Synthesis and Stereochemistry of the 3,3-Difluoro-2,4-dialkyloxetane System[1]

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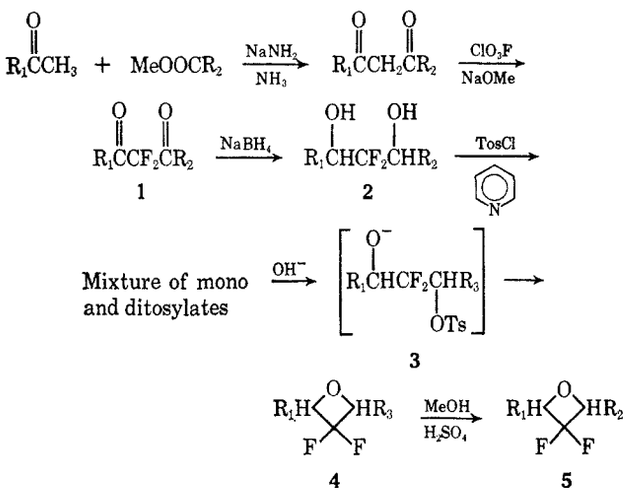
Methyl 11,11-difluoro-10,12-dihydroxyoctadecanoate was synthesized and separated into *erythro* and *threo* isomers, which were stereospecifically converted (*via* a monotosylate) into *trans* and *cis* isomers of 2-(ω-carboxyoctyl)-4-hexyl-3,3-difluorooxetane. The separated geometric isomers were assigned configurations on the basis of fluorine magnetic resonance spectra. Formation of the 3,3-difluorooxetane is a unique example of a relatively facile displacement reaction occurring on carbon adjacent to a *gem*-difluoro group.

Fluorooxetanes have been synthesized by carbonyl addition to fluoroolefins,[2] but to our knowledge there is no example of a fluorooxetane formed by 1-oxide ion displacement of a substituent in the 3 position. In this article we will describe such a synthesis and the accompanying stereochemistry.

Scheme I shows the steps that were used in the synthesis of 2-(ω-carbomethoxyoctyl)-4-hexyl-3,3-difluorooxetane, **5**.

SCHEME I

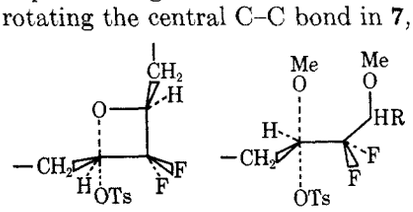
$R_1 = n$-hexyl; $R_2 = \omega$-carbomethoxyoctyl; $R_3 = \omega$-carboxyoctyl



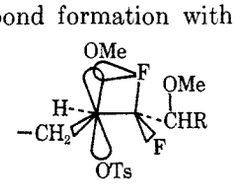
The conversion of **3** into **4** is superficially analogous to the ring closure of 2,2-disubstituted 1,3-bromohydrins,[3] but certain factors influencing ring formation appear to be different. The intramolecular reaction of 1,3-bromohydrins competes with a bimolecular displacement, and significant yields of oxetane are obtained only when the rate of bimolecular reaction is reduced relative to that of the ring closing reaction.[3] Alkyl substituents at the 2 position of 1,3-bromohydrins contribute sufficient steric effects so that ring closure becomes the predominant reaction.

As with reactions leading to other small ring systems,[4a] the formation of **4** can be rationalized on steric grounds by considering that in the transition state between **3** and **4**, the F–C–F bond angle is enlarged enough to relieve the steric compression of the geminal fluorines. However, the van der Waals radii of fluorine (1.35 Å) compared to hydrogen (1.2) and methyl (2.0) suggest that the steric effect is not much greater in the geminal difluoro than in methylene and would be certainly less than for geminal dimethyl. Bond angle measurements on *gem*-difluoro compounds show that there is actually a decrease in the F–C–F angle compared to the corresponding H–C–H angle,[5-7] and that the C–C–C angle in polytetrafluoroethylene[8] is larger than the normal tetrahedral angle suggesting that the F–C–F angle is smaller. These measurements do not support a model in which the fluorines are responsible for the facile formation of **4** because of relief of steric strain or because of electrostatic repulsion of the fluorines.

