Full Characterization and Some Reactions of 1-(2-Adamantyl)-3-(1-adamantyl)aziridin-2-one

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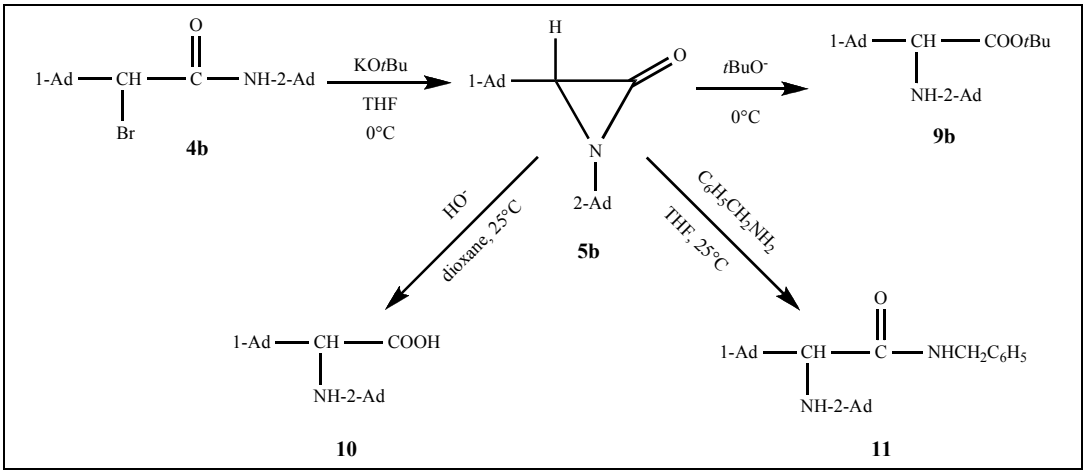

We found that 1-(2-adamantyl)-3-*tert*-butylaziridin-2-one (**5a**) is unstable. It slowly decomposes at room temperature, although detectable by IR spectroscopy (1840 cm^{-1} band in CCl_4). On the other hand, a closely related analogue, 1-(2-adamantyl)-3-(1-adamantyl)aziridin-2-one (**5b**), is very stable, in concurrence with an earlier report [1]. We fully characterized aziridinone **5b**, identified its thermal decomposition products (**7** and **8**) and reacted it with two aprotic ionic (*t*BuO$^-$ and HO$^-$) and one protic non-ionic nucleophile (benzylamine). All three products (**9b**, **10**, and **11**) result from exclusive cleavage of the lactam (1-2) bond.

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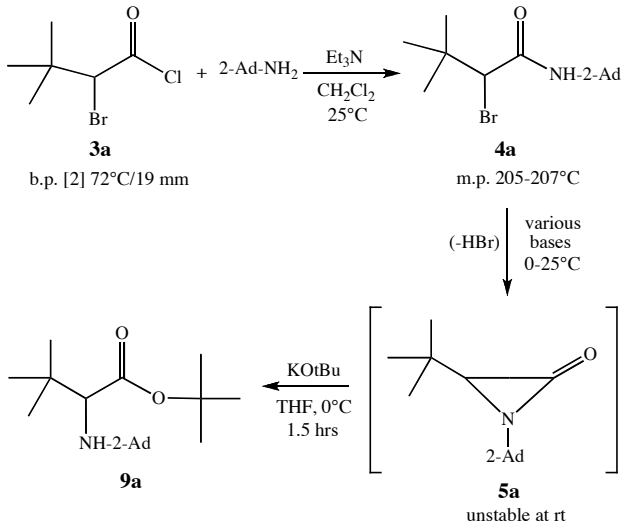
INTRODUCTION

Recently we attempted the synthesis of 1-(2-adamantyl)-3-*tert*-butylaziridin-2-one (**5a**), a new α-lactam having a particularly bulky secondary cycloalkyl substituent on the nitrogen. We devoted a substantial study to finding a satisfactory synthesis of α-lactam **5a** from α-bromoamide **4a** (Scheme 1).

Scheme 1. Attempted synthesis of α-lactam **5a**.



Four different published procedures were examined: (1) The dehydrobromination of α-bromoamide **4a** with 1 equivalent of KO*t*Bu in dry THF at 0°C [3], (2) Varying amounts (1-3 equivalents) of NaO*t*Bu in ether at 0°C or THF at 25°C [2], (3) Excess KOH, in conjunction with 18-crown-6 ether as phase transfer catalyst (PTC), in benzene at 25°C or toluene at 0°C [4], (4) Three equivalents of NaH in the presence of 15-crown-5 ether as PTC, in CH_2Cl_2 at room temperature [5].

α-Lactam **5a** is readily detectable in the IR (an 1840 cm^{-1} band in CCl_4 solution), but decomposes at room temperature because the bases react with it faster than with the α-bromoamide, which precludes its isolation. Nonetheless, we isolated, purified and characterized one of the follow-up products (**9a**) resulting from reaction of the α-lactam with *tert*-butoxide. The formation of such α-aminoacid *tert*-butyl esters had been observed before, both from stable and unstable α-lactams [3, 6].

Next we conducted a comprehensive literature search, which revealed only one short communication [1] reporting a stable α-lactam with a secondary alkyl substituent on the nitrogen, 1-(2-adamantyl)-3-(1-

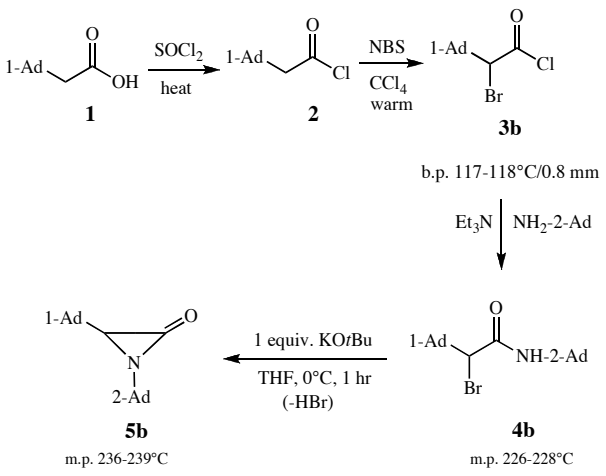
adamantyl)aziridin-2-one (**5b**). Alas, the characterization of α-lactam **5b** [1] is incomplete: there is no elemental analysis, no mass spectrum, no ^{13}C-NMR and APT, no yield, no TLC R_f, the thermal decomposition products are not identified, the experimental details of the synthesis are insufficient, the amount of base used, the reaction time and the exact method of isolation are not described, and no reactions of **5b** are reported.

