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2-(Perfluoroalkyl)ethanols by Thermal Alkylation of Ambidentate Lactams with 2-(Perfluoroalkyl)-1-iodoalkanes, in the Presence of Added Water. A Change in Mechanism and Stoichiometry of the Reaction. Isolation of a Water Adduct of the Lactim Ether Intermediate

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Thermal alkylation of *amides* by an alkyl halide gives alcohols and esters, and the intriguing behavior of ambidentate lactams in this reaction with 2-(perfluoroalkyl)-1-iodoethanes and lactam **2** is summarized in Scheme 1. 2-(Perfluoroalkyl)ethanols (**3**) are the principal alkylation product, and there is obtained a range of coproducts in varying amounts. A lactim ether salt (**6**·HI) is the first reaction intermediate in a sequence of reactions. For δ-valerolactam (**8**) or ϵ-caprolactam (**11**), conversion to **3** falls precipitously and $R_FCH{=}CH_2$ (**4**) becomes a major product. However, when water is introduced, alkylation rate of **2** by iodoalkane **1** increases, the conversion to **3** and **4** decreases, and a new lactim ether salt, **7**·HI (the water adduct of **6**·HI), is formed. Conversion to **3** is suppressed because coproduct **2** is weakly basic and the equilibrium lies on the side of the basic amine salt (**7**·HI). The mass spectrum of 2-hydroxy-2-[[(2-(perfluorohexyl)ethyl]oxy]pyrrolidine (**7**) includes the parent ion and a fragment ($m/z = 131$) of the intact pyrrolidine ring with an attached hydroxy group. Basic hydrolysis of product mixtures containing **7**·HI in a protic solvent gives a high yield of **3** and **2**. The higher lactams, **8** or **11**, with **1** and water give the lactam salts efficiently; yield of **4** is low and yield of **3**, by subsequent reaction with base, is high. With water present, the reaction rates of **8** and **1** are greater than for **2** and **1**; water increases both the alkylation step and the water displacement step. Improved homogeneity of reaction mixtures and a specific solvent effect in which water stabilizes the bipolar transition state may be responsible for improved rates and yields.

Introduction

Previous papers on thermal alkylation of *amides* by a variety of alkyl halides define key intermediates and the effect of reaction parameters on the panoply of products obtainable.[1−4] In the most recent study,[1a] the intriguing behavior of ambidentate lactams in this reaction is explored in the case of 2-(perfluoroalkyl)-1-iodoethanes. As summarized in Scheme 1, 2-(perfluoroalkyl)ethanols are the principal alkylation product, and there is obtained a range of coproducts in varying amounts. It is demonstrated that a lactim ether salt (**6**·HI) is the first reaction intermediate in a sequence of reactions. Indeed, when **6** is heated with the lactam **2**, the predicted products, $R_FCH_2CH_2OH$ (**3**) and iminolactam **5**, are formed in excellent yield.[1] By contrast, for higher lactams with six- and seven-membered rings, conversion to **3** falls precipitously and side product $R_FCH{=}CH_2$ (**4**) becomes a major product.[1a,5]

In an exploratory experiment, when water was introduced as a second nucleophile in the alkylation reaction of **2** with **1**, the formation of **3** was greatly suppressed,[1c] but the utilization rate of iodoalkane **1** was not slowed and thus, **6**·HI was not being converted to **3**. Similarly, in scouting experiments, the higher lactams, δ-valerolactam (**8**) or ϵ-caprolactam (**11**), with **1** and water gave a higher yield of alcohol **3**, and the yield of side-product **4** was much less than that found previously[1a] in comparable reactions *without* water.[1c] In view of these unforeseen effects of water on the alkylation process, a more comprehensive study of these novel systems was undertaken and this paper presents the results in full detail.

Results

In the new alcohol synthesis water is used as a second nucleophile, and the lactam alkylation process is summarized in Scheme 2. Only 1 equiv of lactam **2** is required for complete conversion of **1** to alcohol **3**, but addition of water to the alkylation reaction alters the amounts and the distribution of products from that of Scheme 1, and the mechanism is changed as well. In

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(1) (a) Brace, N. O. *J. Org. Chem.* **1995**, *60*, 2059−2071. (b) Brace, N. O. Reaction of Ambidentate Lactams with 2-(Perfluoroalkyl)-1-iodoethanes. Paper (No. 75) read at Ninth Winter Fluorine Conference, American Chemical Society, St. Petersburg, FL, Feb. 3, 1989. Poster No. 43, Fluorine Division of the 203rd National American Chemical Society Meeting, San Francisco, April 6, 1992. (c) Reference 29 of Brace, N. O. *J. Org. Chem.* **1995**, *60*, 2059−2071.

(2) Brace, N. O. *J. Fluorine Chem.* **1986**, *31*, 151−174.

(3) (a) Brace, N. O. *J. Org. Chem.* **1993**, *58*, 1804. (b) See Correction in *J. Org. Chem.* **1994**, *59*, 3242.

(4) DesLongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; Chapter 4.

(5) A recent paper[1a] reports some important reaction parameters for the alkylation of homologous lactams by 1-iodo-2-(perfluoroalkyl)ethanes. The rate of alkylation and conversion to products decreases with *increasing* ring size (five > six > seven). Heating of 2-pyrrolidinone (**2**) and $C_6F_{13}CH_2CH_2I$ (**1**) under favorable reaction conditions gives 2-(perfluorohexyl)ethanol in 83% yield, and the yield of **3** is increased to 94% by treating the reaction mixture with K_2CO_3. Scheme 1 shows iminolactam **5** (30−80% yield), the lactim ether salt **6**·HI, and 2-(perfluorohexyl)ethene (**4**) as coproducts of **3**. In this system, nucleophilic attack of lactam **2** on lactim ether salt **6**·HI produces alcohol **3** and the iminolactam **5**. Side product **4** is probably derived from lactim **6** by intramolecular elimination. Selectivity (mol ratio of **3**:**4**) to the desired 2-(perfluorohexyl)ethanol (**3**) over side-product **4** fell precipitously in the ring size series: (n = 5:6:7) = 18.4:0.73:0.13.

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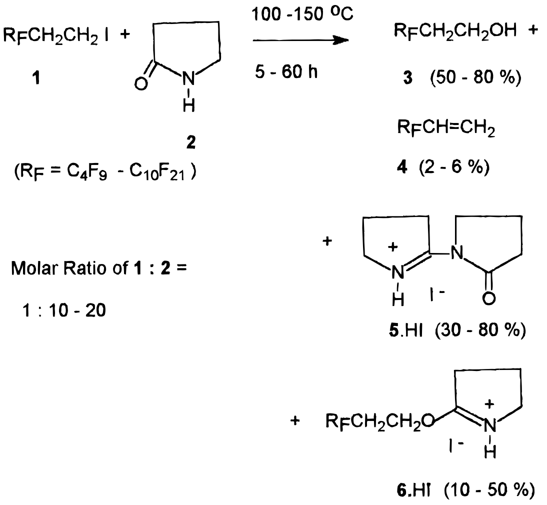
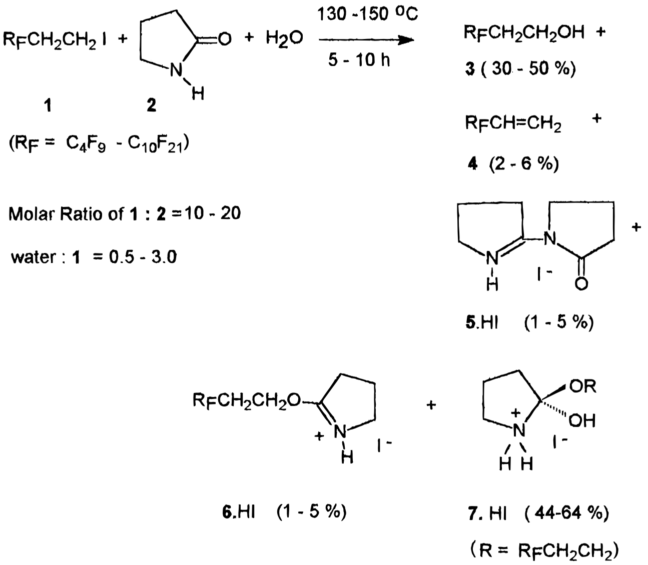
Scheme 1. Synthesis of 2-(Perfluoroalkyl)-1-ethanols by Thermal Alkylation of 2-Pyrrolidinone (2) with 2-(Perfluoroalkyl)-1-iodoethanes (1)



Scheme 2. Alkylation of Lactam 2 with Water Present



order to ascertain the kinetics and the mechanism of the process, the time course of reaction and rate constants for the principal substances were obtained under conditions used formerly for reaction without water.

Presentation of Results and Methods Used. The general method of attack follows that of the previous paper.[1a] Alkylation experiments were performed in sealed tubes at a constant temperature, and the substances present were determined quantitatively[1,2] by capillary GC to give percent conversion based on *mol of product/mol of limiting reactant.* Only the minimum number of experiments needed to define the essential properties of the alkylation system were performed in this study.

Alkylation of Lactam 2 by Iodoalkane 1 with Water Present. The Effect of Mol Ratio on Rates of Reaction and Products Formed. In comparison with a similar reaction without water (Table 6 of ref 1a), a reaction run at 140 °C with mol ratio of **2**:**1** = 14.8:1 *and* mol ratio of water:**1** = 0.562 gave the results listed in Table 1A. After 5 h of reaction time, nearly all (98.6%) of **1** had been consumed, but only 32.2% of **1** had been converted to alcohol **3**. The reaction intermediates **6**·HI and **7**·HI (Scheme 2) reached 70 mol % in 2 h and slowly decreased to 60 mol % in 8 or in 13.5 h. Thus, water greatly suppressed the conversion of the intermediate lactim salts to the desired alcohol. Previously,[1a] *without water* (mol ratio of **2**:**1** = 14.8), 98.3% of **1** had reacted in 6 h, and of this, 81.8% had been converted to **3**.

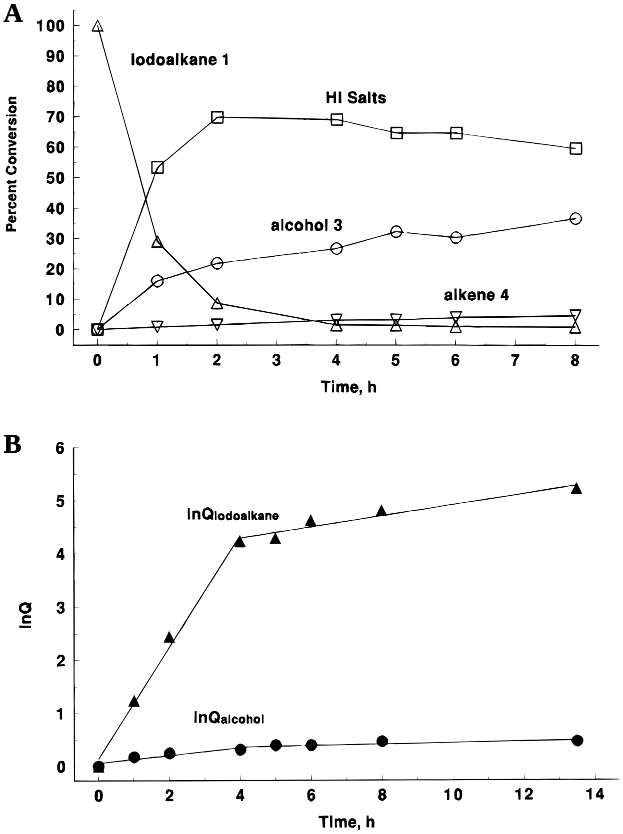


Figure 1. (A) Reaction of lactam **2** with **1** and water at 140 °C (mol ratio **2**:**1** = 14.8; water:**1** = 0.562). (B) Reaction of lactam **2** and **1** and water at 140 °C (mol ratio **2**:**1** = 14.8; water:**1** = 0.562).

