was the desired lactam **4**. This waxy solid, 70 mg, mp 77–79 °C, was removed with a spatula and stored under dry nitrogen. Two successive sublimations at 25 °C (0.05 torr) yielded 25 mg of **4**: mp 82–83 °C; IR (film) 2915 (s, CH_2), 2860 (m, CH_2), 1680 (s, C=O), 1460 and 1370 (s), 1245, 1020 (s), no OH or NH; NMR ($CDCl_3$) δ 1.53 (6 H, br m, methylene H's at C_4, C_6, C_7), 2.35 (4 H, one peak, CH_2 at C_3 and axial H's at C_8 and C_9), 3.10 (2 H, two peaks, equatorial H at C_9 and C_5), 4.10 (1 H, br d, equatorial H at C_8); mass spectrum, *m/e* 139 (parent; calcd 139.2), 111 (M − C=), 83 [base, M − CH_2CH_2C=O (leaving the positively charged piperidine ring)], 55 (M − CH_2CH_2C=O − CH_2=CH_2). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.15; H, 9.62; N, 9.89.

Hydrolysis Studies. Lactam **4** was unchanged after 1 week at 28 °C in D_2O (by NMR) or after 6 h at 100 °C.

Lactam **4** was dissolved in D_2O and gaseous hydrogen chloride was passed in. An exothermic reaction occurred. The NMR spectrum of the resulting solution was identical with that of an authentic sample of β-(3-piperidyl)propionic acid hydrochloride, and the doublet at δ 4.40 in the spectrum of **4** had vanished.

Polymerization Studies. Lactam **4**, 35 mg, was placed in a vial to which was added 20 mg of 85% phosphoric acid (1 drop) by pipet. Infrared analysis immediately after mixing afforded a spectrum with broad absorption at 1640 cm^{-1}, indicating rapid oligomerization of the lactam. An identical mixture was heated to 100 °C in 20 min and formed polyamide **5**.

Heating **4** with either *p*-toluenesulfonic acid monohydrate or potassium *tert*-butoxide at 125 °C for 6 h gave no polyamide.

Registry No. **3**, 1822-31-7; **4**, 74331-49-0; **5** homopolymer, 74331-33-2; **5** repeating unit, 74331-34-3.

O-(2-Acetoxycyclohexyl)-*N*-isopropylhydroxylamine: A Striking Inertness of Acyl Carbon toward an Intramolecular Hydroxylamine Function

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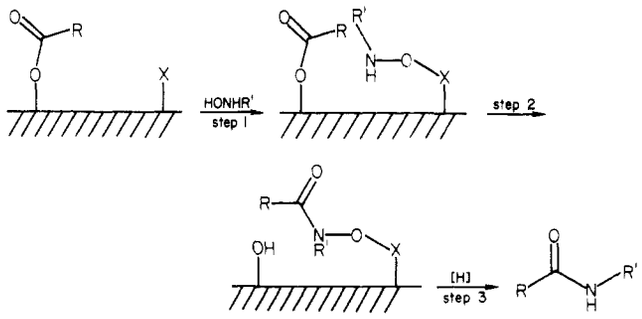
Received September 18, 1979

We have previously outlined a new strategy for peptide bond formation in which the amide function is generated by an intramolecular acylation, preceded by trapping of the nitrogen component of the amide at an electrophilic site of an ester of the acyl component (prior amine capture).[1] Rapid intramolecular O,N acyl transfer is a necessary condition for any structure that can be used with this strategy, and as we have reported for a number of peptide-derived model systems, this condition is difficult to achieve.[2] Accordingly, we are screening a variety of structures that place acyloxy and amino functions in proximity. A structure that allows rapid and clean intramolecular acyl transfer (1) in an unhindered case and (2) in hindered cases[2] (Ala-Val or Val-Val couplings) gives us a promising lead for developing the remaining chemical features that are required for a successful prior amine capture system. In this note we report that a candidate involving N-oxygenated derivatives fails a first test of rapid acyl transfer in an unhindered model case.

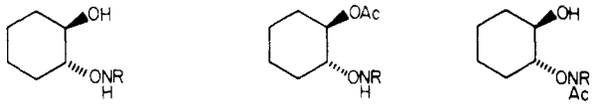
Derivatives of *N*-hydroxy-α-amino acids have been reported.[3] Hydroxylamine itself is noted for the rapidity

Scheme I



of its reactions with both activated and simple esters;[4] moreover, both the nitrogen and oxygen of hydroxylamine exhibit enhanced nucleophilic reactivity. We envisaged a reaction sequence similar to that of Scheme I, in which a capture step (step 1) involves reaction of the unhindered oxygen with an electrophilic site and a cleavage step (step 3) is carried out reductively. Before considering means of achieving these steps, we had to establish that the nucleophilic reactivity of hydroxylamines toward simple esters is retained for an intramolecular reaction involving an *O*,*N*-dialkylhydroxylamine.

