The Effect of Ring Size on Tetrahedral Displacement Reactions of Cyclic Imidates. Synthesis of *O*-(Fluoroalkyl)lactims and Higher *O*-Alkyllactims from Lower *O*-Alkyllactims

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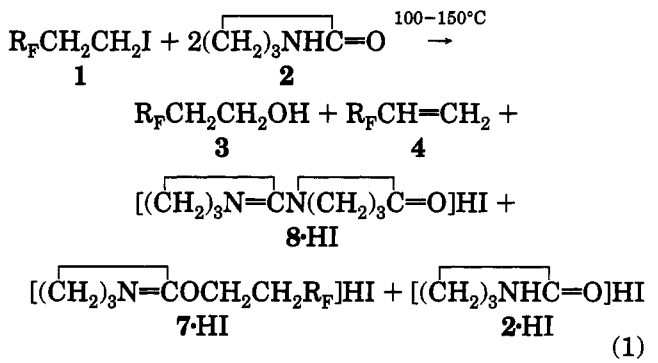
A recently developed synthesis of 2-(perfluoroalkyl)ethanols ($R_FCH_2CH_2OH$) is based on heating 2-(perfluoroalkyl)-1-iodoethanes $R_FCH_2CH_2I$ with an amide, e.g., *N*-methylformamide or a lactam, 2-pyrrolidinone. The presumed *O*-[2-(perfluoroalkyl)ethyl]lactim intermediates have now been prepared in good to excellent yields (60–90%) by heating a lower molecular mass *O*-alkyllactim with a higher-boiling alcohol, e.g., with $R_FCH_2CH_2OH$, to displace the lower boiling alcohol. Competitive rate experiments showed that a 7-membered *O*-methyllactim reacted four to five times faster than did the 5-membered *O*-methyllactim. This difference is attributed to increased eclipsing strain, commonly called "*I-strain*". In a "planar" 5-membered lactim ring, the engendered eclipsing strain appears to be greater than in the more flexible 7-membered ring. Reactant ratio and reaction conditions also affected the yield of lactim ether. Preparatively, reaction of $C_6F_{13}CH_2CH_2OH$ (**3**) with *O*-ethylbutyrolactim (**6**) gave *O*-[2-(perfluorohexyl)ethyl]butyrolactim (**7**) in an 89.2% yield (on unrecovered **3**) at 67.9% conversion. Yield was limited by dealkylation and condensation reactions that occurred during long heating times. By contrast, alcohol **3** with *O*-methylcaprolactim (**10**) gave 7-membered *O*-[2-(*F*-hexyl)ethyl]caprolactim (**11**) in 98% yield at 90% conversion.

Introduction

Hitherto unknown, cyclic imidates of higher molecular mass alcohols (C_8 or greater, and of certain fluorine-substituted alcohols) have potential synthetic and scientific importance. Recently, an imidate $R(CH_2)_2OCH(=NMe)$, where R signifies a perfluoroalkyl (R_F group), was proposed as intermediate in a novel synthesis of $C_6F_{13}CH_2CH_2OH$ (**3**) from $C_6F_{13}CH_2CH_2I$ (**1**) and an ambident amide, e.g., *N*-methylformamide (NMF).[1,2] Alcohol **3** is not readily prepared by classical methods from iodoalkane **1** but is obtained in high yield by thermal alkylation of NMF. The yield of side product 2-(perfluoroalkyl)ethene (**4**) is only 2–4%.[1] Substitution of iodoalkane **1** by typical nucleophiles (^-OH, ^-OAc, or ^-CN) gives a large proportion of side product **4**.[3] In another approach, a lactam such as 2-pyrrolidinone (**2**) is used as the nucleophilic partner with **1** to give an excellent overall yield of alcohol **3** (eq 1).[4,5] In this synthesis of alcohols, 2 mol of ambident lactam **2** are used in forming **3** and the iminolactam coproduct (**8**·HI salt), and there is *no accompanying formate ester*, as is obtained in reaction of **1** with NMF[1] or formamide.[2] Again, alkene **4** is a minor side product. Further elaboration and important elements of this second novel synthesis of fluorinated alcohol **3** and its congenors from lactam **2** are being reported separately.[5c] This paper describes a useful synthesis of *O*-(fluoroalkyl)lactims which are important as the presumed intermediate in thermal alkylation reactions of lactams. These new lactims will aid significantly in our search for understanding these new reactions and to probe the generality of the proposed mechanism.[2]



(1)

Synthesis of *O*-(Fluoroalkyl)lactims and Higher *O*-Alkyllactims. Known methods[6,7] for the synthesis of these model compounds are quite limited in scope. Reaction of dimethyl sulfate or diethyl sulfate with lactam **2** gives only 30–60% yield of *O*-methylbutyrolactim (**5**) or *O*-ethylbutyrolactim (**6**), respectively;[8–11] surprisingly,

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(3) Brace, N. O.; Marshall, L. W.; Pinson, C. J.; van Wingerden, G. *J. Org. Chem.* **1984**, *49*, 2351.

(4) (a) Brace, N. O. 10th International Symposium on Fluorine Chemistry; Vancouver, BC, Canada, Aug 1–6, 1982; Abstract O-19. (b) Brace, N. O. Paper (no. 75) read at Ninth Winter Fluorine Conference, ACS, St. Petersburg, FL, Feb 3, 1989; Reaction of Ambidentate Lactams with 2-(Perfluoroalkyl)-1-iodoethanes.

(5) (a) Brace, N. O. Paper read at Albert S. Jache Symposium, June 16, 1990, Marquette University, Milwaukee, WI. (b) Brace, N. O. Poster no. 43, Fluorine Division of the 203rd National ACS Meeting, San Francisco, April 6, 1992; F-(Alkyl)-substituted Imidates as Intermediates in the Synthesis of F-(Alkyl)-substituted Alcohols. (c) Brace, N. O., Manuscript in preparation.