The present investigation was undertaken, prompted by the apparent uniqueness of α-lactam **5b**, with the following aims: 1. Work out a synthesis of α-lactam **5b**. Isolate, purify and characterize it fully. 2. Determine the limit of its thermal stability, identify and characterize its thermal decomposition products. 3. Carry out three reactions on it, two with aprotic ionic nucleophiles and one with a protic non-ionic nucleophile. Identify the reaction products and determine their physical and spectral properties.

RESULTS AND DISCUSSION

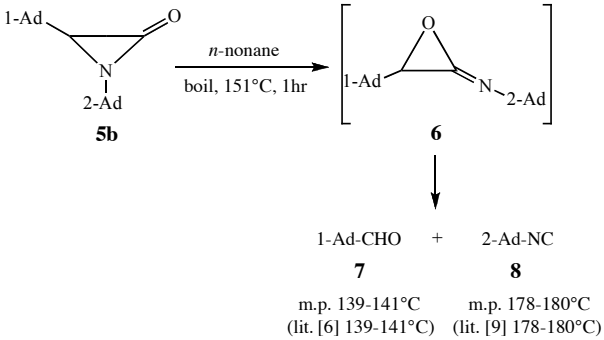
1. Synthesis of α-Lactam 5b. Accordingly, we synthesized the precursor, *N*-(2-adamantyl)-2-(1-adamantyl)-2-bromoacetamide (**4b**), from commercially available 1-adamantaneacetic acid (**1**) in three steps (Scheme 2), following published procedures [7,8], and subjected it to 1,3-dehydrobromination by KO*t*Bu [3]. α-Lactam **5b** forms readily and promptly, although in low yield. Our efforts to increase the yield by adding more base, stirring longer and/or varying the temperature, were not successful because the α-lactam readily reacts with *tert*-butoxide under the reaction conditions, to give ester **9b**.

Scheme 2. Synthesis of α-lactam **5b** (NBS = *N*-bromosuccinimide).



2. The Thermal Decomposition of α-Lactam 5b. Refluxing α-lactam **5b** for one hour in *n*-hexane (b.p. 68-70°C) causes no decomposition whatsoever. Refluxing in *n*-heptane (b.p. 98°C) for one hour results in decomposition of only a very small fraction of the α-lactam. Even refluxing in *n*-octane (b.p. 125-127°C) for one hour results in incomplete decomposition. Only refluxing in *n*-nonane (b.p. 151°C) for one hour brought about complete spontaneous thermal decomposition by quantitative fragmentation into 1-adamantyl aldehyde (**7**) [6] and 2-adamantyl isocyanide (**8**) [9] (Scheme 3), presumably *via* the imino-oxirane intermediate **6** [10].

Scheme 3. The thermal decomposition of α-lactam **5b**.



Characterization of the products was achieved by FT-IR and GC-MS. The IR, MS and retention times of the two thermal decomposition products were identical with those of authentic samples prepared for comparison by independent synthesis (*c.f.* Experimental).

3. Some Reactions of α-Lactam 5b. In general, stability and reactivity are correlated: the most stable α-lactams show very low reactivity. Even though **5b** is the highest-melting of all α-lactams known to date - about 60 compounds in all - it is at the same time also very reactive. It reacts under mild conditions readily and promptly with all common nucleophiles. *What is so astounding is not its high chemical reactivity but the high thermal stability*. To date we are unable to account for this antinomy.

Molecular models and computer drawings indicate that 1. in the most stable configuration the two adamantyl substituents are *trans* to one another. 2. the extent of steric hindrance around the 1-adamantyl group is the same in all rotamers. 3. the extent of steric hindrance generated and imparted on the ring by the 2-adamantyl substituent varies greatly from one rotamer to another. As can be seen from Figure 1, even in the most stable rotamer the ring is largely open to nucleophilic attack either at C_2 or C_3.

We chose to carry out three reactions on α-lactam **5b**: with the aprotic ionic nucleophiles tBuO$^-$ and OH$^-$, and the non-ionic protic nucleophile benzylamine (Scheme 4). Benzylamine was chosen because it is known to react with all α-lactams at room temperature readily and completely [11]. According to two comprehensive reviews [12,13], the general path of ring-opening with ionic nucleophiles occurs *via* 1-2 bond cleavage, while the

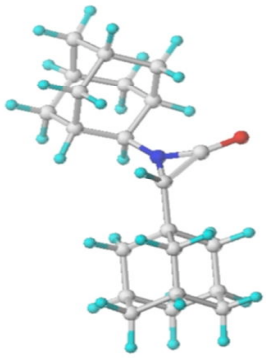
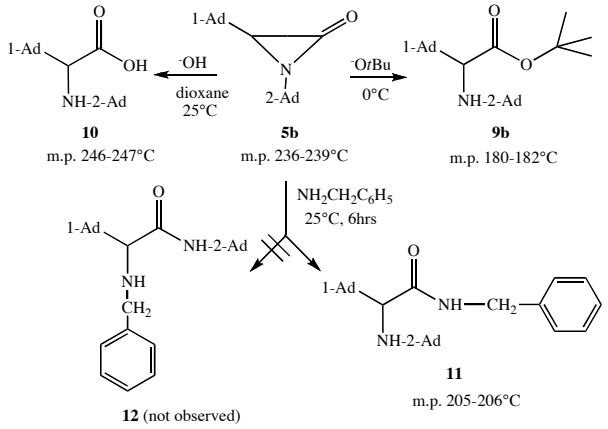


Figure 1. Molecular model of α-lactam **5b** in the most stable conformation.

general path of ring-opening with non-ionic protic nucleophiles proceeds *via* cleavage of the 1-3 bond, although exceptions have been reported [12-15].