Displacement reactions adjacent to carbons containing fluorine substituents either do not proceed[4b] or do so only under vigorous conditions,[9] and our attempts to displace tosyl oxide by methoxide were unsuccessful. Monomethyl ether tosylate of **2** in sodium methoxide in methanol, conditions that convert 2-tosylate into **4**, gave only monomethyl ether and no detectable dimethyl ether of **2**. This suggests that the energy of the transition state, **6**, which yields oxetane, is lower than transition state **7**, which would give 2-dimethyl ether. The apparent differences of steric effects and angle strain between **6** and **7** do not seem adequate to explain the great difference in reactivity of compounds that would pass through these transition states. However, by rotating the central C–C bond in **7**, a fluorine



comes closer to the p orbital of the rehybridized carbon atom. Presumably this proximity permits an orbital overlap of the p electrons of fluorine and the p orbital, **8**, and inhibits bond formation with the nucleophile.



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(1) This work was supported by Public Health Service Research Grant H-4120 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

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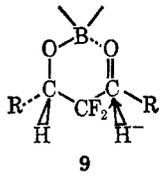
In the rigid system, **6**, which prevents or reduces this overlap because of the ring geometry, there would be no interference with the nucleophile and the reaction could proceed.[10]

The *cis* and *trans* isomers of **4** were separated by a combination of low temperature crystallization and silicic acid chromatography. It was possible to assign configurations to these isomers on the basis of fluorine magnetic resonance spectra, because the spin–spin coupling of the two dissimilar fluorines in *cis*-**4** gave an AB spectrum.

The diastereomeric alcohols, **2**, were isolated in pure form by a combination of crystallization and vapor phase chromatography (vpc). The configurational assignments for the *erythro* and *threo* isomers were based on the determination of which isomer of **4** was formed when each glycol was cyclized. On the assumption that the cyclization proceeds with a single inversion,[11] the *erythro* glycol gives the *trans* oxetane and *threo* gives the *cis*. The ring closure appeared to be completely stereospecific when pure isomers of **2** were used. When **4** was formed (from a mixture of tosylate **2** of unknown diastereoisomeric ratio) in various solvents under identical conditions, the amounts obtained varied over-all be a factor of 2 and were in the order of ethanol > methanol > *t*-butyl alcohol > 80% methanol (aqueous). With the exception of *t*-butyl alcohol of unknown Y value, the amounts of **4** formed were inversely proportional to the Y value of the solvent. This can be rationalized on the basis of a competing tosylate hydrolysis reaction that occurs faster in solvents of higher Y value thereby decreasing the concentration of reactants that give oxetane. An alternative explanation is that the entropy change in excluding solvent in the transition state, **6**, will be less for solvents of low Y, and this change is reflected in a lower free energy of activation. The amounts of *cis*- and *trans*-**4** obtained were also biased by the solvent with relatively more trans formed in *t*-butyl alcohol and aqueous methanol than in ethanol or methanol.

Solvation of β diketones during reduction with sodium borohydride can influence the ratio of diastereomeric glycols obtained.[12] In exploring this possibility, after reduction of **1** with sodium borohydride in methanol, 60% dioxane (aqueous), and *t*-butyl alcohol no large differences were found. The *erythro* to *threo* ratio was 1.5:1, 1.4:1, and 1.4:1 for the three solvents, respectively. As predicted by the rule of steric control of asymmetric induction,[13] in the intermediate complex, **9**, the preferred approach of the hydride ion to the



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remaining keto group is from the less hindered (hydrogen) side of the initially reduced carbonyl group; the choice of solvent evidently does not significantly affect this preference.

(10) The interaction of fluorine p electrons and benzene π electrons has been discussed indetail. W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965).

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Experimental Section[14]

Methyl 10,12-Dioxooctadecanoate.—Methyl 10,12-dioxooctadecanoate, bp 190–205° (300 μm) (37% yield), was prepared by a $NaNH_2$ assisted condensation of 2-octanone and dimethyl sebacate by a method previously described for analogs.[15] The copper salt of the diketo ester, which was used for isolation purposes, crystallized from methanol and melted at 87–88°.

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.90; H, 10.53.

