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ABOUT THE FACTORS WHICH GOVERN THE RING-OPENING OF α-LACTAMS WITH PRIMARY AMINES: II. THE RELATIVE BASICITY OF THE AMINE

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Abstract- The ring-opening reaction of four stable α-lactams, 1-(1-adamantyl)-3,3-di-methylaziridinone **(1a**), 3-(1-adamantyl)-1-triphenylmethyl-aziridinone **(1d)**, 3-*tert*-butyl-1-triphenylmethylaziridinone **(1e)**, and 1-(1-adamantyl)-3-*tert*-butylaziridinone **(1g)** with some substituted benzylamines and other selected primary amines is described. It emerges from the experimental results that the relative basicity of the amine is a decisive factor in determining regioselectivity in the ring-opening.

INTRODUCTION

In a previous paper in this series[1] the reactions of sixteen α-lactams with benzylamine have been reviewed. It was shown that two important factors which determine the regioselectivity in nucleophilic ring-opening of α-lactams are the relative stability of the α-lactam and the substituent on nitrogen. The structural prerequisites necessary for α-lactam stability have been established [2-5] and within the narrow limits of these, it was found[1] that:

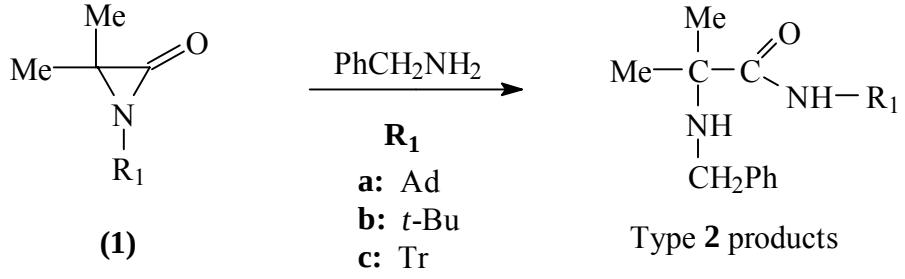
(a) 3,3-Dimethyl-substituted α-lactams **(1a-c)** consistently yield α-benzylamino-*N*-alkylamides (type **2** products) resulting from C_3-N bond cleavage, irrespective of the nature of the *N*-substituent, Scheme 1.

(b) *N*-Trityl-substituted α-lactams **(1d-f)**, irrespective of their relative stability, also give α-benzylamino-*N*-tritylamides (type **2** products), either as the sole or major product, again reflecting C_3-N bond cleavage, Scheme 2.

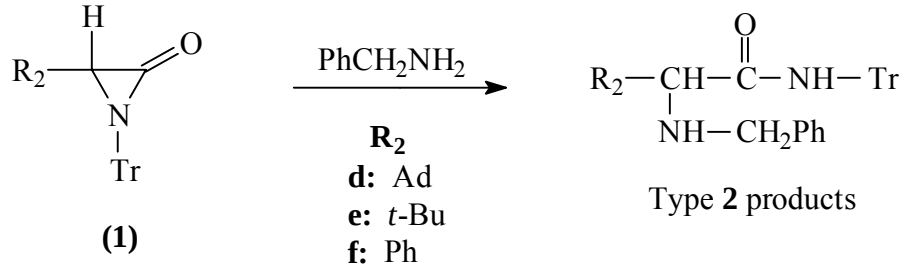
(c) All other stable α-lactams, which have been reacted with benzylamine, give *N*-benzylamides (type **3**

products), arising from C_2-N bond cleavage, Scheme 3.

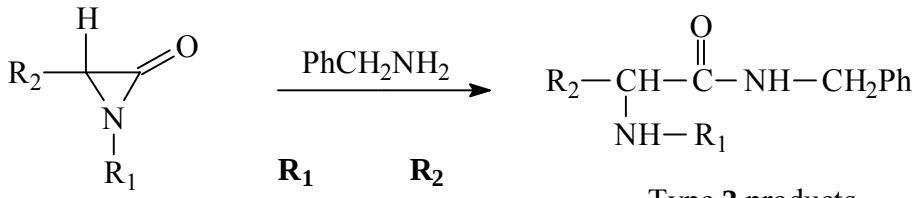
Scheme 1. The reaction of 3,3-dimethyl-substituted aziridinones **(1a-c)** with benzylamine.



Scheme 2. The reaction of *N*-tritylsubstituted α-lactams **(1d-f)** with benzylamine.



Scheme 3. The reaction of other stable α-lactams **(1g-o)** with benzylamine*.



	R_1	R_2
g:	Ad	*t*-Bu
h:	*t*-Bu	*t*-Bu
i:	Dmb	*t*-Bu
j:	Menth	*t*-Bu
k:	Ad	Dmb
l:	*t*-Bu	Dmb
m:	Dmb	Dmb
n:	Ad	Tr
o:	*t*-Bu	Tr

*Ad denotes 1-adamantyl, $C_{10}H_{15}$-
t-Bu denotes *tert*-butyl, C_4H_9-
Dmb denotes α,α-dimethylbenzyl, $C_6H_5C(CH_3)_2$-
Menth denotes *p*-menth-1,8-ylene, -$C_{10}H_{18}$-
Tr denotes triphenylmethyl (trityl), $C_{19}H_{15}$-

RESULTS AND DISCUSSION

1. Objectives

This project was undertaken to determine whether the relative basicity (pK_b) of the amine is a material factor governing regioselectivity in the nucleophilic ring-opening of α-lactams. Our specific objective was to elucidate whether a *product reversal* could be brought about by simply applying amines of sufficiently different basicity. In other words, whether α-lactams which give type **2** products with benzylamine can be induced to give type **3** products when treated with other primary amines of different pK_b values, and *vice versa*.

2. Selection of reactants

The aziridinones **(1a)**,[6] **(1d)**,[5] **(1e)**,[4] and **(1g)**[7] and primary amines chosen for this investigation are depicted in Schemes 1, 2, or 3 and Table 1, respectively.

Table 1. The amines used in this investigation, and their pK_b values.

Amine	**pK_b** (25 °C)
tert-Butylamine	3.32[8]
p-*N*,*N*-Dimethylaminobenzylamine	4.10
p-Methoxybenzylamine	4.55 (lit.,[9] 4.53)
Benzylamine	4.70 (lit.,[10] 4.64)
p-Trifluoromethylbenzylamine	5.35
p-Nitrobenzylamine	5.50[11]
Aniline	9.37[10]

Aziridinones **(1a** and **1e)** were chosen because they react readily with benzylamine and give exclusively type **2** products (C_3-N bond cleavage), **1g** because it gives only the type **3** product (C_2-N cleavage) with benzylamine, and **1d** as a representative that gave a mixture of both types of products when reacted with benzylamine.[1] The amines were selected with the aim to encompass as wide a range of pK_b-s as possible. The pK_b-s of benzylamine, *p*-trifluoromethylbenzylamine, *p*-methoxybenzylamine, and *p*-*N*,*N*-dimethyl-aminobenzylamine were determined experimentally by the general procedure of Albert and Serjeant.[12] The pK_b-s of *tert*-butylamine, *p*-methoxybenzylamine, benzylamine, *p*-nitrobenzylamine, and aniline were obtained from published sources (see Table 1).