Ideally, a model for step 2 of Scheme I should position the carbonyl of the ester function five or six atoms removed from the nitrogen of the hydroxylamine function, which should bear the side-chain residues of a simple amino acid derivative. Since species **1** were expected to be available from the reactions of cyclohexene oxide with oxime salts, followed by reduction, the *O*-acyl derivatives (**2**) were natural choices for models.[5]



1a, R = *i*-Pr
b, R = $CHMeCO_2Et$

2a, R = *i*-Pr
b, R = $CHMeCO_2Et$

3, R = *i*-Pr

Reactions of cyclohexene oxide with the oxime of ethyl pyruvate failed to give the desired product under a variety of reaction conditions. However, acetoxime was found to react under basic conditions with cyclohexene oxide to give the desired *O*-alkyl oxime, which was hydrogenated to yield **1a** (59%, overall). The *O*-acetyl derivative, **2a**, was obtained in a novel two-step procedure in which **1a** is first N-acetylated to form **3**, which is isomerized by treatment with 12 N HCl to the hydrochloride salt of **2a**. The latter is expected to approximate the steric features of an alanine derivative, **2b**.

Neutralization of this salt with triethylamine provided the desired hydroxylamine derivative, **2a**, which proved to be surprisingly resistant to O,N acyl transfer. No transfer was observed in $CDCl_3$ or Me_2SO-d_6 within 24 h, and the substance was recovered unchanged from a Kugelrohr distillation at 100 °C for 30 min (0.001 mm). Although there is clearly a mechanism that allows rapid equilibration of **2a** and **3** under strongly acidic conditions, the nitrogen of **2a** shows no hint of nucleophilicity toward the neighboring ester carbonyl under neutral or mildly basic conditions.

It is clear that this hydroxylamine derivative shows none of the special reactivity exhibited by hydroxylamine itself toward acyl carbon.[4] Instead, the oxygen of this derivative

(1) D. S. Kemp, J. A. Grattan, and J. Reczek, *J. Org. Chem.*, **40**, 3465 (1975).
(2) D. S. Kemp and F. Vellaccio, *J. Org. Chem.*, **40**, 3464 (1975).
(3) For examples, see (a) T. Polański and A. Chimiak, *Tetrahedron Lett.*, 2453 (1974); (b) T. Kolasa and A. Chimiak, *Tetrahedron*, **30**, 3591 (1974); (c) E. Buehler and G. B. Brown, *J. Org. Chem.*, **32**, 265 (1967).
(4) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).
(5) Inspection of models indicates that the tetrahedral intermediate for O → N acyl transfer can assume a strain-free *trans*-decalin-like conformation.

0022-3263/80/1945-3724$01.00/0

appears to be exerting a simple inductive effect, reducing both the basicity and the nucleophilicity of the nitrogen which is chemically similar to that of a sulfenamide.[2]

O- or N-alkylation is known to reduce the nucleophilicity of hydroxylamines toward activated acyl derivatives, but the magnitude of the effect for reactions with unactivated esters, which differ from activated esters in reacting with hydroxylamine at N, not O, has not been determined to our knowledge. However, our observations show that proximity, at least with intramolecular geometries available from **2a**, is not sufficient to overcome the rate-retarding effect of O,N-disubstitution.

Hydrogen bonding in the transition state of acyl transfer and polarizability of the hydroxylamine moiety that is complementary to that of the reacting bonds at the acyl site are possible explanations of the high reactivity of hydroxylamine in acyl-transfer reactions. Accordingly, the inertness of **2a** can perhaps be explained by its poor hydrogen-bonding capacity or the unavailability to it of a conformation that permits mutual polarization of the reacting nucleophile and ester.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 567 grating infrared spectrometer. The ^{1}H NMR spectra were taken on either a Varian T-60, a Perkin-Elmer R-22, or a Hitachi Perkin-Elmer R-24B spectrometer and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were determined on a Varian MAT-44 spectrometer. Ultraviolet spectra were obtained on a Zeiss PMQ-II spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Synthesis of *trans*-1-(*O*-Acetoximino)cyclohexan-2-ol (4). To a solution of acetoxime (1.50 g, 20.5 mmol) in 25 mL of *tert*-butyl alcohol was added sodium hydride (100 mg, 2 mmol). After 10 min, cyclohexene oxide (Aldrich) (2.0 mL, 20 mmol) was added. The solution was heated at reflux under nitrogen for 65 h. It was then cooled, poured into saturated sodium bicarbonate, and extracted with methylene chloride (3 × 100 mL). The combined organic fractions were dried over potassium carbonate, filtered, evaporated, and vacuum distilled in a Kugelrohr apparatus at 100 °C (0.05 mm) to give 2.00 g (65%) of **4**: IR (film) 3420, 2940, 2860, 1450, 1370, 1070, 1040, 935 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.2 (br m, 8), 1.89 (s, 6), 3.75 (br s, 3, 2 with D_2O); mass spectrum (70 eV), *m/e* (relative intensity) 172 (2), 171 (M^+, 0.3), 154 (0.3), 142 (0.4), 128 (0.7), 115 (5), 97 (11), 81 (63), 74 (96), 56 (100), 42 (78), 41 (82).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01. Found: C, 63.18; H, 10.15.