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ϵ-caprolactam (**9**) gives 70%[12] or 93.5%[13] yield of *O*-methylcaprolactim (**10**). Lactim **6** is also obtained from **2** by reaction with triethyl tetrafluoroborate.[7] Regrettably, higher alkyl sulfates cannot be used for this type of alkylation. In most cases they are unavailable, and bis-[2-(perfluoroalkyl)ethyl] sulfates are inert to nucleophiles because of the strongly electron-withdrawing β-perfluoroalkyl group.[14] Higher *O*-alkyllactims have been prepared from caprolactam **9** through the intermediate imidoyl chloride.[15] This method fails, unfortunately, with the simple 5-membered-ring lactim ether **5**. Etienne and Correia[9] heated 2-chloro-1-pyrroline and sodium methoxide in methanol or the imidoyl chloride and alcohol at 140 °C in a sealed tube; neither method gave **5**. Ugi and co-workers,[16,17] in kinetic studies, also observed the extreme unreactivity of 2-chloro-1-pyrroline toward nucleophiles, a fact that had been earlier noted by Tafel amd Wassmuth.[17b] One known, but little practiced, method remained. By heating a lower *O*-alkyllactim with a higher boiling alcohol and removing the more volatile alcohol by careful distillation, Benson[18] obtained *O*-butylcaprolactim (43% yield) and *O*-propyl- or *O*-butylbutyrolactim in 50–60% yield from the corresponding *O*-methyllactims. Etienne and Corriea[9] modified the thermal process by using up to 2 mol of sodium alkoxide to accelerate the reaction with lactim **5** or **6** in toluene solution. Thus, we chose to extend this lactim synthesis, if possible, to higher *O*-alkyl- and *O*-[2-(perfluorohexyl)ethyl]lactims having 5-membered and 7-membered rings. The proposed steps are briefly outlined in Scheme 1.

Results

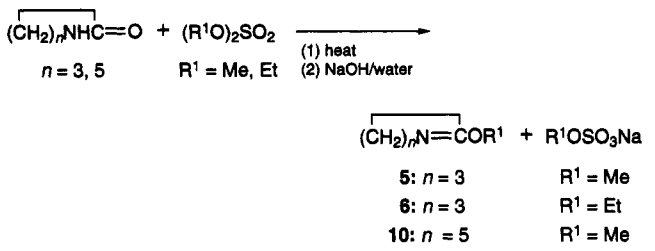
Synthesis of *O*-Octylbutyrolactim (13). Displacement reaction of readily available octanol (**12**) with lactims **5** and **6** was studied as a guide to such reactions with the more expensive fluoro alcohol **3** and also to provide *O*-octylbutyrolactim (**13**) for further studies. Sodium octyloxide (from **12** and NaH) with lactim **6** gave only 11% yield of the desired lactim **13**. Octanol (66%) and 1-(1-pyrrolin-2-yl)-2-pyrrolidinone (**8**) (2%, from reaction of lactam **2** with lactim **6**) were recovered. Next, we heated a mixture of **12** and lactim **5** (mol **12**:**5** = 2.89) in an evacuated, sealed tube at 120 °C (Table 1, expt 1) and obtained an equilibrium mixture containing 45% of **13** in 3 h. Further heating gave no increase in **13**, but dealkylation and condensation products (see below). Very little *N*-methyl-2-pyrrolidinone (**14**) or *N*-octyl-2-pyrrolidinone were found, contrary to previous experience.[9,18]

The reaction equilibrium was shifted by heating the reactants (mol **12**:**6** = 2.89) in a dilute benzene solution and removing the binary azeotrope of benzene and ethanol (bp 68.42 °C[19]) in a spinning band column at a very high reflux ratio. After 20 h, half of **12** had been converted to **13**. Distillation afforded pure (99% by GC) lactim **13** in 84.8% yield at 60.7% conversion of **6** (83% recovery).[20]

Synthesis of *O*-[2-(perfluorohexyl)ethyl]butyrolactim (7). The effect of the *mol ratio of reactants* on the yield of lactim **7** was ascertained experimentally (Table

Scheme 1. Synthesis of the Higher *O*-Alkyllactims from Displacement of the Lower *O*-Alkyllactims with a Higher Boiling Alcohol

Step I: Synthesis of lower *O*-Alkyllactims



Step II: Higher *O*-Alkyllactim by Heating with Higher Alcohol

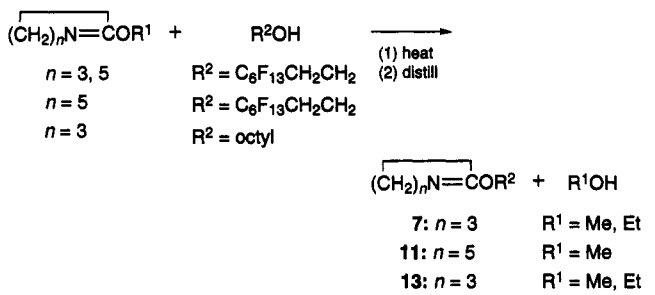


Table 1. Effect of Reactant Ratio of Alcohol and Lactim Ether on Formation of Higher *O*-Alkyllactam Ethers at 120 °C[a]

Expt 1: mol **12**:**5** = 2.89[b]					
time, h	0.5	1.50	3.00	4.00	5.00
lactim ether **13**,[c] mol %	24.6	35.5	44.4	43.4	45.2
Expt 2: mol **3**:**6** = 1.06[d]					
time, h	1.0	2.0	3.0	4.0	
lactim ether **7**, mol %	3.27	4.80	8.80	12.8	
Expt 3: mol **3**:**5** = 1.02[e]					
time, h	1.0	2.0	3.0	5.0	
lactim ether **7**, mol %	3.39	6.01	8.13	11.0	
Expt 4: mol **3**:**5** = 3.03[f]					
time, h	1.0	2.0	4.0		
lactim ether **7**, mol %	49.9	49.7	45.0[g]		
Expt 5: mol **3**:**5** = 11.3[h]					
reaction time, h	1.0	2.0			
lactim ether **7**, mol %	100	94.3[g]			
Expt 6: mol **3**:**6** = 0.298[i]					
time, h	0.5	3.00	5.00	7.00	
lactim ether **7**, mol %	1.26	10.2[g]	17.6[g]	24.6[g]	