The results of Table 1A are plotted in Figures 1A and 1B. In Figure 1A the disappearance of **1** and the formation of **3** were obviously not comparable in rate. A nearly steady state concentration of these substances and the intermediate HI salts of the lactim ether (**6**·HI and **7**·HI) had been reached after 2−3 h (cf. Scheme 2). From the amount of **3** present it appears that half of the water initially present had been used up in 4 h. Figure 1B shows the plots of ln $Q_{\rm iodo}$ and of ln $Q_{\rm alc}$ against time. The abrupt discontinuity in the slope of ln $Q_{\rm iodo}$ after 4 h appears to signal a change in the type of reaction that is occurring with **1**. This could be the attainment of a steady state in the system, as proposed in Scheme 4. The matter is discussed later.[6a] The quantities of $Q_{\rm iodo} = [\mathbf{1}]_o/[\mathbf{1}]_t$ and of $Q_{\rm alc} = 0.721/0.721 - [\mathbf{3}]_t)$ were calculated, and the least squares analysis (LS; Tables 1−1 and 1−2)[7] provided rate constants for the consumption of **1**, for the formation of **3**, and a measure (*r*) of the precision of the data. A comparison of reaction rates showed that, with

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[6] (a) Discontinuity appears in the ln *Q* plots of reactions of **2** and **1** without added water in Figures 3B−6B in ref 1a. The experiment of Table 1A at 140 °C gave $k_{\rm iodo} = 29.1 \times 10^{-5}$ s^{-1} ($r = 0.996$), from 0−4 h reaction time, and $k_{\rm alc} = 1.37 \times 10^{-5}$ s^{-1} ($r = 0.998$). The corresponding rates for the experiment at 140 °C without water[1a] were $k_{\rm iodo} = 14.4 \times 10^{-5}$ s^{-1} ($r = 0.998$) and $k_{\rm alc} = 5.20 \times 10^{-5}$ s^{-1}. (b) In Table 2A, mol ratio of **2**:**1** = 16.2. The corresponding $k_{\rm iodo}$ for the run at 140 °C in Table 11 in ref 1a was obtained by interpolation; it is 15.8 (Table 7B). The rate, $k_{\rm alc}$, without water was unchanged.

[7] See supporting information.

Table 1

A. Lactam 2 with 1 and Water (mol ratio of 2:1 = 14.8; H_2O:1 = 0.562) at 140 °C[a]

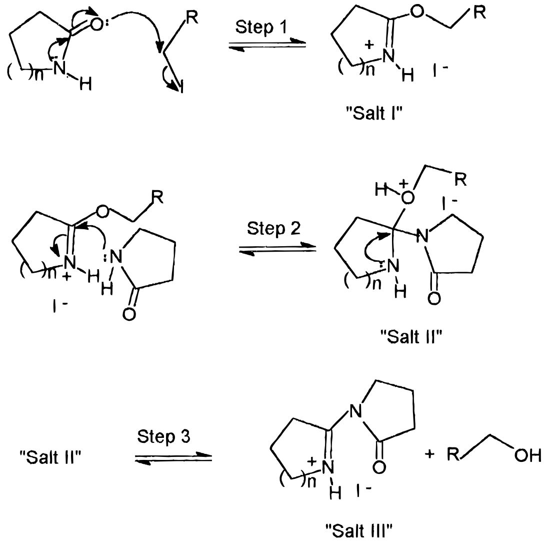
		substances, % conversion by GC				quotients for rates	
entry	time, h	**1**[b]	**3**[c]	**4**[c]	HI salts[d]	ln Q_{iodo}[e]	ln Q_{alc}[f]
1	1.0	29.0	16.0	(0.81)[g]	53.3	1.238	0.174
2	2.0	8.66	21.8	(1.5)[g]	69.7	2.44	0.246
3	4.0[h]	1.46	26.6	3.15	69.0	4.223	0.309
5	5.0	1.38	32.2	(3.2)[g]	64.6	4.285	0.389
6	6.0[i]	1.01	30.3[j]	(4.0)[g]	64.6	4.619	0.361
7	8.0[h]	0.801	36.6	4.61	59.6	4.804	0.456
8	13.5	0.550	35.5	(3.4)[g]	60.6	5.204	(0.44)[j]

B. Reaction of Mixture, Table 1A, entry 8, with K_2CO_3 in $HCCl_3$ and Ethanol at 68 °C[k]

		Substances, % conversn by GC					
entry	time, h	**1**[l]	**3**[m]	**4**[m]	**5**[m]	**6**[n]	**6**·HI and **7**·HI[o]
1	0.0	–	38.7	(3.4)[g]	–	–	57.9
2	7.5	0.19	87.3	4.06	3.5	0.99	7.46
3	7.5	0.13	89.7	3.82	–	1.21	5.14
4[p]	7.5	0.16	88.5	3.94	3.5	1.10	6.30

[a] Materials used were iodoalkane **1** (5.10 g, 10.1 mmol, 94.0% pure, 0.721 M; the sample was not treated to remove iodine and polar impurities; contained 2.62% of C_8 homologue) and lactam **2** (12.80 g, 149.3 mmol, n^{25}_D 1.4856; 99% pure, 10.6 M; contained 0.80 wt% of water; total, 0.102 g, 5.68 mmol, 0.406 M; mol ratio of water:**1** = 0.562). Total volume was 14.1 mL. GC samples of 0.02−0.06 g, toluene (FID ref, 0.02 g) and acetone or $HCCl_3$ (0.2 g) were run two to six times, as indicated, on "DB-5", 30 m column. The substances were identified by time coincidence with known samples; see supporting information. [b] Substance, molar % remaining. [c] Substance, % conversion. [d] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [**1**(used up) − (**3** + **4**)]. GC showed only traces of side-products. [e] See Table 1-1;[7] see Figure 1A for graph of $Q_{iodo} = [\mathbf{1}]_o/[\mathbf{1}]_t$) against time. LS of ln $Q_{iodo} = A + B$(time, s); from 0−4.0 h (4 points, 98.2% of **1** reacted), gave $A = 0.139$, $B(k_{iodo}) = 29.1 \times 10^{-5}$ s^{-1}, and r (correlation) = 0.996. LS from 0−8 h (7 points, 99.2% of **1** reacted) gave $A = 0.809$, $B = 17.0 \times 10^{-5}$ s^{-1}, and $r = 0.932$; LS from 4−8 h (see Figure 1A for plot) gave $A = 3.59$, $B(k_{iodo}) = 4.32 \times 10^{-5}$ s^{-1}, and $r = 0.962$. [f] See Table 1−2; [7] see Figure 1B for graph of $Q_{alc} = 0.721/(0.721 - [\mathbf{3}]_t)$. LS for ln $Q_{alc} = A + B$(time, s), from 0−4.0 h (3 points; 99.0% of **1** reacted), gave $A = 0.126$, $B(k_{alc}) = 1.37 \times 10^{-5}$ s^{-1}, and $r = 1.00$. LS ln Q_{alk} from 0−8 h (6 points; 99.2% of **1** reacted) gave $A = 0.149$, $B = 1.12 \times 10^{-5}$ s^{-1}, and $r = 0.980$. [g] Estimated or interpolated value. [h] GC, average of four determinations. [i] GC, average of six runs. [j] This data point was not used. [k] A portion of the mixture, Table 1A, entry 8 (9.30 g, 0.5201 part, 5.253 mmol of products from **1**) was dissolved in ethanol (0.691 g, 10.5 mmol, 0.88 mL), chloroform (5.0 mL, 7.46 g, 62.5 mmol), and 1,2-dichlorobenzene (1,2-DCB, GC reference; 0.1746 g, 1.188 mmol). K_2CO_3 (anhydrous, 1.4661 g, 10.608 mmol) was added to the mixture while stirring vigorously by magnet bar at 25 °C. A sample (Table 1B, entry 1) was analyzed by GC, and then the mixture was heated to 68 °C. [l] Substance, molar % remaining. [m] Substance, % conversion. [n] Two peaks appeared at 14.6 and 14.7 min (**6**, ret time was 14.6 min in a known mixture); the sum is given here. [o] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [**1**(used up) − (**3** + **4**)]. GC showed only traces of side-products. [p] The two determinations (entries 2 and 3) were averaged.

Scheme 3. Proposed Reaction Steps in the Synthesis of 2-(Perfluoroalkyl)-1-ethanols from Lactams and Iodoalkane 1



(R = $C_6F_{13}CH_2$; n = 1, 2, or 3)

water present, the *initial* rate of **1** consumption had *doubled*, while the rate of **3** production had decreased 3.8-fold from that found without water.[6a] Conversion to alkene **4** was unchanged (both runs, 3−5 mol %). Thus, the presence of even a half mol of water increased the rate of alkylation of **2**, yet retarded the formation of **3** significantly. These rate constants are also summarized in Tables 7A and 7B below.

The unreacted **6**·HI and **7**·HI salts present in the reaction mixture of Table 1A, entry 8, were converted to their hydrolysis products **3** and **2** by reaction with base in a protic solvent mixture. A reaction sample (Table 1A, entry 8) was heated and stirred with K_2CO_3 in $CHCl_3$ and ethanol for 7.5 h at 68 °C (Table 1B, entries 2−4). The conversion to **3** was 88.5% and to iminolactam **5** was 3.46%. Alkene **4** remained unchanged in amount. Reaction of another sample of entry 8 with K_2CO_3 suspended in CCl_4 gave a lower conversion (66.2−71.3%) to **3** (Table 1C).[7] However, part of this decrease in yield resulted from poor extraction of **3** into CCl_4. Since such a small amount of iminolactam **5** was found, it follows that only a small amount of nucleophilic displacement of lactam **2** on intermediate lactim ether **6**·HI (Scheme 3) had occurred during the alkylation reaction. Reasons for this unexpected behavior are offered in the discussion section.

Alkylation at 140 °C with Mol Ratio of 2:1 = 16.2 and Mol Ratio of Water:1 = 3.02. The experiment of Table 2A (Figure 2A) gave more rapid alkylation by **1** and increased conversion to **3** (50% after 6 h) than in Table 1A. Conversion to **4** was very small (ca. 2%), and more of the lactim HI salts were converted to **3**. After 3−4 h, a nearly constant concentration of substances is present when most of **1** has been nearly all consumed (Figure 2A). The equilibria between **3** and lactim HI salts are again in a steady state, though there is more than enough water present to complete the hydrolysis to **3**. Rate constants (k_{iodo} and k_{alc}) were calcd from ln Q_{iodo} and ln Q_{alc} values that are listed in Table 2A. In Figure 2B the discontinuity in the plot of ln Q_{iodo} occurs after about 1.5 h when the concentrations of the products

Table 2

A. Lactam 2 with 1 and Water (mol ratio 2:1 = 16.22; H_2O:1 = 3.02) at 140 °C[a]

		substances, % conversn by GC				quotients for rates	
entry	time, h	**1**[b]	**3**[c]	**4**[c]	HI salts[d]	ln Q_{iodo}[e]	ln Q_{alc}[f]
1	0.33	53.1	10.2	0.92	34.0	0.6330	0.1076
2	0.50	43.1	13.6	0.92	42.4	0.8417	0.1462
3[g]	0.75	24.1	18.6	1.16	55.7	1.423	0.2057
4	1.0	20.7	30.6	2.36	46.3	1.575	0.3654
5	1.5	10.8	36.8	2.07	50.3	2.226	0.4602
6	2.5	6.90	40.0	2.94	50.2	2.674	0.5109
7[g]	4.0	2.68	42.3	1.97	53.1	3.619	0.5498
8[g]	6.0	1.36	50.5	3.30	44.8	4.298	0.7032
9	8.0	0.83	49.6	2.05	47.5	4.791	0.6855

B. Lactam 2 with 1 and Water (mol ratio 2:1 = 16.2; H_2O:1 = 3.00) at 141 °C[h]

	substances, % conversn by GC							
entry	time, h	**1**[i]	**3**[j]	**4**[j]	**X**[k]	**6**[k]	**Y**[k]	HI salts[l]
1[m]	0.5	42.8	26.1	2.47	5.87	–	13.9	8.84
2[n]	2.0	2.34	42.1	2.37	6.45	0.76	16.6	29.4
3[o]	3.0	2.28	53.7	2.04	4.58	0.63	0.35	36.4
4[p]	3.0	1.07	56.9[p]	2.53	6.74	2.64	7.9	22.2
5[q]	3.0	–	48.3	3.13	5.91	1.21	20.8	20.7

