Efficient Synthesis of Azetidine Through *N*-Trityl- or *N*-Dimethoxytritylazetidines Starting From 3-Amino-1-propanol or 3-Halopropylamine Hydrohalides

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Dedicated to the memory of Professor Roland K. Robins

Efficient synthetic routes for the preparation of azetidine starting from commercially available 3-amino-1-propanol or 3-halopropylamine hydrohalides are reported. First, the appropriate *N*-trityl- or *N*-dimethoxytrityl protected tosyloxy- or halopropylamines were prepared. These precursors were then cyclized into the *N*-trityl- or *N*-dimethoxytritylazetidines. The *N*-protecting groups were removed in the presence of perchloric acid giving the hydrogen perchlorate salt of azetidine. The latter compound was transformed into its free base using a strong base under anhydrous conditions. The relatively expensive 4,4'-dimethoxytrityl chloride and less expensive trityl chloride used in these synthetic procedures were recycled in good yields. Azetidine hydrogenperchlorate can be used to prepare *N*-substituted azetidines without the need to isolate the free azetidine.

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Introduction.

Azetidines are valuable compounds in pharmaceutical [1-10], agrochemical [11-13], and polymer [14] research. This interesting class of four-membered *N*-heterocycles has been the subject of many structural studies [15-27]. Very recently, considerable interest has been shown in the use of azetidines in high performance explosives [24,28]. However, azetidines are one of the most difficult amines to synthesize because of the unfavorable enthalpy of activation in four-membered ring formation [29] and the high susceptibility to cleavage of the strained heteroring [30]. Developing effective methods for the synthesis of azetidines have challenged many synthetic chemists for more than one hundred years since the parent azetidine was first prepared in low yield and impure form in 1888 by treatment of 3-bromopropylamine with base [31].

The parent azetidine and its derivatives can be synthesized by several methods [32,33] including the reduction of 2-azetidinones [34]; cyclization of 3-aminopropanols using Mitsunobu-type and related reagents such as triphenylphosphine-diethyl azodicarboxylate [35,36], triphenylphosphine-carbon tetrabromide [35,36], or triphenylphosphine-bromine [2] adducts; cyclization of 3-halopropylamines [36,37]; reduction of 1-substituted azetidine-3-ols [4]; cyclization of 1,3-dihalo- or ditosyloxypropanes with amines [29,38,39]; pyrolysis of 3-hydroxypropenylphosphazenes [40]; and methylene transfer from dimethyloxosulphonium methylide to aziridines [41].

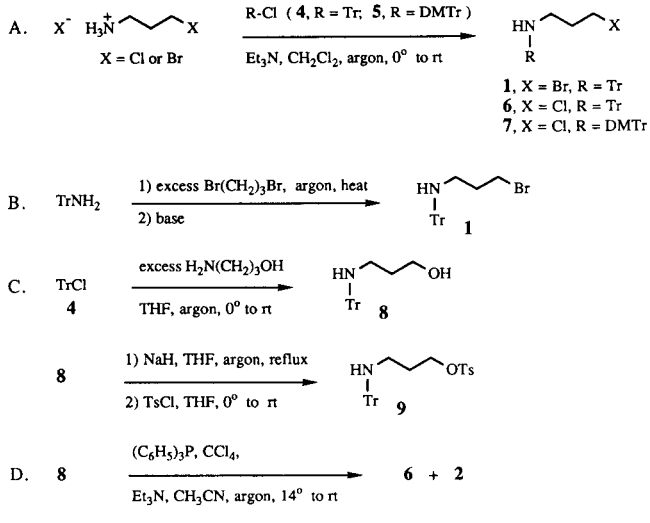
In a study of extension of dimercaptan- or diamine chains with aminopropyl units using 3-bromo-*N*-tritylpropanamine (**1**) and sodium hydride in refluxing dioxane, we noticed that in most cases, *N*-tritylazetidine (**2**), the self condensation product of **1**, was also formed [42]. When this reaction was carried out in the absence of dimercaptan or diamine, **2** was the sole product in an 80% yield [42] (Scheme IIA). It has been well established that bulky *N*-substituents facilitate ring closure of 3-haloalkylamines to azetidines [43]. Considering the latter fact and the possibility of removing the *N*-trityl-protecting group in mild conditions [42,44,45], we felt it important to study this reaction further. It is also important to note that there is a paucity of cheap, general, facile and efficient azetidine syntheses. Azetidine obtained in the final step of most of the reported methods contain considerable amounts of impurities such as water [39], benzene [40] and others [37]. The method reported herein gives pure azetidine in good yields.

Results and Discussion.

Scheme I shows the synthesis of starting materials needed for the preparation of *N*-trityl- and *N*-dimethoxytritylazetidines **2** and **3**. The preparation of 3-halo-*N*-tritylpropanamines **1** and **6** and 3-chloro-*N*-dimethoxytritylpropanamine (**7**) is shown in Scheme IA. We made some changes in the literature procedures described for the preparation of **1** (lit yield, 64% [46]) and (lit yield, 58% [47]), and obtained **1** in 76%, **6** in 90% and **7** in 96% yields. To our knowledge, **6** and **7** have not been reported. Compound **1** was also prepared from tritylamine and 1,3-dibromopropane (Scheme IB) but in a lower yield (45%). Scheme IC shows the preparation of 3-*N*-tritylaminopropyl *p*-toluenesulfonate (**9**). 3-*N*-Tritylamino-1-propanol (**8**) was obtained in a 83% yield from **4** and excess 3-amino-1-propanol. Although **8** has been mentioned in the literature [48] neither

its preparation nor its physical and spectroscopic properties have been reported. Compound **9** was obtained in an 82% yield from **8** by *O*-tosylation using a strong base. It was necessary to reflux **8** with sodium hydride in THF for a long time before adding the tosyl chloride to the reaction mixture, otherwise the yield dropped considerably. Alcohol **8** can also be used for the preparation of **6** (yield, 87%), but in this case 5% of *N*-tritylazetidine also formed as a side product (see Scheme ID).