Methyl 11,11-Difluoro-10,12-dioxooctadecanoate (1).—Using a previously described method for fluorination of active methylene groups,[16] 98.2 g (0.3 mol) of methyl 10,12-dioxooctadecanoate was fluorinated in methanol and sodium methoxide with perchloryl fluoride to give 112 g (0.3 mol) of crude product. A 10-g sample of the product was distilled in a short-path still in an oil bath at 185°, bp 170° (300 μm). After about one-half of the material distilled, the residue was very dark and the distillation was discontinued. An analytical sample was prepared from the crude product by elution from a silicic acid column using 4% (v/v) ether in pentane.

Anal. Calcd for $C_{19}H_{32}O_4F_2$: C, 62.96; H, 8.90; F, 10.48. Found: C, 62.94; H, 8.85; F, 10.52.

Methyl 11,11-Difluoro-10,12-dihydroxyoctadecanoate (2).—A solution of 5.0 g (0.014 mol) of distilled **1** in 25 ml of dioxane was mixed with 0.60 g (0.016 mol) of $NaBH_4$ in 5 ml of H_2O and stirred 15 min. The mixture was acidified with dilute HCl and extracted with ether. The washed and dried ($MgSO_4$) extract was evaporated and dissolved in 50 ml of hot petroleum ether (60–90°). Glycol that crystallized from the petroleum ether weighed 4.41 g. From mother liquor was obtained an additional 0.49 g of oily material. A second crystallization from petroleum ether (60–90°) gave an analytical sample of mixed diastereoisomers.

Anal. Calcd for $C_{19}H_{36}O_4F_2$: C, 62.27; H, 9.90. Found: C, 62.53; H, 10.11.

Isolation of *threo*-2.—Vpc with the nonpolar column showed the first crystal crop of **2** to be homogeneous. Mixed diastereoisomeric glycol diacetates were resolved by vpc on a polar column. The order to elution (based on evidence given below) was *threo* before *erythro*. The diacetates of **2** were made by dissolving 4.0 g of **2** in 20 ml of acetic anhydride containing 10 drops of pyridine. The solution was heated on a steam bath for 1 hr, cooled, hydrolyzed with water, and extracted with ether. After thorough washing, the dried ($MgSO_4$) extract was evaporated and gave 4.8 g of diacetates of **2**. After three crystallizations (−50°, 10% (w/v) acetone solution) **2**-diacetate (8.80 g) gave *threo*-**2**-diacetate (1.36 g). *threo*-**2**-Diacetate was converted into *threo*-**2** by transesterification in refluxing methanol containing 5% sulfuric acid. The *threo*-**2** thus obtained was crystallized from petroleum ether (30–60°), mp 92–93°. Vpc on the polar column of the diacetate of this sample showed no trace of *erythro*-**2**, infrared (KBr) 3.06 μ.[17]

Isolation of *erythro*-2.—*erythro*-**2**-Diacetate (205 mg) was collected from many runs on the preparative vpc column. Material better than 95% *erythro* was combined and eluted from a silicic acid adsorption chromatography column. The material eluded

(14) Elemental analyses were performed at Elek Microanalytical Laboratories, Torrance, Calif. Melting points were observed in a Thomas–Hoover capillary melting point apparatus and are corrected. Infrared absorption spectra were made on a Perkin-Elmer Infracord Model 137B or a Baird Associates Model B instrument with NaCl optics. Silicic acid adsorption chromatographic columns were prepared by pouring a slurry of silicic acid in acetone into a glass chromatographic tube and were activated by washing in sequence with two column volumes each of acetone, ether, and pentane. Analytical vpc was performed with a Barber–Colman Model 10 instrument using a 3 ft column of 0.29% SE-30 on 30–120 mesh glass beads as the nonpolar column, and a 3 ft column of 15% ethylene glycol succinate on acid-washed Chromosorb as the polar column. Preparative vpc was performed with an Aerograph Autoprep equipped with a 10 ft column of 30% diethylene glycol succinate on 60–80 mesh Chromsorb P.

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(16) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Amer. Chem. Soc.*, **80**, 6533 (1958).