[a] Materials used were iodoalkane **1** (0.7912 g, 1.614 mmol, 96.7% pure, GC; 0.6469 M; passed down alumina to remove impurities; contained 2.23% of $C_8F_{17}CH_2CH_2I$); lactam **2** (2.2378 g, 26.187 mmol, 99.6% pure; 10.50 M); and water (0.0878 g, 4.872 mmol; 1.953 M); total volume was 2.495 mL. Sealed tube A was cooled to −196 °C, evacuated, and filled with nitrogen. This process was repeated after each sample was removed. The tube was heated, while stirring by magnet bar in an oil bath at 140 °C for the times given. The reaction mixture formed two layers at 140 °C and after 20 min remained clear throughout the reaction period and when cooled for samples at 25 °C. No weight loss occurred on heating at 140.0 °C. Samples were removed by pipet into a vial and quickly dissolved in $HCCl_3$ for GC. [b] Substance, molar % remaining. [c] Substance, % conversion. [d] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [**1**(used up) − (**3** + **4**)]. [e] $Q_{iodo} = [1]_o/[1]_t$); LS of ln $Q_{iodo} = A + B$(time, s), from 0−1.5 h (5 pts), gave $A = 0.116$, $B(k_{iodo}) = 40.9 \times 10^{-5}$ s^{-1}, and r (correlation) = 0.983. LS of ln Q_{iodo}, from 1.5−8.0 h, gave $A = 1.75$, $B = 11.17 \times 10^{-5}$ s^{-1}, and $r = 0.985$. [f] $Q_{alc} = [0.6469/(0.6469 - [3]_t)]$; LS of ln $Q_{alc} = A + B$(time, s), from 0−1.5 h (6 pts) gave $A = -0.00282$, $B(k_{alc}) = 8.84 \times 10^{-5}$ s^{-1}, and $r = 0.987$. LS from 1.5−6 h (4 pts) gave $A = 0.373$, $B(k_{alc}) = 1.45 \times 10^{-5}$ s^{-1}, and $r = 0.978$. See Figures 2A and 2B. [g] Lactim ether **6** and iminolactam **5** were present: entry 3, 2.01% of **6**, 1.62% of **5**; entry 7, 0.28% of **6**, 0.44% of **5**; entry 8, 0.86% of **6** and 0.72% of **5**. [h] Iodoalkane **1** (2.396 g, 4.920 mmol, 0.6489 M); lactam **2** (6.8158 g, 79.69 mmol, 99.5% pure (contained 0.10 wt %, 0.0682 g, 0.378 mmol of water by Karl Fischer titration), n^{25}_D 1.4865, 10.5 M); water (0.2569 g, 14.26 mmol added; total water, 14.64 mmol, 1.931 M). Total volume, 7.583 mL. The sealed reactor tube A was used. No loss in weight occurred. GC sample (0.1494 g), 1,2-DCB (FID ref, 0.0376 g), toluene (1 mL), and $HCCl_3$ (2 mL) was extracted with 1% $NaHCO_3$ solution (1 mL); the aqueous layer extracted with $HCCl_3$ (1 mL). Poor extraction and severe foaming occurred without toluene. Combined organic liquid dried ($MgSO_4$) and GC run on "DB 1", 15 m, and "DB-5" 15 m and 30 m columns. See Experimental Section for full details. [i] Substance, molar % remaining. [j] Substance, % conversion. [k] On a "DB-5", 30 m column, substances **X** at 10.7 min and 11.0 min, were calcd as **3**; substances **Y** included the lactim water adduct **7** at 16.36 min and an unknown at 14.15 min, both calcd as **6**. [l] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [**1**(used up) − (**3** + **4**)]. [m] Entry 1, 0.5 h sample. [n] Entry 2, 2.0 h sample. [o] Entry 3, 3 h sample, GC on "DB-5", 30 m column, *without washing with bicarbonate solution*, average of two; **7**, 16.5 min (0.35 %), and **Y**, at 17.1 min (1.10%), were present. [p] Entry 4, 3 h sample washed with 1.0% $NaHCO_3$ (1.00 mL) in toluene (0.8531 g) and $HCCl_3$ (1.4687 g) and the aqueous layer extracted again with $HCCl_3$ (1.0 mL); GC on "DB-5" *30 m column* (average of four). Unknown **X**, 9.71 min (7.2%, calcd as **3**), **7** at 16.36 min (8.01%, average of two; and 5.40%, average of two, the next day; or 6.7%, average of four), an unknown **Y**, 14.15 min (1.4%), and **5** (?), 17.0 min (1.1%), were present. Alcohol **3** was obtained in 63.4% conversion (average of two) and in duplicate runs in 56.9% conversion (average of two) the next day. [q] Entry 5, 3 h sample used in entry 4, was also run on "DB-1", 15 m column (average of four runs). Substance **X**, 9.71 min (5.9%), **7**, at 14.0 min (19.3%, calcd as **6**), and **Y**, at 14.6 min (1.5%), were present. The amount of **7** was increased and that of **3** reduced from entry 4.

Table 3

A. Effect of Hydrolysis Conditions on GC Conversion of Table 2B Lactim Ether 6 Mixtures to Products. Reaction with K_2CO_3 in Toluene or in Acetone and CCl_4 at 25−35 °C[a]

			substances, % convsn by GC					
entry	time, h	solvent[b]	**3**[c]	**4**[c]	**X**[d]	**6**[c]	**7**[d]	HI salts[e]
1[f]	3.0	CCl_4/tol	46.6	5.13	5.32	–	19.4	22.8
2[g]	3.0	CCl_4/A	83.0	4.13	1.64	0.98	5.35	3.28
3[h]	3.0	CCl_4/A	85.0	4.34	4.79	0.39	1.23	4.76

[a] A sample of Table 2B, entry 3 reaction mixture was used for reaction; see Experimental Section for full details. [b] Solvent A = acetone. [c] Substance, molar % conversion. [d] On a "DB-5", 30 m column, substances **X**, at 10.7 min and 11.0 min, were calcd as **3**; adduct **7** at 16.36 min, and an unknown **Y** at 14.15 min, were both calcd as **6**. [e] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [**1**(used up) − (**3** + **4**)]. [f] A sample of Table 2B, entry 3, product mixture was stirred with K_2CO_3 (1 equiv) in CCl_4 and toluene suspension at 25−35 °C for 1 h. GC on "DB-5", 15 m column gave unknown **X**, 11.0 min, 5.32%; **7**, 15.1 min, 19.4%; and **Y**, 15.7 min, 0.80%. Thus, without alcohol or water as cosolvent, little or no hydrolysis of the lactim−water adduct, **7**, had occurred. [g] A sample of Table 2B, entry 3, product mixture, CCl_4, and *acetone*, with K_2CO_3 (1.16 equiv), was stirred at 25−35 °C for 1 h. GC was run on "DB-1" and "DB-5" *15 m columns* and averaged. On "DB-1", 15 m column (average of two): unknown **X**, 9.40 min, 1.64%; 1,2-DCB, 9.91 min; **2**, 12.1 min; **6**, 12.2 min; **Y**, 12.48 min, 1.62%; **7**, 12.26 min, 5.35%; and, **5**, 16.0 min, 1.2%. [h] The Table 3A, entry 2, reaction mixture, after GC analysis, was treated with K_2CO_3 (total, *now 2.32 equiv*), and the mixture was stirred at 25−35 °C for 1 h. GC was run on "DB-5", 15 m column (average of two): **3**, 6.72 min, 86.7% and 83.3%; unknown **X**, 11.1 min, 4.79%; 1,2-DCB, 11.32 min; **7**, 15.7 min, 0.72%; **Y**, 0.51%; and, **5**, 1.8%.

3 and the intermediate HI salts have become nearly constant.[6b] As summarized in Table 7A, the *initial* alkylation rate ($k_{iodo} = 40.9 \times 10^{-5}$ s^{-1}) and the alcohol formation rate ($k_{alc} = 8.84 \times 10^{-5}$ s^{-1}) of experiment 2A were greater than in experiment 1A. With the 5-fold increase in water, k_{iodo} increased 1.4-fold and k_{alc} increased 6.5-fold relative to the rates obtained with less water added. The conversion to **3** was 50.5% and

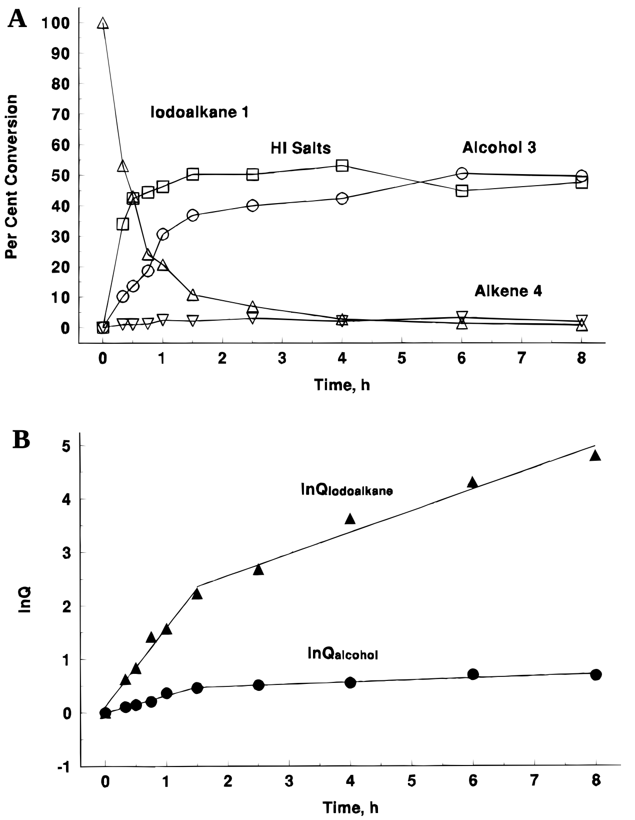


Figure 2. (A) Reaction of lactam **2** with **1** and water at 140 °C (mol ratio **2**:**1** = 16.22; water:**1** = 3.02). (B) Reaction of lactam **2** with **1** and water at 140 °C (mol ratio **2**:**1** = 16.22; water:**1** = 3.02).

conversion to **4** was 2−3%. Table 7B[1,6] gives comparisons for reactions done without water and with water. In a followup experiment of nearly identical conditions (Table 2B), product conversions were very similar to those of Table 2A and new substances, including **7** (Scheme 2), were definitely observed by GC. Hydrolysis studies of these reaction mixtures (Tables 2C[7], 2D,[7] and 3A, 3B,[7] and 3C[7]) are described in the next section.

In a single experiment at 130 °C, (mol ratio of **2**:**1** = 16.2 and mol ratio of water:**1** = 3.32) conversions to products were similar, and reaction rate was half that obtained at 140 °C in conformity with expectation. The results are given in Table 4 and Table 7A. The time course of reaction and LS plots are given as Figures 4A and 4B.[7] In most respects these results parallel those obtained at 140 °C. The Table 4 reaction product mixture was used for the isolation and identification of the reaction intermediates (see below).

Effect of Hydrolysis Conditions on the GC Conversion of Lactim Ether 6 and Water Adduct 7 Mixtures into Products. Some experiments are listed in Table 3A. Treating reaction mixtures from alkylation of **2** by **1** with *anhydrous* K_2CO_3 in a solvent in which it was insoluble gave very little conversion of the lactim salts **6**·HI and **7**·HI to alcohol **3**. In Table 3A, entry 1, stirring a sample with 1 equiv of K_2CO_3 in CCl_4/*toluene* suspension caused an increase in the **7** concentration from 0.35 to 19.4 mol % and an apparent decrease in **3** from 53.7 to 46.6%. In entry 2, stirring a sample with K_2CO_3 in CCl_4/*acetone* mixture for 1 h at 35 °C increased **3** to 83.0 mol % and decreased **7** from 19.4 to 5.4 mol %. In entry 3, further reaction with K_2CO_3 consumed most of **7** and gave a little more of **3**. Thus, acetone (or a protic solvent) assisted the displacement reaction. Variations in final product concentrations were frequently observed in the analysis of reaction samples from alkylation systems that contained **1**, **2**, and water. Optimum conditions for the isolation of **7**, the conversion of **6** or **7** to **3**, or of the HI salts to the free bases were not successfully determined. Results from other samples, treated in various ways, are given in Tables 2C, 2D, and 3B, 3C in supporting information.[7]

Reaction of Lactim 6 with Water in Acetone/$DCCl_3$ Solution. Lactim ethers are notoriously sensitive to nucleophiles such as water.[8] Accordingly, the aqueous hydrolysis of **6** in an NMR solvent was attempted in order to prepare **7** for its NMR spectrum. In one experiment, water and acetone-d_6 were added to **6** dissolved in $DCCl_3$ and CH_2Cl_2 (reference). The mixture was shaken and allowed to stand at 25 °C for 48 h. The NMR spectrum was unchanged from that of pure **6**.[9] To induce reaction with water, the NMR sample of **6** was transferred, with the aid of $DCCl_3$, to a vial with a spin bar, and 6 N HCl was added. The clear liquid sample immediately formed a layer of white gel on the surface. When stirred, a coating of gel formed on the glass surface and the mixture foamed when shaken (surface active **6**·HCl).[1a] The mixture was stirred at 25−30 °C, and samples were removed for GC analysis at intervals of time, as recorded in Table 5. The new compound **7** was not observed during the very slow hydrolysis of **6** to alcohol **3** and lactam **2**; the known substance **5**[10] was formed by the reaction of **6** with lactam **2**.[10c,11] An unknown compound, not **7**, was found in two samples. In view of these results, further work on the preparation of **7** from **6** was deferred to future studies.