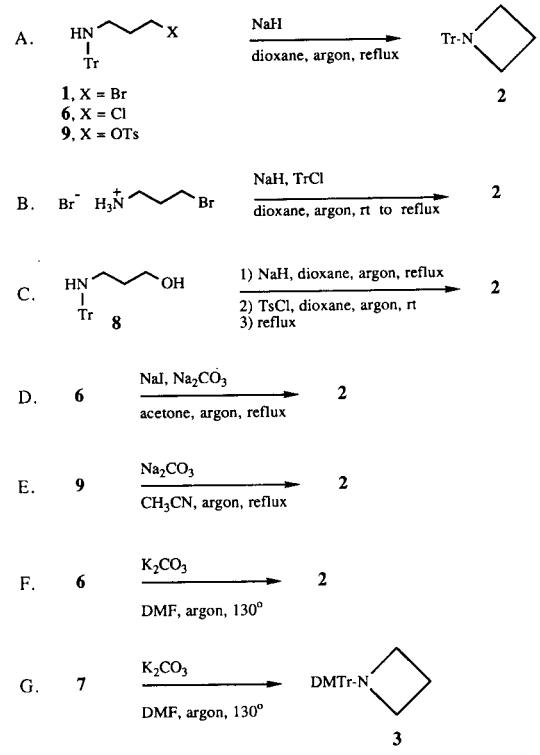
Scheme I[a]



[a] Tr = trityl, DMTr = 4,4'-dimethoxytrityl, Ts = tosyl, rt = room temperature

Scheme II shows the procedures for the preparation of *N*-tritylazetidine (**2**) and *N*-dimethoxytritylazetidine (**3**). As mentioned earlier, **1** produces **2** in an 80% yield [42]. This reaction required reflux temperature for 48 hours. As expected, preparation of **2** from the tosyloxy analogue **9** required less reflux time (32 hours, 83%) and from the chloro compound **6** considerably more reflux time (400 hours, 75%) to get good yields (Scheme IIA). Scheme IIB shows a one pot procedure for preparing **2** from commercially available 3-bromopropanamine hydrobromide and trityl chloride (**4**). In this case, the yield of **2** was low (40%) and column chromatography was necessary to get a pure product. The *N*-tritylated aminopropanol (**8**) was also converted to **2** using a one pot procedure giving a 71% yield (Scheme IIC). It is interesting that when trying to exchange the chloride of **6** for an iodide using sodium iodide and sodium carbonate in refluxing acetone, **2** slowly formed. After 60 hours of reflux only **2** was isolated in an 80% yield (Scheme IID). Using acetonitrile, which has a higher boiling point than acetone, we were able to cyclize **9** into **2** with sodium carbonate in concentrated solution (36 hours: 80%, Scheme IIE). At a higher temperature in DMF, even **6** cyclized into **2** in 90 hours in a 93% yield (Scheme IIF). In the same conditions, **7** (the dimethoxy analog of **6**) was converted into **3** in a 91% yield in only 20 hours (Scheme IIG). Sodium hydride is not only dangerous to handle and costly, it also contains mineral oil and amine **2** prepared by procedures IIA, B and C was contaminated with mineral oil and had to be recrystallized from hexane. In most cases after recrystallization from hexane, another recrystallization from ethanol was necessary to remove other impurities. Procedures IID–F are superior methods to prepare **2** because one recrystallization from ethanol always gave a pure product.

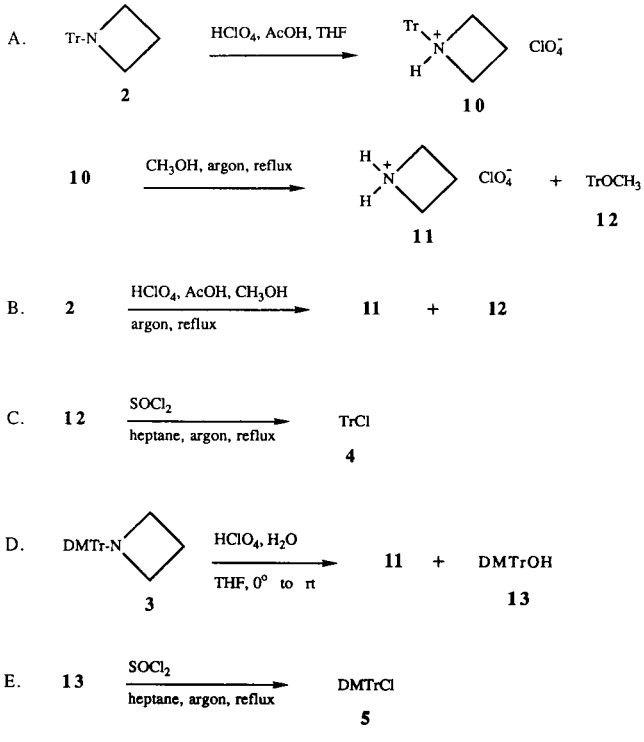
Scheme II



Schemes III (A, B and D) show the preparation of azetidine hydrogenperchlorate salt (**11**) by removal of the *N*-trityl and *N*-dimethoxytrityl groups. Scheme IIIC and E show the transformation of methyl trityl ether (**12**) and dimethoxytrityl alcohol (**13**), products formed from the protecting groups, into the corresponding chlorides **4** (96%) and **5** (91%), respectively. Thus, **4** and **5**, the most expensive starting materials (see Scheme I), can be recycled in good yields. As shown in Scheme IIIA, first, the stable hydrogen perchlorate salt of *N*-tritylazetidine (**10**) was prepared in a 96% yield, then **10** was refluxed in methanol for 60 hours to give **11** (55%) and **12** (86%). Scheme IIIB shows a one pot procedure for the preparation of **11** from **2** with about the same (52%) yield. In this case, 84% of **12** was obtained. Compound **11** was formed *in situ* when azetidine was polymerized [49,50] and was mentioned as a side product in the preparation of *N*-perchlorylazetidine [51], but neither its physical nor its spectroscopic proper-

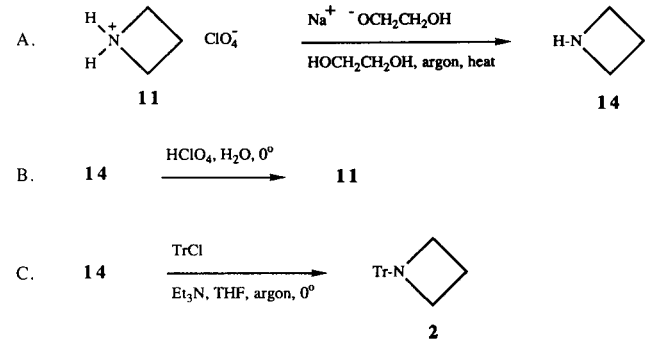
ties were reported. Compound **11** is a stable non-hygroscopic salt containing a non-nucleophilic anion. A deuterium oxide solution of **11** was kept at room temperature in a sealed nmr tube for 6 months with no change in its ^1H nmr spectrum. The moderate yields of **11** in the procedures IIIA and B could be caused by prolonged refluxing in methanol. Lapidot and coworkers reported that the *N*-methoxytrityl group in a peptide was easier to remove than its *N*-trityl counterpart [52]. We used the *N*-4,4'-dimethoxytrityl group, but in this case, methanol was not used to remove the protecting group because, in methanol, the initially formed methyl dimethoxytrityl ether would be reduced [53] and therefore, could not be recycled into **5**. Using an equivalent amount of perchloric acid in a water-tetrahydrofuran mixture at room temperature, **3** was converted to **11** (86%) and **13** (99%) in 24 hours (Scheme IIID). Treating non-methoxy-substituted **2** in the same manner for 6 days gave only traces of trityl alcohol and **11**. Thus, in these syntheses, the dimethoxytrityl species is a superior protecting group.

