filtered off and dried in air at room temperature. The product, 3.2 g, was a yellow–brown solid which contained propanamide **II** and benzimidazole **IV** at a ratio of 93:7 (^{19}F NMR). It was extracted with methylene chloride, and the extract was evaporated. The residue, 2.6 g, was purified by column chromatography on silica gel using methylene chloride–hexane (3:1) as eluent, followed by recrystallization from hexane. Yield of **II** 2.1 g (35%).

d. A glass ampule was charged with 1.8 g (16.7 mmol) of *o*-phenylenediamine and 20 ml of diglyme, the mixture was cooled with dry ice, 2.66 g (8.4 mmol) of compound **I** was added, and the ampule was sealed, allowed to warm up to room temperature, and heated for 1 h on a water bath at ~80°C with intermittent shaking. The ampule was then cooled and opened, the mixture was poured into ice water, and the precipitate was filtered off and dried in air at room temperature. The product, 1.8 g, was a gray–brown

solid containing propanamide **II** and benzimidazole **IV** at a ratio of 25 : 75 (^{19}F NMR). It was extracted with methylene chloride, and the extract was evaporated. The residue, 0.48 g, was purified by column chromatography on silica gel using methylene chloride–hexane (3 : 1) as eluent, followed by recrystallization from hexane. Yield of **II** 0.42 g (12%). The undissolved material remaining after extraction with methylene chloride was treated as described above in *b* to isolate 0.94 g (48%) of benzimidazole **IV**.

2,2,3,3,3-Pentafluoro-*N*-[2-(2,2,2-trifluoro-1-trifluoromethylethylamino)ethyl]propanamide (III). *a*. A glass ampule was charged with 2.52 g (42 mmol) of ethylenediamine and 25 ml of dioxane, the mixture was cooled with dry ice, 6.68 g (21 mmol) of compound **I** was added, and the ampule was sealed, allowed to warm up to room temperature, and heated for 2 h on a water bath at ~80°C with intermittent shaking. The ampule was then cooled and opened, the mixture was poured into ice water, the organic layer was separated and dried over $MgSO_4$, and the product was isolated by fractional distillation. Yield of **III** 3.1 g (41%), colorless viscous liquid, bp 220–222°C. IR spectrum (ATR), ν, cm^{-1}: 3345 (NH); 3093, 2955, 2885 (C–H); 1713 (C=O); 1539 (amide II). ^{1}H NMR spectrum, δ, ppm: 2.94 q (2H, 2′-H, J = 6.4 Hz), 3.28–3.33 m (3H, 1′-H, H′), 4.65 d.sept (1H, 1″-H, $^3J_{HH}$ = 10.5, $^3J_{HF}$ = 7.5 Hz), 9.38 br.t (1H, NH, J = 5.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 39.98 (C$^{1'}$), 46.34 (C$^{2'}$), 59.95 sept (C$^{1''}$, $^2J_{CF}$ = 29.1 Hz), 106.67 t.q (C^2, $^1J_{CF}$ = 265.2, $^2J_{CF}$ = 37.8 Hz), 117.85 q.t (C^3, $^1J_{CF}$ = 286.3, $^2J_{CF}$ = 35.1 Hz), 123.46 q.m (C$^{2''}$, C$^{3''}$, $^1J_{CF}$ = 284.7 Hz), 157.04 t (C^1, $^2J_{CF}$ = 25.4 Hz). ^{19}F NMR spectrum, δ_F, ppm: 71.20 d (6F, 2″-F, 3″-F, $^3J_{HF}$ = 7.5 Hz), 84.70 s (3F, 3-F), 125.07 s (2F, 2-F). Mass spectrum, m/z (I_{rel}, %): 355 (0.2) $[M - H]^+$, 287 (5) $[M - CF_3]^+$, 193 (19), 190 (17), 180 (100), 160 (26), 124 (13), 110 (19), 69 (5.6) $[CF_3]^+$, 58 (2.6). Found, %: C 26.78; H 1.81; F 58.96; N 7.53. $C_8H_7F_{11}N_2O$. Calculated, %: C 26.97; H 1.97; F 58.71; N 7.87. M 356.14

b. A flask equipped with a dry-ice reflux condenser and a magnetic stirrer was charged with 2.28 g (38 mmol) of ethylenediamine and 35 ml of acetonitrile, 6.0 g (19 mmol) of oxirane **I** was added dropwise, and the mixture was heated for 4 h under reflux with stirring, cooled, and poured into ice water. The organic phase was separated, dried over $MgSO_4$, and subjected to fractional distillation. Yield of **III** 2.4 g (36%).

c. As described in *b*, a mixture of 5.0 g (15.8 mmol) of oxirane **I** and 1.9 g (31.6 mmol) of ethylenediamine in 30 ml of acetonitrile was heated for 4 h under reflux with stirring. The mixture was cooled and filtered, the filtrate was passed through a layer of silica gel to remove tarry and salt-like impurities, the solvent was distilled off, and the residue was subjected to fractional distillation. Yield of **III** 2.9 g (52%).

d. A flask equipped with a dry-ice reflux condenser and a magnetic stirrer was charged with 2.84 g (47.3 mmol) of ethylenediamine and 55 ml of diethyl ether, 7.5 g (23.7 mmol) of compound **I** was added, and the mixture was stirred for 3 h at room temperature. A light yellow solid gradually separated and was filtered off, the filtrate was passed through a layer of silica gel to remove tarry and salt-like impurities, the solvent was distilled off, and the residue was subjected to fractional distillation to isolate 5.7 g (67%) of propanamide **III**. According to the ^{19}F NMR data, the light yellow solid contained a small amount of compound **VI** [7].

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