(17) The authors are indebted to Mr. George Alexander, Laboratory of Nuclear Medicine and Radiation Biology, University of California at Los Angeles, for this spectrum.

by 8 and 12% ether in pentane was combined (178 mg) and converted into the glycol (125 mg) by transesterification with 5% H_2SO_4 in methanol. The sample was crystallized at room temperature from 10 ml of petroleum ether (30–60°) to give *erythro*-**2** (70 mg). Two additional crystallizations gave material with mp 57.5–58.5°. Vpc showed that the diacetate of recrystallized erythro-**2** contained less than 1% of the *threo* isomer. Infrared (KBr) showed peaks at 2.95 and 3.06 μ.[17]

Diastereoisomer Ratio Obtained by $NaBH_4$ Reduction of 1.—Approximately 80 mg of **1** in 1 ml of solvent (listed below) was added dropwise to an equal weight of $NaBH_4$ in 3 ml of solvent at room temperature. The solution was stirred for 30 min; excess $NaBH_4$ was destroyed with dilute HCl; and the sample was extracted into ether, washed, and dried ($MgSO_4$). Aliquots were acetylated (as described above) and analyzed for diastereoisomers by vpc. Methanol, *t*-butyl alcohol and 60% (v/v) dioxane (aqueous) gave *erythro* to *threo* ratios, respectively, of 1.53:1, 1.35:1, and 1.42:1.

Mono- and Dimethyl Ethers of 2.—A sample (450 mg) of mixed diastereoisomers of **2** was refluxed 16 hr in a excess of Ag_2O and methyl iodide. Vpc showed only monomethyl ether. Addition of fresh Ag_2O and refluxing 24 hr gave a mixture of mono and dimethyl ether (418 mg) which were separated by silicic acid chromatography. The dimethyl ether was eluted by 7% (v/v) ether in pentane and the monomethyl ether by 15% (v/v).

Anal. Calcd for $C_{20}H_{38}O_4F_2$ (monomethyl ether): C, 63.13; H, 10.06. Found: C, 63.20; H, 10.37. Calcd for $C_{21}H_{40}O_4F_2$ (dimethyl ether): C, 63.93; H, 10.22. Found: C, 64.00; H, 10.26.

Attempted Displacement of Tosyl Oxide by Methoxide from Monomethyl Ether Tosylate 2.—Monomethyl ether **2** (86 mg) (free of diether by criteria of vpc and silicic acid thin layer chromatography) was mixed with *p*-toluenesulfonyl chloride (100 mg) and 0.1 ml of pyridine. After 10 days at room temperature, the product was extracted with ether, washed with dilute HCl, and dried ($MgSO_4$). Evaporation of the solvent gave an oil (86 mg) which was chromatographed on a silicic acid column. The tosylate was eluted by 15% (v/v) ether in pentane, and was not completely free of monomethyl ether. A small sample (1.5 mg) of tosylate in an excess of sodium methoxide in methanol was sealed in a tube and heated at 100° for 2.5 days. The mixture was acidified (HCl), extracted with ether, washed, dried ($MgSO_4$), and treated with diazomethane. Thin layer silicic acid chromatography showed that the tosylate group had disappeared and that the major product was monomethyl ether of **2**. There was no evidence either from vpc or thin layer chromatography that dimethyl ether of **2** was present.

2-(ω-Carbomethoxyoctyl)-4-hexyl-3,3-difluorooxetane (5).—A mixture of **2** (7.8 g, 0.021 mol), *p*-toluenesulfonyl chloride (8.8 g, 0.046 mol), and 25 ml of pyridine was dissolved by warming, and the solution was allowed to stand at room temperature for 4 days. The reaction product was mixed with benzene, and it emulsified to a great extent when washed first with dilute HCl and then with water. The emulsion free portion of the benzene solution was dried (Na_2SO_4) and evaporated to give 11.4 g of crude tosylate **2**. Filtering broke the emulsion, and an additional 0.45 g tosylate was obtained. These conditions did not give completely tosylated product, as evidenced by O–H stretching absorption in the infrared spectrum.

Crude tosylate **2** (8.59 g) was refluxed in 200 ml of *t*-butyl alcohol containing KOH (3.6 g) for 4 days. The mixture was acidified with dilute HCl, and the product was isolated by ether extraction in the usual manner. The yield was 4.11 g of **4** (76% yield based on **2**). A small sample (approximately 1 g) was esterified with methanol containing 1% H_2SO_4, and the product distilled in a short-path still, bp 188–195° (230 μm), to give pure **5** (mixture of isomers). The ir spectrum (CCl_4) for *cis*-**5** showed peaks at 8.0 and 8.8 μ; for *trans*-**5**, 8.3 and 9.4 μ.

Anal. Calcd for $C_{19}H_{34}O_3F_2$: C, 65.49; H, 9.83; F, 10.91. Found: C, 65.50; H, 9.68; F, 10.69.