Scheme III



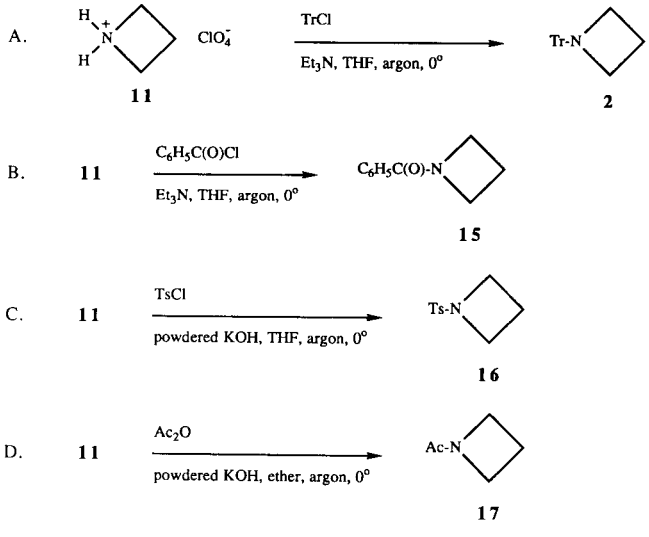
Scheme IVA shows the procedure for obtaining free azetidine (**14**) from its hydrogen perchlorate salt **11**. Sodium metal was dissolved in ethylene glycol to form a base. Salt **11** in ethylene glycol was then added at a temperature below 60° because above this temperature polymerization can take place if both **11** and **14** are present [49,50]. After mixing the two solutions, the temperature of the reaction mixture was gradually raised allowing **14** (81%) to distill. The purity of crude **14** was checked by spectroscopic methods and it was transformed back into crystalline **11** (99%) (Scheme IVB) and **2** (98%) (Scheme IVC).

Scheme IV



Scheme V shows a few examples demonstrating that **11** can be used in place of **14** for many reactions. Thus, *N*-tritylazetidine (**2**, 92%) was prepared from **11** (Scheme VA), as were *N*-benzoylazetidine (**15**, 96%) (Scheme VB), *N*-tosylazetidine (**16**, 92%) (Scheme VC), and *N*-acetylazetidine (**17**, 91%) (Scheme VD). These reactions clearly show that the synthesis of azetidine (**14**) can be accomplished in few steps from readily available starting materials and that **11**, a very stable derivative, can be used for reactions involving this important small heterocyclic compound.

Scheme V



Crystals of **2**, **10**, and **11** were prepared for X-ray studies. These crystal structures give important information allowing a more complete characterization of the azetidine ring. The structure of **11** contains protonated azetidine. Unfortunately the disordered ClO_4^- in the structure reduces the accuracy of the atomic parameters of the atoms and, therefore affects the accuracy of the determination of

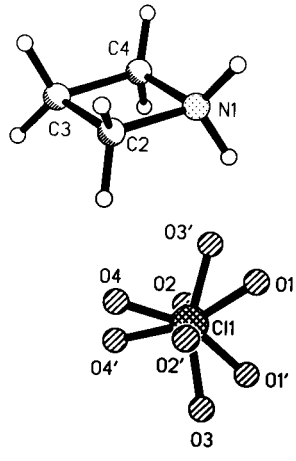


Figure 1. Computer drawing of **11** showing the conformation of the azetidine ring and atom labels.

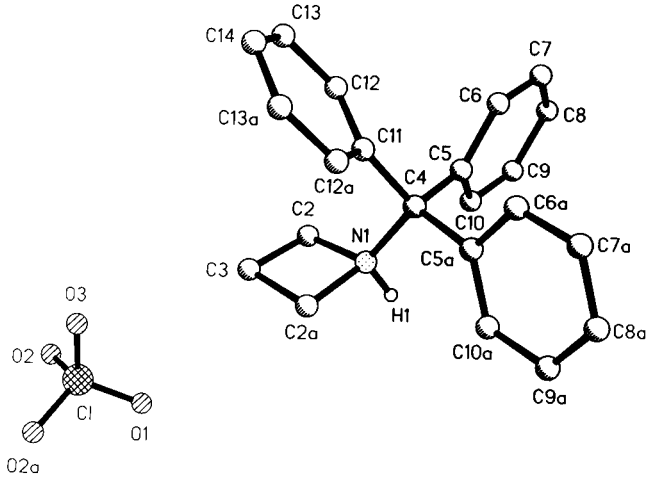


Figure 2. Computer drawing of **10** showing the conformation of the azetidine ring and atom labels. All hydrogens except the one bonded to nitrogen are excluded for clarity.

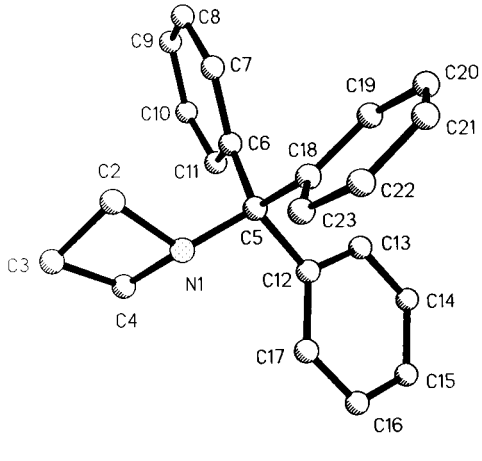


Figure 3. Computer drawing of **2** showing the conformation of the azetidine and atom labels. Hydrogens are omitted for clarity.