Isolation and Characterization of 2-Hydroxy-2-[[2-(perfluorohexyl)ethyl]oxy]pyrrolidine (7). The new substance **7** was found in GC analysis of reaction product mixtures; cf. Tables 2B and 3A. The GC analysis, after washing with $NaHCO_3$ (aqueous), showed several unknown compounds, as given in Tables 3B−D.[7] Dr. Dale Shellhamer[12] examined these samples by GC/MS; however, this required several days for shipping, and a sample of Table 4, entry 5 (sample 4-5, which had been washed with water) now contained none of substance **7**. The sample 4-5 (not exposed to aqueous base treatment) that was submitted at the same time, however, contained the new substances, including **7**, as given in Tables 6A and 6B. In GC/MS analyses, **7** was found just after the lactim **6**,[9] prepared and characterized by elemental analysis, IR, NMR, and GC/MS.[11] Table 6A lists the substances found in sample 4-5, their retention times, and molecular ions, as percent of the base peak. These are the compounds already separated by GC on the capillary "DB-1" and "DB-5" columns; GC/MS, therefore, confirmed the identity and relative retention times of the substances listed. Iminolactam **5** had previously been prepared[1,10a,b] and its mass spectrum reported;[10b] it was

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(10) (a) Dannhardt, G. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311-(4)*, 294; *Chem. Abstr.* **1978**, *89*, 42981p. (b) Mazurkiewicz, R. *Acad. 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.

(11) The MS spectra of substances **2**, **3**, **5**, and **6** are given in the supplementary material of ref 9.

(12) Dr. Dale F. Shellhamer of Point Loma Nazarene College, San Diego, CA, kindly provided GC/MS results for several sample mixtures that contained substances **1**, **2**, **3**, **5**, **6**, and **7**. These results are given in Tables 6A, 6B; and in 6C and 6D.[7]

Table 4. Lactam 2, 1, and Water (mol ratio of 2:1 = 16.08; H_2O:1 = 3.32) at 130 °C[a]

		substances, % conversn by GC				quotients for rates	
entry	time, h	**1**[b]	**3**[c]	**4**[c]	HI salts[d]	ln Q_{iodo}[e]	ln Q_{alc}[f]
1	1.0	57.4	14.9	1.74	26.0	0.555	0.161
2	2.0	28.4	33.1	2.48	36.0	1.26	0.402
3	5.0	2.81	40.2	3.10	54.1	3.57	0.514
4[g]	6.0	1.50	40.7	3.31	56.0	4.20	0.522
5[g]	7.0	1.52	45.0	3.33	50.2	4.20	0.598

[a] Materials used were iodoalkane **1** (2.3923 g, 4.880 mmol, 96.7% pure, GC; 0.6357 M), lactam **2** (6.7054 g, 78.470 mmol, 99.6% pure; 10.22 M), water (0.2918 g, 16.19 mmol; 2.154 M), and toluene (0.1398 g, FID ref). Total volume was 7.677 mL. Sealed tube A was cooled to −196 °C, evacuated, and filled with nitrogen to 10 mm. The liquid mixture became clear and colorless after heating for 0.5 h at 130 °C. No weight loss on heating. Samples were quickly dissolved in $HCCl_3$ or $DCCl_3$ for GC on "DB-5", 30 m column. [b] Substance, molar % remaining. [c] Substance, % conversion. [d] Nonvolatile HI salts were calcd from mol **6**·HI + **7**·HI = [1(used up) − (**3** + **4**)]. [e] $Q_{iodo} = [\mathbf{1}]_0/[\mathbf{1}]_t$); LS of ln $Q_{iodo} = A + B$(time, s) from 0−6 h, gave $A = -0.0984$, $B(k_{iodo}) = 20.0 \times 10^{-5}$ s^{-1}, and r (correlation) = 0.999. [f] $Q_{alc} = [0.6357/(0.6357 - [\mathbf{3}]_t)]$; LS of ln $Q_{alc} = A + B$(time, s) from 0−2 h gave $A = -0.0132$, $B(k_{alc}) = 5.58 \times 10^{-5}$ s^{-1}, and $r = 0.994$. LS from 2−7 h gave $A = 0.326$; $B(k_{alc}) = 1.02 \times 10^{-5}$ s^{-1}, and $r = 0.979$. [g] A separate sample was prepared with 1,2-DCB as FID ref and gave amounts of substances, within experimental error, the same as with toluene reference.

Table 5. Reaction of Lactim 6 with Water and HCl at 25−30 °C in $DCCl_3$ and Acetone-d_6 Solution and Mixture[a]

entry	time, h	**3**[c]	**2**[c]	**6**[c]	**7**[d]	**5**[e]
		Substances, % (area) by GC				
1[b]	0.25	−	0.268	99.2	−	0.52
2	3.0	6.40	0.147	89.9	−	2.66
3[b]	4.0	3.76	0.259	93.8	−	2.21
4	5.0	6.13	0.087	89.9	−	3.71
5	6.0	5.36	0.098	92.2	0.13	2.40
6	23.0	4.50	0.060	95.4	0.077	0.0845
7[b]	52.0	4.04	0.681	92.6	−	2.34
8[f]	69.0	6.47	0.47	90.2	−	2.79
9[b,f]	71.0	3.94	0.72	92.4	−	2.54
		GC Retention Time, Min[g]				
		8.0	13.7	14.6	16.5	18.7

[a] The reaction mixture contained lactim **6** (0.1250 g, 0.2899 mmol as 100%; CH_2Cl_2, 0.0063 g; and $DCCl_3$, 0.6650 g. Water, 0.0008 g (0.04 mmol); and acetone-d_b, 0.01351 g, were added. The composition of the mixture was checked by NMR, which showed no detectable change from the original sample. Thus, to induce reaction with water, the sample was transferred to a vial and 3.0 μL of 6 N HCl was added from a 10 μL syringe. The weight by difference of the vial, however, was 0.013 g. This is 0.072 mmol of water. With the 0.04 mmol above, this is a 0.11 mmol total or 38.6% mol on **6**. The 1.3 × μL of 6 N HCl, calcd 7.8 × μmol of HCl, is 0.0078 mmol of HCl, or 2.7% mol on **6**. The vial was tightly capped, placed inside another tightly capped vial (after the first sample was run), and stirred by magnet bar for the times indicated above. GC samples were run on a "DB-5", 30 m column (or "DB-1" 15 m, below), under conditions previously used with a known mixture. See Table 3B.[7] [b] The GC analysis was run on a "DB-1", 15 m column. [c] These are known compounds: **2** is 2-pyrrolidinone; **3** is 2-(perfluorohexyl)ethanol; **6** is *O*-[2-(perfluorohexyl)ethyl]butyrolactim; **5** is 2-pyrrolinyl-2-pyrrolidinone. [d] This is a new compound (see Table 6B for GC/MS); the retention time did not coincide with that of **7**, and its identity here is questionable. [e] Substance **5** is a known compound that is formed by reaction of a lactim ether with 2-pyrrolidinone. [f] The sample was kept at 5 °C for 17 h in the refrigerator and then run to check the result at 52 h. [g] The ret time of substances **2**, **3**, **5**, **6**, and **7** (?) as run on a "DB-5", 30 m GC column. The (correct) observed ret time of **7** was 16.36 min under these conditions (see Table 2B, footnote k).

confirmed here, as was lactam **2**.[11] The mass spectrum of alcohol **3** was reported previously.[11]

In Table 6B are listed the *m*/*z* values of all ion fragments from **7** with relative abundances greater than 1% of the base peak (*m*/*z* = 30.1), including the molecular ion (449) calculated for substance **7**. The most important fragment has *m*/*z* = 131, since it contains the intact pyrrolidine ring and the 2-hydroxy group of 2-hydroxy-2-(ethyloxy)pyrrolidine, e.g., the free base **7**, less its perfluorohexyl group, having the lactam "hemiketal" structure. This is evidence from its fragmentation pattern that **7** is not the lactim **6** with an associated molecule of water not bonded to the lactim. Such a hydrate of the lactam **2** is well known. Other fragments from **7** such as *m*/*z* = 112, 85.1, 77.0, 56.1, 55.1, 119 ($CF_3CF_2^{\bullet}$), 69.1 ($CF_3^{\bullet}$), and 57.1 are those found in lactim **6**, the precursor of **7**. Still other fragments, so indicated in Table 6B, are found in lactam **2**, a probable fragmentation product of **6** or **7**. Further GC/MS results from other samples (Tables 6C and 6D)[7] gave additional evidence for the existence of substance **7** in these mixtures.

Effect of Water on the Reaction of 1 with Higher Lactams. Extensive studies with δ-valerolactam (**8**) were reported, and an experiment at 140 °C without added water (mol ratio of **8**:**1** = 14.1) is described in Table 12 in ref 1a. The time course and least squares plots appear as Figures 6A and 6B in ref 1a. In 9 h, there was 96.5% consumption of **1**, 20.8% conversion to **3**, and 28% conversion to **4**. Thus, the mol ratio **3**:**4** was only 0.728 (cf. Table 8C). The rate constants were $k_{iodo} = 10.1 \times 10^{-5}$ s^{-1}; $k_{alc} = 0.45 \times 10^{-5}$ s^{-1}; and $k_{alkene} = 1.45 \times 10^{-5}$ s^{-1} (least squares, $r_{avg} = 0.96$). The unusual appearance of the reaction mixture was noted. The homogeneous reaction mixture became cloudy after 4 h, and samples at 25 °C separated into two phases.

Table 8A delineates a similar experiment with water added (mol ratio of **8**:**1** = 14.0 and mol ratio of water:**1** = 2.10 at 140 °C). In just 3.5 h, utilization of **1** had reached 99.5% of theory, conversion of **1** to **3** was 56 molar %, and conversion to **4** was 5.6%. Remarkably, the reaction mixture became homogeneous *immediately* at 140 °C and remained clear throughout the reaction period and when cooled for samples at 25 °C. Table 8C compares directly the conversion of **1** to products from alkylation of **2** with added water and without water after 5 h heating at 140 °C. As summarized in Table 8C, the few data points of Table 8A were superimposed on Figures 6A (in ref 1a) and 2A to show that lactam **8** gave rates of reaction for **1** and **3** that were greater in the experiment *with water* than for either the experiment of Table 12 (ref 1a), or of a comparable experiment of lactam **2** with **1** and water (Table 2A). Estimates of the rate constants also are given in Table 8C. From these results it is clear that water increased both the rate of alkylation of **8** by **1** and conversion to **3** and decreased the rate of formation of **4**.