Aminoacid ester **9b** and aminoacid **10** are the expected products of these reactions with *t*BuO$^-$ and HO$^-$, respectively. Similar derivatives have been isolated from reactions of other α-lactams with these reagents [3,6,12,16]. On the other hand, the product of the benzylamine reaction (**11**, Scheme 4) was less predictable. Even though considerable effort has been expended in trying to determine the factors governing the product of the benzylamine reaction [11], it is not known to date why sometimes C_2-N bond cleavage occurs leading to α-

Scheme 4. Some reactions of α-lactam **5b**.



alkylamino-N-benzylamides (like **11**), while at other times the C_3-N bond breaks, with formation of α-benzyl-aminoamides (like **12**) [17].

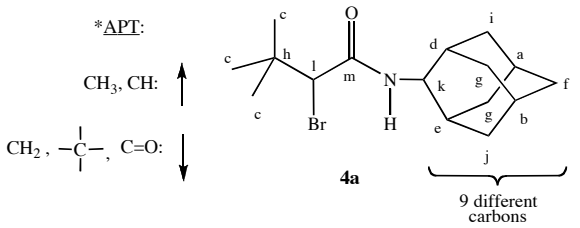
EXPERIMENTAL

General Remarks. Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer Spectrum 1000 FT-IR instrument. Mass spectra (MS) were recorded either on a Hewlett-Packard GC-MS GCD system or a Shimadzu GC-17A gas chromatograph equipped with a GCMS-QP5050A mass spectrometer with direct injection into the EI ion source. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz Bruker instrument with tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ). 2-Adamantylamine hydrochloride, 1-adamantaneacetic acid, 1-adamantanemethanol, sodium hydride, 15-crown-5 ether and pyridinium chlorochromate (PCC) were purchased from Aldrich (Milwaukee, WI). KO*t*Bu and *N*-bromosuccinimide (NBS) were purchased from Lancaster (Windham, NH). For column chromatography, JT Baker silica gel (40 microns) was used. Thin layer chromatography (TLC) was performed with Analtech silica gel glass-backed plates (250 microns). Microanalyses were performed by Atlantic Microlab Inc., Norcross, GA. Molecular modeling was performed with SYBYL version 7.2 [18] on a Dell Precision 470n workstation with RHEL 4.0 operating system. The energy minimization of the compound was carried out using steepest descent followed by conjugate gradient method which gives the local minimum conformation of the compound by Tripos force field (empirical) based geometry optimization.

***N*-(2-Adamantyl)-2-bromo-3,3-dimethylbutanamide (4a).** The procedure of Lengyel and Aaronson [8] was followed. To a solution of 2-adamantylamine hydrochloride (2.29 g, 0.0122 mol) in 60 mL of water was added 10.6 mL of 20% aqueous NaOH (0.05 mol). The mixture was stirred at room temperature for 5 minutes, cooled in an ice-water bath, filtered, and washed three times with 10 mL water. The product was dissolved in 100 mL CH_2Cl_2, dried over Na_2SO_4 and filtered. To the clear CH_2Cl_2 solution was added 1.23 g (0.0122 mol) Et_3N. A solution of the α-bromoacid chloride **3a** [2] (2.59 g, 0.0122 mol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 20 minutes. Then the reaction mixture was stirred at room temperature overnight. Next day the CH_2Cl_2 solution was washed with 25 mL of water, then with 20 mL of 1 *N* HCl solution, then again with 25 mL water. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to yield 3.86 g (97 %) of a solid. It was recrystallized from *n*-hexane: ethyl acetate (9: 1) to yield pure **4a** as a white solid (3.43 g, 89 %), mp 205-207°C. TLC (90 % *n*-hexane: 10 % ethyl acetate): R_f = 0.41. IR (CCl_4): 3431 (N-H of secondary amide); 2910 and 2855 (aliphatic C-H); 1670 (amide C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.16 (s, 9H, protons on the *tert*-butyl group); 1.60-1.95 (m, 14H, protons of the adamantyl moiety); 4.04 (d, J = 8.1 Hz, 1H, C_2-proton of the 2-adamantyl moiety); 4.18 (s, 1H, Br-CH-C=O proton); 6.49 (bs, 1H, N-H proton). ^{13}C-NMR ($CDCl_3$), interpreted with the aid of APT: The molecule contains 13 different carbons (Figure 2).

MS: m/z 327/329 (M^+, $C_{16}H_{26}BrNO$); 312/314 ($M - CH_3\cdot)^+$; 271/273 ($M - C_4H_8)^+$; 248 *base peak*, ($M - Br\cdot)^+$; 192 ($M - Br\cdot - C_4H_8)^+$; 178 Ad-N$^+$H=C=O; 150 Ad-NH$^+$; 135 $C_{10}H_{15}^+$; 93 $C_7H_9^+$; 79 $C_6H_7^+$; 67 $C_5H_7^+$; 41 $C_3H_5^+$. *Anal.*: Calcd for $C_{16}H_{26}BrNO$: C 58.54; H 7.98; Br 24.34; N 4.27. Found: C 58.72; H 8.05; Br 24.47; N 4.36.

Attempted Synthesis of 1-(2-Adamantyl)-3-*tert*-butyl-aziridin-2-one (5a). A mixture of dichloromethane (45 mL), sodium hydride (0.18 g, 0.00457 mol) and 15-crown-5 ether (0.084 g, 0.00038 mol) was stirred at room temperature for 20 minutes, after which *N*-(2-adamantyl)-2-bromo-3,3-dimethyl-



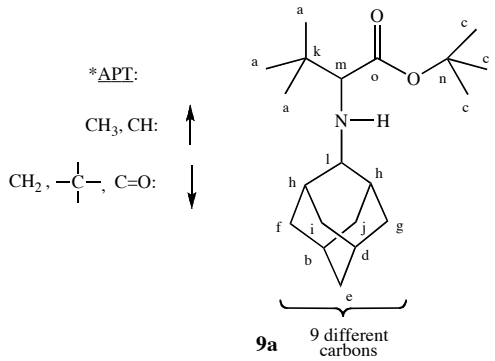
APT *	Carbon	δ	Interpretation #
↑	a	27.08	One CH-carbon in Ad
↑	b	27.19	One CH-carbon in Ad
↑	c	27.69	CH_3-carbons of *tert*-butyl
↑	d	31.72	One CH-carbon in Ad
↑	e	31.95	One CH-carbon in Ad
↓	f	31.98	One CH_2-carbon in Ad
↓	g	32.1	Two CH_2-carbons in Ad
↓	h	35.04	Quaternary carbon in *tert*-butyl
↓	i	37.04	One CH_2-carbon in Ad
↓	j	37.49	One CH_2-carbon in Ad
↑	k	53.83	CH-carbon in Ad attached to N
↑	l	65.08	CH-carbon attached to Br
↓	m	166.8	Carbonyl carbon

Figure 2. The interpretation of the ^{13}C-NMR spectrum of α-bromo-amide **4a**. #Ad = adamantyl

butanamide (**4a**) (0.5 g, 0.00152 mol) was added. The reaction mixture was monitored by IR. The maximum amount of α-lactam detected was 32 %, based on comparison of the carbonyl stretching frequency of the α-lactam (1840 cm^{-1}) and the starting amide (1670 cm^{-1}), after 3 hours. To date, all attempts to isolate α-lactam (**5a**) were unsuccessful.