[a] A Carius-type heavy glass wall tube, 20.0-mL volume, fitted with a Teflon sealing valve, was charged with reactants, sealed, cooled to −196 °C, evacuated, and filled with nitrogen and evacuated to 8 mm and sealed again. Samples were analyzed by capillary GC with either 1,2-dichlorobenzene or toluene reference.[20] [b] Reaction of 1-octanol (**12**) with lactim **5** is described in the supplementary material.[20] [c] *O*-Octylbutyrolactim (**13**). [d] See Table XII[20] for experimental details. [e] See Table XIII.[20] [f] See Tables XIV and XV.[20] [g] Dealkylation and condensation products of the reactive lactim ether were obtained in small amounts. [h] See Table XVI;[20] there was no detectable lactim ether **5** in the product mixture. [i] See Table XVII,[20] increasing amount of side products were observed with reaction time and a corresponding decrease in unreacted lactim **6**.

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(13) Luessi, H. *Chimia* **1973**, *27* (2), 65–68.
(14) Annello, L. G.; Sweeney, R. F. *J. Org. Chem.* **1970**, *35*, 118.
(15) Jurczak, J.; Kozluk, T.; Kulicki, W.; Pietraszkiewicz, M.; Szymanski, J. *Synthesis* **1982**, 382.
(16) Ugi, I.; Beck, F.; Fetzer, U. *Chem. Ber.* **1962**, *95*, 126.
(17) (a) Pure 2-chloro-1-pyrroline may be recrystallized unchanged from *aqueous acetone and is unaffected by aqueous KOH!* "Die Tatsache, dass 2-chlor-Δ^1-pyrrolin sich aus wässrigem Aceton umkristallisieren läszt und selbst gegen Kalium hydroxyd recht stabil ist[17b] demonstriert die extrem geringe S_N2-bzw. AE-Reactionsbereitschaft von Carbonsäureimidchloriden. Umsetzungen nach S_N1 sind hier aus Ringspannungsgrunden unmöglich." (b) Tafel, J. ; Wassmuth, O. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2841.
(18) Benson, R. E. U. S. Patent 2,516,293, to E. I. Du Pont de Nemours and Co., July 25, 1950; *Chem. Abstr.* **1951**, *45*, 640f.
(19) Horsley, L. H. *Anal. Chem.* **1947**, *19*, 508.

1, expts 2–5). A very high reactant ratio (mol **3**:**5** = 11.3) gave complete conversion to lactim **7** in 1 h at 120 °C. At mol **3**:**5** = 3.035, 50% conversion to lactim **7** resulted in 1 h, and the amount of **7** began to decrease after 2 h (expt 4, Table 1; see Tables XIV and XV, also).[20] At mol **3**:**5** = 1.02, 3.4 mol % conversion to **7** was achieved after 1 h and conversion rose to 8.1 mol % in 3 h; a similar reaction of **3** and **6** gave comparable results (expts 2 and 3, Table 1; see also Tables XII and XIII in the supplementary material).[20] If an inverse mol ratio (**3**:**6** = 0.298) was employed (expt 6, Table 1; see also Table XVII in the supplementary material), equilibrium was reached more slowly than with a similar excess of **3** over lactim **5**. In all cases, extending the heating time past the attainment of equilibrium caused loss of lactim **7** and formation of side products.

Accordingly, in these equilibrium reactions,[9,18] two means could be used to shift the equilibrium toward the less volatile lactim ether: first, remove volatile alcohol by distillation, or second, employ a higher molar amount of one (preferably more reactive) of the reactants.[7,9]

The product mixture of expt 4, Table 1 was distilled in a spinning band column to substantiate GC analyses. This gave lactim **7** in 44.8% yield (91.1% purity), *O*-methyllactim **5** (in mixture with **3** and MeOH) in 93.6% recovery, and alcohol **3** in 98.4% recovery. The distilled yield of **7**, based on conversion of alcohol **3**, was 98%. On the basis of the amount of **5** used, the yield of **7** was 93.6%. A complete record of these results is given in Table XV.[20] Alternatively, heating of lactim **6** with **3** (mol **3**:**6** = 1.386) in a short path still and removing ethanol to a cold trap gave lactim **7** in 68.0% yield (79.3% on unrecovered **6**). However, this process required 36 h, or more, to go to completion.

Preparation of *O*-[2-(perfluorohexyl)ethyl]caprolactim (11). Facile reaction occurred when a mixture of *O*-methylcaprolactim (**10**) and alcohol **3** (mol **10**:**3** = 2.03) was heated in a spinning band column. Methanol was removed at high reflux ratio and lactim **11** distilled in 93.4% yield (98.5% purity, GC); 98% of unreacted lactim **10** was recovered. Similarly, lactim **10** and alcohol **3** (2 mol to 1, respectively) was heated at 120–130 °C in a simple still under a slow stream of nitrogen and methanol condensed in a cold trap. Distillation in a Vigreux column gave first a mixture of **10** and **11** and then lactim ether **11** in 52% yield (98% purity). The total distilled yield of **11** was 72%. Side reactions were not observed and distilled **11** remained unchanged on standing. Other preparative experiments are described in the supplementary material.[20]

The Effect of Ring Size on Relative Rates of Displacement Reactions: Direct Competition Experiments. To determine quantitatively the rate difference between 5-membered and 7-membered lactim ethers in these tetrahedral displacement reactions, direct competition experiments were carried out (Table 2). In the first set, equimolar amounts of lactim *methyl* ethers **5** and **10** were heated with alcohol **3** at 120 °C in an evacuated, sealed tube. Molar amounts of lactims were found by GC, and the ratio of **11**:**7** (7:5-membered lactim) decreased linearly over a 5-h time period. The least-squares regression (LS) of this ratio over time gave an intercept of mols **11**:**7** = 4.37 (r = 0.974), which is a measure of the *initial* relative rates of reaction.

