Thermal Alkylation of Ambidentate Lactams with 2-(Perfluoroalkyl)-1-iodoalkanes. The Effect of Reaction Conditions and Ring Size on the Synthesis of 2-(Perfluoroalkyl)ethanols and the Mechanism of Reaction

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The perfluoroalkylated long chain alcohols and their derivatives exhibit strong surface activity in solution and novel surface modification properties as adsorbed layers or films. A new, little known synthesis of 2-(perfluoroalkyl)ethanols ($R_FCH_2CH_2OH$) employs a lactam, e.g., 2-pyrrolidinone (**2**), with an iodoalkane, e.g., $C_6F_{13}CH_2CH_2I$ (**1**). Alkylation of **2** by heating with **1** gives $C_6F_{13}CH_2CH_2$-OH (**3**) in 83% distilled yield, and treating the residual lactim ether salt (**6**·HI) with K_2CO_3 gives additional **3**, up to 94% yield. Rate of alcohol formation (k_{alc}) is unaffected by molar ratio of **2**:**1**, yet rate of **1** reaction (k_{iodo}) increases 2.44 times with doubling of **2**:**1** and side product $C_6F_{13}CH{=}CH_2$ (**4**) decreases from 4 to 2%. For homologous lactams [$(\overline{CH_2})_nNHC{=}O$] ($n$ = 3–5), selectivities (mol **3**:**4**) are as follows: 5-membered ring, 18.4; 6-membered ring, 0.73; 7-membered ring, 0.13. Conversions to **3** are as follows: 6-membered ring, 19.4%; and 7-membered ring, 1.75%, Table 13. A three-step mechanism is proposed: (1) *O*-alkylation of the lactam by **1** gives lactim salt I; (2) *N*-substitution of salt I by another molecule of lactam forms a tetrahedral adduct (II); (3) breakdown of salt II gives **3** and iminolactam salt III. In model experiments, heating of **2** and lactim **6** yields 99% of **3** and iminolactam **5** and 1% of **4**. By contrast, *7-membered* **14** with **2** gives 45% of **3** and iminolactam **12**, besides **4** and ϵ-caprolactam **10** (20%). For higher lactams, two competitive reactions can be discerned: (1) the S_N2 displacement of alcohol by *N*-attack on salt II and a unimolecular, concerted fragmentation of the lactim, to lactam and alkene.

Introduction

Long chain, fluorine-substituted alcohols have unique properties of synthetic and commercial importance. Fluorine substitution affects both their synthesis and properties in many ways. When the perfluoroalkyl groups are C_6F_{13} or longer, such compounds have strong surface activity in solution and exhibit novel surface modification properties as adsorbed layers or films. As a class, fluorocarbon compounds in which all carbon–hydrogen bonds have been replaced by carbon–fluorine bonds possess the lowest surface tensions and surface energies of any substances currently known to science.[1] Remarkably, and of great importance technically, compounds with a long chain perfluoroalkyl (R_F) group connected by a hydrocarbon spacer to a suitable functional group exhibit these same unusual surface properties.[2] For example, salts of phosphate esters $[(R_FCH_2CH_2O)_2P(O)OH$, derived from $R_FCH_2CH_2OH$, give highly surface active solutions in water and are preferentially adsorbed on surfaces such as films or fibers. The coated surface then becomes nonwettable by water, aqueous solutions, and many organic liquids.[3] Further, derivatives of $R_FCH_2CH_2OH$ such as polymers of the acrylate esters are widely used to provide durable, thin coatings that exhibit high contact angles to various liquids.[4] For these reasons, similar novel fluorinated compounds are receiving increased attention.[5-8]

The synthesis of $R_FCH_2CH_2OH$ seldom employs common methods such as oxidation of the Grignard or alkaline hydrolysis of $R_FCH_2CH_2I$ because of competing elimination reaction to alkenes $R_FCH{=}CH_2$.[9] Instead, special methods are used, such as LAH reduction of the adducts $R_FCH_2CHIOAc$, which are prepared by free radical addition of R_FI to vinyl acetate.[10] This gives an

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1995.

(1) Schulman, F.; Zisman, W. A. *J. Colloid Sci.* **1952**, *7*, 465. (b) Hare, E. F.; Shafrin, E. G.; Zisman, W. A. *J. Phys. Chem.* **1954**, *58*, 236. (c) Jarvis, N. L.; Zisman, W. A. *Kirk–Othmer Encycl. Chem. Technol., 2nd Ed.* **1966**, *9*, 506–847.

(2) Brace, N. O. *J. Org. Chem.* **1962**, *27*, 4491. (b) Shafrin, E. G.; Zisman, W. A. *J. Phys. Chem.* **1962**, *66*, 740. (c) Brace, N. O. U.S. Patent No. 3,172,910, to E. I. du Pont de Nemours and Co., Mar 9, 1965; *Chem. Abstr.* **1965**, *63*, P503c.

(3) Brace, N. O.; Mackenzie, A. K. U.S. Patent No.3,083,224, to E. I. du Pont de Nemours and Co., Mar 26, 1963; *Chem. Abstr.* **1963**, *59*, P50238. Pure, crystalline solid $[F(CF_2)_7CH_2CH_2O]_2PO(ONH_4)$ was obtained from $C_7F_{15}CH_2CH_2OH$. The 2-(perfluoroheptyl)-1-ethanol was prepared from $C_7F_{15}CH_2CHIOAc$ (azonitrile initiated addition of $C_7F_{15}I$ to vinyl acetate, 87.2% yield by analysis), followed by zinc and acid reduction.

(4) (a) Ahlbrecht, A. H. U.S. Patent No. 3,171,861 to Minnesota Mining and Manufacturing Co., Mar 2, 1965; *Chem. Abstr.* **1965**, *64*, P1189g. $C_7F_{15}CH_2CH_2OH$ was prepared from $C_7F_{15}CH_2CHIOAc$, by reduction with LAH. (b) Fasick, R. U.S. Patent No. 3,239,557, Mar 8, 1966 to E. I. du Pont de Nemours and Co.; *Chem. Abstr.* **1966**, *64*, P14098c.

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(6) Kunetake,T.; Okahata, Y.; Yasunami, S. *J. Am. Chem. Soc.* **1982**, *104*, 5547.

(7) Jacquemain, D; Wolf, S. G.; Leveiller, F.; Lahav, M.; Leiserowitz, L; Deutsch, M.; Kjaer, K.; Als-Nielsen, J. *J. Am. Chem. Soc.* **1990**, *112*, 7724–7736. (Two-dimensional self-aggregation in a fluorocarbon amphiphile.)

(8) Dagani, R. *Chem. Eng. News* **1993**, *71*, *20*–25. A report on the Nanoscale Technology Symposium of the American Association for the Advancement of Science, Boston, 1993.

(9) Brace, N. O. *J. Fluorine Chem.* **1982**, *20*, 313–327. (b) Brace, N. O.; Marshall, L. W.; Pinson, C. J.; van Wingerden, G. *J. Org. Chem.* **1984**, *49*, 2361–2368.

(10) (a) Brace, N. O. *J. Org. Chem.* **1962**, *27*, 3033–3038. R_FI (R_F = C_3–C_{11}, 12 entries) and vinyl acetate, heated 2–10 h, 50–80 °C, with AIBN initiator (0.6–1.2 mol %) gave adducts in 85–95% yield (by analysis or distillation). $CF_3(CF_2)_6I$ and vinyl acetate (0.1 mol each) and AIBN (1.2 mmol), when heated under nitrogen for 2 h at 80 °C, gave monoadduct at 92% conversion or 100% yield on unrecovered reactants (GC). Reduction by LAH and distillation afforded $CF_3(CF_2)_6$-CH_2CH_2OH in 80% yield and 3.5 g of higher bp residue. (b) U.S. Patent No. 3,145,222, to E. I. du Pont de Nemours, Aug 18, 1964. *Chem. Abstr.* **1964**, *61*, P10589. Many additional examples are provided for this type of process.

0022-3263/95/1960-2059$09.00/0

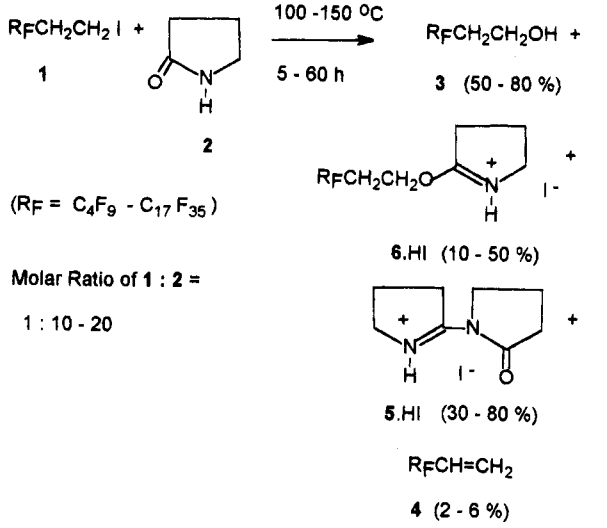
excellent yield of $R_FCH_2CH_2OH$ and has been used successfully by other workers.[11] Because of the reagents required, however, large scale use would be severely limited.

$$R_FI + CH_2{=}CHOAc + AIBN \xrightarrow{70\ °C} R_FCH_2CHIOAc \xrightarrow{LAH} R_FCH_2CH_2OH \quad (1)$$

Other methods, such as oxidative displacement of iodine from $R_FCH_2CH_2I$ by fuming sulfuric acid[12] or by peroxy acids,[13] electrolysis,[14] nucleophilic substitution by weakly basic metal salts,[15] or indirectly from esters thus obtained,[16] have been used with some success. However, these procedures also suffer from inherent drawbacks; the formation of side products and the difficulty in handling the reagants are the most notable. By contrast, higher homologues, $R_F(CH_2)_nOH$ (n = 3–12 or higher), can be readily synthesized by standard procedures.[9]

Large scale synthesis of $R_FCH_2CH_2OH$ requires an efficient process that employs readily available materials. Such requirements account for the utilization of iodoalkane $R_FCH_2CH_2I$, which is chemically reactive and is manufactured on a relatively large scale and low cost in several countries by thermal or free radical addition of R_FI to ethene.[10b,17] Heating a mixture of iodoalkane $R_FCH_2CH_2I$ and *N*-methylformamide (or with DMF and water)[18] provides alcohol and formate ester (combined) in 90–95% yield, and the loss to alkene $R_FCH{=}CH_2$ is only 2–4%.[18,19] Surprisingly, this method fails when *formamide* is used as the nucleophile with $R_FCH_2CH_2I$, though heating of 1-bromooctane with formamide (with or without water) gives an excellent yield of octanol and octyl formate.[20] A new, little known synthesis of $R_FCH_2CH_2OH$ employs a lactam, 2-pyrrolidinone (**2**), as the nucleophilic partner with $R_FCH_2CH_2I$.[21] Lactam **2** is a readily available, inexpensive polyamide precursor unencumbered with the toxicity concerns associated with DMF. Thus, important reaction parameters of the new synthesis are explored in this paper to determine their effect on the rates and yields of $R_FCH_2CH_2OH$. This study also reports the effect of ring size (5, 6, and 7 members) on the outcome of this alkylation reaction and employs a new mechanism to interpret the experimental results.

Scheme 1. Synthesis of 2-(Perfluoroalkyl)-1-ethanols by Thermal Alkylation of 2-Pyrrolidinone (2) with 2-(Perfluoroalkyl)-1-iodoethanes (1)



Results

Preparative Experiments for Complete Product Isolation and Analysis. Heating of $CF_3(CF_2)_5CH_2CH_2I$ (**1**) with lactam **2** in large excess gave $CF_3(CF_2)_5CH_2CH_2OH$ (**3**), 1-(1-pyrrolin-2-yl)-2-pyrrolidinone (as HI salt, **5**·HI), $CF_3(CF_2)_5CH{=}CH_2$ (**4**), and $[(\overline{CH_2})_3N{=}COCH_2CH_2C_6F_{13}]$·HI (the lactim ether salt **6**·HI; Scheme 1). In this synthesis of alcohols, *two* molecules of ambident lactam **2** are used in forming iminolactam **5** and alcohol **3**. A small amount of **1** was converted to alkene **4**; lactim **6**[22] was also found in reaction mixtures. The yields of products varied with reaction conditions as described herein.

A stirred mixture of iodoalkane **1** and lactam **2** (mol **2**:**1** = 10; 0.1 mol scale) was heated for 16 h at 132 °C in a sealed tube, with the results summarized in Table 1. Alcohol **3** distilled in 78.5% yield (with 4.2% of unreacted **1**), and 85.2% of lactam **2** was recovered. The yield of **4** (by GC) was 4.5%. Vigorous stirring of the nonvolatile salt residue of **2**, **5**, and **6** HI salts with an excess of solid K_2CO_3 in acetone/$HCCl_3$ slurry provided **2**, **5**, and **6** in solution (eq 2). When this mixture was heated and

$$\mathbf{2}\cdot HI + \mathbf{5}\cdot HI + \mathbf{6}\cdot HI \xrightarrow{K_2CO_3} \mathbf{2} + \mathbf{5} + \mathbf{6} + HCO_3^- + KI \quad (2)$$

$$\mathbf{6} + H_2O \rightarrow \mathbf{2} + \mathbf{3} \quad (3)$$

stirred for several h, most of **6** was converted to **2** and

(11) (a) Napoli, M.; Scipioni, A.; Conte, L.; Legnaro, E.; Krotz, L. N. *J. Fluorine Chem.* **1994**, *66*, 249. Reaction of $C_6F_{13}I$ and vinyl acetate gave $C_6F_{13}CH_2CHIOAc$ and $C_6F_{13}CH_2CHO$ (3:1 molar ratio) in 100% combined yield. The aldehyde was prepared from this mixture in 91.0% distilled yield by hydrolysis with 15% aqueous H_2SO_4. (b) Napoli, M.; Fraccaro, C.; Conte, L.; Gambaretto, G. P.; Legnaro, E. *Ibid.* **1992**, 219–227. The effect of molar ratio of reactants and reaction conditions upon product yield and conversion was studied. An equimolar amount of R_FI and vinyl acetate, with 2.5% of AIBN initiator at 80 °C for 1 h, gave adduct and 1:1 telomer in 96:4 molar ratio at 80% conversion.