***trans*-*O*-(2-Hydroxycyclohexyl)-*N*-isopropylhydroxylamine Hydrochloride (1a).** A solution of 991 mg (5.8 mmol) of oxime **4** in a mixture of 9.5 mL of 1 N HCl and 20 mL of absolute ethanol was placed in a Parr bottle with 200 mg of PtO and 130 mL of absolute ethanol. The mixture was hydrogenated on a Parr apparatus at 25 °C under 50 psi of hydrogen for 2.5 h. After being filtered, the solution was evaporated, and the salt crystallized slowly on standing to give 1.09 g (90%) of **1a**: mp 84–91 °C; IR (KBr) 3200, 2920, 1570, 1445, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–2.40 (m, 8), 1.51 (d, 6, J = 6 Hz), 3.40–4.70 (m, 3), 5.35 (br s, 2), 8.43 (br s, 1).

The free amine was obtained by washing a methylene chloride solution of the salt with a saturated sodium bicarbonate solution. The organic layer was separated, dried with potassium carbonate, filtered, and evaporated: IR (film) 3350, 2930, 2860, 1450, 1060, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3, J = 6 Hz), 1.08 (d, 3, J = 6 Hz), 1.10–2.10 (m, 8), 3.20 (septet, 1, J = 6 Hz), 3.50 (br m, 2), 5.13 (br s, 2); mass spectrum (70 eV), *m/e* (relative intensity) 173 (M^+, 1), 158 (1), 140 (1), 116 (1), 99 (6), 81 (40), 60 (100), 41 (43); UV (EtOH) λ_{max} 268 (ϵ 7.5).

***trans*-*O*-(2-Hydroxycyclohexyl)-*N*-acetyl-*N*-isopropylhydroxylamine (3).** To a solution of 517 mg (2.46 mmol) of **1a** in 5 mL of dry pyridine (distilled from CaH_2) at 0 °C was added 0.2 mL (2.8 mmol) of acetyl chloride. The resulting mixture was stirred for 4 h at 0 °C under nitrogen and then evaporated. The residue was dissolved in methylene chloride, washed 3 times with 1 N HCl, dried with potassium carbonate, filtered, and evaporated. Chromatography of the 320 mg of crude material on 50 g of silica gel 60 with a chloroform → ethyl acetate gradient elution gave 194 mg (37%) of **3**: IR (film) 3400, 2930, 2860, 1660 cm^{-1}; ^{1}H NMR ($CDCl)_3$ δ 1.20 to 1.90 (br m, 8), 1.25 (d, 3, J = 6 Hz), 1.30 (d, 3, J = 6 Hz), 2.14 (s, 3), 3.58 (br m, 2), 4.22 (septet, 1, J = 6 Hz), 4.84 (br s, 1); mass spectrum (70 eV), *m/e* (relative intenstiy) 216 (M + 1, 3.5), 215 (M^+, 0.21), 198 (0.1), 141 (1), 117 (19), 81 (61), 75 (74), 60 (58), 43 (100).

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.17; H, 9.87; N, 6.46.

***trans*-*O*-(2-Acetoxycyclohexyl)-*N*-isopropylhydroxylamine Hydrochloride (5).** Acetamide **3** (114 mg, 0.53 mmol) was dissolved in 1 mL of 12 N HCl. The resulting pale green solution was evaporated with a rotary evaporator followed by high-vacuum drying to give 98 mg (73%) of crude **5**: IR (film) 3360, 2940, 2860, 2640, 2460, 1740, 1580, 1450, 1375, 1240, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–2.0 (br m, 8), 1.48 (d, 6, J = 6 Hz), 2.13 (s, 3), 3.74 (br m, 1), 4.55 (br m, 2), 7.63 (br s, 1), 11.68 (br s, 1).

***trans*-*O*-(2-Acetoxycyclohexyl)-*N*-isopropylhydroxylamine (2a).** To a solution of 98 mg (0.39 mmol) of **5** in 0.5 mL of $CDCl_3$ was added 55 μL (0.40 mmol) of triethylamine. Evaporation followed by preparative layer chromatography using 1:1 chloroform–ethyl acetate elution afforded 5 mg of **1a** as the free amine, presumably due to some hydrolysis in the preparation of **5**, and 31 mg of **2a**: IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3, J = 6 Hz), 1.06 (d, 3, J = 6 Hz), 1.1–1.9 (br m, 8), 2.08 (s, 3), 3.10 (septet, 1, J = 6 Hz), 3.58 (br m, 1), 4.93 (br m, 2); mass spectrum (70 eV), *m/e* (relative intensity) 215 (M^+, none), 199 (2), 184 (3), 141 (95), 99 (21), 81 (63), 43 (100).

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.53; H, 9.94; N, 6.45.

Acknowledgment. Financial support from the National Institutes of Health (5R01GM13453-14) is gratefully acknowledged.

Registry No. **1a**, 74312-44-0; **1a** free amine, 74312-45-1; **2a**, 74312-46-2; **3**, 74312-47-3; **4**, 74312-48-4; **5**, 74312-49-5; acetoxime, 127-06-0; cyclohexene oxide, 286-20-4; acetyl chloride, 75-36-5.