Table 2. Selectivity for *O*-[2-(Perfluoroalkyl)ethyl]lactims 11 and 7 from Lower *O*-Alkyllactims with Alcohol 3[a]

O-Methylbutyrolactim (**5**) and *O*-Methylcaprolactim (**10**)[b]

5 + **10** + $C_6F_{13}CH_2CH_2OH$ (**3**) → **7** + **11** + MeOH

	mols **10**/**5** = 1.0				
reaction time, h	0.0	1.0	2.0	3.0	5.0
product lactims (**11**:**7**)	(4.37)[c]	4.22	3.76	3.51	3.14

O-Ethylbutyrolactim (**6**) and *O*-Methylcaprolactim (**10**)[d]

6 + **10** + $C_6F_{13}CH_2CH_2OH$ (**3**) → **7** + **11** + MeOH + EtOH

	mols **10**/**6** = 1.1				
reaction time, h	0.0	1.0	2.0	5.0	8.0
product lactims (**11**:**7**)	(5.35)[e]	5.01	4.97	4.23	3.40

[a] Reaction in an evacuated, sealed tube at 120 °C. Amounts of substances were determined by capillary GC (Table III).[20] [b] Reaction mixture contained the following: lactim **5**, 0.4952 g, 4.9958 mmol; lactim **10**, 0.6406 g, 5.001 mmol; alcohol **3**, 1.8467 g, 5.072 mmol. See Table XIII and supplementary material[20] for experimental details. [c] The intercept A of the equation time (h) = $A + B(\mathbf{11}:\mathbf{7})_t$ at zero time was 4.37, B = 0.259, correlation r = 0.974. [d] Reaction mixture contained the following: lactim **6**, 0.5441 g, 4.816 mmol; lactim **10**, 0.6617 g, 5.203 mmol; alcohol **3**, 1.8598 g, 5.108 mmol. See Table XII.[20] [e] The intercept A, by least squares of the equation: time (h) = $A + B(\mathbf{11}:\mathbf{7})_t$ was 5.35, B = 0.238, r = 0.992.

In the second set of experiments, *O-ethyl*lactim **6** and *O*-methyllactim **10** were allowed to react with **3** at 120 °C. LS for the equation, time (h) = A + B (**11**:**7**), gave A (intercept) = 5.35 mol **11**:**7** (r = 0.992). In this instance also, the relative rate was larger in favor of the 7-membered lactim, and these results may be used to calculate an *O*-methyl- to *O*-ethylbutyrolactim partial rate factor of 1.22. The greater reactivity of the 7-membered lactim in displacement reactions with alcohol is mirrored in the higher yields in the alkylation of the corresponding lactam by dialkyl sulfate.

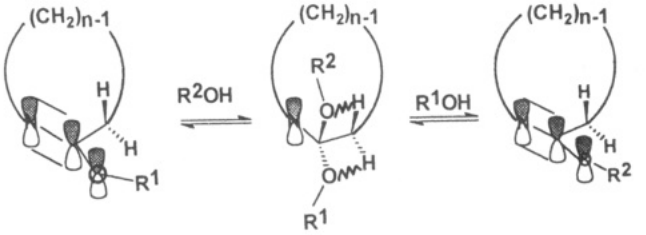
The new compounds of this study were thoroughly characterized by GC, NMR, IR, and MS/GC methods. Tables with complete data for these experiments and the NMR and IR spectra of new lactim ethers **7**, **11**, and **13** (as figures, with peak tables) are given in the supplementary material.[20] Chemistry of these new compounds, already alluded to, is under further study.

Discussion

Tetrahedral Displacement Reactions of Lactims. Deslongchamps has interpreted tetahedral displacements on imino ethers and iminium salts in terms of steric and stereoelectronic effects.[22] In the preparation of *5-membered* and *7-membered* lactims by displacement of alcohol from lactim **5** or lactim **10**, respectively, the intermediates may be depicted as given in Scheme 2. In both cases, the rings have little *angle* strain, but the change of the sp^2 imidate carbon atom to sp^3 configuration would be expected to generate eclipsing strains caused by C–H bonds. In the tetrahedral intermediate the geminal OR groups are flanked by two hydrogen atoms on the adjacent carbon atom, and these strains cannot be readily relieved by the twisting or bending of the *5-membered* ring. Further, the bulky alkoxy groups may impose additional restraints on the usual bending of the 5-membered ring into an envelope form. By contrast, the 7-membered ring "orthoamide" intermediate from lactim **10** can bend into a variety of conformations to relieve the additional eclipsing strain

(20) See supplementary material.
(21) Deslongchamps, P. *Stereoelectronic Effects In Organic Chemistry*; Pergamon Press: New York, 1983; Chapter 4.
(22) Reference 21, Chapter 6, pp 210–221.