***tert*-Butyl 2-(2-adamantyl)amino-3,3-dimethylbutanoate (9a).** 0.500 g (0.00152 mol) of **4a** was dissolved in 25 ml of dry THF at 0°C. To this solution was added 0.597 g (0.00532 mol, 3.5 equivalents) of KO*t*Bu. It was stirred at 0°C for 1.5 hour. The THF was evaporated to give a solid residue which was flash chromatographed (100 % *n*-hexane) to give 0.39 g (80 %) of **9a**, as an oil. TLC (95 % *n*-hexane: 5 % ethyl acetate): R_f = 0.60. IR (CCl_4): 2905 and 2843 (aliphatic C-H); 1724 (ester C=O) cm^{-1}. The absence of a pronounced N-H type band in the IR spectra of α-alkylamino *tert*-butyl esters has been observed previously [3]. ^{1}H-NMR ($CDCl_3$) δ = 0.97 (s, 9H, C-*tert*-butyl); 1.46 (s, 9H, O-*tert*-butyl); 1.56-1.88 (m, 13H, ten CH_2-protons in Ad, two CH-protons in Ad and the N-H proton, exchanges in D_2O); 2.12 (d, 2H, CH-protons in Ad in β-position to the NH); 2.53 (s, 1H, C_2-proton in Ad attached to N); 2.80 (s, 1H, CH-proton between nitrogen and carbonyl). ^{13}C-NMR ($CDCl_3$), interpreted with the aid of APT: The molecule contains 15 different carbons (Figure 3).

MS: m/z 322 $(M + 1)^+$; 321 M^+; 320 $(M - H\cdot)^+$; 306 $(M - CH_3\cdot)^+$; 264 $(M - C_4H_9\cdot)^+$; 250 $[(CH_3)_2C^+CH(NHAd)(COOH)]$; 220 (*base peak*, $[(CH_3)_3CCH=N^+HAd)]$; 208 $[AdN^+H=CHCOOH]$; 162 $[AdN=CH^+]$; 150 $AdNH^+$; 107 $C_8H_{11}^+$; 93 $C_6H_5NH_2^+$; 91 $C_7H_7^+$; 86 $[(CH_3)_3CCH=N^+H_2]$; 79 $C_6H_7^+$; 67 $C_5H_7^+$. *Anal.*: Calcd for $C_{20}H_{35}NO_2$: C 74.72; H 10.97; N 4.36. Found: C 74.64; H 11.09; N 4.51.



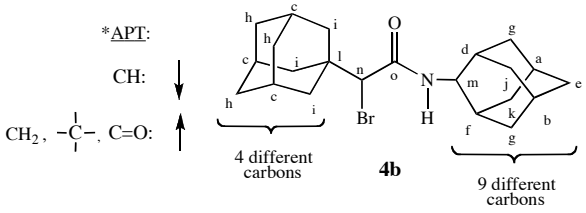
APT*	Carbon	δ	Interpretation#
↑	a	27.09	Three CH_3-carbons in C-*t*-Bu
↑	b	28.05	One CH-carbon in Ad
↑	c	28.43	Three CH_3-carbons in O-*t*-Bu
↑	d	31.02	One CH-carbon in Ad
↓	e	31.31	One CH_2-carbon in Ad
↓	f	31.72	One CH_2-carbon in Ad
↓	g	34.15	One CH_2-carbon in Ad
↑	h	34.73	Two CH-carbons in Ad
↓	i	37.27	One CH_2-carbon in Ad
↓	j	37.95	One CH_2-carbon in Ad
↓	k	38.22	Quaternary carbon in C-*t*-Bu
↑	l	60.84	CH-carbon in Ad attached to N
↑	m	68.42	CH-carbon between NH and C=O
↓	n	80.61	*t*-Bu-carbon attached to O
↓	o	175.22	Carbonyl carbon

Figure 3. The interpretation of the ^{13}C-NMR spectrum of α-amino-acid *tert*-butyl ester **9a**. #Ad = adamantyl

2-Bromoadamantaneacetyl Chloride (3b) [7]. The general procedure of Lengyel *et al.* [7] was followed. A solution of 1-adamantaneacetic acid (**1**) (12.85 g, 0.066 mol) in 7 mL carbon tetrachloride was treated with 31.50 g (0.265 mol) of thionyl chloride, then NBS (14.13 g, 0.0794 mol) and 4 drops of 48% aqueous HBr. After the succinimide byproduct was filtered off (m.p. 121°C) and the CCl_4 was removed on the rotary evaporator, the residual oil was vacuum distilled, b.p. 117-118°C/0.8 mm Hg (lit. [7] b.p. 105-107°C/0.7 mm Hg), to give 17.0 g (88 %) of pure **3b**. IR (CCl_4): 2908 and 2850 (aliphatic C-H); 1797 (C=O of acid chloride) with shoulder at 1765 (weak overtone vibration) cm^{-1}. ^{1}H-NMR (CCl_4) δ = 1.60-1.80 (m, 12H, CH_2-protons of the adamantyl moiety); 2.05 (s, 3H, the CH-protons of the adamantyl moiety); 4.25 (s, 1H, Br-CH-C=O proton).

