Conformational Equilibria in the 1-Amino-1-phenyl-2-propanol and 2-Amino-1-phenyl-1-propanol Systems. III. Nuclear Magnetic Resonance and Infrared Studies[1,2]

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Conformational preferences in the 1-(*N,N*-dialkylamino)-1-phenyl-2-propanol and 2-(*N,N*-dialkylamino)-1-phenyl-1-propanol series of amino alcohols and their benzoate esters have been studied by nuclear magnetic resonance and infrared spectroscopy. The threo amino alcohols reside almost exclusively in the intramolecularly hydrogen bonded form of the anti rotamers, while the erythro alcohols prefer the intramolecularly hydrogen bonded form of the gauche rotamers.

Conformational equilibria in the 2-amino-1,2-diphenylethanol system have been studied in detail by NMR[4] and infrared spectroscopy.[1] These earlier studies led to working hypotheses regarding the factors controlling conformation in that system. The present study was undertaken to test the applicability of these working hypotheses in related systems to further refine our understanding of the controlling factors. The compounds chosen for this study belong to the 1-amino-1-phenyl-2-propanol (I) and 2-amino-1-phenyl-1-propanol (II) systems.

The stereoisomeric *N,N*-dialkylamino alcohols in Table I were prepared by either nucleophilic scission of the C–O bond of *trans*-1-phenyl-1-propene oxide, hydroboration of the appropriate enamine, or reduction of the corresponding amino ketone. The well-documented trans nature of the epoxide opening established the configuration of the erythro[5] amino alcohols in these systems. In each case structure and homogeneity were established by NMR spectroscopy.

The vicinal coupling constants, J_{ab}, were conveniently obtained from the NMR spectra and reflect a weighted mean dependent on the relative populations of the three possible staggered rotamers.[6] This study, as the earlier one, is concerned with identifying trends and evaluating their conformational implications. The calculations of approximate anti to gauche rotamer ratios using the previously suggested working values, J_{anti} = 10.3 and J_{gauche} = 2.6 Hz,[4] are consistent with the objective.

It is apparent from the values of J_{ab} (Table I) that the threo amino alcohols **1** and **3** highly populate the anti rotamers tA and tA′ (Charts I and II), respectively. Intramolecular hydrogen bonding (OH···N) undoubtedly contributes to the stability of these rotamers, already favored on steric grounds. The intrinsic stablizing influence of the division of the four bulkiest groups into two pairs separated from one another by hydrogen atoms has been noted previously in the 2-amino-1,2-diphenylethanol system.[4]

At high dilution in carbon tetrachloride, *only* hydrogen bonded OH stretching bands appear in the infrared spectra of threo piperidino alcohols **1a** and **3a** (Table II); therefore, the highly populated anti rotamers tA and tA′, respectively, exist completely in the intramolecularly hydrogen bonded form. In addition to the strong intramolecular OH···N absorption bands, the corresponding threo pyrrolidino alcohols **1b** and **3b** exhibit weak absorptions at 3590 and 3621 cm^{-1}, respectively. The band at 3590 cm^{-1} (**1b**) assigned to intramolecular OH···π (phenyl), is consistent with a small population of gauche rotamers. Similarly, the appearance of unassociated OH stretching in the spectrum of

Chart I
Rotamers in the 1-Amino-1-phenyl-2-propanol System (I)