Scheme 2. Tetrahedral Displacement Mechanism for the Synthesis of the Higher *O*-Alkyllactims

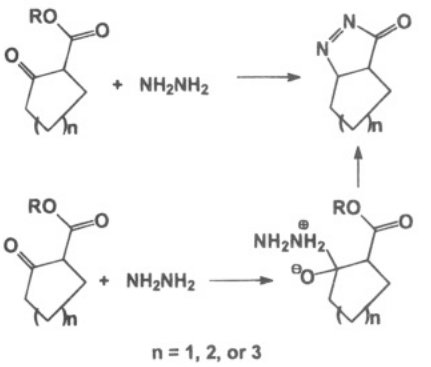


No.	n	R^1	R^2	No.	n	R^2
5	3	Me	$R_FCH_2CH_2$	7	3	$R_FCH_2CH_2$
6	3	Et	Octyl	13	3	Octyl
10	5	Me	$R_FCH_2CH_2$	11	5	$R_FCH_2CH_2$

imposed by two geminal alkoxy groups. In general terms, these effects appear to be consistent with the "I-strain" concept developed by Brown, Fletcher, and Johannesen.[23] Indeed, these authors suggested that an appropriate test of the I-strain concept would be to correlate "the change in reactivities of the common ring compounds with ring size." In the reaction portrayed, an sp^2 carbon atom is converted to a geminally substituted sp^3 carbon atom. I-strain theory predicts that the reaction rate will be slower in the 5-membered ring because of increased crowding and the resulting eclipsing strains in the smaller ring compound.[24,25] There is precedent in the heats of hydrogenation of cyclopentene and cyclohexene and of 1-methylcyclopentene and 1-methylcyclohexene.[26 a,b] The exothermic heat is *less* for the cyclopentenes than for the corresponding cyclohexenes, even though the double bond in the 5-membered ring is more strained than in the 6-membered ring. This is attributed to the "greater residual eclipsing strain" in the cyclopentane hydrogenation products. Comparison of homologous cycloalkenes shows that cyclopentene and cycloheptene release nearly the same amount of heat: heats of hydrogenation, gas phase, 82 °C; $-\Delta H$ (kcal/mol) = −26.92 (C_5), −28.59 (C_6), −26.52 (C_7).[26a] These data indicate, roughly, that hydrogen crowding in cycloheptane causes nearly the same falling off in exothermic heat as does C−H eclipsing in cyclopentane. Heats of combustion of cyclopentane and cycloheptane give the same result: ($-\Delta H$, kcal/CH_2 group, gas phase, 25 °C: −158.7 (C_5), 157.4 (C_6), 158.3 (C_7).[26a]

Though they correlate a different reaction type, these precedents from hydrogen addition to cycloalkenes appear to have the same underlying causes as in the lactim series. Unpublished work by Silversmith and Ekiko[27] on pyrazolone formation from cyclic β-keto esters and hydrazine has a close similarity to the imidate substitution reaction. These workers found that 5-membered keto esters (Scheme 3, $n = 3$) reacted more slowly than 6- or 7-membered keto esters (n = 4 or 5). The additional eclipsing strain

Scheme 3. Five-, Six-, and Seven-Membered Pyrazolones from Cyclic β-Keto Esters and Hydrazine (Silversmith and Ekiko)



generated in the transformation of sp^2 to sp^3 carbon atom during pyrazolone formation appears to have a similar effect on relative reaction rates.

This interpretation is also consistent with the greater reactivity of the *O*-methylbutytrolactim **5** over *O*-ethylbutyrolactim **6**. The larger ethoxy group of **6** may cause greater eclipsing strain. It is planned to carry out molecular mechanics calculations to establish more definitely these tentative conclusions.

Side Reactions in the Lactim Tetrahedral Displacement Reaction. Dealkylation and condensation reactions of imidate intermediates were reported in amide alkylation reactions, and possible reaction steps were proposed.[2] In the case of lactims **5** to **13** of this present work, these reactions (eqs 2 and 3) would result in lactam

$$\underset{\mathbf{5-13}}{(\overbrace{CH_2)_n N{=}C}OR^1} + H^+ \xrightarrow{\text{heat}} \underset{\mathbf{2}}{(\overbrace{CH_2)_n NHC}{=}O} + \underset{\mathbf{4}\text{ (or other)}}{RCH{=}CH_2} \quad (2)$$

$$\mathbf{2} + \underset{\mathbf{5}}{(\overbrace{CH_2)_n N{=}C}OCH_3} \xrightarrow{\text{heat}} \underset{\mathbf{8}}{(\overbrace{CH_2)_3 N{=}C}N(\overbrace{CH_2)_3 C}{=}O} + CH_3OH \quad (3)$$

2 being formed along with an alkene (eq 2). Lactam **2** may then condense with a lactim ether (e.g., **5**) to form iminolactam **8** and the alcohol (eq 3).[28] If the lactim ether being considered were a 2-(perfluoroalkyl)ethyl-substituted lactim ether, the alkene formed would be $R_FCH{=}CH_2$ (**4**, $R_F = C_6F_{13}$), and this substance was identified in the product mixtures in this instance.[20] It is noteworthy that 7-membered lactim **11** was prepared without noticeable loss of *O*-methylcaprolactim (**10**) to side products, such as occurred when the 5-membered ring lactims were employed. This was also true in the direct competition experiments, such as in Table 2 (see also Table XIII);[20] the amounts of products formed and of reactants used were nearly equal for **10** and **11**. An *O*- to *N*-alkyl shift in the caprolactam compounds was not observed, but a significant amount of 1-methyl-2-pyrrolidinone was found in the experiment with *O*-ethylbutyrolactim (**6**) and *O*-methylcaprolactim (**10**); see Table XII.[20]

(23) Brown, H. C.,; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212.
(24) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience Publishers (John Wiley and Sons): New York, 1966; Chapter 4.
(25) Reference 24, p 205.
(26) (a) Turner, R. B.; Meador, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 4133. (b) Turner, R. B.; Garner, R. H. *Ibid.* **1958**, *80*, 1424. (c) Turner, R. B.; Nettleton, D. E.; Perlman, M. *Ibid.* 1430.
(27) Private Communication, June 9, 1993, from Dr. Ernest Silversmith, Morgan State University, Baltimore, MD.
(28) Glickman, S. A.; Miller, D. S. U.S. Patent No. 3,040,004 (to General Aniline and Film Corp., New York, NY), June 19, 1962.