(12) Day, R. I. U.S. Patent 3,283,012 (to E. I. Du Pont de Nemours and Co.), Nov 1, 1966; *Chem. Abstr.* **1967**, *66*, 18507t. (b) Mares, F.; Oxenrider, B. C. *J. Fluorine Chem.* **1976**, *8*, 373.

(13) von Werner, K. German Offenlegungsschritt DE12 3,035,641 A1, to Hoechst AG, May 6, 1982; *Chem. Abstr.* **1982**, *97*, 91725g.

(14) (a) Benefice-Malouet; Blancou, H.; Calas, P.; Commeyras, A. *J. Fluorine Chem.* **1988**, *39*, 125 and 245. (b) Becker, J. Y.; Smart, B. E.; Fukunaga, T. *J. Org. Chem.* **1988**, *53*, 5714.

(15) Knell, M.; Klemchuck, P. U.S. Patent No. 3,671,574 (to CIBA-GEIGY Corp.), June 20, 1972; *Chem. Abstr.* **1972**, *77*, 4960a; 164049p.

(16) Brace, N. O. 10th International Symposium on Fluorine Chemistry, Vancouver, BC, Canada, Aug 1–6, 1982; Abstract O-69, Synthesis of 2-(*F*-Alkyl)ethanols and Esters by Phase Transfer Catalyzed S_N2 Reactions of 2-(*F*-Alkyl)-1-Iodoethanes. (b) Felix, B.; Starflinger, S. German Offenlegungschritt DE No. 3,016,571 (to Hoechst A.-G.), Nov 5, 1981; *Chem. Abstr.* **1982**, *96*, 34546e.

(17) Knell, M. U.S. Patent No. 4,058, 573 (to CIBA-GEIGY Corp.), Nov 15, 1977; *Chem. Abstr.* **1976**, *85*, 93781g; **1978**, *88*, 74021w.

(18) Matsuo, M.; Hayashi, T. *Asahi Garasu Kenkyu Hokoku* **1976**, *26*, 55. German Offen. DE No. 2,318,941 (to Asahi Glass Co., Ltd.), Oct 25, 1973; *Chem. Abstr.* **1974**, *80*(1), 14564a.

(19) Brace, N. O. *J. Fluorine Chem.* **1986**, *31*, 151. This paper describes in detail alternative methods for the synthesis of $R_FCH_2CH_2OH$.

(20) Brace, N. O. *J. Org. Chem.* **1993**, *58*, 317. This paper describes thermal alkylation of amides by *non-fluorinated alkyl halides*. (b) See Correction in *J. Org. Chem.* **1994**, *59*, 3242.

(21) 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. *Ibid.* 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.

(22) Brace, N. O.; Carpenter, B. L.; Shellhamer, D. F.; Daniels, M. *J. Org. Chem.* **1994**, *59*, 3670–3675.

Table 1. Alkylation of Lactam 2 with Iodoalkane 1 at 132 °C for 15.5 h[a]

	substances, % conversn by GC or distillation					
	1[b]	2[c]	3	4	5	6
Sample A and Distilled Products from Reaction						
GC[d]	95.0		80.7	3.7	9.4	2.3
distilled[d]	95.8	(370)[c]	78.7	4.5	tr	1.9
Sample A Treated with Insufficient K_2CO_3[e]						
GC[d]	95.3	(399)	86.1	4.0	47.8	3.0
Sample A Treated with Excess K_2CO_3[e]						
GC[d]	*f*		88.8	8.9	83.2	2.3[g]
Distillation Residue Treated with K_2CO_3[h]						
GC[d]		(63.6)	4.4	4.4	76.1	
distilled[i]		(68.4)[c]	4.4		85.2	
Summary of Products[j]						
	95.3	(438.4)[c]	82.9	4.5	85.2	3.0

[a] Iodoalkane **1** (24.20 g; 49.66 mmol; 98.2% purity, contained homologue C_8F_{17}, 1.94%) and lactam **2** (46.78g, 544.1 mmol; contained 0.10% of water by titration, 0.515 g, 2.86 mmol) was stirred by magnet bar and heated at 132 °C for 15.5 h in a glass reactor tube B; see Experimental Section. [b] The amount of **1** *used up* in percent (mol) of theory. [c] The amount of **2** in mmol recovered by distillation or detected by GC; the total of **2** was 438.4 mmol or 97.8% of the theoretical based on **3**, **4**, and **6** that was found. [d] See the supplementary material.[26] [e] Anhydrous K_2CO_3 (5.1 mg, 0.037 mmol) was added to sample A (0.2333 g, 0.1649 mmol of **1** and products) and stirred for 2 h at 25 °C. Then, K_2CO_3 (37.11 mg, 0.268 mmol) and CCl_4 (0.4839 g) were added to the same GC sample A and stirred for 5 h at 25 °C. [f] All of remaining **1** was dehydrohalogenated to alkene **4**. [g] The lactim ether **6** remaining did not react completely with base at 25 °C. GC also showed some higher retention time substances were present, such as oligomers of **5** or of **2**. [h] The HI salt mixture (21.34 g; ca 49.66 mmol of **1** products) was stirred at 66–75 °C for 16 h in $HCCl_3$/acetone slurry with K_2CO_3 (10.00 g, 72.3 mmol), stripped of solvent, and fractionated by distillation. GC sample B was removed before distiillation. [i] Higher retention time substances were observed, and a high-boiling, viscous residue (2.80 g) was obtained. [j] Amounts based on distilled material.

alcohol **3** (eq 3) as summarized in Table 1. Perhaps the small amount of water present (or absorbed from air by the hygroscopic liquid mixture) hydrolyzed **6** or **6**·HI to lactam **2** and alcohol **3** (eq 3).[23] (Any unreacted **1** was converted to alkene **4**.) The total *distilled conversion* of **3** was then 82.9% (or 87% *yield* based on 95% utilization of **1**), that of **5**[24] was 85.2%, and recovery of **2** was 97.8%. This workup procedure avoided the troublesome emulsions encountered when water washing was used (see next experiment). GC analyses and distillation samples of Table 1 gave consistent results, and this validated the procedures used in this study.

Analogous reaction of **1** and **2** at 150 °C for 6 h gave 97–98% consumption of iodoalkane **1**. However, only a 55.8% conversion to alcohol **3** and 5% to alkene **4** were obtained by distillation; thus, *ca.* 37 mol % of undistillable **6**·HI remained. The residue was dissolved in CH_2Cl_2 and extracted with water and gave a stable, foamy emulsion that only slowly separated. This was caused by highly surface active lactim salt **6**·HI, with its long perfluoroalkyl group. The more polar **5**·HI, along with unreacted lactam **2**, concentrated in the aqueous layer, and most of **6**·HI migrated into the CH_2Cl_2 layer, as shown by spectroscopic properties[25] and GC retention times of

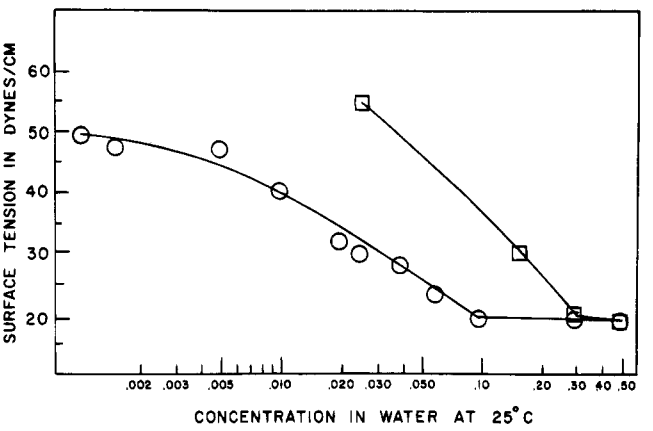
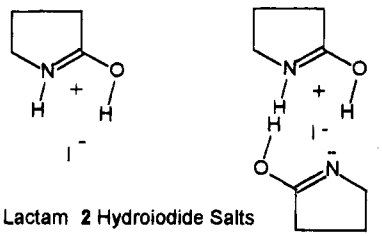


Figure 1. Surface activity in water at 25 °C of 2-(perfluorohexyl)ethylbutryolactim hydroiodide (**6**·HI) in comparison with *N*-[2-(perfluorohexyl)ethyl]pyridinium iodide: open circles, **6**·HI; open boxes, *N*-[2-(perfluorohexyl)ethyl]pyridinium iodide.

samples, in comparison with synthesized **5**[24] and **6**.[22] Eventually an 89.7% (combined) yield of **3**, **6**·HI, and alkene **4** was isolated.[26]

Isolation of Lactam 2 Hydroiodide Salts. A crystalline solid, mp 212–213 °C, was also isolated from the nonvolatile residue. The water-soluble and CH_2Cl_2-soluble salt gave a positive iodide test and the IR of a new substance (not **2**). The C=O band at 1700 cm^{-1} in **2** had shifted to 1670–1650 cm^{-1} in the salt, and this is the reported frequency for the $C{=}N^+$ band of butyrolactim ether salts, e.g., 1669 cm^{-1} in *O*-ethylbutyrolactim tetrafluoroborate salt.[27a] This was not surprising, since the lactim ether salt and the enol form of lactam **2**·HI



Lactam **2** Hydroiodide Salts

have analogous structures. A DIP mass spectrum of the salt gave both the mol ion of **2** and a minor component with $m/z = 170$, the mass of two molecules of **2**. The salt was unstable to loss of HI, as the combustion analysis obtained later, was that of **2**, itself. Other spectroscopic evidence and further experimental results are given in the Experimental Section. Both single and double salts were isolated by Tafel and Wassmuth[27b] from **2** and HCl or from **2** and HBr. The double salt $(C_4H_7ON)_2$·HBr was much more stable than the single salt, which easily decomposed during recrystallization. Salts of **2** with HI have not been reported.

Figure 1 gives a plot of surface tension in water at 25 °C of **6**·HI.[26] In comparison with a similar pyridinium salt,[28a,b] **6**·HI is more effective at lower concentration. Analogous compounds have achieved widespread use as

(23) The amount of **6**·HI salt present was 10.7 mol %, calculated from the equation: **6**·HI = mol [(**1** used up) − (**3** + **4** + **6**)].

(24) a. Glickman, S. A.; Miller, E. S. U.S. Patent No. 3,040, 004 (to GAF Corp.), June 19, 1962 (filed on April 4, 1958); *Chem. Abstr.* **1978**, *57*, 11390. This patent contains claims to composition of matter for iminolactam **5** and related compounds. (b) Ney, W. O., Jr.; Zollinger, J. L. M. U.S. Patent 3,057,874 (to 3M Co.), Oct 9, 1962. This patent describes *meta*phosphoric acid salts of iminolactam **5**.

(25) (a) Dannhardt, G. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311*(4), 294; *Chem. Abstr.* **1978**, *89*, 42981p. (b) Mazurkiewicz, R. *Acta Chim. Hung.* **1984**, *116*(1), 95; *Chem. Abstr.* **1984**, *101*, 191663. (c) Brozek, J.; Roda, J.; Kralecek, J. *Makromol. Chem.* **1988**, *189*, 1–7; *Chem. Abstr.* **1988**, *108*, 113081u. The paper gives a useful comparison of methods for the synthesis of **5** and some of its hydrolysis reactions.

(26) Supplementary material.

(27) Pilotti, A.; Reuterhall, A.; Torssell, K. *Acta Chem. Scand.* **1969**, *10*, 3704. (b) Tafel, J.; Wassmuth, O. *Chem. Ber.* **1907**, *40*, 2831–2842.

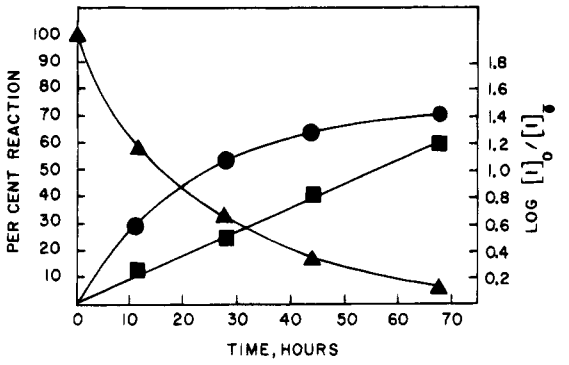


Figure 2. Reaction rate and profile of 2-(perfluorohexyl)-1-iodoethane (**1**) and 2-pyrrolidinone (**2**) at 100 °C: solid triangles, iodoalkane **1**; solid circles, 2-(perfluorohexyl)ethanol (**3**); solid boxes, $\log[\mathbf{1}]_o/[\mathbf{1}]_t$.

Table 2. Lactam 2 with Iodoalkane 1 (Mol 2:1 = 10) at 100 °C[a]

		substances, % conversn by GC				quotients for rates	
entry	time, h	**1**[b]	**3**[c]	**4**[c]	(**6**·HI)[d]	$\ln Q_{iodo}$[e]	$\ln Q_{alc}$[f]
1	12	58.7	28.6	(1.5)[g]	11.2	0.532	0.348
2	28	32.6	54.0	2.5	10.9	1.12	0.790
3	44	15.7	63.1	(2.7)	18.1	1.85	0.998
4[h]	68	6.40	70.6	(3.5)	18.7	2.76	1.26

[a] Iodoalkane **1** (4.82 g, 9.98 mmol, 0.998 M) and **2** (6.46 g, 99.4 mmol, 9.90 M, 99.6% pure) was stirred in a sealed reactor A. Total volume was 10.0 mL. The mixture in 12 h became homogeneous at 100 °C and at 25 °C. GC on "QF-1" fluorosilicone oil. [b] Substance, percent (mol) remaining. [c] Substance, percent (mol) conversion. [d] Nonvolatile **6**·HI was calculated from mol [**1**(used up) − (**3** + **4**)]. GC showed only traces of side products. [e] $Q_{iodo} = ([1]_o/[1]_t)$; least-squares regression (LS) of $\ln Q_{iodo} = A + B$ (time, s) gave $A = 0.0369$, B (k_{iodo}) $= 1.12 \times 10^{-5}$ s^{-1}, and r (correlation) $= 0.999$. [f] $Q_{alc} = (0.998/(0.998 - [\mathbf{3}]_t)$; LS of $\ln Q_{alc} = A + B$ (time, s) gave $A = 0.253$; B (k_{alc}) $= 0.435 \times 10^{-5}$ s^{-1}; $r = 0.972$. [g] Volatile material was lost during sampling; estimated amounts of **4** are bracketed. [h] A sample gave total iodine, 9.7 wt % (calcd, 9.56%), and ionic iodine, 8.6 wt % (90% of theory for complete reaction of **1**).

surfactants to reduce surface tension and interfacial tension of water–hydrocarbon mixtures.[28c]

The Effect of Reaction Parameters on Rates and Yield of Products. A brief study of variables (reaction time, temperature, and reactant ratio) gave rate constants and product conversions, useful for defining an efficient process. Volatile substances were determined quantitatively by GC,[19,20] and are reported as *percent conversion* based on mol of product/mol of limiting reactant. The percent yield is given in the tables *when mol of product / mol of limiting reactant consumed in the reaction* is used for calculation. In the first experiments, a constant ratio of mol **1**:**2** = 10 was employed at 100–140 °C. Then, in subsequent experiments, the molar ratio of reactants was explored as a reaction parameter.