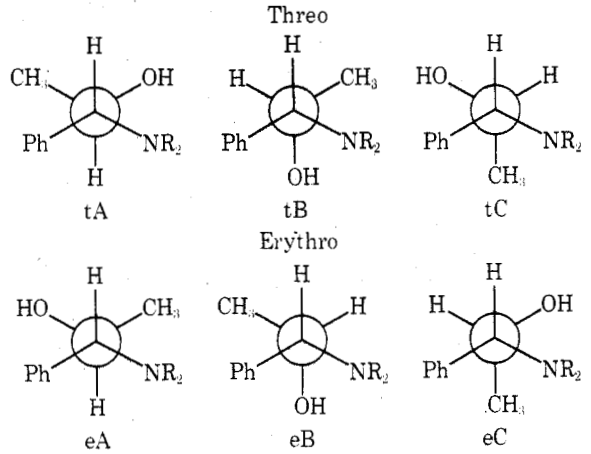
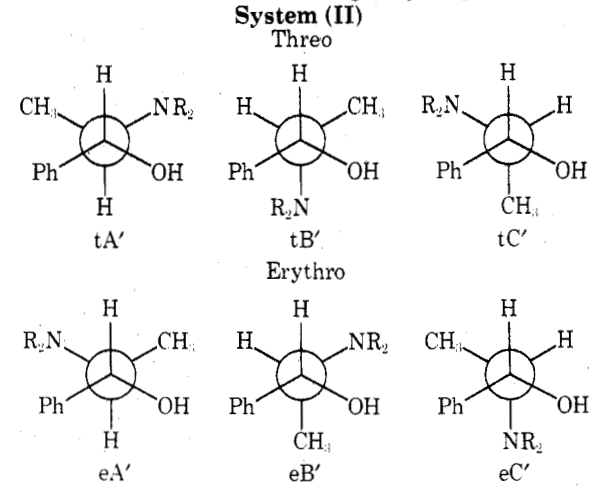


Chart II
Rotamers in the 2-Amino-1-phenyl-1-propanol System (II)



3b is also compatible with the presence of gauche rotamers. These conclusions are consistent with the slightly lower vicinal coupling constants observed for the threo pyrrolidino alcohols, and suggest that the subtle differences in the steric requirements of the piperidine and pyrrolidine groups noted in the more encumbered 2-amino-1,2-diphenylethanol system[4] manifest themselves here as well.

The lower J_{ab} values (<5.1 Hz) observed in the erythro

Table I
Nuclear Magnetic Resonance Data[a]

Compd	Chemical shift[b] Ha thr[e]	Ha er[e]	Hb thr	Hb er	CH_3 thr	CH_3 er	J_{ab}[c] thr	J_{ab} er	[anti]/[gauche][d] thr	[anti]/[gauche] er
				$C_6H_5—CH_a(X)—CH_b(OR)—CH_3$						
				I						
Amino Alcohols										
1, R = H										
a, X = 1-piperidino	186	183	245	260	55	51	10.2	5.1	*f*	0.47
b, X = 1-pyrrolidino	207	179	248	255	49	49	9.8	3.2	*f*	0.09
Esters										
2, R = benzoyl										
a, X = 1-piperidino	204	211	342	344	62	85	8.8	7.9	4.3	2.2
b, X = 1-pyrrolidino	209	189	337	327	70	65	5.3	3.2	0.54	0.09
				$C_6H_5—CH_a(OR)—CH_b(X)—CH_3$						
				II						
Amino Alcohols										
3, R = H										
a, X = 1-piperidino	253	285	*g*	*g*	46	48	9.9	4.1	*f*	0.23
b, X = 1-pyrrolidino	247	301	*g*	*g*	43	48	9.1	3.2	5.3	0.09
Esters										
4, R = benzoyl										
a, X = 1-piperidino	360	366	180	179	53	68	9.0	5.9	4.9	0.75
b, X = 1-pyrrolidino	268	378	185	*g*	54	68	6.1	3.7[h]	0.82	0.16

[a] Spectra were determined at room temperature on a Varian Model A-60A (60 MHz) spectrometer in CCl_4 or $CDCl_3$ solution at a concentration of ca. 15%. [b] In hertz relative to internal tetramethylsilane. [c] An average of ten runs. Values are accurate to an estimated ±0.1 Hz. [d] Ratio of the population of rotamer A or A′ to the gauche rotamers. [e] thr = *dl*-threo; er = *dl*-erythro. [f] >90% anti. [g] Signal overlaps the NCH_2 signal. [h] Spectrum was determined on 10 mg of sample and the value is accurate to an estimated ±0.2 Hz.