Table 1

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 x 10^3) for Nonhydrogen and Isotropic Displacement Coefficients (Å^2 x 10^3) for Hydrogen Atoms of **11**

	x	y	z	U (eq) or U [a]
N1	1993 (5)	984 (3)	5115 (14)	56 (1)
H1A	1514	771	6080	80
H1B	1600	798	4066	80
C2	2067 (7)	1776 (4)	5163 (14)	69 (1)
H2A	1624	2009	6125	80
H2B	1709	1977	4111	80
C3	3677 (8)	1747 (5)	5057 (17)	114 (1)
H3A	4153	1989	4132	80
H3B	4064	1905	6137	80
C4	3602 (7)	960 (4)	5056 (17)	84 (1)
H4A	4078	700	5958	80
H4B	3928	789	3959	80
Cl	1993 (2)	1020 (1)	0	62 (1)
O1	1246	595	1146	92 (1)
O2	3115	636	-671	195 (1)
O3	1089	1225	-1308	270 (1)
O4	2502	1612	845	251 (1)
O1'	1331	628	-1278	133 (1)
O2'	994	1443	810	218 (1)
O3'	2598	562	1179	181 (1)
O4'	3038	1443	-718	206 (1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 x 10^3) for Nonhydrogen and Isotropic Displacement Coefficients (Å^2 x 10^3) Hydrogen Atoms of **10**

	x	y	z	U (eq) or U [a]
C1	1008 (2)	2500	8665 (1)	56 (1)
O1	-347 (8)	2500	8380 (6)	143 (4)
O2	1283 (6)	3431 (5)	9105 (3)	163 (3)
O3	2037 (10)	2500	8060 (4)	130 (4)
N1	-761 (6)	2500	5132 (3)	36 (2)
H1	-1716	2500	5229	37 (18)
C2	-120 (5)	3380 (4)	5664 (2)	44 (2)
H2A	-1028	3737	5895	59 (15)
H2B	521	3931	5391	41 (12)
C3	664 (11)	2500	6121 (5)	68 (3)
H3A	589	2500	6771	103 (32)
H3B	1628	2500	5944	84 (33)
C4	-387 (7)	2500	4271 (3)	35 (2)
C5	-1076 (5)	3523 (4)	3898 (2)	38 (1)
C6	-614 (6)	3871 (4)	3161 (3)	55 (2)
H6	109	3318	2942	105 (23)
C7	-1274 (6)	4731 (4)	2787 (3)	61 (2)
H7	-1038	5024	2244	99 (21)
C8	-2416 (6)	5273 (4)	3125 (3)	54 (2)
H8	-2841	5866	2842	56 (15)
C9	-2877 (5)	4959 (4)	3847 (3)	50 (2)
H9	-3753	5299	4185	81 (18)
C10	-2216 (5)	4083 (4)	4233 (3)	42 (1)
H10	-2548	3787	4759	35 (11)
C11	1254 (7)	2500	4198 (4)	40 (2)
C12	2019 (5)	3483 (4)	4189 (3)	47 (2)
H12	1396	4172	4216	63 (16)
C13	3508 (6)	3481 (6)	4170 (3)	63 (2)
H13	4046	4257	4133	85 (19)
C14	4249 (9)	2500	4154 (5)	68 (3)
H14	5464	2500	4133	90 (28)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 x 10^3) for Nonhydrogen Atoms and Isotropic Displacement Coefficients (Å^2 x 10^3) for Hydrogen Atoms of **2**

	x	y	z	U (eq) or U [a]
N1	3262 (3)	178 (6)	4297(1)	35 (2)
C2	2627 (4)	-1203 (8)	4355 (2)	50 (2)
H2A	2287	-1645	4071	80
H2B	2281	-851	4563	80
C3	3371 (4)	-2417 (8)	4577 (2)	65 (3)
H3A	3327	-3617	4458	80
H3B	3502	-2422	4906	80
C4	3958(4)	-1196 (7)	4367 (2)	51 (3)
H4A	4468	-832	4580	80
H4B	4076	-1633	4086	80
C5	3092 (3)	1366 (7)	3886 (2)	31 (2)
C6	2899 (4)	230 (7)	3446 (2)	35 (2)
C7	2082 (4)	-371 (7)	3257 (2)	47 (2)
H7	1620	76	3380	80
C8	1919 (5)	-1576 (9)	2893 (2)	66 (3)
H8	1354	-2009	2767	80
C9	2580 (7)	-2224 (9)	2720 (2)	75 (4)
H9	2473	-3041	2465	80
C10	3396 (6)	-1658 (9)	2901 (2)	68 (3)
H10	3857	-2121	2780	80
C11	3558 (4)	-429 (8)	3261 (2)	50 (2)
H11	4125	-3	3385	80
C12	3868 (3)	2638 (7)	3921 (2)	32 (2)
C13	4007 (4)	3473 (8)	3532 (2)	52 (2)
H13	3634	3222	3240	80
C14	4671 (4)	4701 (9)	3565 (3)	63 (3)
H14	4769	5241	3291	80
C15	5192 (4)	5102 (9)	3979 (3)	61 (3)
H15	5651	5940	3995	80
C16	5050 (4)	4289 (9)	4369 (3)	55 (3)
H16	5411	4573	4662	80
C17	4389 (3)	3061 (7)	4341 (2)	41 (2)
H17	4291	2498	4612	80
C18	2354 (3)	2640 (6)	3930 (2)	31 (2)
C19	1897 (4)	3570 (8)	3548 (2)	49 (2)
H19	2028	3375	3254	80
C20	1265 (4)	4751 (9)	3594 (3)	64 (3)
H20	964	5403	3331	80
C21	1076 (4)	5062 (8)	4015 (3)	59 (3)
H21	624	5867	4040	80
C22	1527 (4)	4184 (9)	4391 (3)	56 (3)
H22	1398	4382	4685	80
C23	2161 (3)	2952 (8)	4349 (2)	45 (2)
H23	2480	2331	4613	80

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 4

Bond Lengths and Angles Excluding ClO_4^- of **11**

1	2	3	1-2	1-2-3
C2	N1	C4	1.49 (1)	89.0 (5)
C3	C2	N1	1.51 (1)	90.5 (5)
C4	C3	C2	1.48 (1)	89.4 (6)
N1	C4	C3	1.51 (1)	91.0 (5)

Table 5

Bond Lengths and Angles Excluding Phenyl Groups and ClO_4^- of **10**

1	2	3	1-2 (Å)	1-2-3 (°)
C2	N1	C4	1.531 (6)	119.5 (3)
C2	N1	C2A		88.6 (4)
N1	C2	C3		90.4 (4)
C2	C3	C2A	1.516 (8)	89.7 (6)
N1	C4	C5	1.523 (8)	108.1 (3)
C5	C4	C11	1.541 (6)	112.5 (3)
C5	C4	5A		107.6 (5)
C4	C5	C6		119.4 (4)
C4	C5	C10		122.8 (4)
C4	C11	C12	1.539 (9)	120.8 (3)