***N*-(2-Adamantyl)-2-bromo-1-adamantaneacetamide (4b) [1].** The procedure of Lengyel and Aaronson [8] was followed. To a solution of 2-adamantylamine hydrochloride (4.93 g, 0.0263 mol) in 60 mL of water was added 10.6 mL of 20% aqueous NaOH (0.05 mol). The mixture was stirred at room temperature for 5 minutes, cooled in an ice-water bath, filtered, and washed three times with 10 mL water. The product was dissolved in 100 mL CH_2Cl_2, dried over Na_2SO_4 and filtered. To the clear CH_2Cl_2 solution was added 2.63 g (0.026 mol) Et_3N. A solution of the α-bromoacid chloride **3b** (7.29 g, 0.025 mol) in

60 mL of CH_2Cl_2 was added dropwise over a period of 20 minutes. Then the reaction mixture was stirred at room temperature overnight. Next day the clear CH_2Cl_2 solution was washed with three 50 mL portions of water, then with 50 mL of 1N HCl solution, then again with 50 mL water. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to yield a white solid, 10.16 g (100 %), mp 225-227°C (no decomposition). TLC (90 % *n*-hexane-10 % ethyl acetate): R_f = 0.38, essentially single spot. This product was recrystallized from a mixture of 50 mL *n*-heptane, 70 mL acetonitrile, and 50 mL isopropyl alcohol, boiling on the steam bath, cooling to room temperature for 2 hours, then kept in an ice-water bath for 2 hours. The crystalline precipitate was collected on a sintered-disk funnel, washed with 3 x 20 mL *n*-hexane and dried in a vacuum desiccator, to give 8.2 g (80.7%) of pure **4b** as white crystals, mp 226-228°C (no decomposition) (lit. [1] m.p. 237.5-240.0°C [decomposition]). TLC (90 % *n*-hexane: 10 % ethyl acetate): R_f = 0.40. IR (CCl_4): 3430 (N-H of secondary amide); 2914 and 2853 (aliphatic C-H); 1669 (amide C=O); and 1525 (amide II band) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.62-1.89 (m, 22H, the 11 CH_2-groups of the two adamantyl moieties); 1.94-2.03 (s, 7H, seven of the eight CH-protons of the two adamantyl moieties); 4.04 (d, 1H, the C_2-proton of the 2-adamantyl moiety, J= 8Hz); 4.07 (s, 1H, Br-CH-C=O proton); 6.45 (bs, 1H, the N-H proton, exchangeable in $CDCl_3/CF_3COOD$). ^{13}C-NMR ($CDCl_3$), interpreted with the aid of APT: The molecule contains 15 different carbons. There are six non-equivalent CH_2-carbons in the two adamantyl groups combined, four of them in the 2-adamantyl group (e, g, j, k). The reason for this is that the O=C-N-H group is *magnetically strongly anisotropic* (Figure 4).

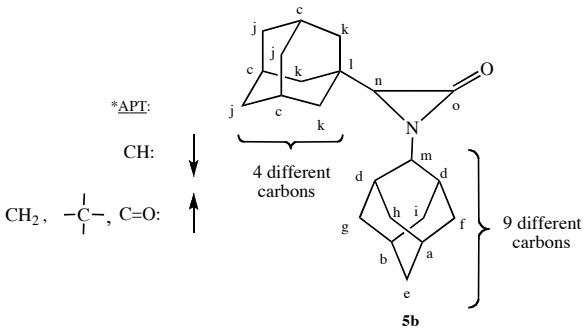


APT*	Carbon	δ	Interpretation#
↓	a	27.08	One CH-carbon in 2-Ad
↓	b	27.19	One CH-carbon in 2-Ad
↓	c	28.42	Three CH-carbons in 1-Ad
↓	d	31.7	One CH-carbon in 2-Ad
↑	e	31.96	One CH_2-carbon in 2-Ad
↓	f	31.99	One CH-carbon in 2-Ad
↑	g	32.11	Two CH_2-carbons in 2-Ad
↑	h	36.07	Three CH_2-carbons in 1-Ad
↑	i	36.56	Three CH_2-carbons in 1-Ad
↑	j	37.02	One CH_2-carbon in 2-Ad
↑	k	37.49	One CH_2-carbon in 2-Ad
↑	l	39.74	C_1-carbon in 1-Ad
↓	m	53.84	CH-carbon attached to N in 2-Ad
↓	n	66.32	CH-carbon attached to Br and C=O
↑	o	166.15	Carbonyl carbon

Figure 4. The interpretation of the ^{13}C-NMR spectrum of α-bromoamide **4b**. #Ad = adamantly.

MS: m/z 405/407 (M^+); 326 (*base peak*, (M – Br·)$^+$, Ad-C$^+$HCONH-Ad); 192 (326 – $C_{10}H_{14}$, $^+CH_2CONHAd$); 150 $C_{10}H_{15}NH^+$; 135 $C_{10}H_{15}^+$; 119 $C_9H_{11}^+$; 108 $C_8H_{12}^+$; 93 $C_7H_9^+$; 91 $C_7H_7^+$; 79 $C_6H_7^+$; 68 $C_5H_8^+$; 41 $C_3H_5^+$. *Anal.*: Calcd for $C_{22}H_{32}BrNO$: C 65.02; H 7.94; N 3.45; Br 19.66. Found: C 64.85; H 8.01; N 3.39; Br 19.57.

Synthesis of 1-(2-Adamantyl)-3-(1-adamantyl)aziridin-2-one (5b). A variation of the procedure of Sheehan and Lengyel [3] was used. 0.610 g (0.0015 mol) of α-bromoamide **4b** was dissolved in 30 mL of dry THF. To this solution was added 0.168 g (0.0015 mol, 1 equivalent) of KO*t*Bu in one portion at 0°C and stirred vigorously for 1 hour. The mixture was then filtered and the filtrate was evaporated to dryness. The residue was taken up into 50 mL of EtOAc and washed with cold phosphate buffer (0.01 M, pH 7.4, 3 x 50 mL). The organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 0.40 g of a white solid which was then flash chromatographed (95 % *n*-hexane: 5 % ethyl acetate) to give 0.088 g (18 %) of α-lactam **5b**, as a white solid with m.p. 236-239°C (decomposition) (lit. [1] m.p. ≈ 226°C). 0.150 g of unreacted α-bromoamide **4b** was recovered from the column. Subtracting this increases the yield of α-lactam **5b** to 24 %. TLC (90 % *n*-hexane: 10 % ethyl acetate): R_f = 0.41. IR (CCl_4): 2908 and 2852 (aliphatic C-H); 1838 (lactam C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.5-2.4 (m, 29H); 2.53 (s, 1H, C_2-proton of 2-adamantyl); 3.15 (s, 1H, CH-proton of lactam). ^{13}C-NMR ($CDCl_3$), interpreted with the aid of APT: The molecule contains