As shown in Table 8B, reaction of the product mixture, Table 8A, entry **4**, with K_2CO_3 in ethanol and $HCCl_3$ suspension at 60 °C for 4.5 h increased the conversion of **3** to 83.3% (avg of two determinations). Evidently, another 11% of lactim ether HI salt (**9**·HI) remained unconverted to **3** and lactam **8**. These results throw a new light on the thermal alkylation of lactam **8** by iodoalkane **1**, and further study of reaction parameters could lead to useful new syntheses of lactims from **8** and

Table 6

A. GC Separation and Mass Spectrum Analysis of Product Mixture from Table 4, Entry 5[a]

entry	subst	ret time[b]	mol ion[c]	base	other ions
1	tol	4.04	92 (61.3)		
2	**3**[d]	5.17	364 (3.2)	31	363 (M − 1;31.5)
3	**2**[d]	9.69	85.1 (100)	85	84.1 (20.8)
4	**7**[e]	14.59	449.2 (7.4)	31	131 (9.0); 85 (62.1); 69 (78.6)
5	**5**[d,f]	15.48	152 (60.8)	41.1	151 (M − 1,61.6); 97 (71); 59 (93.9)

B. Mass Spectrum Analysis of 2-Hydroxy-2-[[2-(perfluorohexyl)ethyl]oxy]pyrrolidine (7) {$[(CH_2)_3NHC](OH)OCH_2CH_2(CF_2)_5CF_3$; FW 449.23; $C_{12}H_{12}F_{13}NO_2$}. Trapped Peak at 15.15 Min in GC Separation of Table 6A

m/*z*	rel %[g]	fragment	*m*/*z*	rel %[g]	fragment
449	7.4	$M^{\bullet+}$ (mol ion)	327	1.2	
131	2.0	$(CH_2)_3NHC(OH)OCH_2CH_2\cdot H^{\bullet+}$	119[h]	1.8	$CF_3CF_2^{\bullet+}$
112[h]	2.3		95.1	1.7	
87.2	8.7		86.1[h,i]	24.1	$(CH_2)_3NH{=}COH^{\bullet+}$
85.1[h,i]	7.2	$(CH_2)_3N{=}COH^{\bullet+}$	84.1[h,i]	6.3	$(CH_2)_3N{=}CO^{\bullet+}$
77.0[h]	4.2		69.1[h]	26.1	$CF_3^{\bullet+}$
65.1	3.2		57.1[h]	2.4	
56.1[h,i]	8.1	$(CH_2)_2C{=}O$	55.1[h,i]	2.3	
55.1[h]	2.3		44.1	9.9	
43.1	7.7		42.1[i]	6.8	$(CH_2)_3^{\bullet+}$
41.1[h,i]	7.4	$C_3H_6^{\bullet+}$ or $CH{=}N{=}CH_2^{\bullet+}$	30.1	100	$CH_2O^{\bullet+}$
29.2[h,i]	5.2	$C_2H_5^{\bullet+}$	28.1[h,i]	19.2	$C_2H_4^{\bullet+}$
27.2[i]	4.0		18.1	3.2	

[a] The reaction sample Table 4-5 was run *as is*, without washing by aqueous $NaHCO_3$ solution. GC/MS analysis was done by Dr. Dale Shellhamer; May 18, 1994 letter.[12] A 30 m methylsilicone coated (Ultraperformance; Hewlett-Packard) column was employed. The initial temperature was held at 50 °C for 2.0 min; then the temperature was raised on a ramp of 10 °C/min to 200 °C. The sample peaks were comparable to those found by GC on a Megabore "DB-5", 30 m column, or a similar "DB-1", 15 m column (see Tables 3B−D). [b] The retention time in minutes. [c] *m*/*z* of the molecular ion, in % of the base peak in parentheses. [d] Mass spectrum data were reported. These new results are consistent. [e] Substance **7** is 2-hydroxy-2-[[2-(perfluorohexyl)ethyl]oxy]pyrrolidine, derived by the addition of water to lactim ether **6** (*O*-[2-(perfluorohexyl)ethyl]butyrolactim). [f] Mazurkiewicz reported the mass spectrum for iminolactam **5**.[10b] [g] The relative abundance in % of base peak; only fragments greater than 1% are listed. [h] These ions are principal fragments in the mass spectrum of lactim ether **6**, the precursor of **7**. [i] These ions are principal fragments in the mass spectrum of lactam **2**, a possible fragmentation product from **6** and **7**; see also the mass spectrum of iminolactam **5**.[10b]

various alkyl halides, as well as new routes to products derived from lactam **8**.

ϵ-Caprolactam. The best results in the previous thermal alkylation process with ϵ-caprolactam (**11**, Table 13, entry 5)[1a] were obtained in toluene solution (mol ratio of **11**:**1** = 12.2; 140 °C, 5.5 h).[1a] A 46% consumption of **1** occurred, along with 1.75% conversion to **3**, and 13.1% conversion to **4**. Thus, **3** was only a minor product. Now, with water present in the alkylation of **11** (mol ratio of **11**:**1** = 11.1; mol ratio of water:**1** = 5.66; 140 °C, 6.5 h), complete consumption of **1** occurred, conversion to **3** was 17.7%, conversion to **4** was 6.48%, and about 80% of the lactim ether salts **14**·HI and **15**·HI remained unconverted to **3** (Table 9). The alkylation of **11** to intermediate salts **14**·HI and **15**·HI was nearly complete, and the loss to alkene **4** was greatly suppressed.

Discussion

Alkylation of a Lactam by an Alkyl Halide in the Presense of Water. A three-step mechanism was proposed for the thermal alkylation of a lactam by iodoalkane **1** (Scheme 3).[1a] A lactim ether salt ("salt I") is first formed from the iodoalkane by the lactam acting as an *O*-nucleophile. In the previous paper,[1a] a steady state concentration of the lactim ether salt was observed and the lactims, prepared by another route, were found in these product mixtures. Then, in step 2, the *ambidentate* lactam, acting as an *N*-nucleophile, adds to the lactim ether double bond to give a tetrahedral intermediate, probably in a slow step followed by a rapid proton transfer to give the substance "salt II". The basis for this behavior 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).[1a] If this intermediate ("salt II") breaks down to alcohol **3** and iminolactam (step 3), the equilibrium reactions of step 2 are shifted to the right, and stable products are obtained. The strong acid HI readily protonates the strongly basic nitrogen of the iminolactam ("salt III").[1a] In product isolation studies, the theoretical amount of the iminolactam was obtained, and the model reaction of the lactim ether with lactam also produced the same result.[1a] Further, the analogous steps were observed in thermal reactions of alkyl halides with formamide and *N*-substituted amides.[2]

Thermal alkylation of the lactam with water present takes a different course, and the proposed mechanism is presented as Scheme 4. Here, in step 1, the lactim ether salt is formed but then reacts with water as an *O*-nucleophile in step 2 to give a new tetrahedral intermediate, and proton transfer once again occurs in step 3. After 1 to 2 h (Figures 1A and 2A) a steady state concentration of lactim salts (e.g., **6**·HI and **7**·HI from lactam **2**) was present in the reaction mixture. The free base **7** from lactam **2** (isolated in GC separations and in GC/MS) is analogous in structure to a hemiketal. Remarkably, under these reaction conditions, water is a sufficiently powerful nucleophile to add to the lactim salt and form a stable compound. In step 4, the protonated "hemiketal" loses alcohol and gives the lactam (as enol form), which, in step 5, with proton transfer, gives again the starting lactam and HI. These steps are all repre-

Table 7

A. A Summary of Alkylation of Lactam 2 with 1 and Water Reaction Temperatures, Molar Ratios, and Reaction Rates[a]

			substances, mol ratio		% conversion by GC			rates of reaction × 10^{-5} s^{-1}		least squares (LS)[d,e]	
entry	temp, °C	time, h	**2:1**	H_2O:**1**	**1**[b]	**3**[c]	**4**[c]	k_{iodo}[d]	k_{alc}[d]	r_{iodo}[e]	r_{alc}[e]
1[f]	130	7	16.2	3.32	98.5	45.0	3.3	20.0	5.58	0.999	0.994
2[g]	140	8	14.8	0.562	99.5	36.6	3.4	29.1[h]	1.37[h]	0.996	0.999
								4.32[i]	–	0.960	–
3[j]	140	8	16.2	3.02	99.2	50.5	2.05	40.9[k]	8.84[k]	0.983	0.987
								11.2[l]	1.45[l]	0.985	0.978
4[m]	141	3	16.2	3.00	97.8	49.4	2.04	–	–	–	–

B. Alkylation of 2 with Iodoalkane 1 at 140 °C, with or without added Water. A Comparison of Molar Ratios with Reaction Rates and Reaction Rate Ratios

	with water: mol ratio **2:1** = 14.8; water:**1** = 0.562	without water: mol ratio **2:1** = 14.8; water = 0
k_{iodo}	29.1 × 10^{-5} s^{-1}	14.4 × 10^{-5} s^{-1}
k_{alc}	1.37	5.20
$k_{\text{iodo}}/k_{\text{alc}}$	21.2	2.77

	with water: mol ratio **2**:**1** = 16.2; water:**1** = 3.02	without water: mol ratio **2**:**1** = 16.2; water = 0
k_{iodo}	40.9	15.8
k_{alc}	8.84	5.1
$k_{\text{iodo}}/k_{\text{alc}}$	4.62	3.1

C. Effect of Added Water on the Thermal Alkylation of Lactam 2 with Iodoalkane 1; Mol Ratio 2:1 = 14.8. Equilibrium Conversions to Products in 8 h at 140 °C

		substances, % conversns by GC			
entry	water:**1**	**1**[n]	**3**	**4**	HI salts
1[o]	none	1.43	81.0	4.7	12.7
2[p]	0.562	0.80	36.6	4.6	59.6
3[q]	3.02	0.83	49.6	2.05	47.5

[a] General procedure: a sealed tube A was used; see table at each entry for specific conditions and GC analysis. [b] Substance, mol % used up. [c] Substance, % conversion. [d] The rates were calcd, using the linear regression equation, ln $Q = A + B$ (time, s); B (slope) = k_{iodo} or k_{alc}, resp. [e] LS is least squares correlation (r) of the pseudo first order reaction. [f] Table 4; and see Figures 4A and 4B.[7] [g] Table 1A, and see Figures 1A and 1B. [h] The segments of the plots of ln Q_{iodo}/time or of ln Q_{alc}/time from 0–4 h; see Figure 1B. [i] The segment of the plot (Figure 1B) of ln Q_{iodo}/time from 4–8 h gave the lower rate of reaction. [j] Table 2A and see Figures 2A and 2B. [k] See Figure 2B; the segment of the plot of ln Q_{iodo}/time from 0–1.5 h. [l] The segment of the plot of ln Q_{alc}/time from 1.5–8.0 h. [m] Table 2B. [n] The mol % of **1** remaining after reaction has occurred. [o] See Table 6 of ref 1. [p] See Table 1A. [q] See Table 2A.

sented as equilibria since the lactim and the intermediate **7** salts were present in a nearly constant concentration. The tetrahedral water adduct **7** of lactim **6** was isolated in several reactions of **1** with **2** and water. Thus, steps 2–4 of Scheme 4 are based on the physical evidence of isolated (by GC) compound **7**.

Surprisingly, with a 0.562 mol ratio of water:**1**, insufficient water to react completely in step 2 of Scheme 4, nucleophilic attack by the lactam **2** does not compete. Iminolactam **5** was only a minor product when water was present (yield of **5** was 3.5% in Table 1B, none in Table 2B, and 0.64% in Table 3B), despite the large excess of lactam (cf. Scheme 2). Water increased the rate of alkylation in step 1, Scheme 4. With 0.562 mol ratio of water:1 at 140 °C, k_{iodo} is doubled, and with 3.02 mol ratio of water:**1** (the mol ratio of **2**:**1** was 16.2), k_{iodo} is 2.6 times over the reaction rate without added water. Many more experiments are needed, of course, to define the rate dependence on the concentration of water.

Secondly, the rate of alcohol elimination from **7** in step 4 of Scheme 4 was retarded more than 7-fold ($k_{\text{iodo}}/k_{\text{alc}}$) by 0.562 mol ratio of water:**1** in reactions at 140 °C (Table 7A, entry 2; Table 7B). Thirdly, perhaps of even greater importance, the equilibrium concentration of alcohol **3** decreased from 81.0% without water to 36.6 mol% when water was present at the 0.562 mol ratio (Table 7C). The rate and extent of iodoalkane **1** consumption with and without added water (Tables 7A–C) were roughly comparable. In both runs, 98–99% of theory of **1** had been consumed. In three reactions (Table 7A), in which the mol ratio of **2**:**1** was 16.2 and mol ratio of water:**1** was 3.0, alcohol formation reached 45–50% of theory, instead of the 80–90% observed when water was not added.

How can the slow formation of alcohol **3** and **7**·HI salt be explained? It is suggested that this may be caused by the weak basicity of lactam **2**. Elimination of **3** from the pyrrolidine salt, **7**·HI, requires the *deprotonation* of the salt by a base stronger than the amide itself. But fragmentation of **7** in step 4 of Scheme **4** gives the alcohol, the lactam, and strongly acidic HI. Lactam **2** would give only a weak salt with HI. By comparison, the analogous cleavage of the pyrrolidine intermediate ("salt II") in Scheme 3 produces an equally strong imine **5** and the alcohol **3**. Since **5** ties up the HI as a salt, both steps 2 and 3 go far to the right.