Table 6

Bond Lengths and Angles Excluding Phenyl Groups of **2**

1	2	3	1-2 (Å)	1-2-3 (°)
C2	N1	C4	1.485 (8)	91.3 (4)
C2	N1	C5		120.2 (4)
C4	N1	C5	1.495 (7)	121.0 (5)
N1	C2	C3		88.2 (4)
C2	C3	C4	1.528 (8)	88.0 (5)
C3	C4	N1	1.540 (10)	87.4 (5)
N1	C5	C6	1.490 (7)	110.2 (4)
C12	C5	N1	1.550 (7)	108.0 (4)
C6	C5	C12	1.537 (7)	113.6 (5)
N1	C5	C18		107.2 (4)
C18	C5	C6	1.547 (7)	113.5 (4)
C12	C5	C18		103.9 (4)
C5	C6	C7		121.3 (5)
C5	C6	C11		120.6 (5)
C5	C12	C13		119.6 (5)
C5	C12	C17		121.2 (5)
C5	C18	C19		120.5 (5)
C5	C18	C23		120.9 (4)

Table 7

Possible H-Bond Data for **11** [a]

D	H	A	D...A (Å)	H...A (Å)	D-H-A (°)	Transformation of A
N1	H1A	O1	2.94	2.07	150	x, y, 1+z
N1	H1A	O3	2.94	2.24	129	x, y, 1+z
N1	H1B	O1	3.14	2.32	161	x, -y, 0.5 + z

[a] The esd values of the D...A distance is approximately 0.01Å while the esd values for the distances and angles involving hydrogen atoms are appoximaely 0.04Å and 2° respectively.

the bond lengths and angles in the ring. The structures of **10** and **2** are significant because they are identical derivatives of azetidine except that **10** is a protonated perchlorate salt while **2** contains the unprotonated ring. Computer drawings of **11**, **10** and **2** are shown in Figures 1, 2 and 3, respectively. Positional and thermal parameters for the three compounds are listed in Tables 1, 2 and 3 and important bond lengths and angles are given in Tables 4, 5 and 6. Because the perchlorate anions of **11** and **10** and the phenyl groups of **10** and **2** are not the focus of this paper, the bond lengths and angles of these groups are not included in the tables.

The two major differences in the protonated ring of **11** and **10** and unprotonated ring of **2** are the bond lengths and the angle θ, which is the dihedral angle between the C N C plane and the C C C plane in the four-membered ring. In protonated compounds **11** and **10**, the C-C and C-N bonds are approximately the same lengths (see Tables 4 and 5). However, in the unprotonated ring of **2**, the C-N bonds are significantly shorter than the C-C bonds (See

Table 8
Crystal Data of **11**, **10** and **2**

	11	**10**	**2**
Formula	$C_3H_8N^+ClO_4^-$	$C_{22}H_{22}N^+ClO_4^-$	$C_{22}H_{21}N$
Crystal size (nm)	0.08 x 0.14 x 0.38	0.3 x 0.4 x 0.4	0.16 x 0.35 x 0.50
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	Iba2	Pnma	C2/c
a (Å)	9.358 (2)	9.349 (2)	16.074 (7)
b (Å)	18.746 (6)	12.159 (3)	7.443 (2)
c (Å)	7.768 (2)	17.220 (4)	29.903 (11)
β (°)	90	90	102.88 (3)
V (Å^3)	1362.7	1957.5	3487
Z	8	4	8
Dx (Mg/m^3)	1.536	1.357	1.134
Absorption Coefficient (mm^{-1})	0.509	0.224	0.065
F (000)	656	840	1280

Table 6). This difference is observed in several other studies of compounds containing protonated and unprotonated azetidine rings [22,24,25].

The rings of the two protonated azetidines are nearly planar since the θ angles of **11** and **10** are 178.2° and 170.2° respectively. The angle in **2** is 155.5°. It has been suggested that the nearly planar ring in the protonated azetidines is a result of hydrogen bonding involving the hydrogens of the azetidine ring nitrogen atom and the anion [23]. However, other factors must be involved. There is good evidence for hydrogen bonds in **11** (see Table 7), but there is no evidence for hydrogen bonds in **10** with all N-O (perchlorate) distances longer than 3.30 Å. It is likely that the energy difference between the planar and bent conformation of the four-membered ring is small as is the case for cyclobutane, where the difference is 5.9 kJ mol^{-1} [23]. Packing and other forces can play an important role in determining conformation in the solid state. The presence of groups of atoms such as phenyl groups or ClO_4^- near the four membered ring may be important factors. For example, one of the phenyl groups, which lies on the mirror plane, is close to the azetidine ring (Figure 2).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Perkin-Elmer FT1600 spectrometer. Nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a Varian Gemini 200 spectrometer in deuteriochloroform using tetramethylsilane as the internal standard unless otherwise indicated. Molecular weights were determined by the electron impact method on a Finnegan 8430 high resolution mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Az. The crystal structural determinations were done on a Nicolet R3 autodiffractometer. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel ALSILG/UV254 (Whatman) plates were used for tlc. Silica Gel 60 (230-400 mesh; EM Science) was used for column chromatography. Developed tlc plates were visualized by uv light or the compounds were detected by using hydrogen chloride gas (in the presence of Tr and DMTr groups) and spraying them with 10% (w/v) phosphomolybdic acid (Spectrum Chemical Company) in ethanol and heating the plates in an oven at 180° for 10 minutes. 4,4'-Dimethoxytrityl chloride (**5**) was prepared as reported [53].

General Procedure for Preparation of 3-Halo-*N*-tritylpropanamines **1** and **6** and 3-Chloro-*N*-4,4'-dimethoxytritylpropanamine (**7**) (Scheme IA).

To a vigorously stirred mixture of 0.47 mole of 3-halopropanamine hydrohalide (dried over phosphorus pentoxide in a vacuum desiccator for 2 days) in 500 ml of dry and pure dichloromethane at 0° and under argon, was added dropwise, first, 150 ml (108.9 g, 1.08 mole) of triethylamine, then 0.42 mole of trityl chloride (**4**), or 4,4'-dimethoxytrityl chloride (in the case of **7**) dissolved in 1000 ml of dichloromethane. After addition, the reaction mixture was stirred at 0° for 3 hours, then the ice bath was removed and stirring was continued for two days. Dichloromethane (1000 ml) was added to the reaction mixture and it was mixed well twice with 1000 ml portions of ice water. The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure to give crude products **1**, **6**, and **7**.