Side Reactions in the Preparation of *O*-alkyllactims. Yields reported for alkylation by dimethyl sulfate of a homologous series of lactams have varied somewhat, but typical results are as follows: *O*-methylbutyrolactim (42%,[29] 45.5%,[30] 48%[8]), *O*-methylvalerolactim (70%,[29] 71%[13]), and *O*-methylcaprolactim (68%,[30,31] 82%,[29] 93.5%[13]). The lower yield of *O*-methyl*butyro*lactim than that of the higher lactims again points up the atypical behavior of the smaller 5-membered ring compound. Our experience[20] in the synthesis of lactims **5** and **6** revealed a probable cause for the lower yield of alkylated product. Contrary to previous reports,[9,13,31,32] isomerization of the *O*-alkyllactim to the *N*-alkyllactam was not the only,[31] or major, side reaction. For lactim **5** the yield of 1-methyl-2-pyrrolidinone (**14**) was 7.9%; for lactim **6**, 1-ethyl-2-pyrrolidinone (**15**) was recovered in 6.8% yield along with an equal amount of an inseparable, probably isomeric, substance. An *oligomeric material* (7.9% yield from **5**, or 11.9% yield from **6**) was isolated as an undistillable, organic-soluble product. This material appears to be the oligomer of lactam **2**, itself; the exact nature of these volatile and nonvolatile side products is being investigated currently.[5]

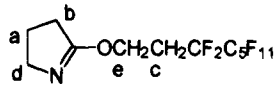
It is known[33,34] that heating of lactam **2** with a catalytic amount of the iminolactam **8**, which is a very effective initiator, causes lactam **2** to oligomerize.[33,34] In this present work, **8** was found to be a significant side product in the preparation of lactims **5** and **6**, as well as in the displacement reactions of **5** or **6** with higher alcohols. These side products are quantitatively reported in Tables VII-XII of the supplementary material.[20]

Experimental Section

Preparation of Starting Materials. Sources and details of preparation of known compounds are given in the supplementary material.[20] **Caution! Many of the substances used in these preparations are irritating and volatile liquids, including the lactim ethers 5, 6, and 10 described below, which have penetrating, offensive odors. In addition, the new lactims 7, 11, and 13 are also volatile, highly reactive compounds of unknown toxicity. Accordingly, great care must be excercised in handling these substances to avoid contact or breathing. All transfers should be made in the absence of air (and moisture) by the use of nitrogen cover and in a well-ventilated space. Protective covering should be worn. These materials should be kept or stored in the dark and cold in tightly closed containers. Lactim ethers are highly reactive to water and other nucleophiles.**

Physical and Instrumental Methods. A 16-in. stainless steel, Nester–Faust total reflux, partial take-off spinning band column with heated jacket (column A) was used for distillation under reduced pressure and for reactions under high reflux ratio. GC analysis employed a 30-m "DB-5" Megabore capillary column, 0.538-mm diameter, coating thickness 1.5 μm with helium carrier gas at 4 mL/min. GC response factors, IR and NMR spectra (as figures and associated peak tables of ^{1}H and ^{13}C resonances), and a listing of MS/GC data and interpretations are given in the supplementary material.[20] The ^{1}H NMR and ^{13}C NMR resonances of lactims **7, 11,** and **13** are given below with the experimental description of these substances. Resonances were decoupled at appropriate frequencies, and the decoupling of associated sets of resonances were noted. This gave the exact chemical shift (in ppm and Hz) of each identified ^{1}H NMR signal and the multiplicity or complexity of each resonance set. From the ^{1}H NMR peak tables[20] the peak of greatest height in each set was taken as the principal line, and the relevant coupling constants were calculated from the frequencies of the associated peaks, where possible.

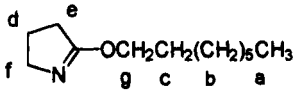
3,4-Dihydro-5-[(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro)-octyloxy]-2*H*-pyrrole (7) from Reaction of *O*-Ethylbutyrolactim (6) with 2-(Perfluorohexyl)ethanol (3) (mol 3:6 = 1.387). Lactim **6** (4.5673 g, 40.347 mmol) and alcohol **3** (20.3574 g, 55.911 mmol) were stirred at 108–95–107 °C (the temperature of the bath during 21 h) in a short path still (50 mL). Ethanol (0.5774 g) was collected in an ice-cooled receiver; ethanol (0.9991 g; 21.70 mmol or 53.9% of theory) was collected in 36 h. See below for distillation. GC samples (total wt removed was 0.8692 g) were taken at 0, 17, 21, and 36 h and showed a steady increase in the amount of **7** formed: 0 h, 0%; 17 h, 50.6%; 21 h, 68.1%; and 36 h, 74.0%. The amounts of **3** and **6** used up were not accurately measured. Distillation (column A; bath temperature at 98 °C) gave fractions: I, bp 36–38 °C/14 mm, 0.60 g; GC, 78.5% of **6**, 20.7% of **3**; II, 62–68 °C/13 mm, 4.91 g; GC, 8.30% of **6**, 88.6% of **3**, and 3.02% of **7**; III, 61–71 °C/9 mm, 3.46 g; GC, 0% of **6**, 98.2% of **3**, and 1.75% of **7**; IV, 72–80 °C/8–6.5 mm, 4.96 g; GC, 25.9% of **3**, and 74.1% of **7**; V, 80 °C/6.5 mm, 5.19 g; n^{25}_D 1.3521; GC, 0.90% of **3**, and 99.1% of **7**; VI, 80 °C/6.5 mm, 2.05 g; GC, 99.9% of **7**; and VII, 50 °C/3.0–0.5 mm, 0.30 g; GC, 0.81 % of **3**, and 99.19% of **7**. Cold trap, 0.21 g (mostly ethanol) and residue, 0.30 g. The total mass recovery was 23.848 g or 95.68% of the materials charged. The mass of **7** in distilled fractions IV–VII was 11.41 g (26.46 mmol) or 67.95% of **6** employed in the reaction; the *yield* of **7**, corrected for GC samples taken and based on unrecovered **6**, was 79.25%. The corrected yield of **7**, based on the amount of **3** used up, was 89.22%. Recovery of ethanol was 1.21 g (26.26 mmol) or 99.25% of the amount of **7** formed in the reaction. IR: C=N band at 1660 cm^{-1}, C–F bands at 1200 to 1250 cm^{-1}. The entire IR spectrum is given in the Supplementary Material.[20] ^{1}H NMR ($CDCl_3$; all resonance sets consisted of two protons and they are listed in alphabetical order of suffixes in lactim **7**; see structure below): δ 2.041 (5