The Effect of Temperature on the Alkylation Reaction. The time course of the reaction of **1** and **2**, mol **2**:**1** = 10, at 100 °C is drawn in Figure 2. Molar amounts of substances, calculated as specified, are given in Table 2, and a summary appears in Table 11. The rate, k_{iodo}, of iodoalkane **1** disappearance obeyed the kinetic law of a pseudo-first-order reaction; least-squares regression (LS) of the equation, $\ln[\mathbf{1}]_o/[\mathbf{1}]_t = A + B$ (time, s), gave $A = 0.0402$, $B = 1.12 \times 10^{-5}$ s^{-1} (the rate constant), and $r = 0.999$. In the tables that follow, $\ln[\mathbf{1}]_o/[\mathbf{1}]_t$ will be given as $\ln Q_{iodo}$ and $\ln[\mathbf{3}]_f/([\mathbf{3}_f - [\mathbf{3}]_t)$ as $\ln Q_{alc}$. From a plot of $\ln Q_{alc} = (0.998/(0.998 - [\mathbf{3}]_t)$ against time (s), LS of $\ln Q_{alc} = A + B$ (time, s) gave $A = 0.253$; B (k_{alc}) $= 0.435 \times 10^{-5}$ s^{-1}; $r = 0.972$. In this experiment $[\mathbf{1}]_i$ was 0.998 M, and this is the *theoretical* final concentration of alcohol **3**.

Table 6. Alkylation of Lactam 2 with 1 (Mol 2:1 = 14.75) at 140 °C[a]

		substances, % conversn by GC				quotients for rates	
entry	time, h	**1**[b]	**3**[c]	**4**[c]	(**6**·HI)[d]	$\ln Q_{iodo}$[e]	$\ln Q_{alc}$[f]
1[g,h]	0.50	41.4	46.2	0.985	11.4	0.882	0.619
2	0.85	25.4	59.5	2.93	12.2	1.37	0.898
3	1.50	17.0	69.5	3.46	10.0	1.77	1.19
4	2.50	9.37	77.1	3.41	10.1	2.37	1.47
5	4.00	4.34	81.3	3.32	11.1	3.14	1.67
6	6.00	1.76	81.8	5.33	11.1	4.04	1.70
7	8.50	1.43	80.1	4.72	13.8	4.25	

[a] See the Experimental Section for quantities and procedures used. "DB-5", 30 m column. In entry nos. 2 and 3, a sample of 0.2 g of $HCCl_3$ (0.50 mL) and dilute salt solution (5.0 mL) was shaken; a foamy emulsion formed and the organic layer was dried ($MgSO_4$) and CCl_4 (0.40 mL) added. In entry nos. 1 and 4–7 a 0.020 g sample in 0.15 mL of $HCCl_3$ was injected. [b] Substance, percent (mol) remaining. [c] Substance, percent conversion. [d] **6**·HI was calculated from [**1**(used up) − (**3** + **4**)]. [e] $Q_{iodo} = ([\mathbf{1}]_o/[\mathbf{1}]_t)$; LS of $\ln Q_{iodo} = A + B$ (time, s) from 0.50–6.0 h gave $A = 0.849$, $B = 15.3 \times 10^{-5}$ s^{-1}, and $r = 0.992$ (six points). From 0–0.5 h the inhomogeniety of the mixture precluded accurate measurement of **1**. [f] $Q_{alc} = 0.7121/(0.7121 - [\mathbf{3}]_t)$; LS from 0.50–4.00 h gave $A = 0.638$, $B = 7.91 \times 10^{-5}$ s^{-1} (this is k_{alc}), and $r = 0.951$ (five points). [g] The sample was homogeneous. [h] Two GC samples and four determinations were averaged.

Table 7. Reaction of Lactam Product Mixture with K_2CO_3 in $HCCl_3$ and Ethanol[a]

		substances, % conversn by GC[b]					
entry no.	time, h	**1**,[c] %	**2**,[d] mmol	**3**,[e] %	**4**,[e] %	**5**, %	**6**, %
1	4	0.487	3.57	89.6	3.1[f]	76.9	0.176
2	5	0.626	8.85	94.2	2.67	89.0	0.216

[a] See the Experimental Section for quantities and procedures used. [b] GC on "DB-5", 30 m column, as described above. [c] Substance **1**, percent (mol) remaining. [d] The amount of lactam **2**, calcd in mmol, that remained in $HCCl_3$ solution, after extraction with dilute $NaHCO_3$ solution. [e] The conversion to product, including the original amount present (see Table 6, entry 7). [f] A single determination only.

The alcohol **3** formation rate ($k_{alc} = 0.435 \times 10^{-5}$ s^{-1}) was about half that of **1** consumption, and the conversion to **3** reached 70.6% after 68 h. At the same time, 90% (I^-) or 93.6% (GC) of **1** had reacted, and about 3% of alkene **4** had been formed. Thus, a constant amount of lactim ether **6**·HI (11%) was present during the first 28 h of the reaction. The analogous reactions and their rate constants at 120 °C (Table 3)[26] and at 130 °C (Table 4)[26] are summarized in Table 11. At 140 °C, consumption of **1** was 96.9% (GC) or 95% (I^-) in 7.5 h. Table 5[26] lists the quantities of substances and rate constants: $k_{iodo} = 9.56 \times 10^{-5}$ s^{-1}; LS, $r = 0.991$; and, $k_{alc} = 5.27 \times 10^{-5}$ s^{-1}, $r = 0.992$.

The Effect of Reactant Molar Ratio on Rates and Products of Reaction at 140 °C. An increase in lactam **2** concentration gave a marked increase in the consumption rate of iodoalkane **1**, but not in the formation rate of **3**. After only 30 min with mol **2**:**1** = 14.75, the lactim ether salt **6**·HI had already reached the steady state conversion of 11.4% (Table 6). Lactim **6**·HI remained constant until 98.3% of iodoalkane **1** had been consumed

(28) (a) Comparison with a pyridinium salt of analogous structure[28b,28c] showed that both surfactants lower the surface tension of water below 20 dyn/cm, but **6**·HI was much more effective at lower concentrations. (b) Brace, N. O. U.S. Patent No. 3,257,407 (to E. I. du Pont de Nemours and Co.), June 21, 1966; *Chem. Abstr.* **1966**, *65*, P12108b. (c) Foulletier, L.; Lalu, J.-P. U.S. Patent 4,062,849 (to Produits Chimiques Ugine Kuhlmann), Dec 13, 1977.

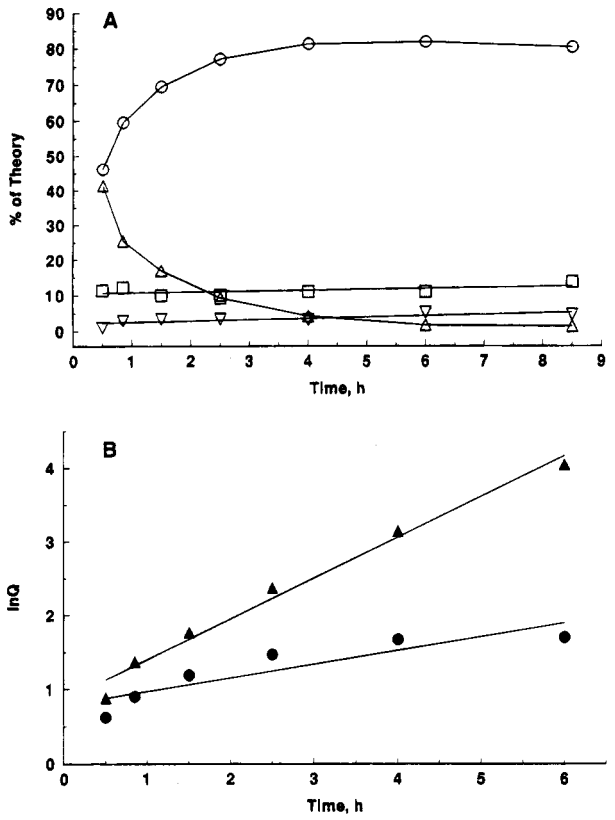


Figure 3. (A) Lactam **2** with iodoalkane **1** (mol **2:1** = 14.75) at 140 °C: open triangles, up, iodoalkane **1**; open circles, 2-(perfluorohexyl)ethanol (**3**); open triangles, down, alkene **4**; open boxes, **6**·HI. (B) Linear regression ln$Q$ plots of lactam **2** with iodoalkane **1** (mol **2:1** = 14.75) at 140 °C: solid triangles, up, $\ln Q_{iodo}$; solid circles, $\ln Q_{alc}$.

and an 82% conversion of **3** had been achieved; Figure 3A. The curves for the formation of alcohol **3** and the disappearance of **1** were nearly asymptotic. Plots of $\ln Q_{iodo}$ and of $\ln Q_{alc}$ are shown in Figure 3B. Regression analysis gave the rate constants, $k_{iodo} = 14.4 \times 10^{-5}$ s^{-1} (LS, A = 1.00, and r = 0.998; five points, 0.85–6.0 h) and $k_{alc} = 5.52 \times 10^{-5}$ s^{-1} (LS, A = 0.944, and r = 0.978; four points, 0.85–4 h).

Treatment of the Reaction Product Mixture with K_2CO_3. To validate these results at 140 °C, the product mixture (entry 7, Table 6) containing **2**, **5**·HI, and **6**·HI was stirred and heated with K_2CO_3 in $HCCl_3$ and gave additional **3**, up to 94% total yield (Table 7). Some of the volatile alkene **4** was lost and, as in Table 1, the iminolactam **5** was released from its salt, in an 89% yield.

At a 19.6 Molar Ratio of 2:1. Increasing the reactant ratio to near 20:1 further increased the reaction rate of iodoalkane **1** (Table 8). However, conversion to alcohol **3** was only 49% after 6 h, with 99.6% conversion of **1**; Figure 4A. At the same time, conversion to **6**·HI remained nearly constant at 44.7% (standard deviation SD, 2.14%) from 1–6 h. This is a value 3.8 times as high as found at the 14.8 molar ratio. Alkene **4** decreased significantly (1.5–2.0% instead of 3–5% at mol **2:1** = 14.8). $\ln Q_{iodo}$ was linear with time (Figure 4B), and k_{iodo} was 23.2×10^{-5} s^{-1} (LS, A = 0.501, r = 0.999, 10 points). The initial rate constant k_{alc}, from 0.33–2.0 h, was 4.95×10^{-5} s^{-1} (LS, A = 0.167, r = 0.953, six points). Rate constant, k_{alc}, calculated from $\ln Q_{alc}$ against time from 3–8 h was 0.479×10^{-5} s^{-1}, r = 0.942 (five points), and this segment of the $\ln Q_{alc}$ plot paralleled that of $\ln Q_{6\cdot HI}$ from 1–6 h.

Table 8. Alkylation of Lactam 2 with 1 (Mol 2:1 = 19.61) at 140 °C[a]

entry	time, h	substances, % conversn by GC 1[b]	3[c]	4[c]	5	(6·HI)[d]	quotients for rates $\ln Q_{iodo}$[e]	$\ln Q_{alc}$[f]	$\ln Q_{6\cdot HI}$[g]
1	0.33	52.4	13.8	0.57	4.64	33.2	0.646	0.148	0.398
2	0.50	40.9	20.9	0.85	7.38	37.4	0.895	0.235	0.460
3	0.75	33.2	28.9	1.04	4.49	36.8	1.10	0.340	0.453
4	1.00	25.5	30.9	1.09	10.0	42.5	1.37	0.370	0.545
5	1.50	16.1	38.9	2.00	15.8	43.0	1.84	0.493	0.553
6	2.00	10.1	44.1	1.56	17.2	44.2	2.29	0.576	0.576
7	3.00	4.69	47.5	1.81	17.1[h]	46.6	3.06	0.644	0.609
8	4.00	1.91	49.1	1.67	24.4	47.3	3.96	0.675	0.633
9	6.00	0.44	49.3	1.63	24.9[h]	48.6	5.43	0.679	0.658
10	8.00	*i*	52.3	2.59	35.7	45.2		0.740	0.601

[a] Iodoalkane **1** (2.5851 g, 5.3329 mmol, 97.6% by GC, 0.5544 M), lactam **2** (8.9664 g, 104.35 mmol, Aldrich, distilled, GC, 99.89% pure, 10.87 M), and 1,2-dichlorobenzene (0.1589 g, GC reference) were charged to reactor tube A. Total volume was 9.602 mL (the liquids did not mix). The mixture became a clear, colorless liquid after 10 min at 140 °C, but separated at 25 °C. After 20 min, the light brown liquid was clear at 140 and at 25 °C. GC on "DB-5", 30 m column. [b] Substance, percent (mol) remaining. [c] Substance, percent conversion. [d] Nonvolatile **6**·HI was calculated from mol [**1**(used up) − (**3** + **4**)]; the mean value of **6**·HI, from 1.0–6.0 h, was 44.7% (standard deviation of 2.14%). [e] $Q_{iodo} = ([\mathbf{1}]_0/[\mathbf{1}]_t)$; LS of $\ln Q_{iodo} = A + B$ (time, s) over 0–6.0 h, gave A = 0.501, B (k_{iodo}) = 23.2×10^{-5} s^{-1}, and r = 0.999. [f] $Q_{alc} = 0.5544/(0.5544 - [\mathbf{3}]_t)$; LS of $\ln Q_{alc} = A + B$ (time, s), from 0.33–2.0 h, gave A = 0.116, $B = 6.63 \times 10^{-5}$ s^{-1} (this is k_{alc}), and r = 0.979 (six points). From 2.0–8.0 h, $\ln Q_{alc}$ against time gave A = 0.556, $B = 0.643 \times 10^{-5}$ s^{-1}, and r = 0.929 (six points). [g] From 0.33–2.0 h, LS of $\ln Q_{6\cdot HI}$ against time gave A = 0.396, B ($k_{6\cdot HI}$) = 2.74×10^{-5} s^{-1}, and r = 0.906 (six points); from 2.0–6.0 h, LS of $\ln Q_{6\cdot HI}$ against time gave A = 0.544, B ($k_{6\cdot HI}$) = 0.550×10^{-5} s^{-1}, and r = 0.972 (four points). [h] Entry 7, **5** = 32.0 mol %, and entry 9, 34.4 mol %, in a second run. [i] Less than 0.1% (mol).