3-Bromo-*N*-tritylpropanamine (**1**) (Scheme IA).

This compound was prepared following the general procedure using 102.5 g (0.47 mole) of 3-bromopropanamine hydrobromide and 117.9 g (0.42 mole) of trityl chloride. The crude product was recrystallized from 1,2-dichloroethane-methanol to give 122.1 g (76%) of **1** as white crystals, mp 102-103°, (reported 98-101° [46] and 100-102.5° [47]); Rf (tlc): 0.4 (toluene/hexane = 1/1); ir (potassium bromide): 3295, 3084, 3055, 3028, 1595, 1490, 1474 cm^{-1}; ^{1}H nmr: δ 1.49 (s, broad, 1 H, disappeared in deuterium oxide), 2.01 (quin, 2 H, J = 6 Hz), 2.29 (t, 2 H, J = 6 Hz), 3.57 (t, 2 H, J = 6 Hz), 7.11-7.57 (m, 15 H).

Compound **1** was also prepared as follows (see Scheme IB). A mixture of 6.1 g (23.5 mmoles) of tritylamine and 35 ml (69.6 g, 345 mmoles) of 1,3-dibromopropane was stirred at 120° under argon for 30 hours. The excess 1,3-dibromopropane was removed under reduced pressure. The residue was dissolved in a mixture of 160 ml of dichloromethane and 80 ml of saturated potassium carbonate solution. The phases were shaken well and separated. The organic phase was shaken with 80 ml of water, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was triturated with 70 ml of methanol and the mixture containing a white pre-

cipitate was stored at room temperature for 2 hours and in a refrigerator for 1 day. The crystals were filtered, dried and recrystallized from 1,2-dichloroethane-methanol to give 4.02 g (45%) of **1**, which was identical to **1** above.

3-Chloro-*N*-tritylpropanamine (**6**) (Scheme IA).

This compound was prepared following the general procedure using 60.9 g (0.47 mole) of 3-chloropropanamine hydrochloride and 117.9 g (0.42 mole) of trityl chloride (**4**). The amine product was recrystallized from 1,2-dichloroethane-ethanol to give 127.8 g (90%) of **6** as white crystals, mp 108-109°; Rf (tlc): 0.45 (toluene/hexane = 1/1); ir (potassium bromide): 3295, 3085, 3053, 3030, 1596, 1490, 1474 cm^{-1}; ^1H nmr: δ 1.54 (s, broad, 1 H, disappeared in deuterium oxide), 1.93 (quin, 2 H, J = 6 Hz), 2.28 (t, 2 H, J = 6 Hz), 3.69 (t, 2 H, J = 6 Hz), 7.02-7.61 (m, 15 H).

Compound **6** was also prepared as follows (see Scheme ID). To a vigorously stirred mixture of 23.4 g (73.8 mmoles) of 3-*N*-tritylaminopropanol (**8**, its preparation is described below) and 23.4 g (89.3 mmoles) of triphenylphosphine in 65 ml of acetonitrile under argon and in a cold water bath was added dropwise, first, 12.46 ml (9.04 g, 89.3 mmoles) of triethylamine, then 8.62 ml (13.7 g, 89.3 mmoles) of carbon tetrachloride. The reaction mixture was stirred in a cold water bath for 14 hours then at room temperature for 1 day. The solvent was evaporated under reduced pressure and the residue was triturated with 300 ml of anhydrous ethyl alcohol. The mixture containing a white precipitate was stored at room temperature for 4 hours and then in a refrigerator for 1 day. The white crystals were filtered and dried to give 20.4 g (82%) of pure **6**. The mother liquor was evaporated under reduced pressure and the residue was triturated with 250 ml of diethyl ether. The mixture, containing triphenylphosphine oxide as a white precipitate, was stored at room temperature for 2 hours and in a refrigerator for 2 days. After filtering the triphenylphosphine oxide, the mother liquor was evaporated to dryness under reduced pressure, and the residue was purified by column chromatography on silica gel using a 1/100 tetrahydrofuran/hexane mixture as an eluent to give 1.23 g (5%) of pure **6** [Rf (tlc): 0.15 (tetrahydrofuran/hexane = 1/100)] and 1.08 g (5%) of *N*-tritylazetidine (**2**) [Rf (tlc): 0.23 (tetrahydrofuran/hexane = 1/100)]. Compound **2** had the same properties as **2** prepared by the procedure in Scheme IIA (below). The combined yield for **6** was 21.6 g (87%) and it was identical to **6** prepared above.

3-Chloro-*N*-4,4'-dimethoxytritylpropanamine (**7**) (Scheme IA).

Compound **7** was prepared following the general procedure using 60.9 g (0.47 mole) of 3-chloropropanamine hydrochloride and 143.3 g (0.42 mole) of 4,4'-dimethoxytrityl chloride (**5**). Crude **7** (160.5 g, 96%), a viscous oil, was reasonably pure according to its tlc and ^1H nmr and ir spectra so it was used in the next step without further purification; Rf (tlc): 0.4 (tetrahydrofuran/hexane = 1/10); ir (neat): 3315, 3056, 3032, 1606, 1580, 1507, 1461 cm^{-1}; ^1H nmr: δ 1.47 (s, broad, 1 H, disappeared in deuterium oxide), 1.91 (quin, 2 H, J = 6 Hz), 2.27 (t, 2 H, J = 6 Hz), 3.67 (t, 2 H, J = 6 Hz), 3.75 (s, 6 H), 6.80 (d, 4 H, J = 10 Hz), 7.10-7.50 (m, 5 H), 7.36 (d, 4 H, J = 10 Hz); ms: (CI) m/z 396 (M + 1), 303, 304.

3-*N*-Tritylamino-1-propanol (**8**) (Scheme IC).

To a vigorously stirred solution of 90 g (1.2 moles) of 3-aminopropanol in 600 ml of pure and dry tetrahydrofuran under argon and in an ice bath, was added dropwise, 139.4 g (0.5 mole) of trityl chloride dissolved in 600 ml of tetrahydrofuran. After addition, the reaction mixture was stirred at 0° for 4 hours then at room temperature for 2 days. During the reaction, an oil separated from the reaction mixture. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 800 ml of ice water and 1200 ml of dichloromethane. The phases were mixed well and separated. The aqueous phase was shaken twice with 400 ml portions of dichloromethane. The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Crude **8** was recrystallized from toluene-hexane to give 131.5 g (83%) of pure crystals, mp 120-121°; Rf (tlc): 0.1 (anhydrous ethyl alcohol/toluene = 1/80); ir (potassium bromide): 3368, 3054, 3018, 1595, 1490, 1445 cm^{-1}; ^1H nmr: δ 1.69 (quin, 2 H, J = 6 Hz), 2.37 (t, 2 H, J = 6 Hz), 2.7 (s, very broad, 2 H, disappeared in deuterium oxide), 3.85 (t, 2 H, J = 6 Hz), 7.13-7.56 (m, 15 H).