lines, J = 7.5 Hz), 2.462 (t, J = 8 Hz), 2.542 [complex, J = 7 Hz, J_{CCF} = 17.63 Hz (decoupling of H–F resonances gave the following: 781.05–763.42 = 17.63 Hz; and 763.42–745.80 = 17.62 Hz)], 3.678 (t, J = 7 Hz), and 4.455 (t, J = 6.5 Hz). A second irradiation experiment (decoupling) of the quintuplet resonance at δ 2.041 (CH_2, a) showed coupling to the triplets at δ 2.462 (CH_2, b) and δ 3.678 (CH_2, d). This establishes CH_2(a) as the methylene group on the ring opposite the $CHOCH_2$-$CH_2C_6F_{13}$ group. Also, decoupling of the signal at δ 2.542 (CH_2, c) caused the signal at δ 4.455 (CH_2, e) to collapse, which confirmed the assignment of these resonances in lactim **7**. ^{13}C NMR ($CDCl_3$, decoupled; ^{13}CF and $DCCl_3$ resonances are omitted): δ 9.773, 17.455, 17.616, 41.696, 46.360, 97.395, 159.04. ^{1}H and ^{13}C NMR spectra of lactim **7** (as figures) with peak tables, additional preparative experiments, MS/GC data, and assignments are found in the supplementary material.[20] Anal. Calcd for $C_{12}H_{10}F_{13}NO$: C, 33.42; H, 2.34; F, 57.28; N, 3.25. Found: C, 33.3; H, 2.2; F, 53.2; N, 3.8.

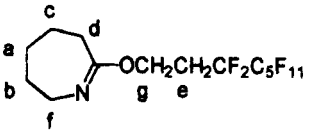
(29) Fujii, T.; Yoshifuji, S.; Yamada, Y. *Chem. Pharm. Bull.* **1978**, *26*(7), 2071–2080.
(30) Results from this work; see supplementary material.[20]
(31) Benson, R. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1948**, *70*, 2115.
(32) Ralls, J. W. *J. Org. Chem.*, **1961**, *26*, 66–8. Using the same conditions as Benson and Cairns'[31] valerolactam gave *O*-alkyllactim, but butyrolactam gave the *N*-alkyllactam. The same pattern was observed when using diazoalkane and the lactams.
(33) Brozek, J.; Marek, M.; Roda, J.; Kralicek, J. *Makromol. Chem.* **1988**, *189*(1), 17–27; *Chem. Abstr.* **1988**, *108*, 113033e.
(34) Brozek, J.; Roda, J.; Kralicek, J. *Makromol. Chem.* **1988**, *189*(1) 29–43; *Chem. Abstr.* **1988**, *108*, 113034f. (Please note: code no. **8** was inserted to aid in the understanding of this abstract.) Polymerization of Lactams. 84. The role of 1-(1-pyrrolin-2-yl)-2-pyrrolidone (**8**) in the anionic polymerization of 2-pyrrolidone. "The incorporation of **8** into the polymer was followed by the change in isotope concentration and the apparent rate constants were derived from some elementary reactions in the investigated polycondensation. The interchange reaction between **8** and monomer was also measured."

3,4-Dihydro-5-(*n*-octyloxy)-2*H*-pyrrole (13): Heating of Octanol (12) and *O*-Ethylbutyrolactim (6) (mol 6:12 = 2.90) with Benzene To Give Azeotrope of Ethanol (bp 68.2 °C) with Shifting of Equilibrium. Alcohol **12** (6.51 g, 50.0 mmol, 99.2% pure, wt corrected), benzene (4.37 g, 5.00 mL, 55.9 mmol; used to rinse **12** from the vial), and lactim **6** (16.40 g, 144.9 mmol, 99.02% pure, wt corrected), followed by benzene (4.37 g, as above) were charged to a 50-mL distillation flask, while purging with nitrogen. The reaction mixture was attached to column A and heated by an oil bath; the ice-cooled cold trap was protected by an oil seal bubbler to keep out air and moisture under positive nitrogen pressure. At high reflux ratio, the ethanol/benzene azeotrope[19] and benzene were distilled and analyzed by capillary GC. Samples (Table VI[20] nos. 1–3) of the *pot liquid* were removed after each fraction (I–III) was collected. Distillation temperature, time, and weights for fractions I–III were as follows: I, bp 65–72 °C, pot temperature of 110–115 °C, 6 h, 3.03 g; (benzene, 5.0 mL, was returned to the reaction flask and distillation was continued); II, bp 70–72 °C; 105–120 °C, 7 h; 1.90 g; III, bp 75 °C; 120–130 °C, 6 h; 5.75 g. GC of fractions I–III gave 19.51 mmol (total) of ethanol and none of **6**, **12**, or **13**. Sample no 3 showed that 55.2% of **12** and 63.2% of **6** had been consumed; 53.6% of **13** had been formed. Evidently, part of the ethanol had been lost. At this point, the cold trap was cooled by liquid nitrogen and distillation was continued under reduced pressure; any remaining benzene, alcohol, and unreacted **6** were slowly removed during 7.5 h. Some reaction occurred during this time period. Comparison of sample no. 3 with sample no. 4, Table VI,[20] which was removed after fraction VI, showed an increase in the concentration of lactim **13**. The distillation record of fractions and the summation of products are given in Table VII.[20] Unreacted **6** of 95 to 99.5% purity, **12** of 96.7% purity, and lactim **13** of 98.1% purity were recovered. Summation of **12** and **13** gave consistent amounts, but the wt of **6** in distilled fractions and calcd from Table VI[20] varied significantly from that of **12** and **13**, for no apparent reason. Not all of **13** in sample no. 4 (37.0 mmol, 74.1% yield) was recovered by distillation because some remained as holdup and pot residue. Yield of **13** in Table VII,[20] fractions IX–XII, was 30.4 mmol or 60.9%, while the amount of **12** used up was 35.8 mmol or 69.0% of theory. GC showed that iminolactam **8** was present in fractions VII–XII, e.g., 0.54–0.84% in distilled **13**. The total of these amounts of **8** was 0.98 mmol or 1.35% yield based on lactim **6** charged to the reaction, corrected for stoichiometry. The complete description of this preparation, including Tables VI and VII of reaction samples, GC analyses, and distillation of the product mixture, and the entire IR spectrum are given in supplementary material.[20] Lactim **13** was characterized as follows. IR: C=N band at 1660 cm^{-1}. ^1H NMR ($CDCl_3$; resonances are listed in alphabetical order of suffixes in lactim **13**, see structure below): δ