Alkylation of Lactam 2 in Diluted Solution. In one experiment at 140 °C, the mixture of **1** and **2** (mol **2:1** = 12.6) was diluted with 1,2-dichlorobenzene (mol **1,2-DCB:1** = 2.44). 1,2-DCB served both as GC reference and diluent. The reaction rates were slowed, but other aspects of the reacting system were essentially unchanged. Relevant quantities are given in Table 9.[26] The stirred mixture became homogeneous (at 25 °C) after heating for 20 min at 140 °C, and $\ln Q_{iodo}$ over time was linear [$k_{iodo} = 10.5 \times 10^{-5}$ s^{-1}; r = 0.999 (six points)].

An experiment at 150 °C with mol **2:1** = 15.22 gave an increased rate of reaction. The results are given in Table 10 and Figure 5A. Instead of the 82% conversion to **3** at 140 °C, the maximum conversion to **3** at 150 °C was 60.4% at 99% conversion of **1**. Intermediate **6**·HI was nearly constant at 27–34%, and alkene **4** was greater (6.0%) than at 140 °C. The increase in reaction temperature was thus deleterious to selectivity to **3** (*selectivity = mol of 3 to mol of 4 and 6·HI*) and gave inefficient use of **1**. The rate constants (Figure 5B) of $k_{iodo} = 36.5 \times 10^{-5}$ s^{-1} (LS, A = 0.0650, r = 0.998, seven points) and of $k_{alc} = 13.3 \times 10^{-5}$ s^{-1} (LS, r = 0.950) were both greater than at 140 °C; Table 10 and Table 6. Unreacted lactim salt **6**·HI was reacted with K_2CO_3 in $HCCl_3$ and ethanol at 60–70 °C and increased the total conversion to **3** from 59% to 89.5% (Table 10B). In entry 6, iminolactam **5** was hydrolyzed[25c] or oligomerized[30] by prolonged exposure to aqueous base at 25 °C.

Summary of Reaction Rate Experiments. The effects of temperature and molar ratio on this alkylation reaction of **1** with **2** are summarized in Table 11. Increasing temperature from 100–130 °C at mol **2:1** = 10:1 increased the overall rate of reaction, without affecting the selectivity to alcohol **3** and alkene **4** appreciably (entries 1–4). *Conversion* to alcohol **3** increased

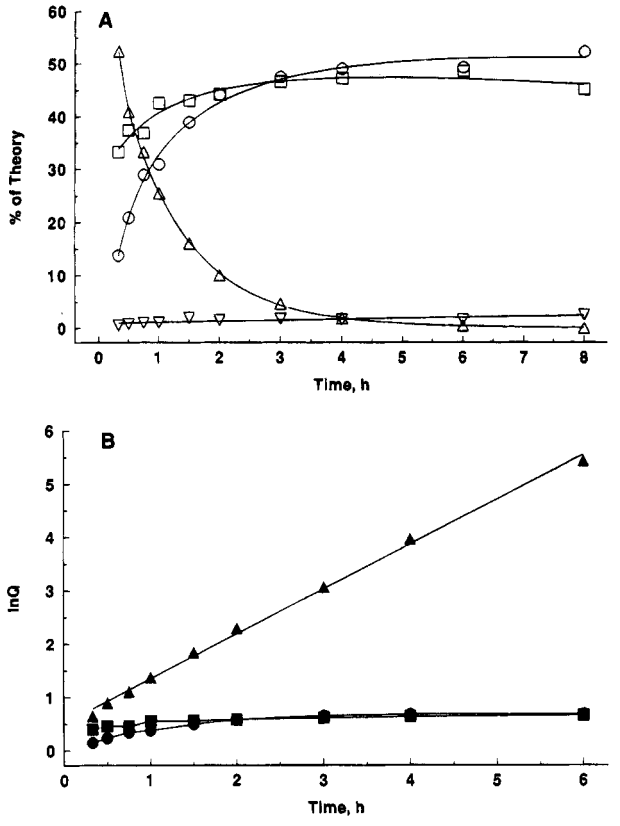


Figure 4. (A) Lactam **2** with iodoalkane **1** (mol **2:1** = 19.6) at 140 °C: open triangles, up, iodoalkane **1**; open circles, 2-(perfluorohexyl)ethanol (**3**); open triangles, down, alkene **4**; open boxes, **6**·HI. (B) Linear regression ln$Q$ plots of lactam **2** with iodoalkane **1** (mol **2:1** = 19.61) at 140 °C: solid triangles, up, lnQ_{iodo}; solid circles, lnQ_{alc}; solid boxes, ln$Q_{lactim6\cdot HI}$.

above 130 °C (enries 3–5), and unconverted lactim ether **6**·HI decreased from about 20 to 10%. An increase in temperature to 150 °C reversed these favorable trends, as conversion to **3** decreased and that of **4** increased.

The effect of mol **2:1** on rates of reaction was significant, as seen in a comparison of entries 5–8 of Table 11. The reaction rates, k_{iodo}, increased progressively with an increase in mol **2:1** from 10–20, while the reaction rate of k_{alc} *remained essentially constant* over this range of reactant ratios. Significantly, in reactions at 140 °C, the loss to unwanted alkene **4** was reduced from 6.0 to about 2 mol % as mol **2:1** was doubled (from 10 to 20). A doubling of the rate of **1** consumption also occurred, and there was no indication of unwanted side reactions. However, a striking effect on conversion to alcohol **3** was observed. As mol **2:1** was raised from 10 to 14.8 at 140 °C, a small increase in the amount of unreacted **6**·HI occurred (entry 5 with 7). Further increase of mol **2:1** to 20 gave a large decrease in conversion to **3** and a concomitant increase in residual lactim **6**·HI (entries 7 and 8). The utilization of **1** reached 99.5% in 6 h at 140 °C; accordingly, in using the higher molar ratio, further processing would be required to convert **6**·HI to **3** and lactam **2**.

Comparison of Lactam 2 with Higher Homologous Lactams in the Novel Synthesis of $R_FCH_2CH_2OH$ (3) from $R_FCH_2CH_2I$ (1). For homologous lactams [$(\overline{CH_2})_nNHC{=}O$ (n = 3–5), *selectivity* to **3** and *conversions* of **1** depended strongly on ring size. The 5-membered ring lactam **2**, under favorable conditions, gave an 83% *conversion* to distilled **3**, and the *selectivity ratio* of **3** to **4** (mol/mol) was 18.4. This conversion to **3** could be raised to 94% (Table 7) by reacting of **6**·HI with K_2CO_3. Heating of δ-valerolactam (**7**) with **1** (mol **7:1** = 14.1) at 140 °C for 6 h gave 19.0% conversion to **3** and 26.1% to alkene **4**; the selectivity ratio of **3** to **4** was thus 0.728 (Table 12). The reaction mixture became homogeneous immediately at 140 °C, but after 4 h a second liquid layer separated at 25 °C. The results as pictured in Figure 6A were striking. Iodoalkane **1** disappeared

Table 10. (A) Alkylation of Lactam 2 with 1 (Mol 2:1 = 15.22) at 150 °C[a] and (B) Reaction of Product Mixture of Table 10 with K_2CO_3 in $HCCl_3$ and Ethanol at 60–70 °C[b]

		(A) substances, % conversn by GC					quotients for rates	
entry	time, h	**1**[c]	**3**[d]	**4**[d]	**5**[d]	(**6**·HI)[e]	lnQ_{iod}[f]	lnQ_{alc}[g]
1	0.167	79.9	14.3	2.26	0.91	3.6	0.225	0.158
2	0.333	63.6	24.5	2.92	3.44	9.0	0.452	0.288
3	0.50	48.1	30.6	2.66	3.51	18.6	0.731	0.376
4	1.00	23.3	45.7	3.76	13.2	27.3	1.46	0.630
5	1.50	12.0	54.1	6.30	21.5	27.6	2.12	0.807
6	2.00	6.41	54.1	5.3	28.8	34.1	2.75	0.807
7	2.50	3.95	57.9	6.02	29.9	32.2	3.23	0.897
8	4.00	1.06	60.4	5.32	40.9	33.2	4.55	0.964
9[h]	7.00	0.00	58.7	5.09	36.2	36.3		0.917

(B) substances, % conversn by GC

entry	time, h	**1**[i]	**3**[j]	**4**[j]	**5**[j]
1	0.00		58.7	5.1	36.2
2[k]	4.00		72.9	3.8[l]	58.6
3[k]	6.00		80.1	3.8	48.7
4[m]	8.00		88.6	4.1	48.1
5[m]	10.00		89.5	4.0	46.6
6[n]	16.00		87.4	4.5	3.63[n]

[a] Iodoalkane **1** (2.6121 g, 5.4722 mmol, 99.3% by GC, 0.6960 M), lactam **2** (7.0984 g, 83.32 mmol, 99.89% pure, by GC; 10.60 M (contained *ca.* 0.10% of water), and 1,2-dichlorobenzene (0.2265 g) were charged to reactor tube A. Total volume was 7.862 mL (the liquids did not mix). It became a clear, brown liquid after 10 min at 150 or 25 °C. GC on "DB-5", 30 m column. [b] The sample of Table 10 (entry 9) products (4.99 g; 0.503 part of total reaction mixture; 5.47 mmol of products from **1**), ethanol (0.33g, 0.72 mmol); $HCCl_3$ (3.06 g; 25.6 mmol); and K_2CO_3 (0.84 g, 6.08 mmol) was a cloudy liquid/solid slurry, stirred by magnet bar in a Fischer tissue culture tube. Samples (0.40 g) were drawn by pipet from the $HCCl_3$ layer at 25 °C and extracted with 2 mL of 1% $NaHCO_3$ solution, the aqueous layer was extracted with $HCCl_3$ (0.30, 0.10 mL), and the oil layer was dried ($MgSO_4$). GC on "DB-5", 30 m capillary column. [c] Substance, molar % remaining. [d] Substance, percent conversion. [e] Nonvolatile **6**·HI was calculated from mol [**1**(used up) − (**3** + **4**)]; the mean value of **6**·HI, from 1.0–4.0 h, was 30.9% (SD 3.2%). [f] $Q_{iodo} = ([\mathbf{1}]_0/[\mathbf{1}]_t)$; LS of ln$Q_{iodo} = A + B$ (time, s) from 10 min to 2.5 h, gave $A = 0.0650$, B (k_{iodo}) = 36.5×10^{-5} s^{-1}, and $r = 0.998$ (seven points). [g] $Q_{alc} = 0.6960/(0.6960 - [\mathbf{3}]_t)$; LS of ln$Q_{alc} = A + B$ (time, s), from 0.167–1.5 h, gave $A = 0.116$, $B = 13.3 \times 10^{-5}$ s^{-1} (this is k_{alc}), and $r = 0.993$ (five points). [h] The sample was used in part B for reaction with K_2CO_3. [i] None of **1** was detected in any of the samples. [j] Substance, percent (mol) coversion. [k] The reaction temperature was 60.0 °C; after 6 h, water (0.50 g, 28 mmol) was added to increase the K_2CO_3 solubility and the temperature was raised to 70 °C. [l] Alkene **4** was lost in sampling the original reaction mixture. [m] After 8 h, K_2CO_3 (0.50 g, 3.6 mmol) was added. [n] The reaction mixture, after 16 h at 25 °C, formed a mass of solid. Water (10 mL) was added, and an oil layer separated during 5 days. Most of iminolactam **5** had been destroyed during this time.[30]

(29) Brace, N. O. Manuscript in preparation.

(30) (a) Brozek, J.; Marek, M.; Roda, J.; Kralicek, J. *Makromol. Chem.* **1988**, *189*(1), 17–27; *Chem. Abstr.* **1988**, *108*, 113033e. (b) Brozek, J.; Roda, J.; Kralicek, J. *Ibid.* **1988**, *189*(1), 29–43; *Chem. Abstr.* **1988**, *108*, 113034f. (Please note: substance no. **5** was inserted to aid in the understanding of this abstract.) Polymerization of Lactams. 84. The role of 1-(1-pyrrolin-2-yl)-2-pyrrolidone (**5**) in the anionic polymerization of 2-pyrrolidone. "The incorporation of **5** 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 **5** and monomer was also measured."