APT*	Carbon	δ	Interpretation#
↓	a	27.25	One CH-carbon in 2-Ad
↓	b	27.51	One CH-carbon in 2-Ad
↓	c	28.29	Three CH-carbons in 1-Ad
↓	d	31.95	Two CH-carbons in 2-Ad
↑	e	32.1	One CH_2-carbon in 2-Ad
↑	f	32.27	One CH_2-carbon in 2-Ad
↑	g	33.73	One CH_2-carbon in 2-Ad
↑	h	36.61	One CH_2-carbon in 2-Ad
↑	i	36.76	One CH_2-carbon in 2-Ad
↑	j	36.86	Three CH_2-carbons in 1-Ad
↑	k	37.55	Three CH_2-carbons in 1-Ad
↑	l	40.19	C_1-carbon in 1-Ad
↓	m	57.76	CH-carbon attached to N in 2-Ad
↓	n	67.36	CH-carbon of lactam
↑	o	163.18	Carbonyl carbon

Figure 5. The interpretation of the ^{13}C-NMR spectrum of α-lactam **5b**. #Ad = adamantyl

15 different carbons. There are four in the 1-adamantyl group and nine in the 2-adamantyl group (Figure 5).

MS: m/z 325 M^+; 297 $(M - CO)^+$; 162 $(Ad\text{-}CHN)^+$; 135 $C_{10}H_{15}^+$; 93 $C_6H_5NH_2^+$ and/or $C_7H_9^+$; 91 $C_7H_7^+$; 79 $C_6H_7^+$; 77 $C_6H_5^+$; 67 $C_5H_7^+$. *Anal.*: Calcd for $C_{22}H_{31}NO$: C 81.18; H 9.60; N 4.30. Found: C 80.98; H 9.75; N 4.29.

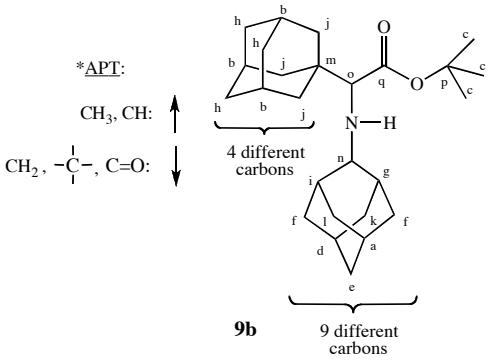
The Thermal Decomposition of α-Lactam 5b. 0.100 g (0.000307 mol) of α-lactam **5b** was dissolved in 20 mL of *n*-nonane (b.p. 151°C) and refluxed for 1 hour. Then the mixture was cooled to room temperature and subjected to analysis by FT-IR and GC-MS. The reaction yielded 1-adamantyl aldehyde (**7**) and 2-adamantyl isocyanide (**8**) as the only products, in agreement with prior observations [10, 12, 16]; IR (nonane): 1725 cm^{-1} (aldehyde C=O); 2129 cm^{-1} (N≡C); GC-MS: two components; first peak molecular ion at m/z 164 (1-adamantyl aldehyde), second peak molecular ion at m/z 161 (2-adamantyl isocyanide).

The IR and GC-MS of the two thermal decomposition products were identical with those of authentic **7** and **8**. **7** was synthesized by the oxidation of 1-adamantanemethanol with PCC [19] and had m.p. 139-141°C (lit. [6] m.p. 139-141°C). **8** was synthesized by a modified Hofmann carbylamine synthesis [9] from 2-adamantylamine and had m.p. 178-180°C (lit. [9] m.p. 178-180°C).

Reactions of α-Lactam 5b.

a. Reaction with KO*t*Bu. 0.100 g (0.000307 mol) of α-lactam **5b** was dissolved in 20 mL of dry THF. To this solution was added 0.103 g (0.000922 mol, 3.0 equivalents) of powdered KO*t*Bu in one portion and stirred vigorously at room temperature. After five hours the THF was removed under reduced pressure, the residue taken up in 50 mL of CH_2Cl_2 and washed with water (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was flash chromatographed (100 % *n*-hexane), to give 0.105 g (86 %) of pure *tert*-butyl 2-(2-adamantyl)amino-1-adamantaneacetate (**9b**), m.p. 180-182°C. TLC: (95 % *n*-hexane: 5 % ethyl acetate) R_f = 0.56. IR (CCl_4): 2906 and 2849 (aliphatic C-H); 1720 (ester C=O) cm^{-1}. The absence of a pronounced N-H type band in the IR spectra of α-alkylamino *tert*-butyl esters has been observed previously [3]. ^{1}H-NMR ($CDCl_3$) δ = 1.46 (s, 9H, O-*tert*-butyl); 1.48-1.84 (m, 22H, the eleven CH_2- groups in the two adamantyl moieties); 1.96 (s, 3H, CH-protons in the 1-adamantyl group); 2.12 (d, 5H, the five CH-protons in the 2-adamantyl moiety); 2.51 (s, 1H, amine N-H, exchangeable in D_2O); 2.66 (s, 1H, HN-CHC=O, CH proton attached to nitrogen and carbonyl). ^{13}C-NMR ($CDCl_3$): The molecule has 17 different carbons; four in the 1-adamantyl group and nine in the 2-adamantyl group (Figure 6). MS: m/z 399 M^+; 342 $(M - C_4H_9\cdot)^+$; 298 (*base peak*, $(M - COOC_4H_9\cdot)^+$, [AdCH=N$^+$HAd]); 240 $(AdCH=N^+HC_6H_5)$; 236 $(M - AdCHNH\cdot)^+$; 164 $(298 - C_{10}H_{14})^+$; 135 $C_{10}H_{15}^+$; 93 $C_7H_9^+$; 79 $C_6H_7^+$; 67 $C_5H_7^+$; 41 $C_3H_5^+$. *Anal.*: Calcd for $C_{26}H_{41}NO_2$: C 78.15; H 10.34; N 3.51. Found: C 78.24; H 10.41; N 3.54.