3. Reactions of the aziridinones (**1a, d, e, g**) with various amines

To elucidate whether a product reversal can be brought about by simply applying amines of sufficiently

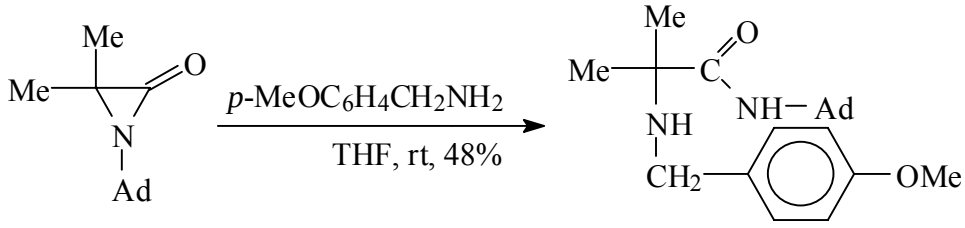
different basicity, two types of amines were used:

(a) Substituted benzylamines. The substituents included two electron-donating groups [-N(CH_3)$_2$ and -OCH_3] and two electron-withdrawing groups (-NO_2 and –CF_3).

(b) Aliphatic and aromatic primary amines unrelated to benzylamine.

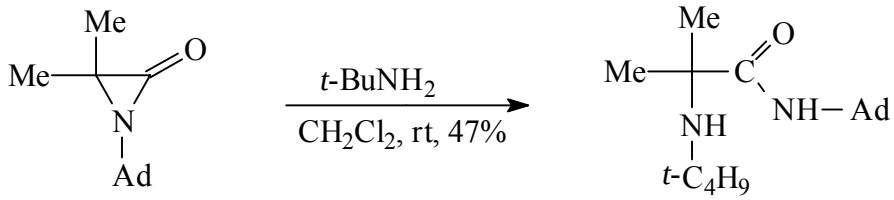
Not surprisingly, it was found that the basicity difference between benzylamine (pK_b= 4.64) and *p*-methoxybenzylamine (pK_b = 4.53) is not large enough to engender product reversal (type **3** product) with aziridinone (**1a)**, (see Schemes 1 and 4). Both amines reacted with **1a** to give type **2** products. Even reaction of **1a** with the more basic *tert*-butylamine (pK_b = 3.32) did not yield the type **3** reverse product, Scheme 5.

Scheme 4. The reaction of aziridinone **(1a)** with *p*-methoxybenzylamine.



(1a) **(2g)**

Scheme 5. The reaction of aziridinone **1a** with *tert*-butylamine.



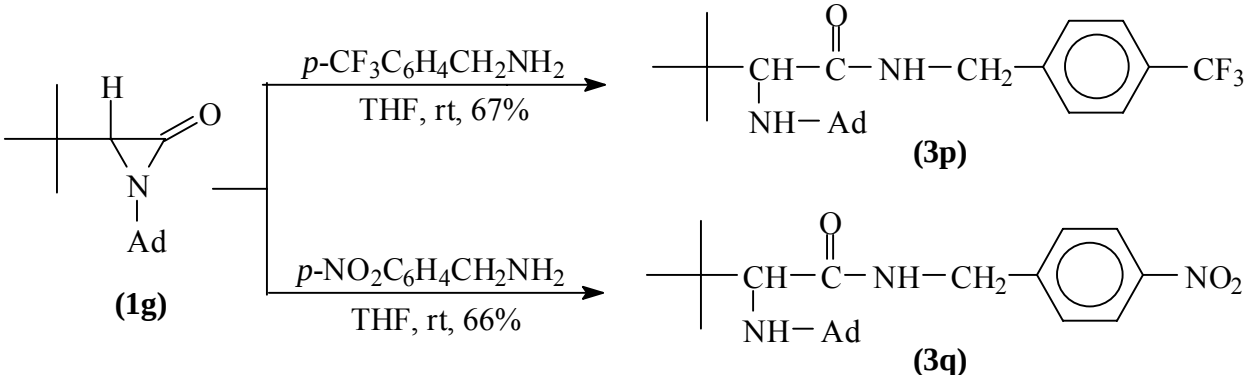
(1a) **(2h)**

Similarly, the basicity difference between benzylamine on the one hand, and *p*-trifluoromethylbenzylamine (pK_b = 5.35) and *p*-nitrobenzylamine (pK_b = 5.50) on the other, is not sufficient to cause product reversal (type **2** products) with aziridinone **(1g)**, Scheme 6. Both of these amines, like benzylamine, give type **3** products resulting from C_2-N bond cleavage.

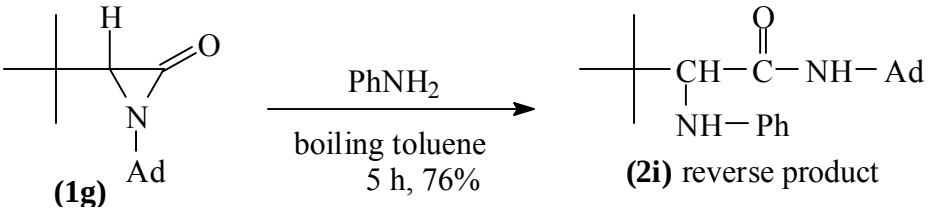
However, when α-lactam **(1g)** was reacted with the much weaker base, aniline (pK_b = 9.37), clean product reversal (type **2** product) was observed, with the α-anilino-*N*-(1-adamantyl)amide **(2i)** being isolated in 76% yield, Scheme 7. This finding tallies with the recent report of Talaty and Yusoff[13] that 1,3-di-*tert*-

butylaziridinone **(1h)**[14] gave the α-anilino-*N*-*tert*-butylamide with aniline, in 95% yield.

Scheme 6. The reaction of aziridinone **(1g)** with *p*-trifluoromethylbenzylamine and *p*-nitrobenzylamine.



Scheme 7. The reaction of aziridinone **(1g)** with aniline.



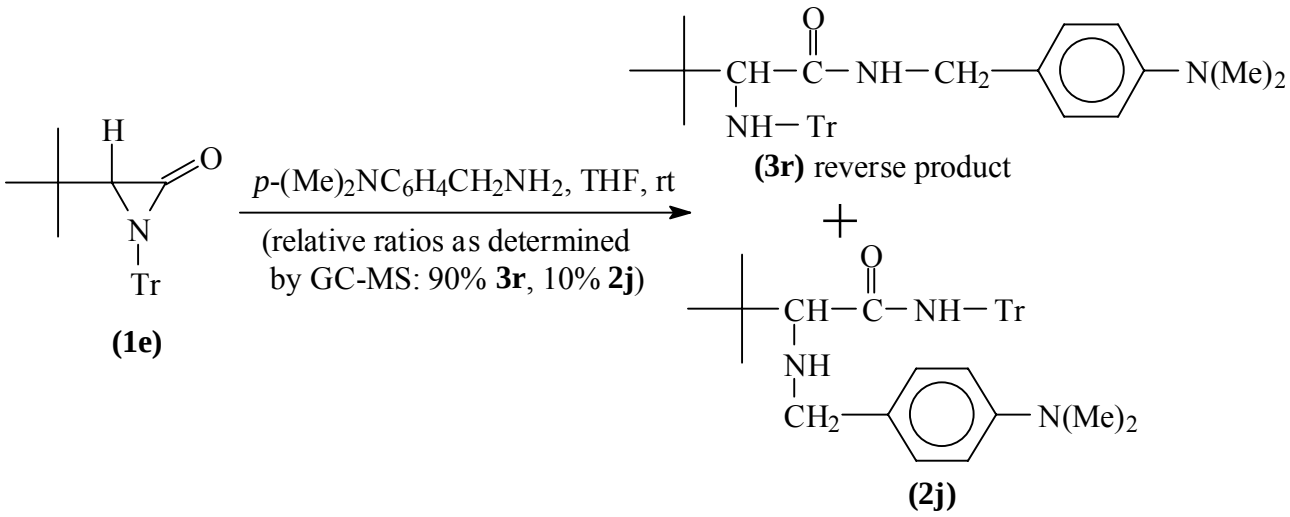
As mentioned earlier, α-lactam **(1e)** with benzylamine yields the α-benzylamino-*N*-tritylamide **(2e)** as sole product, in 92% isolated yield.[4] Substitution of the benzylamine in *para* position with a strong [-$N(CH_3)_2$] or moderately strong (-OCH_3) electron-donor group engenders overwhelming product reversal (90:10), Schemes 8 and 9, respectively.