Table II
Infrared Spectral Properties of Amino Alcohols[a]

Compd	ν[b] OH	OH···π	OH···N[d]	$\Delta\nu$, cm^{-1}[c] OH···π	OH···N
threo-1a			3415		206
1b		3590 (w)	3425	31	196
3a			3355		266
3b	3621 (w)		3385		236
erythro-1a		3600 (s)	3475	21	156
1b		3595 (w)	3515	31	106
3a	3621 (m)		3425		196
3b	3621 (w)		3480		141

[a] All spectra were determined in carbon tetrachloride solution (<0.005 *M*). [b] s = strong; m = medium; w = weak. Probable errors: ±1.5 cm^{-1} for unassociated OH; ±2.5 cm^{-1} for bonded OH absorptions. [c] 3621 cm^{-1} for the free OH stretch is used in calculating these values. [d] Strong, broad absorptions in all cases.

amino alcohols 1 and 3 reflect the dominance of gauche rotamers. In the erythro series, in contrast to the threo amino alcohols, intramolecular hydrogen bonding and steric factors act as opposing forces, with the former effect dominating. This observation serves to underscore the profound role of intramolecular hydrogen bonding in the control of conformation in poor hydrogen acceptor solvents. As in the 2-amino-1,2-diphenylethanol system, the conformational bias toward gauche rotamers is greater in the pyrrolidine than in the piperidine compounds. Space-filling CPK molecular models suggest that this phenomenon has a common origin in the systems studied.[4]

At high dilution the infrared spectra of the erythro amino alcohols **1a** and **1b** confirm the importance of intramolecular hydrogen bonding. In addition to the presence of strong OH···N stretching bands, absorption characteristic of OH···π (phenyl) appears in the spectra of both compounds. The OH···π peak of **1a** is more intense than the OH···N band, but that of **1b** is less intense than the OH···N band. This is consistent with the conclusion, derived on the basis of NMR, that the substitution of pyrrolidine for piperidine in 1 leads to a decrease in the population of the anti rotamer tA, believed responsible for intramolecular OH···π.

The high-dilution spectra of erythro amino alcohols **3a** and **3b** exhibit absorption characteristic of intramolecular OH···N and unassociated OH. The fact that the unassociated OH absorption peak is weaker in **3b** than in **3a** again implicates the greater conformational bias of the pyrrolidine compound for the gauche rotamers.

The reported vicinal coupling constants of the benzoate esters (Table I) permit an analysis of the factors controlling conformation in the absence of the superimposed influence of intramolecular hydrogen bonding. In contrast to the corresponding amino alcohols, both threo and erythro benzoates **2a** heavily populate the anti rotamers tA and eA, respectively, most likely as a result of the stabilization conferred by division of the four bulky groups into two groups separated by hydrogen atoms. However, in the corresponding pyrrolidino esters **2b**, this control is apparently offset by other factors, as gauche rotamers are preferred. An examination of space-filling CPK models suggests a possible explanation of this discrepancy.

Molecular models of the erythro benzoates **2a** and **2b**

Table III
Effect of Substituents on the Coupling Constant in $PhCH_a(OR)CH_b(X)R'$[a]

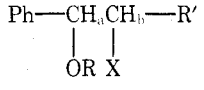
Entry	X	R'	R	$J_{erythro}$[b]	J_{threo}
1	1-Piperidino	Ph	Ms[c]	9.6	10.4
2	1-Piperidino	Ph	Ac	8.7	10.7
3	1-Piperidino	Ph	CH_3	7.7	9.2
4	1-(*N*-Methylpiperidino)	Ph	H	2.9	10.7
5	1-(*N*-Methylpiperidino)	Ph	CH_3	2.2	10.4
6	1-Piperidino	CH_3	Bz	5.9	9.0

[a] Data are taken from ref 4 and Table I of this paper. [b] J_{ab} in hertz. [c] Ms = mesitoyl.

suggest, as in the cases of the erythro pyrrolidino esters in the 2-amino-1,2-diphenylethanol system,[4] that the dominance of the gauche rotamers in the pyrrolidino compound **2b** is the result of unfavorable steric interactions between the pseudo-axial hydrogens at positions 2 and 5 of the pyrrolidine ring and the carbon atoms of phenyl in the anti rotamer eA. In contrast, in the gauche rotamer eB, the most favorable orientation of the amino group about the C–N bond leads to greater steric interaction in the piperidine compound, while the pyrrolidine moiety is relatively strain-free in this conformation.[7] Similar, but apparently not as pronounced, steric influences account for the more highly populated gauche rotamers in threo ester **2b**.