3-*N*-Tritylaminopropyl *p*-Toluenesulfonate (**9**) (Scheme IC).

To a vigorously stirred mixture of 12.0 g (0.4 mole, 80% dispersion in mineral oil) of sodium hydride and 50 ml of dry and pure tetrahydrofuran under argon and in an ice bath, was added dropwise, 31.7 g (0.1 mole) of **8** dissolved in 300 ml of tetrahydrofuran. After addition, the reaction mixture was stirred at 0° for 10 minutes, at room temperature for 1 hour and then it was refluxed for 2 days. The reaction mixture was cooled to 0° and 23.8 g (0.13 mole) of tosyl chloride dissolved in 100 ml of tetrahydrofuran was added dropwise. After addition, the reaction mixture was stirred at 0° for 1 hour then at room temperature for 2 days. The solvent was evaporated under reduced pressure and the residue was treated cautiously with 200 g of ice. After the excess sodium hydride was destroyed, 600 ml of dichloromethane and 100 ml of ice water was added to the mixture and the phases were mixed well and separated. The aqueous phase was shaken twice with 200 ml portions of dichloromethane. The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Crude **9** was recrystallized from 1,2-dichloroethane-anhydrous ethanol to give 38.6 g (82%) of pure crystals, mp 127-128°; Rf (tlc): 0.65 (anhydrous ethanol/toluene = 1/80); ir (potassium bromide): 3301, 3060, 3026, 1596, 1557, 1491, 1463, 1449, 1357, 1173 cm^{-1}; ^1H nmr: δ 1.46 (s, broad, 1 H, disappeared in deuterium oxide), 1.79 (quin, 2 H, J = 6 Hz), 2.15 (t, 2 H, J = 6 Hz), 2.42 (s, 3 H), 4.18 (t, 2 H, J = 6 Hz), 7.12-7.48 (m, 17 H), 7.73 (d, 2 H, J = 8 Hz).

Anal. Calcd. for $C_{29}H_{29}NO_3S$: C, 73.86; H, 6.20. Found: C, 73.72; H, 6.25.

General Procedure for Preparation of *N*-Tritylazetidine (**2**) From **1**, **6** and **9** Using Sodium Hydride in Dioxane (Scheme IIA).

To a vigorously stirred mixture of 4.0 g (133.3 mmoles, 80% dispersion in mineral oil) of sodium hydride and 200 ml of dry and pure dioxane at room temperature and under argon, was added dropwise, 52.6 mmoles of 3-halo-*N*-tritylpropanamine, **1** or **6**, or its tosyloxy analogue **9** dissolved in 800 ml of dioxane. After addition, the reaction mixture was stirred at room temperature for 10 minutes and refluxed for the time indicated below for each individual compound **1**, **6** or **9**. The solvent was evaporated under reduced pressure and the residue was treated cautiously (in small portions) with 100 g of ice. After the excess sodium hydride was destroyed, 300 ml of diethyl ether was added to the mixture and the phases were mixed well and separated. The aqueous phase was shaken twice with 100 ml of portions of diethyl ether. The

combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to give crude **2**.

N-Tritylazetidine (**2**) From **1** (Scheme IIA).

Following the general procedure, 20.0 g (52.6 mmoles) of **1** and 4.0 g (133.3 mmoles) of sodium hydride was refluxed in 1000 ml of dioxane for 48 hours. Crude **2** was recrystallized from hexane to give 12.6 g (80%) of pure, white crystals, mp 115-116°; Rf (tlc): 0.25 toluene/hexane = 1/1); ir (potassium bromide): 3054, 3000, 1594, 1486, 1448 cm^{-1}; ^1H nmr: δ 1.78 (quin, 2 H, J = 6 Hz), 3.00 (t, 4 H, J = 6 Hz), 7.09-7.53 (m, 15 H); ms: (CI) 300 (M + 1), 244.

Anal. Calcd. for $C_{22}H_{21}N$: C, 88.25; H, 7.07. Found: C, 88.19; H, 7.14.

N-Tritylazetidine (**2**) From **6** (Scheme IIA).

Following the general procedure, a mixture of 17.7 g (52.6 mmoles) of **6** and 4.0 g (133.3 mmoles) of sodium hydride was refluxed in 1000 ml of dioxane for 400 hours. Crude **2** was recrystallized, first from hexane, then from anhydrous ethyl alcohol to give 11.8 g (75%) of pure white crystals, mp 118-119°. The Rf (tlc) value, ir and ^1H nmr spectra of **2** prepared from **6** were identical to those of **2** prepared above.

N-Tritylazetidine (**2**) From **9** (Scheme IIA).

Following the general procedure, a mixture of 24.8 g (52.6 mmoles) of **9** and 4.0 g (133.3 mmoles) of sodium hydride was refluxed in 1000 ml of dioxane for 32 hours. Crude **2** was recrystallized, first from hexane, then from anhydrous ethyl alcohol to give 13.1 g (83%) of **2** which was identical to **2** prepared above.

N-Tritylazetidine (**2**) From **4** and 3-Bromopropanamine Hydrobromide (Scheme IIB).

To a stirred mixture of 4.4 g (20 mmoles) of dried and powdered 3-bromopropanamine hydrobromide, 5.6 g (20 mmoles) of trityl chloride (**4**) and 3 g (100 mmoles, 80% dispersion in mineral oil) of sodium hydride under argon and in a cold water bath, was added dropwise, 120 ml of dry and pure dioxane. After addition, the reaction mixture was stirred in the cold water bath for 4 hours, at room temperature for 2 days and then it was refluxed for 2 days. The reaction mixture was treated as described above. Crude **2** was first purified by column chromatography on silica gel using tetrahydrofuran/hexane = 1/100 as eluent then it was recrystallized from anhydrous ethyl alcohol to give 2.4 g (40%) of pure **2** which was identical to **2** above.

N-Tritylazetidine (**2**) from **8** and Tosyl Chloride (Scheme IIC).