The only α-lactam, which gave a mixture of both adducts when reacted with benzylamine, was **1d** (64% type **2**, 36% type **3**).[1] It was therefore of great interest to us to find out whether and under what conditions a partial or complete product reversal can be brought about.

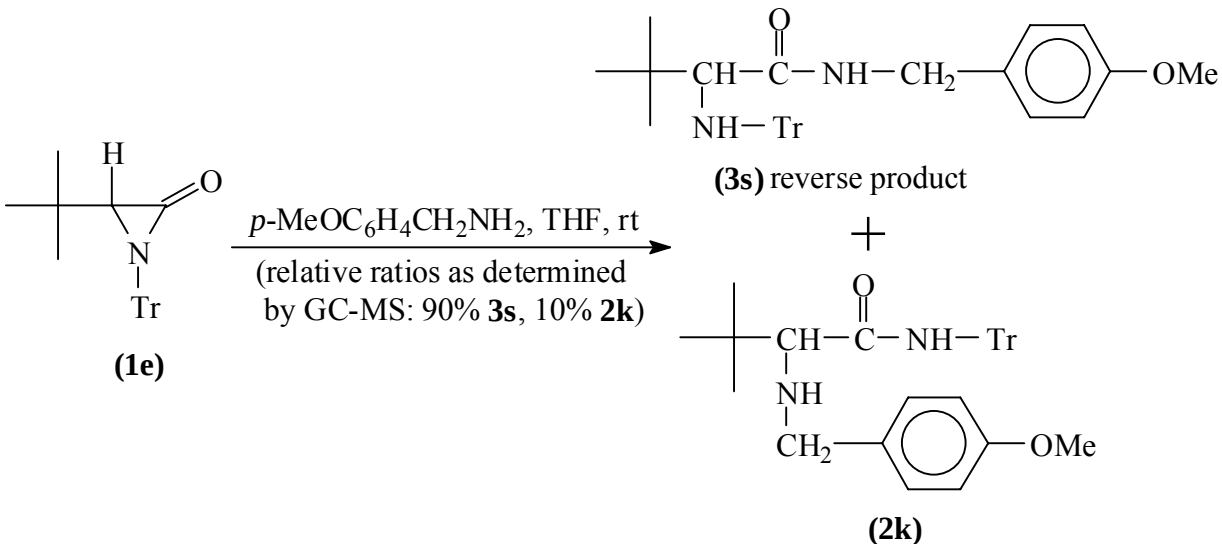
As anticipated, reaction with the less basic *p*-nitrobenzylamine ($pK_b = 5.5$) led to a product mixture in which the type **2** regular adduct predominates, Scheme 10, while reaction with the more basic *p*-methoxybenzylamine ($pK_b = 4.55$) gave a mixture in which the type **3** reverse adduct was the major component, Scheme 11. In both cases, the NMR spectral signals of the benzylic protons were used to determine the relative product ratios.

Only with *tert*-butylamine ($pK_b = 3.32$) did the reaction give a single product, but no product reversal, Scheme 12.

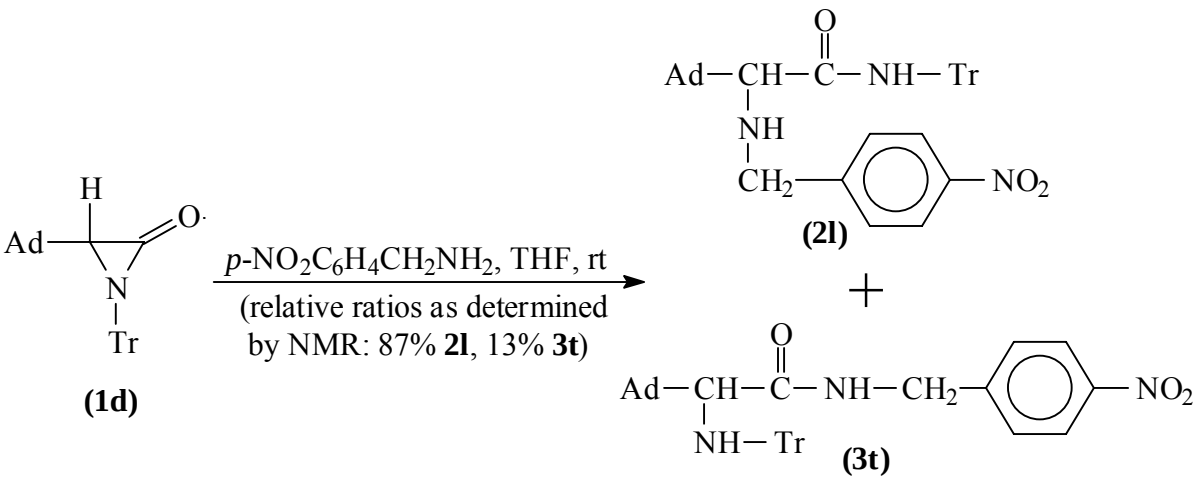
Scheme 8. Reaction of aziridinone **(1e)** with *p*-*N*,*N*-dimethylaminobenzylamine.