As expected on steric grounds, the NMR data for the threo piperidino ester **4a** reveals a heavily populated anti rotamer tA′. In the erythro piperidino ester **4a** the concentration of the gauche rotamers slightly exceeds that of the anti rotamer. In the absence of intramolecular hydrogen bonding this is unexpected, since in rotamer eA′, just as in tA, the four bulky groups are divided into two pairs separated by hydrogen atoms. This contrasting behavior is explicable in the disposition of the two bulkiest vicinal groups, phenyl and amine; anti in tA′ and gauche in eA′. This unfavorable latter interaction is relieved in eB′, but not in eC′, which is probably negligibly populated.

If the above analysis is valid, conformational equilibria should be quite sensitive to the steric requirements of OR, X, and R′ in *erythro*-**5**, but not in *threo*-**5**. The compounds



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listed in Table III demonstrate that this is indeed the case. In the erythro series (a) a decrease in the steric requirement of the ester group favors rotamer eB′ (entries 1–3); (b) an increase in the size of the amino group increases the proportion of gauche rotamer eB′ (entries 3 and 5); and (c) an increase in the size of R′ favors rotamer eA′ (entries 1, 2, and 6).

The gauche rotamers of the pyrrolidino benzoates (*threo*- and *erythro*-**4b**) are more highly populated than in the corresponding piperidino benzoates **4a**. Inspection of molecular models suggests that in the anti rotamers of ester **4**, the methyl and amino groups occupy the same relative orientation toward one another as the phenyl and amino groups in the tA and eA rotamers of esters **2**. Consequently, the less favorable methyl–amine interaction in the pyrrolidino compounds should destabilize the anti rotamers. Models suggest that the effect should be less pronounced than in ester series **2**, where the more severe amine–phenyl interactions operate. This view is supported by the data, since the anti/gauche ratio for both *threo*- and *erythro*-**4b** is greater than that for *erythro*-**2b**.

Table IV
Properties of the Amino Alcohols and Their Benzoate Esters[a]

Compd	% yield	Mp, °C, or eluent
threo-**1a**	71	95.5–96.5
erythro-**1a**	63	82–83
threo-**1b**	20	81–82
erythro-**1b**	69	82.5–83.5
threo-**2a**	66	Hexane
erythro-**2a**	68	Hexane
threo-**2b**	78	3% EtOAc
erythro-**2b**	80	10% EtOAc
threo-**3a**	39	55–56
erythro-**3a**	1	84–85
threo-**3b**	12	60–61
erythro-**3b**	6	70–71
threo-**4a**	75	10% EtOAc
erythro-**4a**	34	3% EtOAc
threo-**4b**	82	4% EtOAc
eryt hro-**4b**	34	7% EtOAc

[a] Satisfactory analytical data were obtained for all compounds listed in the table.

Experimental Section

All melting points are uncorrected and were determined on a Mel-Temp melting point apparatus. The nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide or as a thin film on a Perkin-Elmer 137 spectrophotometer. High-dilution infrared studies were carried out on a Beckman IR-12 spectrophotometer using previously described techniques.[1] The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind.

Ring Opening of *trans*-1-Phenyl-1-propene Oxide with Pyrrolidine. A solution of 2.0 g (0.015 mol) of *trans*-1-phenyl-1-propene oxide and pyrrolidine (5 ml) was heated at the reflux temperature for 41 hr. The solvent was removed in vacuo and the residue poured into water (40 ml). The material which solidified was isolated by filtration. Fractional crystallization from hexane afforded the crystalline, isomeric amino alcohols: 2.12 g (69%) of *dl-erythro*-1-(1-pyrrolidino)-1-phenyl-2-propanol (**1b**) and 0.184 g (6%) of *dl-erythro*-2-(1-pyrrolidino)-1-phenyl-1-propanol (**3b**).

Ring Opening of *trans*-1-Phenyl-1-propene Oxide with Piperidine. Using the above procedure with a reaction time of 54 hr, the following amino alcohols were prepared: *dl-erythro*-1-(1-piperidino)-1-phenyl-2-propanol (**1a**) in 50% yield and *dl-erythro*-2-(1-piperidino)-1-phenyl-2-propanol (**3a**) in 1% yield.