The effect of solvent on formation of 4 was determined by dissolving 250-mg samples of tosylate **2** (of unkonwn diastereoisomer content) in 20 ml of solvents (listed below) containing 100 mg of KOH. The samples (in sealed tubes) were heated at 80° for 18 hr. The acidified product was isolated by ether extraction in the usual manner. Silicic acid chromatography separated **4** (eluted by 10% (v/v) ether in pentane) from unreacted starting material (eluted by ether). The amounts of **4** recovered were 66 mg from methanol, 42 mg from 80% methanol (aqueous), 86 mg from ethanol, and 50 mg from *t*-butyl alcohol. Vpc of the methyl esters (diazomethane) of these isolated samples of **4** showed that equal amounts of *cis* and *trans* formed in methanol and ethanol, but in *t*-butyl alcohol and aqueous methanol the *trans* to *cis* ratio was 1.4:1.

Separation of *cis*- and *trans*-4.—Vpc was used to monitor the separation of isomers of **4** (as the corresponding methyl esters, **5**). On a polyester column *cis*-**5** is eluted before *trans*. **4** (4.0 g of crude material) was crystallized four times from a 10% (w/v) acetone solution at Dry Ice–acetone temperature to give 95% pure *trans*-**4** (0.61 g). This *trans* fraction was eluted by 10% (v/v) ether in pentane from a silicic acid chromatographic column. The *trans* isomer was eluted slightly faster than the contaminating *cis*, and 0.30 g of 98% pure *trans*-**4**, mp 30.5–33.5°, was collected. This material was used for fluorine magnetic resonance spectra.

The *cis* isomer of **4** was purified by successive silicic acid chromatography of mother liquor material from crystallizations described above. By eluting the sample with 5 and then 10% (v/v) ether in pentane, 0.12 g (oil) of the slower moving *cis* isomer was obtained 90% pure (contaminated by 10% *trans* isomer). This was used for fluorine magnetic resonance spectra.

Configuration Assignment of *cis*- and *trans*-4.—The fluorine magnetic resonance spectra[18] of CCl_4 solution of 98% pure *trans*-**4** and 90% pure *cis*-**4** were obtained with a varian HR 60 instrument working at 56.4 mc. Calibration was by the side-band technique. The isomer defined as *cis* gave an AB spectrum with a coupling constant of 273 cps and chemical shifts upfield from trifluoroacetic acid of 28.6 and 70.9 ppm for the centers of the two doublets. The *trans* isomer gave an upfield shift from trifluoroacetic acid of 47.6 ppm.[19]

Stereospecificity of 2 Forming 4.—Samples of *threo*-**2** (9.2 mg) and *erythro*-**2** (9.6 mg) were each dissolved in 25 ml of pyridine containing 30 mg of *p*-toluenesulfonyl chloride. After 5 days at room temperature, the tosylates were ether extracted, washed with dilute H_2SO_4 and water, and then dried ($MgSO_4$). One milliliter of a solution of 140 mg of KOH in 5 ml of methanol was added to each tosylate. The samples in sealed tubes were heated at 65° for 18 hr. Isolation was made by ether extraction after acidification of the samples with dilute H_2SO_4. The extracts were washed and dried ($MgSO_4$), and the solvent was evaporated. Esterification with diazomethane and chromatography on silicic acid as described above served to remove unreacted tosylate. Vpc showed that *threo*-**2** forms *cis*-**4** and that *erythro*-**2** forms *trans*-**4** with stereospecificity not less than 98% (based on estimated limiting sensitivity of vpc analysis).

Registry No.—17414-54-9; **2** (*threo*), 17393-51-0; **2** (*erythro*), 17393-52-1; **4** (*cis*), 17393-53-2; **4** (*trans*), 17393-54-3; **5** (*cis*), 17393-55-4; **5** (*trans*), 17393-56-5; methyl-10,12-dioxooctadecanoate, 17414-55-0.

(18) The authors are indebted to Dr. F. A. L. Anet, Chemistry Department, University of California at Los Angeles, for these spectra.

(19) These data are consistent with values reported earlier for geminal fluorines by N. Muller, P. C. Lauterbur, and G. F. Svatos, *J. Amer. Chem. Soc.*, **79**, 1807 (1957), and W. D. Phillips, *J. Chem. Phys.*, **25**, 949 (1956).