In the aqueous system, after a sufficient concentration of alcohol, lactam, and coproduct HI have been formed, the reversible steps 2–5 of Scheme 4 reach an equilibrium state that depends on the temperature and the free energies of the substances. The amount of alcohol **3** obtained, for example, was increased when a larger concentration of water was present (Table 7C). Addition of base to the product mixture gave nearly complete conversion to the desired final product alcohol **3**. In this way, the equilibria of steps 2–5 go to completion with the formation of a stable salt (i.e., KI from K_2CO_3). Thus, in Scheme 5, where step 5 of Scheme 4 is replaced with an irreversible new step 5, the strong base, hydroxide ion, reacts with the lactam salt of HI. The result is the shifting of the prior steps 3 and 4 of Scheme 4 also to

Table 8

A. δ-Valerolactam (8) with 1 and Water (mol ratio 8:1 = 14.0; water:1 = 2.10) at 140 °C[a]

		substances, % conversn by GC				
entry	time, h	**1**[b]	**3**[c]	**4**[c]	**8**[d]	**9**.HI[e]
1	1.25	(4.4)[d]	39.8	4.39	–	51.4
1	(1.25)[f]	7.13	50.1[f]	4.52	–	38.3
3	3.5	0.49	56.0	5.59	–	31.0
4	5.0	(0.01)[g]	62.9	6.13	–	25.3

B. Reaction of Entry 4 Sample with K_2CO_3 at 60 °C in Ethanol and Chloroform (Mol Ratio K_2CO_3:1 = 2.61)[h]

		substances, % conversn by GC				
entry	time, h	**1**[i]	**3**[j]	**4**[j]	**8**[k]	**9**·HI[l]
1	0.0	(0.94)[m]	67.1	7.63	–	24.3
2[n,o]	4.5	(0.56)[m]	76.4	5.68	–	18.4
3[n,o]	4.5	(0.0)[m]	83.8	5.38	–	10.8

C. δ-Valerolactam (8) with 1 and Water (mol ratio of 8:1 = 14.0; water:1 = 2.10) at 140 °C.
A Comparison of Rates and Conversion with Lactam 2 and Water, and with Lactam 8 for Reactions without Added Water

		substances, % conversn by GC[p]			least squares, rate constants, × 10^{-5} s^{-1}		
entry	time, h	**1**	**3**	**4**	k_{iodo}	k_{alc}	k_{alkene}
1[q]	5.0	10.4	17.8	23.0	10.1	0.45	1.45
2[r]	5.0	0.05	65.0	6.88	>40.9	>8.84	<1.45
3[s]	5.0	2.02	46.4	2.55	40.9	8.84	<0.5

[a] Iodoalkane **1** (0.9038 g, 1.861 mmol, corrected, 96.7% pure by GC, 0.40 mL; 0.604 M; contained 2.23% of $C_8F_{17}CH_2CH_2I$); lactam **8** (2.60 g, 26.0 mmol, 99%), water (0.0704 g, 3.91 mmol, 0.070 mL), and 1,2-DCB (0.1500 g, GC ref) were charged to reactor tube A. The reaction tube was cooled to −196 °C, evacuated, and filled with nitrogen as in tables above. This process was repeated after each sample was removed. The tube was heated, while stirring by magnet bar in an oil bath at 140 °C for the times given. The reaction mixture became homogeneous *immediately* at 140 °C and remained clear throughout the reaction period and when cooled for samples at 25 °C. The remaining reaction mixture, allowed to stand for 7 days, formed long needles in the viscous mixture. GC samples were drawn with a Pasteur pipet and weighed, the pipet was rinsed out with 12 drops of $HCCl_3$, and a "DB-5", 30 m column was used; average of two determinations. A mixture of **8** (0.0602 g), 1,2-dichlorobenzene (1,2-DCB, 0.0231 g), and acetone (0.15 g) gave FID of 0.644 for **8**. Tables 8-0 and 8-1[7] give concentrations and quantities for rate calculations. See also Table 8C. [b] Substance, mol % remaining. [c] Substance, % conversion. [d] The amount of substance was not determined accurately. [e] Nonvolatile **9**·HI (or HI salts derived from **1**) was calcd from mol [**1**(used up) − (**3** + **4**)]. [f] After standing for 24 h, the reaction sample showed an increase in **3**, probably by the hydrolysis of **9**·HI. [g] The amount present was too small to measure accurately under these conditions. [h] A portion (0.67 g, 0.180 part, 0.335 mmol as **1**) of the viscous reaction mixture from Table 8A, entry 4, ethanol (0.050 g; 1.0 mmol), $HCCl_3$ (1.95 g, 1.30 mL), and K_2CO_3 (0.1210 g, 0.8755 mmol; or mol ratio of K_2CO_3:**1** = 2.61), in this order, were placed in a Fisher tissue culture tube that was fitted with a Teflon-lined screw cap and a small magnet bar. *Before mixing or heating the reaction mixture, a sample was removed for GC (Table 8B, entry 1) for a zero point measure of substances. The sample composition changed significantly from that of Table 8A, entry 4.* [i] Substance, molar % remaining. [j] Substance, % conversion. [k] The amount of substance was not determined accurately. [l] Nonvolatile **9**·HI (or HI salts derived from **1**) was calcd from mol [**1**(used up) − (**3** + **4**)]. [m] The amount present was too small to measure accurately under these conditions. [n] The GC sample (10 drops) was diluted with $HCCl_3$ (10 drops), water was added (10 drops), and the sample was shaken and then dried over $MgSO_4$. [o] A new major substance appeared at 16.43 min; as the δ-valerolactim ether **9**, this is a conversion of ca. 6.3−18%. The amount found varied widely with the GC run. [p] The % conversion of **1** is the mol % remaining; for **3** and **4**, the % conversion is the mol % formed. [q] Previous paper (Table 12),[1a] no water was added; mol ratio of **8**:**1** = 14.0; samples were taken over a 9 h reaction time; results at 5.0 h were interpolated from the data presented. Figures 6A and 6B[1a] show the time course and least squares plots of the data points; r(avg) = 0.960. [r] See the results from Table 8A. The data points of Table 8A were superimposed on Figure 6A.[1a] This simple exercise shows that the estimated rate for k_{iodo} and k_{alc} of Table 8A are greater than those found in the previous experiment of Table I2.[1a] The rate, k_{alkene}, is less in Table 8A than in Table I2. [s] Table 2A; mol ratio of **2**:**1** = 16.22; mol ratio of water:**1** = 3.02. The results at 5 h were interpolated at the midpoint between 4 and 6 h, and the value for **4** is the avg of four taken from entries 6−9. The few data points from Table 8A were superimposed on Figure 2A to show that the estimated rates for k_{iodo}, k_{alc}, and k_{alkene} are greater in Table 8A than for the data of Table 2A.

alcohol **3**, lactam **2**, and iodide ion. The lactim ether hydrate **7** has a structure analogous to that of a hemiketal, and having a basic nitrogen atom, its concentration as an HI salt *in the absence of added base* could increase until all of iodoalkane was used up. Thus, under these conditions, **7**·HI would only slowly convert to **3** and **2**.

A Rationalization of the Effect of Water on Reaction Rates and Conversions to Products. Reasons for the increased conversions and rates of reaction induced by the presence of water in reactions of a lactam and iodoalkane may be proposed. (1) Water is a dipolar substance with a large dielectric constant (twice that of DMF, for example) and is able to interact with changes in charge distribution that occurs during nucleophilic substitution reactions.[13] As explained in the text of *Mechanism and Theory in Organic Chemistry*,[14] the reaction of step 1 in Schemes 3 or 4 belongs to the class of "charge type 2" nucleophilic substitutions, in which a neutral nucleophile and a charged leaving group are involved.[14a] In this reaction type a developing charge is present, and the dipolar transition state may be represented by Figure 3.[14b] The transition state complex when solvated by water gives an increased reaction rate, owing to the lowering of the activation energy as represented in the usual reaction coordinate diagram.[13] The associated water molecules form a strongly coordinated shell around the ions in the solvent sphere[14c] which stabilizes the transition state and causes the increase in reaction rate. Water molecules because of their small size would be better able to solvate the transition state compound than would the larger lactam molecules.

(2) A second possible reason for the increase in reaction rate, is that water may improve the homogeneity of the reaction medium. This was true, at least in the case of

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[13] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A; Structure and Mechanisms*; Plenum Press: New York, 1977; pp 158−160.

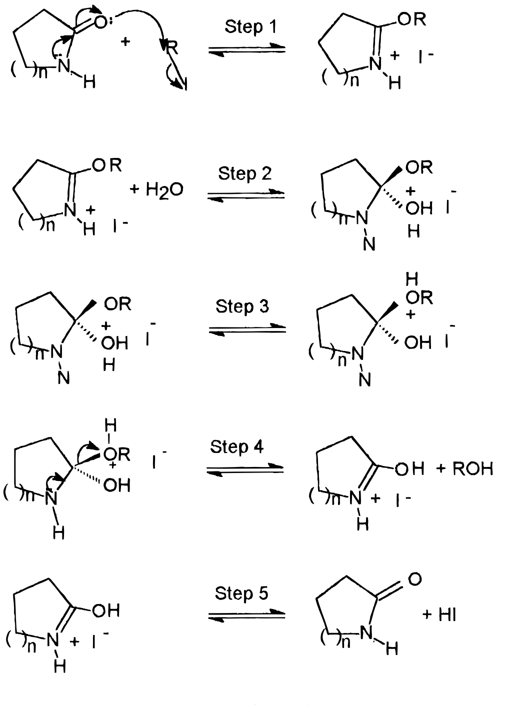
[14] Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row Publishers: New York, 1981. (a) p 292; (b) p 325; (c) p 169.

Table 9. ε-Caprolactam (11) with Iodoalkane 1 and Water (mol ratio of 11:1 = 11.11; mol ratio of water:1 = 5.664) at 140 °C[a]

		substances, % conversn by GC			
entry	time, min	**1**[b]	**3**[c]	**4**[c]	**14**·HI[d]
1	35	66.5	5.64	1.25	26.6
2	150	10.1	11.3	5.51	73.1
3	210	3.38	12.7	4.6	79.3
4	390	*e*	17.7	6.48	75.8[f]

[a] Materials used were iodoalkane **1** (0.7048 g, 1.451 mmol, 96.7% pure, by GC; 0.589 M; passed down alumina to remove impurities; contained 2.32% of C_8 homologue); lactam **11** (1.8244 g, 16.12 mmol, 96% pure; 0.73 M); and water (0.1481 g, 8.2118 mmol; 0.061 M); total volume was 2.46 mL. Sealed tube A was cooled to −196 °C, evacuated, and filled with nitrogen. This procedure was repeated after each sample was removed. The reaction mixture at 140 °C became a clear liquid, light yellow in color immediately. The liquid remained clear throughout the reaction period at 140 °C and at 25 °C. No wt loss on heating at 140.0 °C. Samples (0.02 g) were removed by Pasteur pipet into a vial and quickly dissolved in $HCCl_3$ (0.14 g) and ethanol (0.02 g) to give a clear solution for GC. [b] The molar % of substance remaining. [c] The % conversion. [d] Nonvolatile **14**·HI (and HI salts derived from **1**) was calcd from mol [**1**(used up) − (**3** + **4**)]. Substance **14** is *O*-[2-(perfluorohexyl)ethyl]caprolactim, or as the water adduct, **15**, 2-hydroxy-2-[[2-(perfluorohexyl)ethyl]oxy]-3,4,5,6,7-hexahydro-2*H*-azepin. [e] The amount of **1** was too small to measure under the conditions used. [f] GC showed several higher reaction time substances were present of 2−5% relative amount. Thus, the calcd amount of **14**·HI was not accurately determined.

Scheme 4. Proposed Reaction Steps in the Synthesis of 3 from Lactams and 1 in the Presence of Water



$R = C_6F_{13}CH_2CH_2$; n = 1, 2 and 3

the higher lactams, where a homogeneous mixture was present throughout the entire reaction period (Tables 8A and 9). With **8** and **1** the fastest reaction was observed (see Table 8C). However, this is not a general effect, since, in reactions of **2** and **1**, an initial phase separation occurred either without water or with water, before the mixtures became clear.