1-Phenyl-2-(1-piperidino)-1-propene. Using the method of Munk and Kim,[8] 16.0 g (0.12 mol) of phenylacetone and 34.5 g (0.41 mol) of piperidine afforded 10.9 g (45%) of the enamine: mp 40–42°C; NMR (CCl_4) δ 7.1 (m, 5, Ph), 5.48 (s, 1, CH=), 2.9 (m, 4, CH_2N), 1.89 (s, 3, CH_3), and 1.5 (m, 6, CH_2). Short-path distillation followed by crystallization afforded the analytical sample.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.51; H, 9.53. Found: C, 82.88; H, 9.80.

Hydration of 1-Phenyl-2-(1-piperidino)-1-propene. To a solution of 0.507 g (0.013 mol) of sodium borohydride and 2.057 g (0.010 mol) of 1-phenyl-2-(1-piperidino)-1-propene in dry THF (25 ml) was added dropwise 1.59 g (0.014 mol) of boron trifluoride etherate in THF (7 ml). The solution was heated at the reflux temperature for 1 hr and cooled in an ice bath and water (10 ml) was added followed by 6 ml of sodium hydroxide (1 *N*) and 30% hydrogen peroxide (4 ml). The solution was heated at the reflux temperature for 4 hr, poured into a solution of saturated sodium chloride (50 ml), and extracted with three 50-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Crystallization of the residue afforded 0.894 g (39%) of *dl-threo* **3a**.

Hydration of 1-Phenyl-1-(1-piperidino)-1-propene. The above procedure afforded *dl-threo* **1a** in 71% yield.

Hydration of 1-Phenyl-1-(1-pyrrolidino)-1-propene. To a solution of 0.544 g (0.014 mol) of sodium borohydride in dry THF (15 ml) was added dropwise 1.5 ml (0.012 mol) of boron trifluoride

etherate in THF (10 ml). The solution was stirred at room temperature for 2 hr and cooled in an ice bath and 0.953 g (0.053 mol) of 1-phenyl-1-(1-pyrrolidino)-1-propene in THF (10 ml) was added dropwise. The solution was stirred at room temperature for 5 hr and cooled and a solution of 1 *N* sodium hydroxide (4 ml) was added simultaneously with a solution of 30% hydrogen peroxide (3 ml). The solution was stirred for 12 hr, poured into a saturated sodium chloride solution, and extracted with three 50-ml portions of 1 *M* hydrochloric acid and the combined acid extracts were made basic by the addition of sodium hydroxide pellets. The basic solution was extracted with ether and dried ($MgSO_4$) and the solvent was removed in vacuo. Crystallization of the residue from hexane afforded 0.207 g (20%) of *dl-threo*-**1b**.

Reduction of 2-(1-pyrrolidino)-1-phenyl-1-propanone. The sodium borohydride reduction of the amino ketone in methanol afforded a mixture of *dl-threo-* and *dl-erythro*-**3b** in high yields. The *dl*-threo and *dl*-erythro amino alcohols (Table IV) could be isolated in low yields from the mixture by fractional crystallization from hexane.

Benzoate Esters 2 and 4. A solution of benzoic anhydride (0.01 mol), pyridine (2 ml), and amino alcohol (ca. 0.002 mol) was heated on a steam bath for 2–24 hr. The solution was poured into a mixture of saturated sodium bicarbonate (50 ml) and ether (25 ml). The solution was magnetically stirred for ca. 1 hr, extracted with three 50-ml portions of ether, and dried ($MgSO_4$) and the solvent was removed in vacuo. The oily benzoates were purified by chromatography over alumina.

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Registry No.—*threo*-**1a**, 56571-81-4; *erythro*-**1a**, 56571-82-5; *threo*-**1b**, 56571-83-6; *erythro*-**1b**, 56571-84-7; *threo*-**2a**, 56571-85-8; *erythro*-**2a**, 56571-86-9; *threo*-**2b**, 56571-87-0; *erythro*-**2b**, 56571-88-1; *threo*-**3a**, 56571-89-2; *erythro*-**3a**, 56571-90-5; *threo*-**3b**, 56571-91-6; *erythro*-**3b**, 56571-92-7; *threo*-**4a**, 56571-93-8; *erythro*-**4a**, 56571-94-9; *threo*-**4b**, 56571-95-0; *erythro*-**4b**, 56571-96-1; *trans*-1-phenyl-1-propene oxide, 23355-97-7; pyrrolidine, 123-75-1; piperidine, 110-89-4; 1-phenyl-2-(1-piperidino)-1-propene, 56571-97-2; 1-phenyl-1-(1-piperidino)-1-propene, 25076-80-6; 1-phenyl-1-(1-pyrrolidino)-1-propene, 31889-28-8; 2-(1-pyrrolidino)-1-phenyl-1-propanone, 19134-50-0.