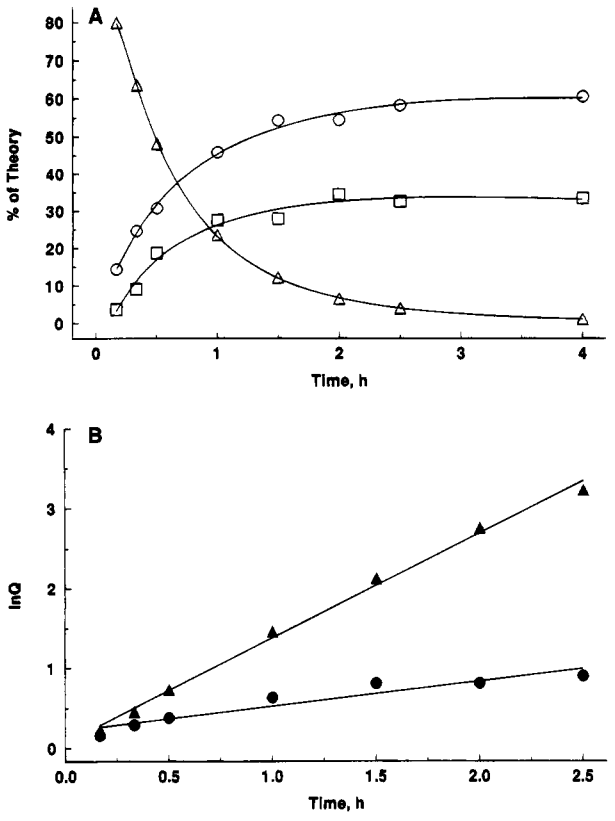


Figure 5. (A) Lactam **2** with iodoalkane **1** (mol **2:1** = 15.22) at 150 °C: open triangles, up, iodoalkane **1**; open circles, 2-(perfluorohexyl)ethanol (**3**); open boxes, **6**·HI. (B) Linear regression ln$Q$ plots of lactam **2** with iodoalkane **1** (mol **2:1** = 15.22) at 150 °C: solid triangles, up, lnQ_{iodo}; solid circles, lnQ_{alc}.

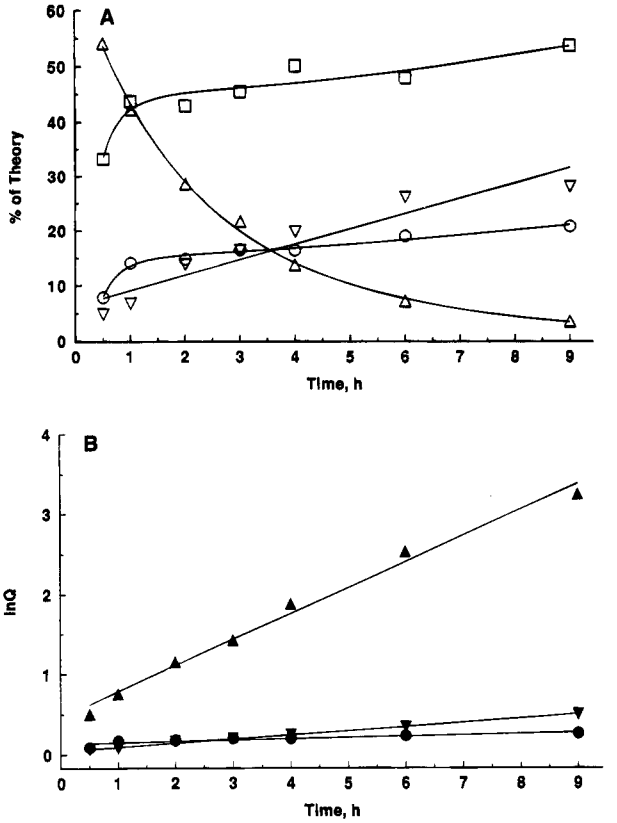
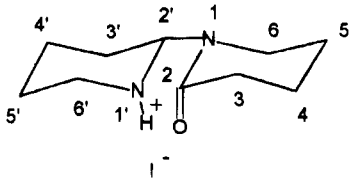


Figure 6. (A) Iodoalkane **1** with lactam **7** (mol **7:1** = 14.1) at 140 °C: open triangles, up, iodoalkane **1**; open circles, 2-(perfluorohexyl)ethanol (**3**); open triangles, down, alkene **4**; open boxes, **6**·HI. (B) Linear regression ln$Q$ plots of iodoalkane **1** with lactam **7** (mol **7:1** = 14.1) at 140 °C: solid triangles, up, lnQ_{iodo}; solid circles, lnQ_{alc}; solid triangles, down, ln$Q_{alkene4}$.

at 140 °C, after 0.5 h, at a constant rate (k_{iodo} = 10.1 × 10^{-5} s^{-1}; LS, r = 0.998); alcohol **3** was formed at a much slower rate (k_{alc} = 0.45 × 10^{-5} s^{-1}, r = 0.887, seven points); and alkene **4** at a rate somwhat greater than that of **3** (k_{alkene} = 1.45 × 10^{-5} s^{-1}, r = 0.992, seven points); Figure 6B. (By comparison, for **2** and **1** at 140 °C, k_{iodo} = 14.4 × 10^{-5} s^{-1}; entry 7, Table 11.) Conversion to lactim **9**·HI was 43.7% in 1 h and slowly increased to 50% in 4 h. When treated with K_2CO_3, the lactim **9**·HI was converted to more alcohol **3** and lactam **7**.[29] However, the loss to alkene **4** renders this route to alcohol **3** unsatisfactory.

The expected iminolactam **8**·HI was isolated as a pure crystalline salt and was fully characterized by elemental analysis and spectroscopic means. The ^{1}H NMR was



Iminolactam Hydroiodide Salt **8**.HI

especially useful, as indicated in the Experimental Section. Hence, reaction of **1** with lactam **7** probably followed the anticipated sequence of reactions given in Scheme 2. The equilibration of lactim salt **9**·HI with the large excess of lactam **7** would give some free base lactim **9**. Then, thermal fragmentation of **9** at 140 °C could occur to give alkene **4** and lactam **7**. The significance of these results for the mechanism of the reaction is discussed below in connection with other lactams. Further experiments are being reported separately.[29]

Alkylation of ϵ-Caprolactam (10). Table 13 lists some representative results with lactam **10** and lactams **2** and **7**. In summary, **10** provided little or no **3** but mostly $R_FCH{=}CH_2$ (**4**) when heated with **1**. In entry 3, a mixture (mol **10:1** = 10) was heated at 150 °C for 6 h. Distillation gave very little of **3**, and the solid remaining contained **1** (48.8% by iodine analysis, also identified by TLC), the iminolactam **13**·HI, the lactim ether **14**·HI[22] (50% by I^-), and unreacted **10**. An experiment (entry 4, Table 13) with mol **10:1** = 5.06 and 5.01 M in toluene solution gave no detectable reaction after 1, 3, or 6 h. Increasing the amount to mol **10:1** = 12.2 (entry 5, Table 13) gave conversions as follows: 1.75% to **3**, 13.1% to **4** (selectivity of mol **3:4** = 0.134), and 34.1% to **14**·HI. Meanwhile, 46.3% of **1** was consumed. Other experiments, with water added to the reaction mixture, increased the conversion to alcohol **3** and *decreased* the loss to alkene **4**. These results are being reported separately.[29]

Nucleophilic Displacement Reactions in the Homologous Lactim Ether Series. Simple heating of lactam **2** with lactim **6** either neat, or 0.395 M in toluene solution at 140 °C (Table 16[26] and Scheme 3), gave nearly quantitative yield of **3** and iminolactam **5**. Conversion of lactim **6** in the neat mixture in 3 h was 90% to **3** and 1% to alkene **4**. The rate constant (in toluene) for consumption of **6** was $k_{lactim6}$ = 4.40 × 10^{-6} s^{-1} (r = 0.996). Similarly, two reactions without solvent, at 120 and 130 °C, gave analogous, consistent results found in Tables

Table 11. Summary of Alkylation Reactions of Lactam 2 with Iodoalkane 1: Effect of Change in Temperature and Mol Ratio on Conversion to Products and Rates[a]

				substances, % conversn by GC				rates of reaction			
										LS, r	
entry	temp, °C	time, h	mol **2**:1	**1**[b]	**3**[c]	**4**[c]	**6**·HI[c]	k_{iodo} 10^{-5} s^{-1}	k_{alc} 10^{-5} s^{-1}	iodo	alc
1[d]	100	68	10	93.6	70.6	*e*	20.0	1.12	0.436	0.999	0.972
2[f]	120	14	10	93.3	69.2	*e*	21.1	4.17		0.985	
3[g]	130	10	10	94.3	68.0	*e*	23.3	6.60		0.991	
4[h]	132	15.5	10	95.0	82.9	4.5	10.6				
5[i]	140	7.5	10	95.0	79.3	6.0	9.7	9.56	5.27	0.991	0.992
6[j]	140	9	12.6[j]	95.3	74.2	4.0	17.1	10.5	4.00	0.999	0.967
7[k]	140	6	14.8	98.3	81.8	3.32	13.2	14.4	5.20	0.998	0.978
8[l]	140	6	19.6	99.5	49.3	1.7	48.6	23.3	4.95	0.999	0.953
9[m]	150	4	15.2	99.0	60.4	6.0	33.2	36.5	13.3	0.998	0.993

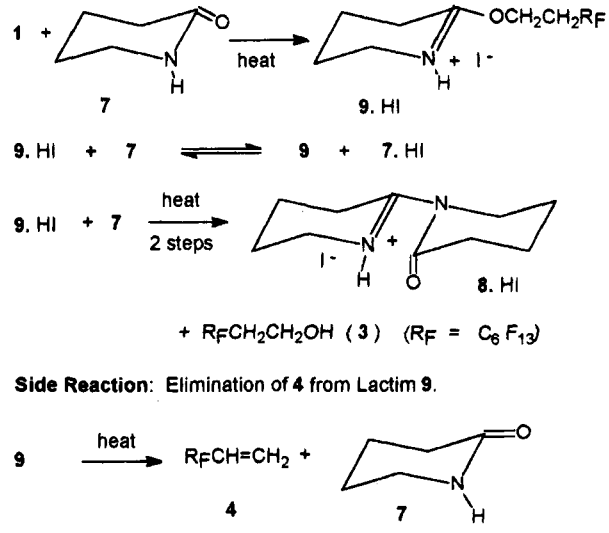
[a] General procedure: reactions were run in reactor tube A; see each table for specific conditions and GC analysis. [b] Substance, percent (mol) used. [c] Substance, percent (mol) conversion. [d] Table 2. [e] Alkene **4** was estimated to be ca. 3.0%. [f] Table 3.[26] [g] Table 4.[26] [h] Table 1. [i] Table 5; [**2**] = 9.93. [j] Table 9;[26] 1,2-dichlorobenzene (2.44 mol, 1.634 M) was used as diluent and GC reference. [k] Table 6; [**2**] = 10.5. [l] Table 8; [**2**] = 10.9. [m] Table 10.

Table 12. Iodoalkane 1 with Lactam 7 (Mol 7:1 = 14.1) at 140 °C[a]

		substances, % (mol) conversn by GC					quotients for rates		
entry	time, h	**1**[b]	**3**[c]	**4**[c]	**7**[b]	(**9**·HI)[d]	$\ln Q_{iodo}$[e]	$\ln Q_{alc}$[f]	$\ln Q_{alkene}$[g]
1	0.50	54.1	7.85	4.82	30.6	33.2	0.506	0.09145	0.0552
2	1.00	42.2	14.1	6.72	32.6[h]	43.7	0.755	0.170	0.0779
3	2.00	28.6	14.8	13.8	32.2	42.9	1.15	0.180	0.167
4	3.00	21.7	16.5	16.4	32.1	45.4	1.42	0.203	0.201
5[i]	4.00	13.7	16.4	19.8	33.4[h]	50.0	1.88	0.202	0.250
6[i]	6.00	7.17	19.0	26.1	32.3[h]	47.8	2.53	0.237	0.343
7[i]	9.00	3.52	20.8	28.0[j]	32.5	53.3	3.24	0.264	0.374[j]

[a] See the Experimental Section for quantities and procedures used. [b] Substance, percent (mol) remaining. [c] Substance, percent (mol) conversion. [d] **9**·HI was calculated from mol [**1**(used up) − (**3** + **4**)]. [e] LS gave $A = 0.479$, B (k_{iodo}) $= 10.1 \times 10^{-5}$ s^{-1}, $r = 0.998$ (six points). [f] LS gave $A = 0.134$, B (k_{alc}) $= 0.450 \times 10^{-5}$ s^{-1}, $r = 0.887$ (seven points). [g] LS gave $A = 0.0386$, B (k_{alkene}) $= 1.45 \times 10^{-5}$ s^{-1}, $r = 0.992$ (seven points). [h] The amount of lactam **7** found by GC was sensitive to the sample size and gave a sloping peak on "DB-5" column. The result was less accurate than required for a determination by difference. [i] The GC sample was taken from a two-layer mixture that was shaken to give a cloudy liquid. [j] An extrapolated value.

Scheme 2. Preparation of Alcohol 3 from 1 and Lactam 7; Side Reaction Gave Alkene 4 by Elimination from Lactim 9



14 and 15.[26] Approximate rate constants were determined as well.

By contrast, lactam **2** with caprolactim **14**[22] at 140 °C (Table 17; Scheme 4), afforded a complex mixture of products. After 24 h, 67.8% of **14** had been consumed; conversion to products was as follows: 45% to **3**, 47.4% to **12**, 20.3% to lactam **10**, and 9% to **4**. During the first 12 h, molar amounts of **3** and iminolactam **12**[25] were nearly equal, as they should be, from Scheme 4. However, after 12 h, conversion of **14** and formation rates of **3** and **12** slowed while that of side products **4** and **10** continued at a steady pace; Figure 7A. A plot of $\ln Q_{lactim14}$ against time (Figure 7B) had two linear segments (as calculated by LS): from 3−12 h, $k_{lactim14} = 1.62 \times 10^{-5}$ s^{-1}; and from 12−32 h, $k_{lactim14} = 0.733 \times 10^{-5}$ s^{-1} (r = 0.99 and 0.998, respectively). This suggests that two concurrent reactions, but of different rates, consumed lactim **14**. The slower reaction may have been the intramolecular elimination depicted in Scheme 4 that produces lactam **10** and alkene **4**. Molar amounts of **10** and **3** equalled the amount of **14** consumed over the entire time period. It was noted above that 6-membered lactim **9** may have suffered a fate similar to that of lactim **14**. Implications for the mechanism of reaction are discussed below.