In the related system of **1**, DMF, and water, the reaction rate is independent of water concentration, but *selectivity* (mol of alcohol and ester/alkene) is strongly dependent on the DMF/water molar ratio.[15] On the basis of kinetic evidence, Hayashi and Matsuo postulated a transition state intermediate [**1**·$(DMF)_2$] for the slow, rate-determining step of reaction, followed by a fast reaction step with water.[15] However, an increase in rate of reaction was observed in the alkylation of *N*-(2-propenyl)formamide (NPF) by **1**, when water was added to the reaction.[2] In this case, the products were altered as well, shifting from alcohol to formate ester.[16]

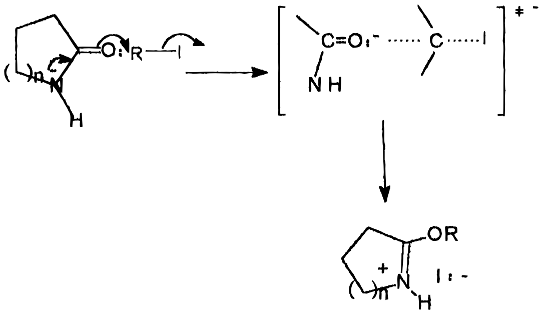
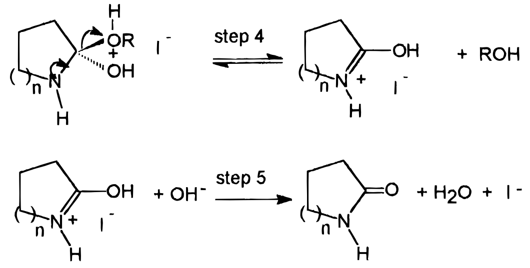


Figure 3. Transition state complex formed during reaction.

Scheme 5. Reaction of the Lactim Ether Hemiketal Salts with Base in the Presence of Water. Elimination of Alcohol and Neutralization of Acid



$R = C_6F_{13}CH_2CH_2$; n = 1, 2 and 3

An analogy with the thermal alkylation reaction of **1** and DMF may be given: in the presence of water, formation of alcohol **3** is suppressed, but the rate of an ester intermediate is greatly accelerated.[2,4] Available evidence indicates that a methanimino ether salt (*salt I*)[2,4] is formed reversibly from **1** and DMF (as for **1** and lactam **2**), but then water, acting as a nucleophile, gives a tetrahedral intermediate that breaks down to ester and *amine salt* (see Scheme 2 in refs 2 and 3). This is in conformity with the theories of Deslongchamps,[4] based on the effect of nonbonded electron pair interactions in the tetrahedral intermediates.

Another observation of complexes from the reaction of DMF or *N*-methylformamide (NMF) with alkylating agents comes from the early work of Bredereck and coworkers.[17] Solid addition compounds were isolated from NMF or DMF and dimethyl sulfate, analogous to that mentioned above. When the substance from NMF and

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(15) Matsuo, M.; Hayashi, T. *Asahi Garasu Kenkyu Hokoku* **1976**, *26*, 55. Ger. Offen. DE No. 2,318,941 (to Asahi Glass Col, Ltd.), Oct 25, 1973; *Chem. Abstr.* **1974**, *80*(1), 14564a. Rate equations are reported: $rate_{alcohol,\ formate\ ester} = k_{a,f}[\mathbf{1}][DMF]^2$; $rate_{alkene} = k_e[\mathbf{1}][DMF][H_2O]$. DMF:water mol ratios of 5−20 were used, with DMF:1 mol ratios of 10−40. Selectivity rose to 97% yield of alcohol and formate ester at the highest DMF:water mol ratio; a mol ratio of water:**1** = 6 was used.

(16) When **1** is used to alkylate an amide such as *N*-(2-propenyl)formamide (NPF),[2] water speeds up both the consumption of **1** and the formation of **3** and the formate ester. At 140 °C, with NPF:**1** = 15.0, water:**1** = 2.2, $k_{iodo} = 5.2 \times 10^{-5}\ s^{-1}$; without water, same conditions, $k_{iodo} = 3.2 \times 10^{-5}\ s^{-1}$.

(17) Bredereck, H.; Gompper, R.; Theilig, G. *Chem. Ber.* **1954**, *87*, 537−546; and references therein.

dimethyl sulfate is heated to a higher temperature, methyl formate and the methanimide are obtained; however, heating of the DMF compound did not produce methyl formate. These addition compounds react with nucleophiles such as water and amines, giving displacement reactions similar to that of steps 2 and 3 of Scheme 3.

Water as a Second Nucleophile in the Alkylation Reaction with the Higher Lactams. The behavior of higher lactams in the thermal alkylation reaction was extensively examined.[1a] In Scheme 3, higher lactams were unable efficiently to pass over step 2, for reasons of size or poor nucleophilicity, and consequently, the synthesis of **3** from **1** and the higher lactam was unsatisfactory.[1] Now, with water as a second nucleophile in the alkylation process, we find lactams **8** and **11** (Tables 7 and 8) show a remarkable increase in rate and efficiency of the alkylation step (Step 1 of Scheme 4) *and* of the alcohol displacement steps (steps 2−5 of Scheme 4). Just as for lactam **8**, thermal alkylation of **11** in the presence of water was greatly accelerated and loss of the intermediate lactim ether **14** to alkene **4** was no greater than for **8**. With both of the higher lactams the decrease in formation of alkene (lactam **8**, 4−6% conversion to **4**; lactam **11**, 6.5% conversion to **4**) is especially significant. These results may have their basis in the greater stability of the water adduct of the intermediate lactim ether toward elimination of the alkene. For lactam **11**, the water adduct **15** (2-hydroxy-2 [[2-(perfluorohexyl)ethyl]-oxy]-3,4,5,6,7-hexahydro-*2H*-azepin) would have a greatly reduced rate of intramolecular elimination. This would be consistent with the mechanism proposed previously[1a] in which lactim ether **14** undergoes a "concerted" reaction through an intermediate ring structure that leads to the loss of alkene and formation of the lactam. If most of lactim ether **14** is converted to **15** in the reaction mixture, loss to alkene **4** would be expected to be reduced, since **15** does not have the requisite structure for concerted elimination of **4**.

Finally, a patent disclosure[18] to synthesis of alcohol **3** by heating of **1** with *N*-methylpyrrolidinone (NMP) and water contains a provocative experimental confirmation of steps of Schemes 4 and 5. The reaction mixture (mol ratio of **1**:water:NMP = 1:3:22) is typically heated for 14 h at 140−150 °C until all of **1** is consumed. The product mixture is then worked up by heating and stirring the two-phase mixture with a large excess of water at 70 °C for 0.5−1 h. The organic phase can then be separated and **3** distilled in an excellent yield; conversion to **4** is ca. 9%. The reason for the extended hydrolysis reaction time is not disclosed, but it may be inferred from an experiment[1b] not described in this disclosure.[19] Reaction of **1**, NMP, and water (mol ratio of **1**:water:NMP = 1:3.14: 22.2) at 140 °C for 7.5 h gave 66.4% consumption of **1** but only 30.6 mol % conversion to alcohol **3**, and 16.9 mol % to alkene **4** by GC. The reaction mixture was not hydrolyzed by heating with a large excess of water.[19] The difference of 18.9 mol % between the consumption of **1** and the formation of volatile products represents the lactim HI salts that were unconverted to alcohol or alkene, analogous to that found in reactions of **1** and **2** and water. The reaction appeared to be much slower with NMP than with **2**, however. In other unpublished work,[20] it was found that the vigorous hydrolysis workup conditions converts the lactam (NMP, in this instance) with ring opening to a salt $[MeNH_2^+(CH_2)_3COOH]I^-$. This substance was treated with Na_2CO_3 to give the zwitterion $MeNH_2^+(CH_2)_3COO^-$ which was characterized thoroughly,[20] and formation of the HI salt is probably responsible for driving the process to completion.

Conclusions. Thermal alkylation of ambidentate lactams of ring sizes 5, 6, or 7 occurs readily by a 2-(perfluoroalkyl)-1-iodoalkane in the presence of 0.5−3.0 mols of water. Only 1 mol of lactam is used (and then recovered), and the rate and yield of the alkylation reaction are increased by the presence of water. A mechanism is devised that accounts for the main features of this water-induced substitution process. A lactim ether water adduct, 2-hydroxy-2-[[2-(perfluorohexyl)-ethyl]oxy]pyrrolidine (**7**) is isolated for the first time. The structure of **7** is based on its behavior and on its mass spectrum, including the parent ion, and a fragment (*m*/*z* = 131) of **7** less its perfluorohexyl group (2-hydroxy-2-(ethyloxy)pyrrolidine). Basic hydrolysis of product mixtures containing **7·**HI in a protic solvent gives a high yield of **3** and **2**. Higher lactams are also readily alkylated by this method to the lactim salt, and in the presence of water the reaction is speeded up over that of the anhydrous process. High temperature hydrolysis in a large excess of water hydrolyzes the lactim salt and its water adduct; the lactam is saponified, with ring opening, to a salt with HI. These results open up a new field of alkylation reactions of lactams with water as a coreactant and may prove to be useful for synthetic and mechanistic studies.

Experimental Section

Materials, physical methods, and standard reaction procedures have been described.[1a]

Alkylation Experiments of 1 and Lactam 2 in Reactor Tube A. Reaction of Iodoalkane 1 with Lactam 2 and Added Water at 130 °C (Table 4). Iodoalkane **1** (2.3923 g, 4.880 mmol, 96.7% pure, GC; 0.6357 M; passed over alumina to remove impurities; contained 2.67% of C_8 homologue), lactam **2** (6.7054 g, 78.470 mmol, 99.6% pure; 10.22 M), water (0.2918 g, 16.19 mmol; 2.154 M), and toluene (0.1398 g, FID ref) were charged to tube A. Total volume was 7.677 mL. Sealed tube A was cooled to −196 °C, evacuated, and filled with nitrogen to 10 mm. The liquid mixture became clear and colorless after heating for 0.5 h at 130 °C. No weight loss occurred on heating. Samples were quickly dissolved in $HCCl_3$ or $DCCl_3$ for GC on "DB-5", 30 m column, as given in Table 4. Alcohol **3** reached 45% conversion, while 99.5% of iodoalkane **1** was consumed in 6 or 7 h.

Reaction of 1 and 2 with Water Present at 141 °C (Table 2B). Reactor tube A was charged with **1** (2.3996 g, 4.920 mmol, 97.2%; contained 0.57% of C_8 homologue; the sample was not treated to remove iodine and polar impurities, as above), lactam **2** (6.8158 g, 79.69 mmol, 99.5%; contained 0.10% of water impurity, by titration), and water (0.2569 g, 14.26 mmol; with the water in **2**, total weight was 0.2644 g, 14.67 mmol). The total volume of reactants was 7.56 mL and mol ratio of **1**:**2** = 1:16.2; mol ratio of water:**1** = 3.00. The reactor tube was heated at 144 °C (inside temp, 141 °C). A dark reddish color formed immediately, and the liquid mixture became clear and lightly colored in 15 min. After 0.5 h, a sample (0.2076 g, Table 2B, entry 1, calcd 0.1494 g of **2** and 0.0525 g of **1**, 0.111 mmol)) was removed, and 1,2-dichlorobenzene (0.0376 g, GC ref) and CCl_4 (2.0 mL) were added to give a clear solution, which was shaken with water (1.0 mL) to give

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(18) Schwenk, U.; König, I.; Streitberger, A. U.S. Patent (to Hoechst Aktiengesellschaft, Fed. Rep. of Germany), August 26, 1980; *Chem. Abstr.* **1980**, *93*, 7656x.

(19) Brace, N. O. Unpublished.

(20) von Werner, K.; Hoechst Aktiengesellschaft, Fed. Rep. of Germany; private communication. The zwitterion was isolated after neutralization with Na_2CO_3 and was characterized by elemental analyses (C,H,N), IR, and NMR.

a thick, foamy emulsion that slowly separated. GC showed incomplete recovery had occurred. To the aqueous layer was then added 1% aqueous NaHCO$_3$ (pH now 9), the mixture was extracted with toluene (1 mL), and the clear extract was combined with the CCl$_4$ layer. The mixture was dried and diluted with acetone, and GC ("DB-5", 15 m) was run (average of two). See Table 2B, entry 1. After 2 h, a sample (0.4732 g) and 1,2-DCB (0.0800 g) were similarly treated with water (2 mL), toluene (1 mL), and HCCl$_3$ (2 mL). To the aqueous layer was added NaHCO$_3$ (1 mL), and it was shaken with HCCl$_3$ (1 mL). The combined extracts were used for GC. Results (average of two) are given in Table 2B, entry 2 (GC on "DB-5", 15 m). Both runs showed substantial amounts of unknown substances, as listed. Samples after 3 h of reaction were run on GC before and after being treated with aqueous aqueous NaHCO$_3$ solution. Variable amounts of **3**, **6**, and **7** were found, as listed in Table 2B.