References and Notes

(1) For previous paper in this series see M. K. Meilahn and M. E. Munk, *J. Org. Chem.*, **34**, 1440 (1969).
(2) M. K. Meilahn, C. N. Statham, J. L. McManaman, and M. E. Munk, Abstracts, First Rocky Mountain Regional Meeting of the American Chemical Society, Fort Collins, Colo., June 1972, p 39.
(3) Taken in large part from the senior research project of C. N. Statham, University of Northern Colorado, 1972.
(4) M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968).
(5) The term threo and erythro as used in this paper indicate *dl*-threo and *dl*-erythro.
(6) Footnote 7, ref 4, defines the term "rotamer" as used in this paper.
(7) These interactions have been previously discussed and Figures 1 and 2 in ref 4 show these interactions.
(8) M. E. Munk and Y. K. Kim, *J. Am. Chem. Soc.*, **86**, 2213 (1964).

Reactions of Amines. XVIII. The Oxidative Rearrangement of Amides with Lead Tetraacetate[1,2]

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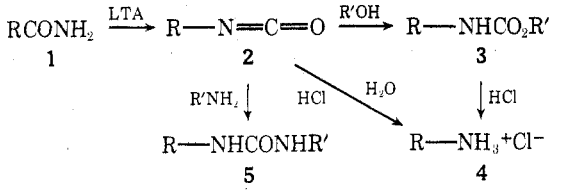
Fourteen primary amides of varying structures were converted to isocyanates by treatment with lead tetraacetate. Generally the isocyanates were not isolated but were converted to carbamates by using a reaction solvent such as benzyl or, preferably, *tert*-butyl alcohol. Alternatively, the reaction was run in dimethylformamide and the isocyanate was converted to the *unsym*-urea by treatment with *tert*-butylamine. The carbamates could be easily cleaved to the corresponding amines (as the hydrochlorides) by treatment with HCl in alcohol, ether, or acetic acid. The rearrangement was shown to proceed with retention of configuration about the migrating carbon atom.

Some years ago we reported[3] the oxidative rearrangement of *N*-aminooxindole to 3-cinnolinol using lead tetraacetate (LTA) as the oxidant. Because this rearrangement appeared to resemble in some aspects the classical Hofmann rearrangement of *N*-halo amides, we next showed[4] that the rearrangement of *N*-aminooxindole could be carried out via the *N*-chloro derivative. These observations led logically to the conclusion and subsequent demonstration[5] that a Hofmann-like oxidative rearrangement of amides (**1**) could be brought about with LTA. By a somewhat different



pattern of reasoning Beckwith[6-9] and his coworkers came independently to the same conclusion. They have described in some detail their investigations of this quite general and immensely practical version of the Hofmann rearrangement.[10]

Even earlier Tscherniac[11] had noted an apparent similarity in the behavior of iodosobenzene and the hypohalites and reported the first example known to us of a Hofmann-like rearrangement using a two-electron oxidant other than positive halogen. This communication describes some of our efforts to explore the scope and limitations of the rearrangement as a practical synthetic method.

As was reported in the preliminary communication,[5] the rearrangement can be run very rapidly in dimethylformamide solution in such as a way as to permit isolation of the intermediate isocyanate (**2**) or to proceed directly via acid hydrolysis to the amine hydrochloride (**4**). However, for many amides isolation of **2** is tedious, if not difficult,[6] and acid-catalyzed hydrolysis of **2** without isolation may result in lower yields of **4** than may be obtained by the less direct routes described here. Nevertheless, the use of dimethylformamide is very advantageous in those rearrangements involving a subsequent reaction with an amine to form a urea[5] (**5**) or a subsequent cyclization of the isocyanate