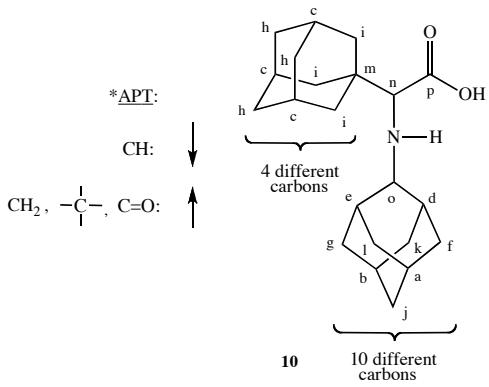
b. Reaction with KOH. 0.100 g (0.000307 mol) of α-lactam **5b** was dissolved in 25 mL of dioxane and to this solution 0.172 g (0.00307 mol, 10 equivalents) of finely powdered KOH was added. The resulting suspension was stirred vigorously for 18 hours at room temperature. The dioxane was removed under reduced pressure, the residue taken up in 100 mL of CH_2Cl_2 and washed with 1N HCl (2 x 25 mL) followed by water (4 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure to give 0.091 g of a white crystalline residue. This was flash chromatographed on silica gel with 65% EtOAc: 35% *n*-hexane as mobile phase, to give 0.075 g (71 %) of 2-(2-adamantyl)amino-1-adamantaneacetic acid (**10**) as a white solid, m.p. 246-247°C (no decomposition). The compound readily sublimes undecomposed. TLC (70% *n*-hexane: 30% ethyl acetate): R_f = 0.23. IR (KBr): 3416 (broad band); 2908 and 2853 (aliphatic C-H); 1719 (carbonyl of the carboxylic acid) cm^{-1}. ^{1}H-NMR (CD_3OD) δ = 1.62-2.10 (m, 29H, all eleven CH_2-groups and seven of the eight C-H protons of the two adamantyl moieties); 2.14 (d, 1H, CH-proton in the 2-adamantyl moiety adjacent to the nitrogen); 2.27 (s, 1H, amine N-H, exchangeable in D_2O); 3.13 (s, 1H, methine proton adjacent to the carbonyl, N-CH-C=O); the carboxyl proton is absent, because of exchange with the solvent, CD_3OD. ^{13}C-NMR (CD_3OD) (Figure 7). MS: m/z 343 (M^+); 342 $(M - H\cdot)^+$; 298 $(M - COOH\cdot)^+$; 208 $(M - C_{10}H_{15}\cdot)^+$; 176 $(1\text{-}Ad\text{-}CH=C=O)^+$; 164 $(1\text{-}Ad\text{-}CH=NH_2)^+$; 162 $(2\text{-}AdNHC)^+$; 135 ($C_{10}H_{15}^+$, 162 – HCN)$^+$; 107 ($C_8H_{11}^+$, 135 – C_2H_4); 93 $C_7H_9^+$; 91 $C_7H_7^+$; 79 $C_6H_7^+$; 67



APT*	Carbon	δ	Interpretation #
↑	a	28.06	One CH-carbon in 2-Ad
↑	b	28.5	Three CH-carbons in 1-Ad
↑	c	28.81	Three CH_3-carbons in *t*-Bu
↑	d	30.89	One CH-carbon in 2-Ad
↓	e	31.28	One CH_2-carbon in 2-Ad
↓	f	31.74	Two CH_2-carbons in 2-Ad
↑	g	34.78	One CH-carbon in 2-Ad
↓	h	35.94	Three CH_2-carbons in 1-Ad
↑	i	37.23	One CH-carbon in 2-Ad
↓	j	37.41	Three CH_2-carbons in 1-Ad
↓	k	37.93	One CH_2-carbon in 2-Ad
↓	l	38.22	One CH_2-carbon in 2-Ad
↓	m	39.42	C_1-carbon in 1-Ad
↑	n	60.67	CH-carbon in 2-Ad attached to N
↑	o	69.28	CH carbon adjacent to C=O
↓	p	80.57	$(CH_3)_3CO$
↓	q	174.69	Carbonyl carbon

Figure 6. The interpretation of the ^{13}C-NMR spectrum of α-aminoacid *tert*-butyl ester **9b**. #Ad = adamantyl

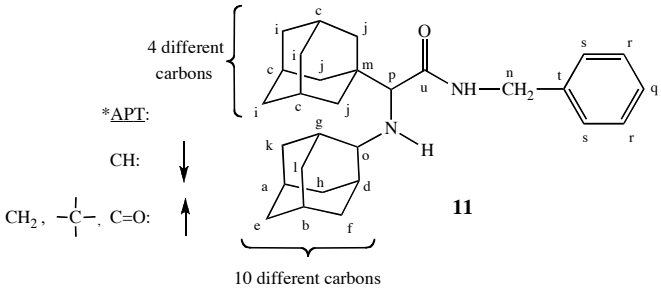
$C_5H_7^+$. *Anal.*: Calcd for $C_{22}H_{23}NO_2$•1/8 H_2O: C 76.42; H 9.71; N 4.05. Found: C 76.40; H 9.67; N 4.04.



APT*	Carbon	δ	Interpretation#
↓	a	27.25	One CH-carbon in 2-Ad
↓	b	27.44	One CH-carbon in 2-Ad
↓	c	28.72	Three CH-carbons in 1-Ad
↓	d	29.78	One CH-carbon in 2-Ad
↓	e	30.35	One CH-carbon in 2-Ad
↑	f	30.83	One CH_2-carbon in 2-Ad
↑	g	30.97	One CH_2-carbon in 2-Ad
↑	h	35.27	Three CH_2-carbons in 1-Ad
↑	i	36.64	Three CH_2-carbons in 1-Ad
↑	j	36.99	One CH_2-carbon in 2-Ad
↑	k	37.07	One CH_2-carbon in 2-Ad
↑	l	37.23	One CH_2-carbon in 2-Ad
↑	m	38.43	C_1-carbon in 1-Ad
↓	n	65.17	CH carbon adjacent to COOH
↓	o	72.4	CH-carbon in 2-Ad attached to N
↑	p	170.98	Carbonyl carbon