Reaction of 1 and 2 with Water Present (mol ratio of 1:2 = 1:15.2; mol ratio of Water:1 = 2.25) at 141 °C. Isolation of Products by Distillation. A heavy wall glass reactor tube A was charged with **1** (2.4045 g, 4.930 mmol, 97.2%; contained 0.57% C$_8$ homologue and some polar impurities), lactam **2** (6.4467 g, 74.99 mmol, 99.5%; contained 0.10% water impurity), and water (0.1939 g, 10.76 mmol; with the water in **2**, total wt, 0.2003 g, 11.11 mmol, 1.543 M); total volume of reactants, 7.199 mL. After processing as above, the reactor tube was heated in a stirred bath at 144 °C (inside temperature was 141 °C) for 3 h. A dark reddish color appeared as above. The reaction mixture was transferred to a distillation flask (8.85 g, 0.9787 part, 4.825 mmol of **1** products) and volatile material distilled through a 10-in. Vigreux column, with bad foaming at first. Fractions collected were the following: I, bp 93−131 °C/10 mm, 5.02 g. GC gave alcohol **3**, 30.9%; **1**, 0.68%; lactam **2**, 46.9 mmol recovered, and lactim **6**, 0.75%. II, bp 83−101 °C/0.65 mm, 0.69 g, which was chiefly lactam **2**. Fractions I and II combined were analyzed by GC. Lactam **2** increased to 63.3 mmol recovered, and iminolactam **5** was 0.78%. Holdup in the column was 0.27 g. The viscous brown residue of **2**, **3**, **5**, and **6** HI salts was 2.44 g. The cold-trap liquid was 0.04 g. The residue of HI salts was converted to lactam **2**, alcohol **3**, iminolactam **5**, and higher retention time products (probably oligomers of **5**) by reaction with K$_2$CO$_3$ (1.36 g, 9.86 mmol) in acetone (2.0 mL) and HCCl$_3$ (8.0 mL), as a stirred mixture in sealed tube at 66 °C for 4 h. A GC sample ("DB-5" capillary column) gave **3** (2.21 mmol), 46.9 mol %, a trace of **1**, recovered lactam **2** (5.24 mmol, or 2 mols to 1 of **2**:**3**); **5**, (0.547 mmol) 11.3 mol %, and higher ret time substances. HCCl$_3$ and acetone were distilled (up to 90 °C pot temp) from the filtered mixture (16.50 g), and the pot liquid (4.25 g) on a "DB-1" capillary column gave **3**, 45.6 mol % yield (on **1** used up); lactam **2**, 5.08 mmol; and **5**, 8.06 mol % on **1**. Further distillation gave a mixture of **2** and **3**, bp 75−115/10 mm, 1.12 g, and a residue of 0.46 g. Isolation of **2** and iminolactam **5** is consistent with two pathways for conversion of lactim **6** to alcohol **3**.

Reaction of Alkylation Product Mixture of Table 1A, Entry 8, with K$_2$CO$_3$ (mol ratio of K$_2$CO$_3$:1 products = 0.989) in CCl$_4$ at 52 °C (Table 1C).[7] Sample entry no. 8 of Table 1A (2.6882 g, 0.1503 part, 1.518 mmol of **1** products), GC reference, 1,2-dichlorobenzene (0.1386 g), CCl$_4$ (5.00 mL, 7.97 g), and K$_2$CO$_3$ (0.2073 g, 1.501 mmol) were stirred at 52 °C under total reflux head, with a trap to the bubbler tube. Samples (1.0 g) of the tan-colored slurry were filtered, and the GC run was on a "DB-5", 30 m column. The CCl$_4$ solution was washed with water (1.0 mL) to give a foamy mixture and a partial emulsion. GC results (Table 1C) for **3** are the average of two determinations.

Reaction of Alkylation Product Mixture of Table 1A, Entry 8, with K$_2$CO$_3$ (mol ratio of K$_2$CO$_3$:1 products = 2.00) in HCCl$_3$ and Ethanol at 68 °C (Table 1B). Sample entry 8 of Table 1A (9.30 g, 0.5201 part, 5.233 mmol of **1** products) was used for reaction; the sample contained 38.7% of alcohol **3** by GC (Table 1B, entry 1). To this sample were added ethanol (0.691 g, 10.5 mmol, 0.88 mL), HCCl$_3$ (5.0 mL, 7.46 g, 62.5 mmol), and 1,2-DCB (0.1746 g), and K$_2$CO$_3$ (1.465 g, 10.61 mmol) was added while the mixture was stirred vigorously at 25 °C. Stirring was continued at 68 °C for 7.5 h, and the mixture was cooled to 25 °C. A GC sample (2.0 mL) was washed with 1% NaHCO$_3$ solution (2.0 mL), and the aqueous layer was extracted twice with HCCl$_3$ (10 d) and dried over K$_2$CO$_3$. GC results are given in Table 1B, entries 2−4, individually and averaged.

Reaction of Product Mixture (Table 4) with Aqueous Sodium Bicarbonate and Extraction into CCl$_4$. Subsequent Extraction of Aqueous layers with HCCl$_3$ (Table 3B).[7] A sample (Table 4; 7 h) was recovered from the reaction tube by acetone rinse and evaporated. A portion (0.3739 g; 3.982% of the total reaction mixture; 0.1934 mmol of products from **1**) and 1% NaHCO$_3$ solution (1.00 mL) were shaken with CCl$_4$ (1.2 mL, 1.9 g) and formed a foamy emulsion (pH ca. 9, same as NaHCO$_3$ solution). Surface active **6**·HI was probably responsible for the foaming emulsion. After 5 min a cloudy CCl$_4$ layer (sample 4-5R-1; 1.8259 g) was drawn for GC ("DB-1", 15 m col) analysis (see Table 3B). Besides **2**, **3**, and **7**, 18.3 area % of four unknowns were observed. Lactam **2** comprised 48.70 area % of the total. The aqueous layer was shaken with HCCl$_3$ (1.00 mL; 1.49 g) for 1 min; the foamy aqueous layer separated quickly and the lower layer (sample 4-5R-2; 1.4818 g) was drawn after 2 min. GC gave **2**, 87.8 area %, **3**, 4.44%, and unknowns (six) comprised the remaining 7.3%. A second extraction with HCCl$_3$ (0.50 mL; 0.75 g) gave a cloudy layer drawn after 5 min (4-5R-3; 0.6307 g). GC gave **2**, 91.54 area %; **3**, 4.29%; and **7**, 3.90%. A third extraction with HCCl$_3$ (0.50 mL; 0.75 g) gave 4-5R-4 (0.60 g). GC gave 95.5% of **2** and smaller amounts of **3** and **7**. There was an increasing amount of **2** extracted into CHCl$_3$, and the amount of **3** remaining diminished with each extraction. However, the extraction did not completely recover the organic products.

In Table 3B[7] the GC analysis of sample 4-5-1 is given for reference. It is clear that the aqueous bicarbonate reaction with this sample converted part of the unreacted lactim ether salt **6**·HI into **3** and the new compound **7** and into the two unknown compounds at 9.65 and 9.81 min (on the "DB-1" column). Heating of the first extracted mixture 4-5R-1 on the steam bath gave sample 4-5R1-1. This caused the loss of **7** and an increase in **3** and the unknown at 9.65 min, as well as a higher boiling point unknown at 24.3 min. These results are in accord with the expected behavior of **7** and may throw some light on the identity of the other unknowns.

Reaction of Lactam 2 with 1 and Water (mol ratio 2:1 = 16.22; H$_2$O:1 = 3.02) at 140 °C (Table 2A). Materials used were iodoalkane **1** (0.7912 g, 1.614 mmol, 96.7% pure, GC; 0.6469 M; passed down alumina to remove impurities; contained 2.23% of C$_8$F$_{17}$CH$_2$CH$_2$I), lactam **2** (2.2378 g, 26.187 mmol, 99.6% pure; 10.50 M), and water (0.0878 g, 4.872 mmol; 1.953 M); total volume was 2.495 mL. Sealed tube A was cooled to −196 °C, evacuated and filled with nitrogen. This process was repeated after each sample was removed. The tube was heated, while stirring by magnet bar in an oil bath at 140 °C, for the times given. The reaction mixture formed two layers at 140 °C and after 20 min remained clear throughout the reaction period and when cooled for samples at 25 °C. No weight loss occurred on heating at 140.0 °C. Samples were removed by pipet into a vial and quickly dissolved in HCCl$_3$ for GC. The results are given in Table 2A; the time course of the reaction is plotted in Figure 2A, and the least squares plot appears as Figure 2B.

Reaction of δ-Valerolactam (8) with 1 and Water (mol ratio 8:1 = 14.0; water:1 = 2.10) at 140 °C (Tables 8A−C). Iodoalkane **1** (0.9038 g, 1.861 mmol, corrected, 96.7% pure by GC, 0.40 mL; 0.604 M; contained 2.23% of C$_8$F$_{17}$CH$_2$I), lactam **8** (2.60 g, 26.0 mmol, 99%), water (0.0704 g, 3.91 mmol, 0.070 mL), and 1,2-DCB (0.1500 g, GC ref) were charged to reactor tube A. The reaction tube was cooled to −196 °C, evacuated, and filled with nitrogen as in the tables above. This process was repeated after each sample was removed. The tube was heated, while stirring by magnet bar in an oil bath at 140 °C, for the times given. The reaction mixture became homogeneous *immediately* at 140 °C and remained clear throughout the reaction period and when cooled for samples at 25 °C. The remaining reaction mixture, allowed to stand for 7 days, formed long needles in the viscous mixture. GC samples were drawn with a Pasteur pipet and weighed, and the pipet was rinsed with 12 drops of HCCl$_3$. A "DB-5", 30 m column was employed, and two determinations were averaged. The GC data and results are given in Table 8A. A mixture of **8** (0.0602 g), 1,2-dichlorobenzene (1,2-DCB, 0.0231 g), and acetone (0.15 g) gave FID of 0.644 for **8**. Tables 8-0 and 8-1[7] give concentrations and quantities for rate calculations. See also Table 8C.

Treatment of Lactam 8 (Table 8A) Reaction Product Mixture with K_2CO_3 in $HCCl_3$ and Ethanol at 60 °C (Table 8B). A portion (0.67 g, 0.180 part, 0.335 mmol as **1**) of the viscous reaction mixture of Table 8A, entry 4, ethanol (0.050 g; 1.0 mmol), $HCCl_3$ (1.95 g, 1.30 mL), and K_2CO_3 (0.1210 g, 0.8755 mmol), in this order, were placed in a Fisher tissue culture tube and fitted with a Teflon-lined screw cap and a small magnet bar. Before mixing or heating of the suspension, a 2-drop sample was diluted 5-fold with $HCCl_3$ and GC run for a zero point measure of substances (Table 8B, entry 1). The sample composition had changed. After stirring the suspension for 4.5 h at 60 °C, a sample (10 drops), $HCCl_3$ (10 drops), and water (10 drops) were shaken. The two cloudy layers were separated, and the lower layer ($HCCl_3$) was dried for GC (Table 8B, entry 2). A new major substance appeared at 16.43 min; as the δ-valerolactim ether **9**, this is a conversion of ca. 6.3−18%. The amount found varied widely with the GC run. See Table 8B for the results.

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Supporting Information Available: Table of Contents, alternative names for substances, substance numbers, *Chemical Abstracts* registry numbers, and GC methods for analysis. For reactions of lactam **2** and iodoalkane **1**, quantities for rate calculations (Tables 1-1 to 2-2, Tables 4-2 and 4-3, and Figures 4A and 4B). Further work on alkylation reactions, isolation of reaction products after aqueous hydrolysis reactions (Tables 2C and 2D and Table 3B), and attempted hydrolysis reaction for NMR analysis of **6** and **7** (Table 3C). GC/MS separation and analysis of lactam **2** and **1** product mixtures (Tables 6C and 6D). Reaction of lactam **8** with **1**, molar concentrations, and quantities for rate calculations (Tables 8-0 and 8-1) (26 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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