The unimolecular elimination of an alkene fron an *O*-alkyllactim was observed by Ralls and Elliger.[31b] They found that the compound, *O*-ethylcaprolactim of high purity, is unchanged on heating at 193 °C; it produces trace amouts of *N*-ethylcaprolactam and moderate amounts of lactam **10** during 21 h of heating at 237 ± 5 °C. The major thermal transformation of *O*-ethylcaprolactim at 285 ± 1 °C is a first-order ($k = 0.033$ min^{-1}) formation of **10** and ethene. Lactam **10** is stable under these conditions. The reaction is 94% complete in 3 h. Ralls[31c] also reported that *O*-methylvalerolactim is unchanged by heating at 250 °C for 5 h. The instability of lactim **14** to heating was previously noted;[22] the alkene **4** and lactam **10** were obtained. It was found, in confirmation of the literature,[25b] that heating of *O*-methylcaprolactim **11** with lactam **10** gave no methanol,

(31) (a) Glushkov, R. G.; Granik, V. G. In *The Chemistry Of Lactim Ethers*; Katritsky, A. R., Boulton, A. J., Eds.; Advances in Heterocyclic Chemistry; Academic Press: New York, 1970; Vol. 12, p 191. (b) Ralls, J. W.; Elliger, C. A. *Chem. Ind.* **1961**, 20. (c) Ralls, J. W. *J. Org. Chem.* **1961**, *26*, 66−67.

Table 13. Comparison of Homologous Lactams 7 and 10 with Lactam 2 in the Synthesis of Alcohol 3 from Iodoalkane 1

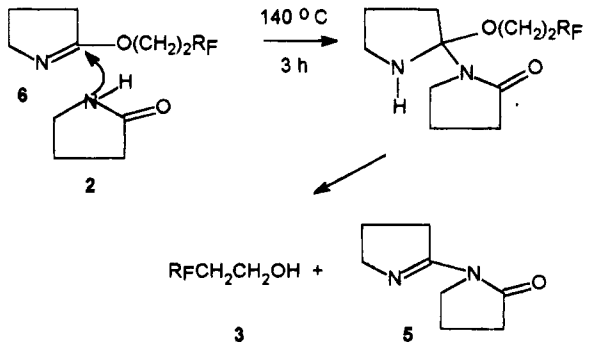
$$\underset{\mathbf{1}}{R_FCH_2CH_2I} + \underset{\mathbf{2, 7, 10}}{(\overbrace{CH_2)_n NHC}{=}O} \xrightarrow{140\ ^\circ C} \underset{\mathbf{3}}{R_FCH_2CH_2OH} + \underset{\mathbf{X}\cdot HI\ (\mathbf{5}, n = 3; \mathbf{8}, n = 4; \mathbf{13}, n = 5)}{[(\overbrace{CH_2)_n N}{=}C\overbrace{N(CH_2)_n C}{=}O]HI} +$$

$$(\overbrace{CH_2)_n N}{=}CO(CH_2)_2R_F.HI\ (\mathbf{Y}.HI;\ \mathbf{6}, n = 3;\ \mathbf{9}, n = 4;\ \mathbf{14}, n = 5)$$

				substances, % conversn by GC[a]				
entry	lactam code, *n*	lactam:**1**, mol	time, h	**1**[b]	**3**[c]	**4**[c]	**Y**·HI[d]	*n*
1[e]	**2**, 3	14.8	7.5	1.7	81.8	3.32	13.2	3
2[f]	**7**, 4	14.1	6.0	7.17	19.0	26.1	47.8	4
3[g]	**10**, 5	10.0	6.0	48.8	0.47	*h*	50	5
4[i]	**10**, 5	5.06	6.0	100	*h*	*h*	*h*	5
5[j]	**10**, 5	12.2	5.5	53.7	1.75	13.1	34.1	5

[a] Reaction samples were analyzed on "DB-5", 30 m column. [b] Substance, percent (mol) remaining. [c] Substance, percent (mol) conversion. [d] Nonvolatile **6**·HI (or homologous lactim ether salt) was calculated from mol [**1** (used up) − (**3** + **4**)]. [e] Table 6 with Table 11. [f] Table 12. [g] At 150 °C; *total* iodine was 100%, and iodide ion was 50% of theory, by titration, for consumption of **1**. TLC: **1**, **2**, and two unknown spots (**X**·HI and **Y**·HI) of major concentration, besides lesser amounts of unknown substances. See supplementary material.[26] [h] None detected by GC or below detection limits. [i] **1** (0.4843 g, 1.02 mmol, 0.521 M), **10** (0.5676 g, 5.00 mmol, 2.64 M), toluene (0.8749 g, 9.495 mmol, 5.013 M) and 1,2-dichlorobenzene (0.1093 g, 0.744 mmol; total volume was 1.89 mL) in reactor tube A gave a clear, colorless liquid mixture at 140 °C and at 25 °C. Reaction samples analyzed as in Table 6. A sample of the original mixture and samples taken after 1, 3, and 6 h were unchanged in GC analysis. [j] **1** (0.6365 g, 1.311 mmol, 0.329 M), **10** (1.8149 g, 16.04 mmol, 4.58 M), toluene (0.1097 g, 1.190 mmol, 0.3404 M, GC ref), and 1,2-dichlorobenzene (0.1043 g, 0.7095 mmol, 0.2828 M; total volume of liquid was 3.50 mL) in reactor tube A gave a clear, colorless liquid at 140 °C that turned to a light brown color after 1 h at 140 °C. The reaction mixture crystallized when cooled to 25 °C. $HCCl_3$ (1.00 mL) was added and the mixture heated to give a clear, brown solution. Samples for GC and spectroscopic examination were clear.

Scheme 3. Displacement of Alcohol 3 from Lactim 6 by Lactam 2



Substances: Used Up, **2**, 88.8 %; **6**, 91.6 %.

Formed, **3**, 89.2 %; **4**, 1.08 %; **5**, 97.4 %

and the lactim was recovered unchanged. Other aspects of these reactions are being reported separately.[29]

Discussion

The striking effect of ring size of the lactam on the synthesis of **3** was found to depend on the rate and efficiency of an intermediate displacement step. This finding was not anticipated from previous knowledge in the area of lactam/lactim chemistry.[31a] A new mechanism is proposed to account for these new results.

Mechanism of the Thermal Alkylation Reaction. Scheme 5 gives the proposed reaction steps for the synthesis of alcohols by the alkylation of ambidentate lactams.[19,20] In the case of lactam **2**, isolation of lactim **6**·HI, the spectroscopic evidence for its presence in reaction mixtures, and conversion to the expected products (namely, **6** and I^-, then **3** and lactam **2**) by reaction with base all provide support for intermediate lactim **6**·HI as salt I ($n = 1$) in step 1. Quantitative product and rate studies showed that the first step of the three step sequence was reversible (Tables 6, 8, and 10), in experiments where a steady state concentration of **6**·HI was obtained for a major part of the reaction period. The necessity for a large excess of lactam and the rate

Table 17. Heating Lactim 14 with Lactam 2 in Toluene Solution at 140 °C to Displace Alcohol 3 and Other Products[a]

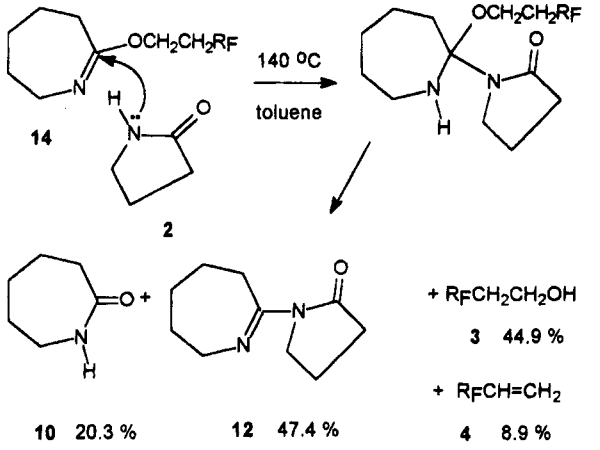
	time,	substances, % conversn by GC[a]					quotient for
entry	h	**3**[b]	**4**[b]	**14**[c]	**12**[b]	**10**[b,d]	rate $\ln Q_{\text{lactim14}}$[e]
1	3	19.9	2.47	77.1	21.0	4.88	0.235
2	8	32.8	5.03	55.9	36.2	8.97	0.593
3	12	38.3	6.77	46.8	43.1	11.8	0.756
4[f]	24	44.9	8.90	33.2	47.4	20.3	1.10
5[f]	24	44.3	(8.9)	33.9	50.1	19.0	(1.1)
6	32	42.7	12.3	34.0[g]	52.0[g]	23.9	1.28

[a] (2-(Perfluorohexyl)ethyl)caprolactim (**14**), 1.3822 g, 3.010 mmol, 97.5% by GC, 0.248 M in toluene; **14** contained **10**, 0.0793 mmol; **2** (1.305 g, 15.33 mmol, 99%, 1.27 M); 1,2-dichlorobenzene (0.3773 g, 2.568 mmol), and toluene (8.67 g, 94.1 mmol, 10 mL) were charged to reactor tube A and processed as above. Total volume was 12.1 mL. GC on "DB-5", 15 m capillary column. See Figure 7A,B for graphs of data. [b] Substance, percent conversion on **14** (limiting reactant). [c] **14**, percent (mol) remaining. [d] The amount of **10** initially present in **14** is not included. [e] $\ln Q_{14}$ is $\ln[\mathbf{14}]_o/[\mathbf{14}]_t$; LS of the equation, $\ln Q_{\text{lactim14}} = A + B$ (time, s), for the interval of 3−12 h, gave a straight line, with $A = 0.0799$, $B = 1.62 \times 10^{-5}$ s^{-1}, $r = 0.989$ (3 points); for the time interval of 12−32 h, the straight line segment gave $A = 0.447$, $B = 7.33 \times 10^{-6}$ s^{-1}, and $r = 0.998$ (three points). [f] To show consistency, two samples, differing in dilution, were analyzed by GC. [g] Extrapolated value.

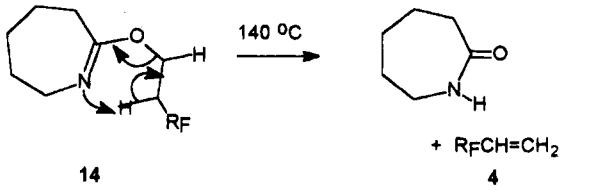
increase caused by an increase in lactam concentration are also consistent with reversibility of step 1. The steady state concentration of intermediate **6**·HI made possible the calculation of rates for the consumption of iodoalkane in the first step of the reaction. The effects of reaction temperature and dilution on the rate of reaction, previously observed for the alkylation of amides,[19,20] were confirmed in the current study.

The second and third steps of Scheme 5 can be reversed by heating a mixture of iminolactam **5** with methanol,[25b,c] and the products (*O*-methylbutyrolactim and lactam **2**) are isolated in quantitative yield.[25c] Thus, the excess of lactam **2** used in the alkylation reaction with **1** probably is needed to drive the equilibria of steps 2 and 3 to completion. Since shifting of the equilibrium by removing the volatile alcohol in the presence of volatile alkyl halide is not possible, part of the driving force for steps 2 and 3 may be the formation of salt II of step 2 and salt III of step 3, as a "sink" for the strong acid HI. A

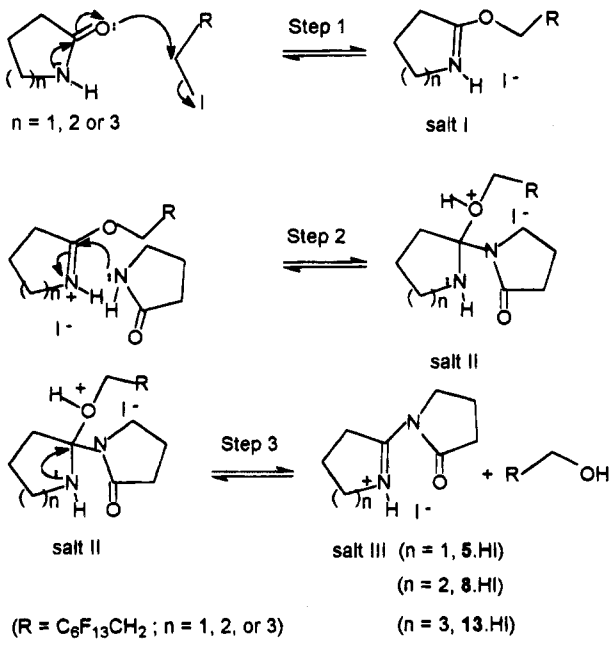
Scheme 4. Displacement of Alcohol from Lactim 14 by Lactam 2. Proposed Transition State for Elimination of Alkene 4 from Lactim 14 (Table 17)



Proposed Transition State for Elimination of Alkene 4



Scheme 5. Proposed Reaction Steps in the Synthesis of 2-(Perfluoroalkyl)-1-ethanols from Lactams and Iodoalkane 1



somewhat different interpretation is proposed below for the higher homologous lactams.

The expectation is for oxygen, the stronger nucleophile in the lactam, to bring about the condensation reaction of step 2 just as it does in step 1. The unexpected mode of action with the nitrogen electron pair acting as the nucleophile illustrates the ambidentate nature of the amide (lactam) linkage. Early reports[32] give dilactim ether structures for the condensation products.[31,32] The correct iminolactam structures are securely defined,[25,33]

(32) Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278.
(33) Mazurkiewicz[25b] gave an extensive list of references for dilactim ether structures and iminolactam structures.