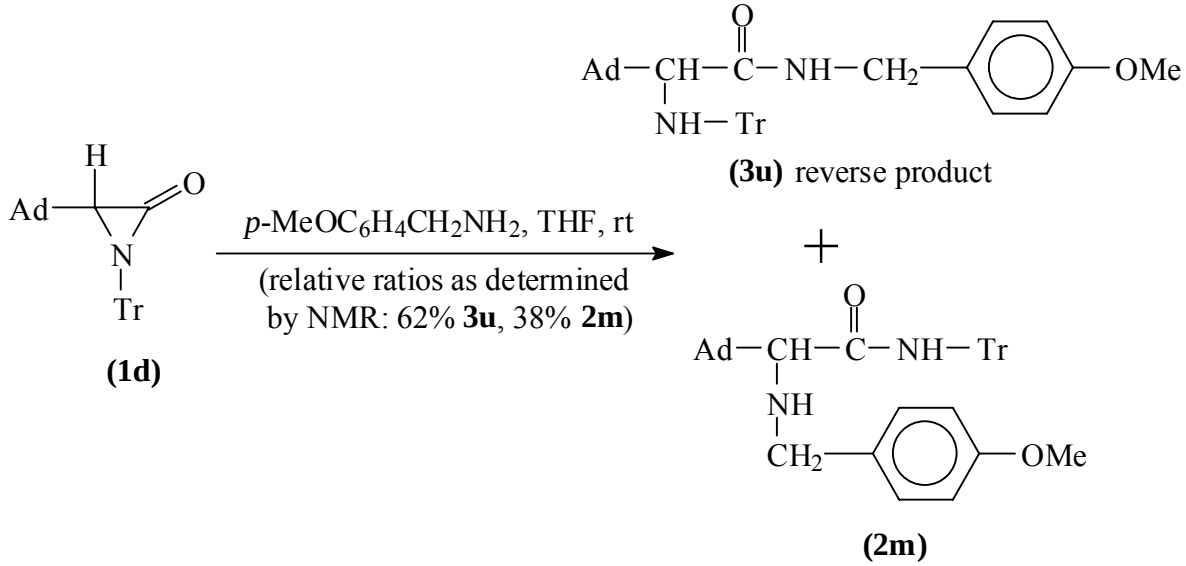
Scheme 9. Reaction of aziridinone **(1e)** with *p*-methoxybenzylamine.



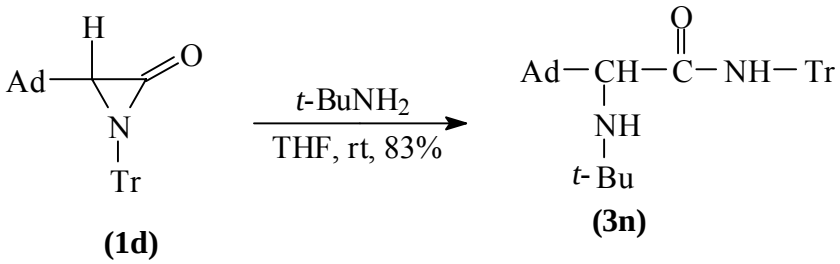
Scheme 10. Reaction of aziridinone **(1d)** with *p*-nitrobenzylamine.



Scheme 11. Reaction of aziridinone **(1d)** with *p*-methoxybenzylamine.



Scheme 12. Reaction of aziridinone **(1d)** with *tert*-butylamine.



For over 30 years, it has been known[2] that in the nucleophilic ring-opening of α-lactams both C_2-N and C_3-N bond cleavage can occur. Yet, the factors affecting regioselectivity have not been fully elucidated. Nucleophilic substitution is known[15] to take place more readily at an acyl carbon than at a saturated carbon, so C_2-N bond cleavage should be more prevalent. However, X-Ray crystallographic measurements performed on 1,3-di-(1-adamantyl)-2-aziridinone,[16] affirms that the C_2-N bond is significantly shorter than the C_3-N bond, having partial double bond character due to amide-resonance. Hence, the C_2-N bond is a stronger bond than the C_3-N bond, which explains why some C_3-N bond cleavage also occurs.

CONCLUSION

The results presented herein indicate that the relative basicity of the amine is an important additional factor influencing regioselectivity in the ring-opening of α-lactams. Weakly basic primary amines tend to lead to C_3-N bond cleavage and the formation of type **2** adducts, while reaction with more basic primary amines

leads to adducts of type **3**, resulting from C_2-N bond cleavage.

EXPERIMENTAL

Melting points are uncorrected and were measured on a Thomas-Hoover capillary melting point apparatus. Thin layer chromatography (TLC) was performed with Analtech Silica gel glass backed plates (250 microns) and recorded in terms of R_f values. Flash chromatographic separations were performed under N_2 stream and using silica gel (JT Baker, 40 μm) as the stationary phase. IR spectra were recorded using a Perkin Elmer Fourier Transform (FTIR) Spectrum 1000 Spectrophotometer. NMR Spectra (^{1}H and ^{13}C) were recorded on a 400 MHz Bruker Spectrometer. NMR spectra are presented using TMS as the internal standard and peak positions are given in ppm as δ values. Elemental analyses were performed by Atlantic Microlab, Inc (Norcross, Georgia). GC-MS studies were performed on a Hewlett Packard G1800A GCD System.

In the determination of the pK_b-s a Fisher Scientific accumet pH meter 10 was used. Biphthalate, phosphate, and borate buffer solutions were purchased from JT Baker (Phillipsburg, NJ) as was 0.01 N HCl solution. The reagents *tert*-butylamine, aniline, *p*-*N*,*N*-dimethylbenzylamine dihydrochloride, and *p*-nitrobenzylamine hydrochloride were purchased from Aldrich (Milwaukee, WI). *p*-Trifluoromethyl-benzylamine was purchased from Lancaster (Windham, NH). Benzylamine was purchased from Sigma (St. Louis, MO). *p*-Methoxybenzylamine was purchased from Alfa Aesar (Ward Hill, MA).

Reaction of *N*-(1-adamantyl)-3,3-dimethylaziridinone (1a)[6] with *p*-methoxybenzylamine

α-Lactam **(1a)** was generated *in situ* and reacted with *p*-methoxybenzylamine by the following procedure. 1.00 g (0.0033 mol) of *N*-(1-adamantyl)-2-bromo-2-methylpropanamide was dissolved into 33 mL of anhydrous benzene. 0.182 g (0.00069 mol) of 18-crown-6 ether and 1.03 g (0.0184 mol) of finely powdered KOH were added and stirred for 1.5 h at rt (an IR spectrum showed an 1846:1676 cm^{-1} band ratio of 80% to 20%). The reaction mixture was centrifuged and the supernatant was dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give a white solid. This was dissolved into 5 mL of THF; 0.905 g (0.0066 mol) of freshly distilled *p*-methoxybenzylamine was added at rt and the solution