0.879 (t, 3H, J = 6.5 Hz), 1.277 (m, 10H), 1.677 (5 lines, 2H, J = 7.0 Hz, J = 7.0 Hz), 2.004 (m, 2H), 2.445 (t, 2H, J = 8.3 Hz), 3.656 (t, 2H, J = 6.5), 4.115 (t, 2H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, decoupled; $CDCl_3$ resonances omitted): δ 8.48, 11.81, 14.72, 14.88, 15.05, 15.13, 16.91, 17.63, 40.89, 53.91, 54.08, 159.13. See also the complete ^1H and ^{13}C NMR spectra and peak tables in the supplementary material.[20] The NMR parameters of **13** were similar to those of lactim **6**,[11] or of lactim **7**, for which double resonance results were available for assignment of protons.[20]

3,4,5,6-Tetrahydro-7-[2-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro)octyloxy]-2*H*-azepine (11) (mol 3:10 = 0.4929). Column A was employed, with an ice-cooled receiver and trap; the column jacket was kept at 90–110 °C. A constant temperature bath was used to maintain reflux as needed. A 50-mL flask was charged with alcohol **3** (18.00 g, 49.44 mmol) and *O*-methylcaprolactim (**10**; 12.76 g, 100.3 mmol). The reaction mixture was stirred and heated to boiling at a high reflux ratio. At 80–110 °C no reflux occurred, but at 120–130 °C, methanol (0.66 g, 20.6 mmol) slowly distilled. At this point, the pressure was cautiously reduced to 200–165 mm, and unreacted **3** and **10** were removed by distillation, bp 88 °C/200 mm to 85 °C/100 mm, 7.05 g. A fraction was collected, bp 98 °C/25 mm to 101 °C/15 mm, 6.16 g; GC, **3**, 2.8%, **10**, 56.8%, and **11**, 34.7%. The liquid remaining (17.23 g) was distilled without column, bp 94 °C/2.00 mm, 16.45 g; GC, 98.5% of **11**; 0.95% of unknown. From GC, the yield of **11** was 93.4% in all distilled fractions; recovery of **10** was 102% of theory. Total mass recovery was 100%. Lactim **11** was redistilled, bp 92–93 °C/2.00 mm, pot temperature 95 °C; 16.11 g, n^{25}_D 1.3671. GC: 0.942% of **10**, 98.5% of **11**, and 0.11% of an unknown substance. A complete record of the experiment is given in Table X.[20] IR: **11**, C=N band at 1660 cm^{-1} and CF bands at 1200–1250 cm^{-1}. ^1H NMR ($CDCl_3$; all resonance sets consisted of two protons and they are listed in alphabetical order of suffixes in lactim **11**, see structure below):



δ 1.612 (m), 1.671 (m), 1.868 (5 lines), 2.515 (t, J = 5.6 Hz), 2.575 (2 t, J = 6.6 Hz, J_{CCF} = 18.7 Hz), 3.514 (m), 4.363 (t, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, decoupled; ^{13}CF and $DCCl_3$ resonances are omitted): δ 9.91, 14.38, 17.14, 17.80, 18.66, 35.21, 43.66, and 155.34. Low-resolution GC/MS analysis gave M(+1) ion, m/z = 460 (relative abundance, 3.6%); the M^+ ion, m/z = 459 (17.7%); and the M+(−1) ion, m/z = 458 (2.0%). The entire IR spectrum, ^1H and ^{13}C NMR spectra and peak tables, decoupling experiments, and mass spectrum analysis, including mol ion and fragmentation products, and additional preparative experiments are given in the supplementary material.[20]

Acknowledgment. We thank Dr. Brian E. Miller and Dr. George E. Gaines III for assistance in obtaining 300-MHz spectra suitable for reproduction. We thank Dr. Ernest Silversmith for helpful comments and a valuable Communication.

Supplementary Material Available: Alternative names, code number, and Chemical Abstract registry numbers. Preparation of starting materials, GC methods, and FID response factors (Table III). Copies of ^1H and ^{13}C NMR spectra and table peaks and IR spectra of **7**, **11**, and **13**. Table of decoupling frequencies and results for **11**. MS fragmentation products, GC analyses, and additional preparations of **7**, **11**, and **13** (Tables IV, V–IX, and XII–XVII, respectively) (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.