Figure 7. The interpretation of the ^{13}C-NMR spectrum of α-amino acid **10**. #Ad = adamantyl

c. Reaction with Benzylamine. 0.100 g (0.000307 mol) of α-lactam **5b** was dissolved in 20 mL of dry THF. To this solution was added 0.132 g (0.00123 mol, 4 equivalents) of freshly distilled benzylamine and stirred at room temperature. After six hours the THF was distilled off under reduced pressure. The residue was flash chromatographed (90% *n*-hexane: 10% ethyl acetate), to give 0.113 g (85 %) of pure *N*-benzyl-2-(2-adamantyl)amino-1-adamantaneacetamide (**11**), m.p. 205-206°C. TLC: (90% *n*-hexane: 10% ethyl acetate) R_f = 0.28. IR (CCl_4): 3448 (N-H of amide); 3363 (N-H of amine), 3030 (aromatic CH); 2909, 2851 (aliphatic CH); 1674 (amide carbonyl); 1525 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 1.26 (s, 1H, N-H proton of 2-Ad); 1.5-1.9 (m, 26H, 12 CH_2-protons of 1-Ad, plus 10 CH_2-protons and 4 CH-protons in 2-Ad); 1.99 (s, 3H, CH-protons in 1-Ad); 2.42 (s, 1H, C_2-proton in 2-Ad); 2.77 (s, 1H, CH-proton adjacent to C=O); 4.37 (dd, 1H, J = 14.5, 5.1 Hz) and 4.56 (dd, 1H, J = 14.4, 6.3 Hz) diastereotopic benzylic protons; 7.29-7.32 (m, 5H, aromatic protons); 7.43 (s, 1H, N-H proton of amide). ^{13}C-NMR ($CDCl_3$): There are 21 different carbons in the molecule, four in the 1-adamantyl group, ten in the 2-adamantyl group (Figure 8).



APT*	Carbon	δ	Interpretation#
↓	a	27.57	One CH-carbon in 2-Ad
↓	b	27.77	One CH-carbon in 2-Ad
↓	c	28.72	Three CH-carbons in 1-Ad
↓	d	30.25	One CH-carbon in 2-Ad
↑	e	31.81	One CH_2-carbon in 2-Ad
↑	f	31.91	One CH_2-carbon in 2-Ad
↓	g	34.56	One CH-carbon in 2-Ad
↑	h	35.65	One CH_2-carbon in 2-Ad
↑	i	37.16	Three CH_2-carbons in 1-Ad
↑	j	37.64	Three CH_2-carbons in 1-Ad
↑	k	37.9	One CH_2-carbon in 2-Ad
↑	l	38.02	One CH_2-carbon in 2-Ad
↑	m	39.86	C_1-carbon in 1-Ad
↑	n	43.19	Benzylic CH_2-carbon
↓	o	60.85	C_2-carbon attached to N in 2-Ad
↓	p	71.24	CH-carbon attached to carbonyl
↓	q	127.47	*para* -carbon in phenyl ring
↓	r	128.01	*meta* -carbons in phenyl ring
↓	s	128.75	*ortho* -carbons in phenyl ring
↑	t	139.09	C_1-carbon of phenyl group
↑	u	173.29	Carbonyl carbon

Figure 8. The interpretation of the ^{13}C-NMR spectrum of α-alkylamino-N-benzylamide **11**. #Ad = adamantyl

MS: m/z 432 (M^+); 431 ($M - H\cdot)^+$; 298 (*base peak*, 1-Ad-CH=N^+H-2-Ad); 164 (298 – $C_{10}H_{14}$)$^+$; 162 ($C_{10}H_{15}CHN)^+$; 150 ($C_{10}H_{15}NH)^+$; 135 $C_{10}H_{15}^+$; 106 ($C_6H_5CH_2NH^+$); 91 $C_7H_7^+$; 79 $C_6H_7^+$; 67 $C_5H_7^+$. *Anal.*: Calcd for $C_{29}H_{40}N_2O$: C 80.51; H 9.32; N 6.47. Found: C 80.34; H 9.37; N 6.41.

REFERENCES AND NOTES

[1] Talaty, E. R.; Madden, J. P.; Stekoll, L. H. *Angew. Chem.* **1971**, *83*, 848; also *Angew. Chem. Internat. Ed. Engl.* **1971**, *10*, 753.

[2] Lengyel, I.; Cesare, V.; Karram, H.; Taldone, T. *J. Heterocycl. Chem.* **2001**, *38*, 997.

[3] Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356.

[4] Scrimin, P.; D'Angeli, F.; Veronese, A. C. *Synthesis* **1982**, 586.

[5] Cesare, V.; Lyons, T. M.; Lengyel, I. *Synthesis* **2002**, 1716.

[6] Bott, K. *Liebigs Ann. Chem.* **1972**, *755*, 58.

[7] Lengyel, I.; Cesare, V.; Adam, I.; Taldone, T. *Heterocycles* **2002**, *57*, 73.

[8] Lengyel, I.; Aaronson, M. J. *Can. J. Spectroscopy* **1974**, *19*, 95.

[9] Sasaki, T.; Eguchi, S.; Katada, T. *J. Org. Chem.* **1974**, *39*, 1239.

[10] Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 746.

[11] Lengyel, I.; Cesare, V.; Chen, S.; Taldone, T. *Heterocycles* **2002**, *57*, 677.

[12] Lengyel, I.; Sheehan, J. C. *Angew. Chem.* **1968**, *80*, 27; also *Angew. Chem., Internat. Ed. Engl.* **1968**, *7*, 25.

[13] Backes, J. Houben-Weyl, *Methoden der Organischen Chemie*, Vierte Auflage, Band E16b, Georg Thieme Verlag, Stuttgart, New York, 1991, p. 1.

[14] Talaty, E. R.; Dupuy, Jr., A. E.; Utermohlen, C. M. *Chem. Commun.* **1971**, 16.

[15] Yusoff, M. M.; Talaty, E. R. *Tetrahedron Lett.* **1996**, *48*, 8695.

[16] Lengyel, I.; Cesare, V.; Taldone, T.; Uliss, D. *Synth. Commun.* **2001**, *31*, 3671.

[17] The empirically deduced correlations [11] based on structural parameters, relative stability and reactivity, substitution pattern and the rate of reaction, may be used to predict the actual product with a high degree of accuracy.

[18] SYBYL 7.2, Tripos Inc., 1699 South Hanley Rd., St. Louis, Missouri, 63144.

[19] Farooq, O.; Marcelli, M.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1988**, *110*, 864.