was stirred for 12 h. The solvent was evaporated under reduced pressure to give 1.83 g of an oil which was dissolved into 25 mL of ethyl acetate and washed with 3 x 15 mL of distilled water, dried with Na_2SO_4, and the solvent was evaporated under reduced pressure to give 1.23 g of a slightly colored oil which crystallized upon standing. This was chromatographed (60% *n*-hexane: 40% ethyl acetate) to give 0.57 g (48% overall yield) of pure *N*-(1-adamantyl)-2-(*p*-methoxy-benzylamino)-2-methylpropanamide **(2g)**, mp 105-109 °C with sintering from 95 °C. TLC (60 % *n*-hexane: 40 % ethyl acetate): $R_f = 0.42$. IR (CCl_4): 3354 (N-H of amine), 2909 and 2851 (aliphatic C-H), 1679 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.34 (s, methyl protons, 6H), 1.68 (s, methylene protons of adamantane moiety farther away from N, 6H), 2.00 (s, methylene protons of adamantane moiety closer to N, 6H), 2.07 (s, methine protons of adamantane moiety, 3H), 3.59 (s, benzylic protons, 2H), 3.80 (s, methoxy protons, 3H), 6.88 (d, J = 8.4 Hz, *meta* protons on benzene ring, 2H), 7.23 (d, J = 8.4 Hz, *ortho* protons on benzene ring, 2H), 7.35 (s, N-H proton of amide, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H). The amine N-H is not clearly observable. ^{13}C-NMR (interpreted with the aid of the APT): δ = 26.22 (methyl carbons), 29.87 (methine carbons of the adamantane moiety), 36.85 (methylene carbons of the adamantane moiety farther away from N), 42.01 (methylene carbons of the adamantane moiety closer to N), 47.79 (benzylic carbon), 51.16 (C_1 carbon of the adamantane moiety), 55.69 (methoxy carbon), 59.51 (carbon adjacent to carbonyl carbon of amide), 114.42 (carbons in *meta* position of phenyl ring), 129.48 (carbons in *ortho* position of phenyl ring), 132.90 (C_1 carbon of phenyl ring), 159.21 (carbon in *para* position attached to the methoxy group on the phenyl ring), 175.89 (amide carbonyl). GC/MS: m/z 341 $(M - CH_3)^+$; 325 $(M - OCH_3)^+$; 298 $(M - C_4H_{10})^+$; 178 (*base peak*, $[(CH_3)_2C{=}NH\text{-}CH_2C_6H_4OCH_3])^+$; 136 $(CH_3OC_6H_4CH_2NH)^+$; 135 $(C_{10}H_{15})^+$; 121 $(CH_3OC_6H_4CH_2)^+$. Anal. Calcd for $C_{22}H_{32}N_2O_2$: C 74.12, H 9.05, N 7.86. Found: C 73.92, H 9.27, N 7.85.

Reaction of *N*-(1-adamantyl)-3,3-dimethylaziridinone (1a)[6] with *tert*-butylamine

α-Lactam **(1a)** was generated *in situ* and reacted with *tert*-butylamine by the following procedure. 1.00 g (0.0033 mol) of *N*-(1-adamantyl)-2-bromo-2-methylpropanamide was dissolved into 33 mL of anhydrous benzene. 0.182 g (0.00069 mol) of 18-crown-6 ether and 1.03 g (0.0184 mol) of finely powdered KOH were added and stirred for 1.5 h at rt (An IR spectrum showed an 1846:1676 cm^{-1} band ratio of 83% to

17%). The reaction mixture was centrifuged and the supernatant was dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give a white solid. This was dissolved into 4 mL of *tert*-butylamine and 4 mL of methylene chloride and allowed to stir at rt for 3.5 h. Methylene chloride and excess *tert*-butylamine were evaporated under reduced pressure to give 1.04 g of a clear oil which crystallized upon standing. This was chromatographed [80% *n*-hexane: 20% ethyl acetate (with 1% Et_3N)] to give 0.45 g (47% overall yield) of pure *N*-(1-adamantyl)-2-*tert*-butylamino-2-methylpropanamide **(2h)**, mp 112-114 °C. TLC: (70% *n*-hexane: 30% ethyl acetate) R_f= 0.39. IR (CCl_4): 3453 (N-H of amide), 3349 (N-H of amine), 2908 and 2851 (aliphatic C-H), 1677 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.17 (s, methyl protons of *tert*-butyl moiety, 9H), 1.33 (s, methyl protons, 6H), 1.71 (s, methylene protons of adamantane moiety farther away from N, 6H), 2.00 (s, methylene protons of adamantane moiety closer to N, 6H), 2.07 (s, methine protons of adamantane moiety, 3H), 7.41 (s, N-H of amide, exchanges for deuterium in $CDCl_3$/CF_3COOD, 1H). The amine N-H is not clearly observable. ^{13}C-NMR (interpreted with the aid of the APT): δ = 28.79 (methine carbons of the adamantane moiety), 29.48 (methyl carbons of *tert*-butyl moiety), 31.89 (methyl carbons), 36.52 (methylene carbons of the adamantane moiety farther away from N), 41.48 (methylene carbons of the adamantane moiety closer to N), 50.60 (quaternary carbon of *tert*-butyl moiety), 51.79 (C_1 carbon of the adamantane moiety), 58.44 (carbon adjacent to carbonyl carbon of amide), 177.77 (amide carbonyl). GC/MS: m/z 293 $(M + H)^+$; 277 $(M - CH_3)^+$; 178 $(AdNH{=}C{=}O)^+$; 150 $(AdNH)^+$; 135 $(C_{10}H_{15})^+$; 114 $[(CH_3)_2C{=}NHC(CH_3)_3]^+$; 93 $(C_7H_9)^+$; 79 $(C_6H_7)^+$; 58 (*base peak*, $[(CH_3)_2C{=}NH_2)]^+$; 41 $(C_3H_5)^+$.

Anal. Calcd for $C_{18}H_{32}N_2O$: C 73.92, H 11.03, N 9.58. Found: C 73.89, H 11.14, N 9.63.

Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (1g)[7] with *p*-trifluoromethylbenzylamine

0.14 g (0.00057 mol) of **1g** and 0.20 g (0.00114 mol) of freshly distilled *p*-trifluoromethylbenzylamine were dissolved into 2 mL of THF and stirred at rt for 30 h. THF and excess *p*-trifluoromethylbenzylamine were removed under reduced pressure to give 0.35 g of a light green solid. This was chromatographed (80% *n*-hexane: 20% ethyl acetate) to give 0.16 g (67%) of pure *N*-(*p*-trifluoromethylbenzyl)-2-(1-adamantylamino)-3,3-dimethylbutanamide **(3p)**, mp 133-137°C with sintering from 122°C. TLC: (80% *n*-

hexane: 20% ethyl acetate) R_f = 0.39. IR: 3447 (N-H of amide), 3352 (N-H of amine), 2909 and 2851 (aliphatic C-H), and 1675 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.99 (s, methyl protons of *tert*-butyl moiety, 9H), 1.39-1.63 (m, methylene protons of the adamantane moiety, 12H, and N-H proton of amine, 1H, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H), 2.01 (s, methine protons of the adamantane moiety, 3H), 3.10 (s, methine proton adjacent to amide carbonyl, 1H), 4.42 (dd, *J* = 24 Hz, *J* = 6.5 Hz, benzylic proton of the benzylamide group, chemically non-equivalent to the other benzylic proton, 1H), 4.54 (dd, *J* = 24 Hz, *J* = 6.5 Hz, the other benzylic proton, 1H), 7.46 (d, *J* = 7 Hz, *ortho* protons on benzene ring, 2H), 7.60 (d, *J* = 7 Hz, *meta* protons on benzene ring, 2H), 7.80 (t, *J* = 6.5 Hz, N-H proton of amide, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H). ^{13}C-NMR (interpreted with the aid of the APT): δ = 27.95 (methyl carbons of *tert*-butyl moiety), 29.97 (methine carbons of the adamantane moiety), 34.04 (quaternary carbon of *tert*-butyl group), 36.80 (methylene carbons of the adamantane moiety farther away from N), 43.05 (benzylic carbon of benzylamido moiety), 43.21 (methylene carbons of the adamantane moiety closer to N), 51.56 (C_1 carbon of the adamantane moiety), 64.13 (methine carbon adjacent to carbonyl carbon of amide), 123.18 (carbon in *para* position attached to the trifluoromethyl group on the phenyl ring), 125.85 (carbons in *meta* position of the phenyl ring), 128.67 (carbons in *ortho* position of the phenyl ring), 129.90 (q, the CF_3 carbon), 143.37 (C_1 carbon of the phenyl ring), 175.66 (amide carbonyl). GC/MS: m/z 407 $(M - CH_3)^+$; 365 $(M - C_4H_9)^+$; 220 $[(CH_3)_3CH{=}NHAd]^+$; 159 $(CF_3C_6H_4CH_2)^+$; 135 (*base peak*, $(C_{10}H_{15})^+$); 93 $(135 - C_3H_6)^+$; 79 $(C_6H_7)^+$. Anal. Calcd for $C_{24}H_{33}N_2OF_3$: C 68.22, H 7.87, N 6.63, F 13.49. Found: C 68.02, H 7.77, N 6.51, F 13.34.

Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (1g)[7] with *p*-nitrobenzylamine

0.215 g (0.00114 mol) of *p*-nitrobenzylamine hydrochloride and 0.121 g (0.0114 mol) of Na_2CO_3 were dissolved into 5 mL of water and stirred for 5 min. 5 mL of methylene chloride was added to this and it was all poured into a seperatory funnel and the organic layer was collected. Extraction was performed with an additional 5 mL of methylene chloride. The organic layers were combined, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved into 2 mL of THF and 0.14 g (0.00057 mol) of **1g** was added and the reaction mixture was stirred at rt for 162 h. THF was evaporated to yield

0.30 g of a light yellow solid. This was chromatographed (70% *n*-hexane: 30% ethyl acetate) to give 0.15 g (66%) of pure *N*-(*p*-nitrobenzyl)-2-(1-adamantylamino)-3,3-dimethylbutanamide **(3q)**, mp 163-165°C. TLC: (70% *n*-hexane: 30% ethyl acetate) R_f = 0.44. IR (NaCl): 3313 (N-H of amine), 2904 and 2848 (aliphatic C-H), 1647 (amide C=O), 1521 (amide II band) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ = 0.85 (s, methyl protons of *tert*-butyl moiety, 9H), 1.41-1.59 (m, methylene protons of the adamantane moiety, 12H), 1.68 (s, N-H proton of amine, exchanges for deuterium in $CDCl_3$/CF_3COOD, 1H), 1.94 (s, methine protons of the adamantane moiety, 3H), 2.91 (s, methine proton adjacent to amide carbonyl, 1H), 4.35 (dd, *J* = 23 Hz, *J* = 6 Hz, benzylic proton on the benzylamide group, chemically non-equivalent to the other benzylic proton, 1H), 4.44 (dd, *J* = 23 Hz, J = 6 Hz, the other benzylic proton, 1H), 7.56 (d, *J* = 9 Hz, *ortho* protons on benzene ring, 2H), 8.20 (d, *J* = 9 Hz, *meta* protons on benzene ring, 2H), 8.49 (t, *J* = 6 Hz, N-H proton of amide, exchanges for deuterium in $CDCl_3$/CF_3COOD, 1H). ^{13}C-NMR (interpreted with the aid of the APT): δ = 27.01 (methyl carbons of *tert*-butyl moiety), 29.16 (methine carbons of the adamantane moiety), 33.97 (quaternary carbon of *tert*-butyl moiety), 36.41 (methylene carbons of the adamantane moiety farther away from N), 42.02 (methylene carbons of the adamantane moiety closer to N), 42.97 (benzylic carbon of benzylamido moiety), 50.06 (C_1 carbon of the adamantane moiety), 61.31 (methine carbon adjacent to carbonyl carbon of amide), 123.50 (carbons in *ortho* position of the phenyl ring), 129.01 (carbons in *meta* position of the phenyl ring), 146.60 (C_1 carbon of the phenyl ring), 147.80 (carbon in *para* position attached to the nitro group on the phenyl ring), 175.53 (amide carbonyl). GC/MS: m/z 398 $(M - H)^+$; 384 $(M - CH_3)^+$; 342 $(M – C_4H_9)^+$; 220 (*base peak*, $[(CH_3)_3CH=NHAd]^+$); 135 $(C_{10}H_{15})^+$; 93 $(C_7H_9)^+$; 79 $(C_6H_7)^+$. Anal. Calcd for $C_{23}H_{33}N_3O_3$: C 69.14, H 8.33, N 10.52. Found: C 69.11, H 8.35, N 10.43.

Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (1g)[7] with aniline

0.37 g (0.0015 mol) of **1g** is dissolved into 15 mL of toluene. To this is added 0.696 g (0.00748 mol, 5 eq) of freshly distilled aniline and the solution is refluxed for 5 h. Toluene and excess aniline were removed under reduced pressure to give 0.42 g of a white solid. This was chromatographed (90% *n*-hexane: 10% ethyl acetate) to give 0.39 g (76%) of pure *N*-(1-adamantyl)-3,3-dimethyl-2-phenylaminobutanamide **(2i)**,

mp 152-154°C. TLC: (85% *n*-hexane: 15% ethyl acetate) R_f = 0.39. IR (CCl_4): 3433 (N-H of amide), 3383 (N-H of amine), 3053 (aromatic C-H), 2909 and 2851 (aliphatic C-H), and 1675 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.09 (s, methyl protons of *tert*-butyl moiety, 9H), 1.64 (s, methylene protons of adamantane moiety farther away from N, 6H), 1.94 (s, methylene protons of adamantane moiety closer to N, 6H), 2.03 (s, methine protons of the adamantane moiety, 3H), 3.20 (s, methine proton adjacent to amide carbonyl, 1H), 4.02 (s, amine proton, exchanges for deuterium in $CDCl_3$/CF_3COOD, 1H), 6.21 (s, N-H of amide, exchanges for deuterium in $CDCl_3$/CF_3COOD, 1H), 6.64 (d, *J* = 8 Hz, *ortho* protons on benzene ring, 2H), 6.78 (t, *J* = 7 Hz, *para* proton on benzene ring, 1H), 7.19 (t, *J* = 7.8 Hz, *meta* protons on benzene ring, 2H). ^{13}C-NMR (interpreted with the aid of the APT) δ = 27.37 (methine carbons of the adamantane moiety), 29.40 (methyl carbons of *tert*-butyl moiety), 33.96 (quaternary carbon of *tert*-butyl moiety), 36.36 (methylene carbons of the adamantane moiety farther away from N), 41.40 (methylene carbons of the adamantane moiety closer to N), 51.47 (C_1 carbon of the adamantane moiety), 69.27 (methine carbon adjacent to carbonyl carbon of amide), 113.94 (carbons in *ortho* position of the phenyl ring), 118.77 (carbon in *para* position of the phenyl ring), 129.24 (carbons in *meta* position of the phenyl ring), 147.60 (C_1 carbon of the phenyl ring), 170.65 (amide carbonyl). GC/MS: m/z 340 (M^+, $C_{22}H_{32}N_2O$); 325 (M – CH_3)$^+$; 283 (M – C_4H_9)$^+$; 226 (M – 114); 190 [$(CH_3)_3CCH(NHC_6H_5)C{=}O$]$^+$; 162 (*base peak*, $(CH_3)_3CCH{=}NHC_6H_5$)$^+$, 135 ($C_{10}H_{15}$)$^+$; 94 ((C_6H_5)NH_3)$^+$; 77 (C_6H_5)$^+$; 41 (C_3H_5)$^+$. Anal. Calcd for $C_{22}H_{32}N_2O{\cdot}1/8H_2O$: C 77.09, H 9.48, N 8.17, Found: C 77.02, H 9.48, N 8.23.