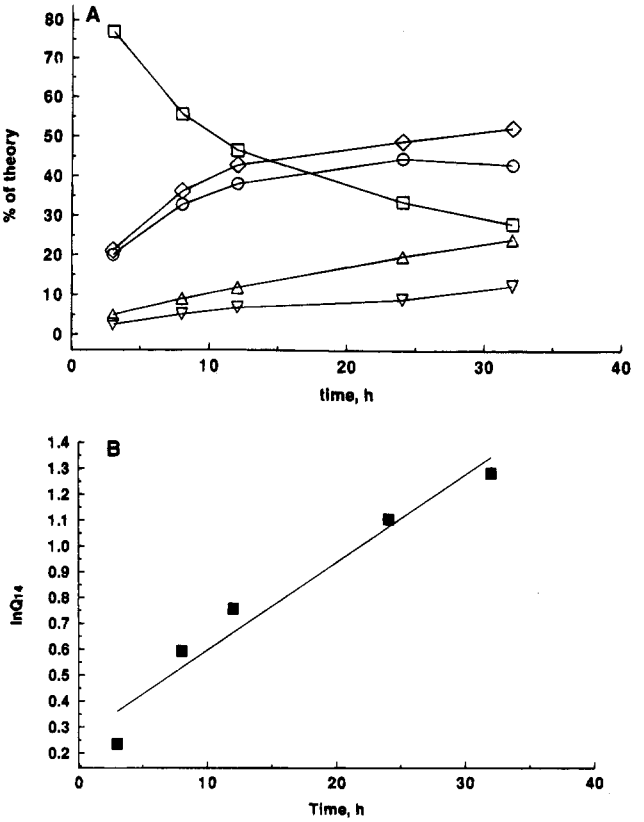


Figure 7. (A) Lactim **14** with lactam **2** in toluene at 140 °C: open boxes, lactim **14**; open triangles, up, lactam **10**; open circles, 2-(perfluorohexyl)ethanol (**3**); open triangles, down, alkene **4**; open diamonds, iminolactam **12**. (B) Linear regression ln$Q$ plot of lactim **14** with lactam **2** in toluene at 140 °C: solid boxes, $\ln Q_{\text{lactim14}}$.

however, and are strictly analogous to the imidamides [HC(=NR)NHR$^+$ X$^-$], obtained as the coproduct from alkylation of amides by alkyl halides.[19,20] The basis for this mode of reaction may be the tendency for a "softer" nucleophile (the N electron pair) to combine with the "softer" electrophile (the electron-deficient carbon of the C=N π-bond). This point is further illustrated with the higher lactams, given below.

The observed rate constants, $k_{\text{iodo}} > k_{\text{alc}}$ (Table 11) in the present alkylation process suggest that step 2 may be the rate-determining step. The measured pseudo-first-order rate constants for the thermally induced nucleophilic displacement reaction of lactam **2** on lactim **6** of Scheme 3 (Tables 14–16)[26] did not differ greatly from the analogous rates for k_{alc} of Table 11. In any case, the displacement of alcohol **3** from *neutral* lactim **6** bears a close analogy to steps 2 and 3. Finally, in the case of lactam **2**, the iminolactam salt **5**·HI of step 3, isolated both as its HI salt and as free base, gives a complete accounting for the products of Scheme 5.

As previously cited,[19,20] an imidate salt was prepared from reaction of *N*-methylformamide and dimethyl sulfate and was isolated and characterized.[34] If this imidate salt is heated, displacement of methyl formate and formation of an amidine salt occurs.[34] These reactions are closely analogous to those given as steps 1–3 in Scheme 5. It cannot be stated for certainty that steps 2 and 3 actually exist as separate steps; the intermediate salt II, not isolated, may be only a "transition state

(34) Bredereck, H.; Gompper, R. Rempfer, H.; Klemm, K. Keck, H. *Chem. Ber.* **1959**, *92*, 329–337.

complex". Additional evidence on this point is being sought experimentally.[29]

Higher Homologues. It is clear from the results with **7** and **10** that the larger ring lactams are unsuitable for the synthesis of alcohol **3**. The reasons for this behavior have been partially uncovered. Using Scheme 5 as a guide, and the results from Scheme 3, it may be concluded that retardation, or failure, of step 2 partially, or completely, blocks the overall synthesis. Instead, elimination of alkene **4** from the intermediate lactim ether (e.g., **9** or **14**) intervenes. Thermal elimination of **4** and displacement of **3** by nucleophilic S_N2 attack by the lactam are considered to be competitive reactions. Their relative rates would thus determine the relative amounts of **3** and **4** produced in a given system.

In Scheme 3 the 5-membered lactim **6** (as free base) readily reacted with **2** at 140 °C to give alcohol **3** in 90% conversion in 3 h. In Scheme 4 the analogous reaction of 7-membered lactim **14** with **2** gave **3** (44.9%), lactam **10** (20.3%), and **4**. A model transition state (TS) structure for thermal elimination of **4** from **14** is pictured in Scheme 4. It is now proposed that, consistent with known principles of conformational analysis, the activation energy needed to pass over the TS barrier may be somewhat reduced by minimizing the eclipsing and torsional strains in a six-membered ring fused to the 7-membered parent ring of lactim **14**. In this TS the hydrogen atoms of $R_FCH_2CH_2$ are assumed to occupy noneclipsed positions, and the $(CH_2)_5$ linkage in **14** *is twisted* to allow the planar imine linkage to be held in the approximate chair of the newly forming ring. Lactim **6**, if it were to be held in a planar form, would be less able to accommodate the additional angle and eclipsing strains imposed on the TS structure of the two fused 5- and 6-membered rings. The valerolactim **9**, for these reasons, may be expected to lie somewhere between lactims **6** and **14** in its ability to achieve the necessary TS structure for concerted elimination of **4**. It is assumed in the foregoing discussion that the lactim would react only as the free base, with its lone pair of electrons on nitrogen free to abstract the proton from the relatively acidic carbon atom attached to the strongly electron withdrawing perfluoroalkyl group.[9b]

However, in Scheme 2, where steps in the synthesis of alcohol **3** from lactam **7** are proposed, *equilibration* of lactim ether salt **9**·HI with the *large* excess of lactam **7** gives a small but definite concentration of free base lactim **9**. Then, in a separate step, thermal dealkylation of **9** can occur to give **4** and the lactam. A comparison of the synthesis of alcohol **3** from **1** and the homologous lactams shows a steep decline in the selectivity to alcohol **3**. In reaction of **1** with **2** the selectivity ratio of mol **3**:**4** = 18.4 fell to mol **3**:**4** = 0.73 with lactam **7** and further to mol **3**:**4** = 0.134 with lactam **10**.

Nucleophilicity of Lactams. The relative reactivity of lactims **6**, **9**, and **14** in the nucleophilic displacement reactions with a lactam differ in another important respect. The nucleophile in step 2 of Scheme 5 has nucleophilic properties that differ significantly with ring size. This was demonstrated by the model reactions carried out with lactams **2** and **10**, acting as a nucleophile with lactim ether **14** or with *O*-methylcaprolactim. The latter reaction had already been studied by Brozek *et al.*,[25] and was confirmed in this work. The 7-membered ring lactam **10** is inert as a nucleophile in these reactions in contrast to the butryolactam **2**. The origin of this difference in nucleophilicity may be more difficult to determine. The 7-membered lactam may be insufficiently nucleophilic because the less strained ring has a weaker dipole momemt of the NHC=O group or because of increased steric repulsion of the two larger rings in the tetrahedral intermediate. The subject apparently has not been examined in any detail. Preliminary results will be communicated in a forthcoming report.[29]

Summary. Schemes that rationalize the synthesis of alcohols by the thermal alkylation of homologous lactams are proposed.[19,20] The nucleophilic displacement on the iodoalkane by *O*-attack of the ambidentate lactam reversibly forms a lactim salt in step 1; this is followed by *N*-attack of the lactam on the lactim salt I to give a tetrahedral intermediate salt II in step 2. In step 3 the salt II fragments to alcohol and an iminolactam salt III. Several lines of evidence are followed: (1) isolation of, and confirmation by synthesis,[22] of lactim ether **6**; (2) model reactions of lactam **2** with lactam **6** or with 7-membered lactim **14** to give alcohol and iminolactims; (3) failure of displacement of alcohol from 7-membered lactims by 7-membered lactam **10**; (4) quantitative product and rate studies that provided rate constants for steps 1 and 2 of the alkylation reaction. Results with the 6- and 7-membered lactams gave additional insight into these thermal alkylation reactions. Two competitive reactions can be discerned: (1) the S_N2 displacement of alcohol by *N*-attack of lactam on the intermediate lactim and (2) the unimolecular, concerted fragmentation of the lactim to lactim and the alkene. These competitive reactions appear to occur in both reacting systems, since in the model reaction of lactim **12** with lactam **2** alkene elimination occurred just as it did in the alkylation reaction of **7** with **1**. The two competitive reactions were defined by rates and product formation and showed that the alcohol was formed at a faster rate initially but that alkene was formed at a faster rate after a substantial amount of the iodoalkane, or of the lactim, respectively, had been consumed. In reaction studies underway, these novel results will be more fully explored.[29]

Advantages and Disadvantages of the Lactam Alcohol Synthesis. The synthesis of **3** from iodoalkane **1** and lactam **2** has distinct advantages over present methods and some drawbacks as well. The thermal alkylation process is simple to perform and will give a high yield alcohol **3** in a few hours. Strong acids, strong oxidizing agents, or heavy metal salts are not required. There is no need to hydrolyze the formate ester of **3**, as in the alkylation of DMF by **1**, in the presence of water. The loss in yield to alkene **4** is as low or lower than any known process, and the recovery of unreacted lactam **2** can be readily achieved. In the "anhydrous" process, coproduct iminolactam **5** may be separated from **2** with some difficulty, and then **5**, which is a valuable initiator of lactam polymerization,[30] may be used for this or other purposes. An alternative is to hydrolyze the salt mixture of **5**·HI and **2** by heating with aqueous base to recover the iodine as iodide salt and the lactam **2** as volatile product.

Disadvantages are, firstly, a large molar excess of **2** is required, though this is offset to some degree by the low molecular mass of **2**. At a 15 mol excess this is 2.5 parts by wt of **2**:**1**. Secondly, an efficient distillation apparatus is needed to separate **3** from the less volatile **2**. Loss of **1** to hydrolysis (in an aqueous workup procedure) can be minimized by carrying the reaction to 98% conversion (6 h, 140 °C, mol **2**:**1** = 15). In a closely related process, to be presented in a companion paper,[29] some of these disadvantages are minimized.

Experimental Section

Materials and physical methods are given in the supplementary material.[26]

Standard Reaction Procedures. These methods were previously described.[19,20] Most frequently, a heavy-walled Pyrex glass reactor tube A (1.8 by 11 cm; volume, 18.5 mL), fitted with a vacuum-tight, Teflon valve was used. The tube A was chilled (−78 or −196 °C), evacuated to a low pressure, and filled with nitrogen several times. The tube was sealed, weighed, and immersed in a stirred, constant temperature oil bath; the inhomogeneous reaction mixtures were stirred vigorously by a magnet bar. After intervals of time, the tube was cooled, weighed, and opened. A GC sample was drawn out by Pasteur pipet and processed as described in representative experiments and tables that follow. Reaction tube B was a heavy wall, 90-mL glass tube, fitted with a metal cap and valve, sealed by a Teflon "O" ring and locking device (Fischer-Porter tube). The reactor tubes may be used up to 150 °C without loss of vacuum.

Alkylation Experiments of 1 and Lactam 2 in Reactor Tube A. Reaction Rate of Iodoalkane 1 and Lactam 2 at 140 °C; Mol 2:1 = 14.75. Iodoalkane **1** (2.4639 g, 5.073 mmol, 0.7121 M, 97.6% of C_6 homologue; polar impurities removed by activated alumina), lactam **2** (6.3924 g, 74.807 mmol, 99.5% purity, 10.50 M, contained 0.10% water, 0.006 39 g, 0.355 mmol, 0.0500 M), and 1,2-dichlorobenzene (0.1812 g, GC reference) were charged to reactor tube A and processed as described above. The total volume was 7.124 mL. The sealed tube was immersed in a stirred oil bath at 140 °C, and the two-layer solution was stirred by a magnet bar. After 10 min at 140 °C the mixture became clear; after 20 min, the liquid remained clear at 25 °C. Samples for GC analysis were removed, as indicated in Table 6; after 8.5 h, GC gave the following: **1**, 0.041 mmol, 1.43 mol %; alkene **4**, 0.244 mmol, 4.72 mol %; and alcohol **3**, 4.16 mmol, 80.1 mol %. Thus, it was estimated that lactim salt **6**·HI comprised 0.700 mmol or 13.8 mol % of the total products.

B. Treatment of Reaction Product Mixture from 1 and 2 with K_2CO_3 in Ethanol and $HCCl_3$. The reaction product mixture above (8.5 h reaction time; 5.00 g, 0.5533 part; 2.875 mmol of products; see Table 6 for GC analysis) with K_2CO_3 (0.80 g, 5.75 mmol), ethanol (0.33 g, 5.0 mmol) and $HCCl_3$ (4.78 g, 40.0 mmol) was stirred at 68 °C for 4 h. At 25 °C a sample (0.39 g) of clear, supernatant liquid was shaken with 2.00 mL of aqueous $NaHCO_3$ solution and extracted with $CHCl_3$ twice (0.30 and 0.1 mL). The cloudy liquid was dried over anhydrous $MgSO_4$. Samples 2 and 3, after 5 and 6 h, respectively, were similarly treated. GC results are given in Table 7. Alcohol **3** was found in 89−94% yield, and coproduct iminolactam **5** was recovered in 77−89% yield. There was 3−4% yield of alkene **4** (unchanged from Table 6).