Reaction of 3-*tert*-butyl-1-triphenylmethylaziridinone (1e)[4] with *p*-*N*,*N*-dimethylaminobenzylamine

0.669 g (0.003 mol) of *p*-*N*,*N*-dimethylbenzylamine dihydrochloride and 1.5 g (0.014 mol) of Na_2CO_3 are dissolved into 20 mL of water and stirred for 5 min. 20 mL of methylene chloride was added to this and it was all poured into a seperatory funnel and the organic layer was collected. Extraction was performed with an additional 20 mL of methylene chloride. The organic layers were combined, dried with Na_2SO_4, and evaporated under reduced pressure to give 0.44 g of an oily residue. The residue was dissolved into 5 mL of THF and 0.355 g (0.001 mol) of **1e** was added and the reaction mixture was stirred at rt for 16 h. THF was evaporated to yield 0.77 g of an oil which was determined to consist of a relative ratio of 90% *N*-

benzylamide **(3r)** (MS: m/z 328 $[(CH_3)_3CCH{=}NHC(C_6H_5)_3]^+$) to 10% *N*-tritylamide **(2j)** (MS: m/z 219 $[(CH_3)_3CCH{=}NHCH_2C_6H_4N(CH_3)_2]^+$) by GC-MS, among other impurities. This was chromatographed (90% pentane: 10% acetone) to give 0.33 g (66%) of pure *N*-(*p*-*N*,*N*-dimethylbenzyl)-3,3-dimethylamino-2-triphenylmethylaminobutanamide **(3r)**, mp 73-75°C with sintering from 60°C. TLC: (80% *n*-hexane: 20% methylene chloride) $R_f = 0.32$. IR: 3449 (N-H of amide), 3060 (aromatic C-H), 2956 (aliphatic C-H), 1673 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) $\delta = 0.95$ (s, methyl protons of *tert*-butyl moiety, 9H), 1.68 (s, amine proton, exchangeable in $CDCl_3/D_2O$, 1H), 2.83 (d, $J = 7.1$ Hz, methine proton adjacent to amide carbonyl, 1H), 2.91 (s, methyl protons attached to nitrogen, 6H), 3.71 (dd, $J = 9$ Hz, $J = 5$ Hz, benzylic proton, 1H), 3.75 (dd, $J = 9$ Hz, $J = 5$ Hz, benzylic proton, 1H), 5.29 (t, $J = 5$ Hz, amide proton, exchangeable in $CDCl_3/CF_3COOD$, 1H), 6.62 + 6.64 (d, $J = 8.8$ Hz, *meta* protons of benzylamido moiety, 2H), 6.92 + 6.94 (d, $J = 8.8$ Hz, *ortho* protons of benzylamido moiety, 2H), 7.19 (t, $J = 7.7$ Hz, *para* protons of triphenylmethyl moiety, 3H), 7.25 (t, $J = 7.7$ Hz, *meta* protons of triphenylmethyl moiety, 6H), 7.45 (d, J=7.1 Hz, *ortho* protons of triphenylmethyl moiety, 6H). ^{13}C-NMR (interpreted with the aid of the APT) $\delta = 28.09$ (methyl carbons of *tert*-butyl moiety), 35.73 (quaternary carbon of *tert*-butyl moiety), 41.04 (methyl carbons attached to N), 43.70 (benzylic carbon), 65.87 (methine carbon adjacent to carbonyl carbon of amide), 71.48 (quaternary carbon of triphenylmethyl moiety), 113.02 (*meta* carbons of benzylamido moiety), 126.08 (C_1 carbon of benzylamido moiety), 126.95 (*para* carbons of triphenyl-methylamino moiety), 127.98 (*meta* carbons of triphenylmethyl moiety), 129.51 (*ortho* carbons of benzylamido moiety), 130.00 (*ortho* carbons of triphenylmethyl moiety), 146.41 (C_1 carbons of triphenylmethyl moiety), 150.38 (*para* carbon attached to the dimethylamino group of the benzylamido moiety), 173.11 (amide carbonyl). Anal. Calcd for $C_{34}H_{39}N_3O{\cdot}1/4H_2O$: C 80.04, H 7.80, N 8.24. Found: C 80.14, H 7.96, N 8.07.

Reaction of 3-*tert*-butyl-1-triphenylmethylaziridinone (1e)[4] with *p*-methoxybenzylamine

0.35 g of **1e** is dissolved into 4 mL of THF and 0.274 g (0.002 mol) of freshly distilled *p*-methoxy-benzylamine is added. The reaction mixture was stirred for 16.5 h and THF was removed under reduced pressure to give 0.60 g of an oil which was determined to consist of a relative ratio of 90% *N*-benzylamide

(3s) (MS: m/z 328 $[(CH_3)_3CCH{=}NHC(C_6H_5)_3]^+$) to 10% *N*-tritylamide **(2k)** (MS: m/z 206 $[(CH_3)_3CCH{=}NHCH_2C_6H_4OCH_3]^+$) by GC-MS, among other impurities. This was chromatographed (90% pentane: 10% acetone) to give 0.22 g (45%) of pure *N*-(*p*-methoxybenzyl)-3,3-dimethyl-2-triphenyl-methylaminobutanamide **(3s)**, mp 68-72°C with sintering at 60°C. TLC: (80% pentane: 20% acetone) R_f = 0.60. IR (CCl_4): 3450 (N-H of amide), 3394 (N-H of amine), 3061 and 3034 (aromatic C-H), 2956 (aliphatic C-H), and 1675 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 0.96 (s, methyl protons of *tert*-butyl moiety, 9H), 2.85 (d, *J* = 6.8 Hz, benzylic proton of the benzylamide group, non-equivalent to the other benzylic proton, 1H), 2.93 (d, *J* = 6.8 Hz, the other benzylic proton, 1H), 3.74 (s, methine proton adjacent to amide carbonyl, 1H), 3.75 (d, *J* = 1.4 Hz, amine proton, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H), 3.77 (s, methoxy protons, 3H), 5.41 (t, *J* = 5 Hz, N-H of amide, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H), 6.79 (d, *J* = 8.7 Hz, *meta* protons of benzylamido moiety, 2H), 6.97 (d, *J* = 8.7 Hz, *ortho* protons of benzylamido moiety, 2H), 7.19 - 7.44 (m, protons of triphenylmethyl moiety, 15H). ^{13}C-NMR (interpreted with the aid of the APT) δ = 27.69 (methyl carbons of *tert*-butyl moiety), 35.31 (quaternary carbon of *tert*-butyl moiety), 43.09 (benzylic carbon), 55.24 (methoxy carbon), 65.52 (carbon adjacent to carbonyl carbon of amide), 71.05 (quaternary carbon of triphenylmethyl moiety), 113.92 (*meta* carbons of benzylamido moiety), 126.57 (*para* carbons of triphenylmethyl moiety), 127.58 (*meta* carbons of triphenylmethyl moiety), 129.31 (*ortho* carbons of benzylamido moiety), 129.57 (*ortho* carbons of triphenylmethyl moiety), 130.21 (C_1 carbon of benzylamido moiety), 145.93 (C_1 carbons of triphenylmethyl moiety), 158.85 (*para* carbon attached to the methoxy group on the benzylamido moiety), 172.79 (amide carbonyl). GC/MS: m/z 415 $(M - C_6H_5)^+$; 328 $[(CH_3)_3CCH{=}NHC(C_6H_5)_3]^+$; 243 $[(C_6H_5)_3C]^+$; 165 $(C_{13}H_9)^+$, 136 $(CH_3OC_6H_4CH_2NH)^+$; 121 $(CH_3OC_6H_4CH_2)^+$. Anal. Calcd for $C_{33}H_{36}N_2O_2$: C 80.45, H 7.37, N 5.69. Found: C 80.19, H 7.49, N 5.56.

Reaction of 3-(1-adamantyl)-1-triphenylmethylaziridinone (1d)[5] with *p*-nitrobenzylamine

0.131 g (0.000692 mol) of *p*-nitrobenzylamine hydrochloride and 0.147 g (0.00138 mol) of Na_2CO_3 are dissolved into 5 mL of water and stirred for 5 min. 5 mL of methylene chloride was added to this and it was all poured into a seperatory funnel and the organic layer was collected. Extraction was performed

with an additional 2 x 5 mL of methylene chloride. The organic layers were combined, dried with Na_2SO_4, and evaporated under reduced pressure to give an oily residue, which crystallizes upon standing. The residue was dissolved into 4 mL of THF and 0.15 g (0.000346 mol) of **1d** was added and the reaction mixture was stirred at rt for 9 days. THF was evaporated and the residue was dissolved into 25 mL of methylene chloride and washed with 3 x 15 mL of H_2O. The organic layer was dried with Na_2SO_4, and rotary evaporated to yield 0.22 g of an oil. This was chromatographed (75% *n*-hexane: 25% ethyl acetate) to give 0.14 g (69%) of a mixture of **2l** (87%) and **3t** (13%). The relative ratios were determined by comparing the integrals associated with the benzylic protons.

2l (3.69 δ, dd, J = 14 Hz, J = 14 Hz, benzylic protons; 52.94 δ, benzylic carbon)

3t (4.13 δ, dd, J = 7 Hz, J = 7 Hz, benzylic protons; 39.89 δ, benzylic carbon)

Reaction of 3-(1-adamantyl)-1-triphenylmethylaziridinone (1d)[5] with *p*-methoxybenzylamine

0.300 g (0.0007 mol) of **1d** was dissolved into 7 mL of THF. To this was added 0.288 g (0.0021 mol) of freshly distilled *p*-methoxybenzylamine and the solution was stirred at rt for 40 h. THF was evaporated under reduced pressure to give 0.54 g of a clear oil. The oil was dissolved into 40 mL of methylene chloride, washed with 3 x 15 mL of distilled water, dried with Na_2SO_4, and evaporated under reduced pressure to give 0.47 g of a clear oil. This was chromatographed (85% *n*-hexane: 15% ethyl acetate) to give 0.29 g (73%) of a mixture of **3u** (62%) and **2m** (38%). The relative ratios were determined by comparing the integrals associated with the benzylic protons.

3u (3.55 δ, dd, J = 12.6 Hz, J = 12.6 Hz, benzylic protons; 43.43 δ, benzylic carbon)

2m (2.82 δ, dd, J = 7 Hz, J = 7 Hz, benzylic protons; 53.56 δ, benzylic carbon)

Reaction of 3-(1-adamantyl)-1-triphenylmethylaziridinone (1d)[5] with *tert*-butylamine

0.250 g (0.000577 mol) of **1d** was dissolved in 4 mL of *tert*-butylamine and stirred at rt for 24 h. The excess *tert*-butylamine was evaporated to yield 0.37 g of a white solid. This was chromatographed (90% *n*-hexane: 10% ethyl acetate) to give 0.24 g (83%) of pure *N*-triphenylmethyl-2-(1-adamantyl)-2-*tert*-butylaminoethanamide **(2n)**, mp 175-176°C with sintering from 170°C. TLC (85% *n*-hexane: 15% ethyl acetate): R_f = 0.37. IR (CCl_4): 3414 (N-H of amide); 3061 (aromatic C-H), 2906 and 2850 (aliphatic C-

H),1683 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.01 (s, methyl protons of *tert*-butyl moiety, 9H), 1.26 (s, N-H proton of amine, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H), 1.55 (d, *J* = 11 Hz, methylene protons of the adamantane moiety farther away from the quaternary carbon, 6H), 1.63 (d, *J* = 11 Hz, methylene protons of the adamantane moiety closer to the quaternary carbon, 6H), 1.92 (s, methine protons of the adamantane moiety, 3H), 2.66 (s, methine proton adjacent to the amide carbonyl, 1H), 7.20-7.31 (m, aromatic protons of the triphenylmethyl amide moiety, 15H), 8.91 (s, N-H proton of amide, exchanges for deuterium in $CDCl_3/CF_3COOD$, 1H). ^{13}C-NMR (interpreted with the aid of the APT) δ = 28.56 (methine carbons of the adamantane moiety), 29.45 (methyl carbons of *tert*-butyl moiety), 36.25 (methylene carbons of the adamantane moiety closer to the quaternary carbon), 36.90 (methylene carbons of the adamantane moiety farther away from the quaternary carbon), 39.64 (C_1 carbon of the adamantane moiety), 50.96 (quaternary carbon of *tert*-butyl moiety), 66.99 (methine carbon adjacent to carbonyl carbon of amide), 69.84 (quaternary carbon of triphenylmethyl moiety), 126.74 (*para* carbons of triphenylmethyl moiety), 127.68 (*meta* carbons of triphenylmethyl moiety), 128.80 (*ortho* carbons of triphenylmethyl moiety), 145.27 (C_1 carbons of triphenylmethyl moiety), 172.23 (amide carbonyl). GC/MS: m/z 243 $[(C_6H_5)_3C]^+$; 220 $[AdCH{=}NHC(CH_3)_3]^+$; 164 $(AdCH{=}NH_2)^+$. LC/MS m/z 506.7 (M^+, *base peak*, $C_{35}H_{42}N_2O$); 449.3 $(M\text{-}C_4H_9)^+$; 243 $((C_6H_5)_3C)^+$; 165.2 $(C_{13}H_9)^+$; 100 $((CH_3)_3CNH{=}C{=}O)^+$. Anal. Calcd for $C_{35}H_{42}N_2O$: C 82.96, H 8.35, N 5.53. Found: C 82.99, H 8.57, N 5.46.

Determination of pK_b-s

The pK_b-s of benzylamine, *p*-trifluoromethylbenzylamine, *p*-methoxybenzylamine, and *p*-*N*,*N*-dimethylaminobenzylamine were determined potentiometrically by the general procedure of Albert and Serjeant.[12] 50 mL of a 0.01 M solution of amine in distilled water was titrated with 0.01 N HCl. The pH was recorded at 0.5 mL intervals. The pH meter was initially standardized using biphthalate (pH = 4), phosphate (pH = 7), and borate (pH = 10) buffer solutions. The results are summarized in Table 1.

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