Reaction of Iodoalkane 1 with Lactam 7 (Mol 7:1 = 14.1) at 140 °C. The sealed tube technique was used. All materials were pipetted into reactor tube A, and the tube was cooled to liquid nitrogen temperature and then evacuated and sealed. Iodoalkane **1** (1.0937 g, 2.288 mmol, 99.2% pure by GC, 4.642 M), lactam **7** (3.2305 g, 32.26 mmol, 99.3% pure by GC, with three impurities observed, 7.904 M (the solid lactam was melted and transferred with the aid of heated pipet, by use of a heat gun), and 1,2-dichlorobenzene (0.2838 g, 1.931 mmol, 0.4731 M, GC reference) were charged to the reactor tube and sealed as above. The tube was heated and stirred at 140.0 °C for time periods given in Table 12. The reaction mixture was clear immediately. Samples of 0.03 g were diluted with $HCCl_3$ (0.30 g) and analyzed by GC ("DB-5" column). Clean separation was achieved, and only traces of unknown products appeared. GC samples were quickly dissolved in order to minimize loss of the volatile alkene **4**. Response factors for each substance are given in the supplementary material.[26]

Isolation of Lactam 2 Hydroiodide Salt. A 25-mL flask was charged with **1** (4.82 g, 9.98 mmol) and **2** (12.76 g, 150 mmol), and the clear solution was stirred and heated at 150 °C for 6 h, under a spiral, water-cooled reflux condenser. The dark colored mixture was cooled, a Dean-Stark trap and receiver were set in place, and steam was carefully admitted. The entire mixture foamed up and over into the receiver in a short time. The cooled mixture was extracted with CH_2Cl_2 (13 mL, then 4 mL, two times). The dry CH_2Cl_2 extract in a short path still gave **3**, bp 75−80 °C, 1.94 g (53.4% yield): **2**, bp 81−123 °C/11 mm, 0. 28 g and bp 131 °C/11 mm, 1.79 g (16.2% recovery); and residue, 1.75 g (dark brown viscous liquid). The aqueous layer above was made basic by the addition of NaOH (3 M, 10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The extract was evaporated off to an oil (0.6100 g): IR heavy NH, 3500−3100 cm^{-1}, and C=O bands of **2** and **5** at 1730, 1700−1640 cm^{-1}; also 1290 (**2**) and at 1250 and 1200 cm^{-1} (**5**). Bands for **2**·HI could not be distinguished in this mixture, though present. The oil crystallized on standing in a closed vial, in part, to long needles (sample **A-1**), 0.1156 g. The crystals were washed with ligroine and dried, mp 212−213 °C (sample **A-2**). The solid **2**·HI salt was soluble in benzene and in water, and gave a positive test for I^-. The solid was dissolved in benzene and evaporated on KBr plates for IR and the spectrum differed from that of lactam **2** or of **5**: NH/OH, broad, 3400−3200 cm^{-1}; $C{=}N^+$ (vs), 1690−1670 cm^{-1}; rocking vibrations at 1490, 1460, 1440, and 1420 cm^{-1}; ^1H NMR (sample **A-1** or **A-2**, $CDCl_3$, δ) 2.08, m, 2 H; 2.27, t, 2 H; 3.37, t, 2 H; and 7.02, broad, exchangeable, 1 H. These are the resonances of **2**. An anomalous, exchangeable signal was present at 2.9 in **A-1**, however, with an integral of *ca.* one-half proton, and this and another signal at 4.1 in **A-2** of similar size also appeared. Heating the sample in $CDCl_3$ solution to 60 °C caused the two unassigned signals to broaden and shift, as did the resonance for NH at 7.02. This behavior suggests the presence of another substance, perhaps a salt of **2**. The mass spectrum of sample **A-1** by GC/MS showed a large component, m/z = 85, the molecular ion of **2**; however, DIP/MS revealed a minor component with m/z = 170, the mass of two molecules of **2**.

A crystalline solid containing an HI salt of **2** was isolated from a similar reaction mixture of **1** and **2** by column chromatography (SiO_2, Aldrich, grade 60, 230−400 mesh; column 19 mm inside and 530 mm long, loaded with hexane slurry). The nonvolatile residue of salts (**2**·HI, **5**·HI, and **6**·HI; 4.33 g) dissolved in CH_2Cl_2 was mixed with and absorbed on $MgSO_4$ (22 g) to give a slurry that was dried and placed on top of the column. Soluble material was adsorbed on the column by washing with CH_2Cl_2 (50 mL) and then eluted by washing with methanol. This gave six fractions (50 mL each). Fractions I−III contained only 0.02 g of nonvolatile material. Fraction IV was evaporated (rotary) to give 3.78 g of partly crystalline oil. A slurry in acetone was collected and washed three times. The solid sample B (0.5243 g) gave mp (sinter 176 °C) 182−192 °C, dec. Fraction V gave 0.50 g of oil and solid. Mass spectum analysis of sample B gave m/z = 85, only. ^1H NMR of sample B gave resonances only for lactam **2**. However, the IR of sample B was clearly different from that of **2** or **5** and was similar to that of sample **A-2** above. Lactam **2**, as a film, dissolved in CCl_4 on KBr plates: NH/OH heavy 3210 and 3100 cm^{-1}; CH, 2990, 2970, 2920, 2880; C=O, 1700; rocking frequencies at 1500, 1470, 1430, 1380, 1310, 1290, 1270, 1170; bands at 1380, 1310, 1290, 1270, 1170, 1100, 690, and 490 cm^{-1}. Sample solid B as a *slurry* on KBr plates: NH/OH, heavy resolved lines at 3300, 3240, 3180; CH (s), 2990, 2950, 2900; $C{=}N^+$ (vs), 1670−1650; 1570 (w); rocking CH (s), 1490, 1460, 1420, 1385, 1300, 1280; bands (s) at 1170, 990, 900, 700, 635, 490 cm^{-1}. A Nujol mull of sample B gave the same spectrum, with even sharper resolution of the bands. The bands at 1670 and 1640 bracket the $C{=}N^+$ stretching frequency (1669 cm^{-1}) found in [*O*-ethylbutyrolactim ether·H]$^+$ BF_4^-.[26a] Anal. Calcd for C_4H_8INO (**2**·HI): C, 22.6; H, 2.78; I, 59.6; N, 6.58. Anal. Calcd for $C_8H_{15}IN_2O_2$ (**2**·HI·**2**): C, 32.2; H, 5.07; I, 42.6; N, 9.40. Found (sample **A-2**): C, 54.5, 53.7; H, 8.1, 7.9; N, 15.7, 15.5. Found (sample B): C, 36.1, 36.2; H, 5.3, 5.3; I, 30.2, 30.2; N, 10.4, 10.5. These results indicate that sample **A-2** had decomposed to release all of the HI and that sample B contained about 71% of the double salt (or some other fraction of **2**·HI) and about 29% of **2** (based on iodine analysis). Solid sample B gave a single spot, having R_f = 0.71 on TLC silica plates, eluted with $HCCl_3$, MeOH, NH_3 and H_2O. This R_f value of sample B was identical with the R_f value of a sample of **2**·HI prepared in 100% yield as a soft, white solid,

from **2** (8.51 g, 100 mmol) and HI (27.60 g, 100 mmol, 47% aqueous HI, Fisher) in ligroine (50 mL). Ligroine and water were distilled off with a Dean-Stark trap, until 13.0 mL (100% yield) of water had been removed, with the final bath temperature at 100 °C, and the head and pot temperature at 67 °C. The remaining ligroine was distilled at 65–67 °C. The residue of soft, white solid weighed 21.13 g (100% yield as **2**·HI). Further stripping of volatile material on a rotary evaporator operated at 15 mmHg pressure and 45 °C left 20.31 g of soft solid. TLC gave a single spot, R_f = 0.71 on a "Chromogram" plate. The R_f of **2** was 0.84 on this plate. IR (CCl_4 smear on KBr plates): broad NH/OH, 3500–3100 cm^{-1}; C=N^+, 1690; other bands were poorly resolved and generally similar to **2**.

Preparative Methods: Reaction of Iodoalkane 1 with Lactam 7 (n = 4). Isolation of 1-(3,4,5,6-Tetrahydropyridin-2-yl)-2-piperidinone Hydroiodide Salt [8·HI(H_2O)]. As above in the reaction of **1** with lactam **2**, iodoalkane **1** (4.82 g, 99.8 mmol) and lactam **7** (9.912 g, 100.0 mmol, Karl Fischer analysis, 0.41% water, 2.26 mmol) was stirred at 140.0 °C in sealed tube A. The mixture was cooled to 35 °C after 225 min (3.75 h), and a sample (0.8553 g, 5.79% part, not homogeneous) was taken of the cloudy, two-phase mixture. GC gave **4**, 37.8% yield, **3**, 6.2% yield, and **1**, 45.0% recovery (these amounts are only approximate, owing to the inhomogeneous nature of the sample). The reaction mixture was heated for 225 min at 140 °C, making a total of 435 min (7.25 h). A sample (B, 0.4192 g, 2.84% part) of the stirred, cloudy, warm two-phase mixture was drawn by pipet. Anal. Calcd for I^-: 8.57. Found: I^-, 8.3 (96.8% of theory for consumption of **1**). Most of the remaining product mixture was poured while warm into a vial. A portion (9.67 g, 71.7%) was cooled to 25 °C and gave a white, crystalline mass of solid, which was slurried with acetone (25 mL), filtered, and rinsed with acetone (2 × 5 mL). The colorless solid (0.5955 g, 18.3% yield as **8**·HI) was kept in a desiccator. The filtrate was stripped of volatile material at 72 °C/15 mm and gave a dark oil (8.20 g). The solid was characterized as the monohydrate of 1-(3,4,5,6-tetrahydropyridin-2-yl)-2-piperidinone hydroiodide salt [8·HI(H_2O)] by the following tests. The solid was soluble in water, warm ethanol, acetone, and $HCCl_3$ and was insoluble in benzene, toluene, and ligroine. Substance 8·HI(H_2O) (sample A) sintered at 141 °C and melted at 149–150 °C to a red-colored liquid. It was hygoscopic and gave a strongly acidic water solution. A suspension of 0.070 g in 1.0 mL of toluene was warmed, and chloroform was added at the boil until all of the solid dissolved, during 10 min. When allowed to cool, the slightly yellow solution formed a small cluster of needle-like crystals of **8**·HI (sample B), which weighed 0.0368 g and had mp (sintered at 137 °C) 144–145 °C. A solution in 10 mL of acetone that contained five drops of formic acid gave a single spot on a TLC plate (iodine visualization): IR (either CCl_4 slurry or Nujol mull, on KBr plates) strong NH at 3140 cm^{-1}; CH, 2940, 2860; C=O and C=NH^+, 1660–1640 cm^{-1} (strong); and sharp bands 1480, 1450, 1410, 1370, 1360, 1320, 1310, 1270, 1190, 1100, 1080, 990, 940, 880, and 480 cm^{-1}. Conley[35] gives 1680 cm^{-1} for C=N^+ of imine salts and ca. 1680 cm^{-1} for C=O of 6-membered lactam. Pilotti[27a] reported 1669 cm^{-1} for 5-membered ring and 1663 cm^{-1} for 7-membered ring lactims. Mazurkiewicz reported[25b] 1661 cm^{-1} for C=N and C=O of **8**, with a shoulder to lower frequency. This was attributed to overlap of the two bands:[25b] NMR (DMSO-d_6, sample A) δ 1.65 (complex, 8 H; H-4, H-5; H-4′, H-5′); δ 2.15 (t, J = 8 Hz, 4 H; H-3, H-3′); δ 3.10 (m, 4 H; H-6, H-6′); δ 4.10, s for H_2O; this was a much larger resonance than in DMSO-d_6, itself; δ 7.60 (s, 1 H, exchangeble; H-1 of NH); NMR (D_2O) δ 1.75; 2.33, 3.28, 4.80 (H_2O, large peak); no peak for NH. The NMR in DMSO-d_6 with sample B gave the same results, except that two exchangeble signals for NH appeared at δ 7.65 and 8.60, but no water peak in the spectrum. Mazurkiewicz prepared **8** as free base and reported the UV and the ^1H and the ^{13}C NMR spectra.[25b] The ^1H spectrum was identical to that found for 8·HI(H_2O), except for the δ 3.10 signal of H-6 and H-6′, which was at δ 3.55–3.80, and of course, the absence of exchangeable NH and water. Since the pair of H atoms on H-6 are adjacent to the N atom in the imine ring, it is reasonable that protonation of the ring in 8·HI(H_2O) would lower the chemical shift of H-6 protons to δ 3.10. These results[25b] thus confirm the structural assignments for 8·HI(H_2O).

Sample B of **8**·HI was submitted to FAB mass spectrometry in the positive and negative mode in a glycerol matrix. The results were as follows, where M = lactam **7**, FW 99. Positive ions: m/z = 100 (M + H)$^+$; 192 (M + H + glycerol)$^+$; 199 (2M + H)$^+$; 284 (M + H + 2 glycerol)$^+$; 291 (2M + H + glycerol)$^+$; 298 (3M + H)$^+$; 376 (M + H + 3 glycerol)$^+$; 383 (2M + H + 3 glycerol)$^+$; 390 (3M + H + glycerol)$^+$; 468 (M + H + 4 glycerol)$^+$; 475 (2M + H + 3 glycerol)$^+$; 560 (M + H + 5 glycerol)$^+$; 464 (3M + H + 2 glycerol-H_2O)$^+$. Negative ions: m/z = 219 (I + glycerol)$^-$; 311 (I + 2 glycerol)$^-$; 403 (I + 3 glycerol)$^-$. The EI spectrum was also consistent. The mass spectrum results appear to involve cleavage of **8**·HI to the *lactam* ***7·HI*** as the primary fragment, with the association of two molecules of **7** into a "dimer" or "trimer" protonated species. Mazurkiewicz gave mass spectra for iminolactams **5**, **12**, and **13**.[25b] In all cases, a principal fragment was that of the imine ring, e.g., C_4H_6N from **5**, m/z = 68; the similar fragment from the 7-membered ring compounds **12** and **13** ($C_6H_{10}N$, FW = 96) was even more prominent. Anal. Calcd for $C_5H_{10}IN0$ (**7**·HI): C, 26.5; H, 4.44; I, 55.9; N, 6.2. Anal. Calcd for $C_{10}H_{19}N_2O_2I$ (**8**·HI monohydrate): C, 36.8; H, 5.87; N, 8.57; I, 38.9. Found (8·HI·H_2O, sample A): C, 36.9, 36.9; H, 6.1, 6.1; N, 8.5, 8.5; I, 38.7, 38.6 (total); I (ionic), 38.1, 38.6. These combustion analysis results are consistent with 8·HI·H_2O.

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Supplementary Material Available: Alternative names, substance numbers, and *Chemical Abstracts* registry numbers; GC methods; preparative methods of alcohol **3**, iodoalkane **1** with **7**, and with lactam **10**; isolation and spectroscopic properties (IR, NMR, GC, MS, and GC/MS) of **6**·HI, iminolactam **5**, and **5**·HI; kinetic studies of alkylation reactions of **1** with **2** at 100–140 °C; displacement model reactions of **2** with lactim ether **6** and reaction rates; attempted reaction of lactim ether **6** with iodoalkane **1** and with iodine catalyst; displacement reactions of lactam **2** with lactim **14** and of **10** with *O*-methylcaprolactim; and Tables 3–5, 9, 14–16, and 18–23 (31 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.

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