To a vigorously stirred suspension of 15.0 g (0.5 mole, 80% dispersion in mineral oil) of sodium hydride in 100 ml of dry and pure dioxane under argon and in a cold water bath, was added dropwise, 26.4 g (83.3 mmoles) of **8** dissolved in 450 ml of dioxane. The reaction mixture was stirred in the cold water bath for 10 minutes, at room temperature for 1 hour and refluxed for 2 days. The reaction mixture was cooled in a cold water bath and 22.2 g (116.6 mmoles) of tosyl chloride dissolved in 100 ml of dioxane was added dropwise. After addition, the reaction mixture was stirred in the cold water bath for 4 hours, at room temperature for 2 days and refluxed for 32 hours. The reaction mixture was treated as above for the preparation of **2** from **9** (Scheme IIA). In this case, 17.7 g (71%) of pure **2** was obtained.

N-Tritylazetidine (**2**) From **6** Using Sodium Iodide and Sodium Carbonate in Acetone (Scheme IID).

A vigorously stirred mixture of 21.7 g (64.6 mmoles) of **6**, 8.22 g (77.6 mmoles) of powdered anhydrous sodium carbonate and 9.7 g (64.6 mmoles) of sodium iodide was refluxed in 125 ml of dry and pure acetone under argon for 60 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 200 ml of ice water and 300 ml of ether. The phases were shaken well and separated. The aqueous phase was shaken twice with 100 ml portions of ether. The combined organic phase was shaken with saturated brine (100 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from anhydrous ethyl alcohol to give 15.5 g (80%) of **2** which was identical to **2** above.

N-Tritylazetidine (**2**) From **9** Using Sodium Carbonate in Acetonitrile (Scheme IIE).

A vigorously stirred mixture of 30.5 g (64.6 mmoles) of **9** and 8.2 g (77.6 mmoles) of powdered anhydrous sodium carbonate was refluxed in 150 ml of pure and dry acetonitrile under argon for 36 hours. The reaction mixture was treated as above to give **2** (15.4 g, 80%).

N-Tritylazetidine (**2**) From **6** Using Potassium Carbonate in Dimethylformamide (Scheme IIF).

A vigorously stirred mixture of 43.4 g (0.13 mole) of **6** and 35.7 g (0.26 mole) of powdered anhydrous potassium carbonate was kept at 130° in 300 ml of dry and pure *N,N*-dimethylformamide for 90 hours. The solvent was evaporated under high vacuum. The residue was dissolved in a mixture of 400 ml of ice water and 600 ml of ether. The phases were shaken well and separated. The aqueous phase was shaken twice with 200 ml portions of ether. The combined organic phase was shaken with 200 ml of saturated brine, dried under anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from anhydrous ethanol to give 35.9 g (93%) of **2** which was identical to **2** above.

N-4,4'-Dimethoxytritylazetidine (**3**) (Scheme IIG).

Compound **3** was prepared as described above for the preparation of **2** from **6** with a reaction time of 20 hours and using 51.1 g (0.13 mole) of **7** to give 45.1 g of crude **3**. Crude **3** was stirred under reflux in 550 ml of hexane in the presence of 3.0 g of charcoal under argon for 10 minutes and at room temperature for two hours. After filtering the charcoal, the solvent was evaporated under reduced pressure. The residue was vacuum dried for 14 hours to give **3** (42.1 g, 91%), as a white amorphous solid, mp 44-47°; Rf (tlc): 0.5 (tetrahydrofuran/hexane = 1/10); ir (potassium bromide): 3055, 3031, 1606, 1580, 1505, 1462, 1444 cm^{-1}; ^1H nmr: δ 1.78 (quin, 2 H, J = 6 Hz), 3.01 (t, 4 H, J = 6 Hz), 3.78 (s, 6 H), 6.81 (d, 4 H, J = 10 Hz), 7.09-7.51 (m, 9 H); ms: (CI) m/z 360 (M + 1), 303, 304.

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01. Found: C, 79.96; H, 6.85.

N-Tritylazetidine Hydrogen Perchlorate (**10**) (Scheme IIIA).

To a stirred solution of 59.9 g (0.2 mole) of **2** in 720 ml of dry and pure tetrahydrofuran in an ice bath (the reaction flask was protected from moisture using a calcium chloride tube), was added dropwise, 62.6 ml (0.2 mole) of 3.2 *M* perchloric acid in acetic acid [54]. After addition, the reaction mixture was stirred at 0° for 10 minutes then stored in a refrigerator for 1 day. White crystals were filtered and dried in a vacuum desiccator over phos-

phorus pentoxide to give 76.8 g (96%) of **10**, mp 178-180°. This product was used without purification for the next step. An analytical sample was obtained by recrystallization from acetonitrile, mp 183-184°; Rf (tlc): 0.95 (8% aqueous sodium chloride solution/anhydrous ethanol = 1/10); ir (potassium bromide): 2797, 2606, 2487, 1597, 1500, 1449, 1116, 1044 cm^{-1}; ^1H nmr: δ 1.58-1.80 (m, 1 H), 2.55-2.78 (m, 1 H), 3.86-4.06 (m, 2 H), 4.79-4.99 (m, 2 H), 7.24-7.54 (m, 15 H), 10.04 (s, broad, 1 H, disappeared in deuterium oxide).

Anal. Calcd. for $C_{22}H_{22}ClNO_4$: C, 66.08; H, 5.55. Found: C, 66.24; H, 5.63.

Azetidine Hydrogen Perchlorate (**11**) From **10** (Scheme IIIA).

A vigorously stirred mixture of 37.4 g (93.6 mmoles) of **10** and 600 ml of dry and pure methanol was refluxed under argon for 60 hours. The resulting clear solution was condensed to a volume of 100 ml under reduced pressure, 500 ml of dry and pure ether was added, and the resulting mixture was stirred under argon for 1 hour. The mixture containing white precipitate **11** was kept in a refrigerator for 2 days protected from moisture. Crude **11** was filtered, dried and recrystallized from 2-butanone to give 8.09 g (55%) of **11** as non-hygroscopic crystals, mp 230-232°; Rf (tlc): 0.55 (8% aqueous sodium chloride solution/anhydrous ethanol = 1/10); ir (potassium bromide): 2983, 1451, 1147, 1115, 1087, 637, 627 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.38 (quin, 2 H, J = 8 Hz), 3.95 (t, 4 H, J = 8 Hz), 8.40 (s, broad, disappeared in deuterium oxide).

Anal. Calcd. for $C_3H_8ClNO_4$: C, 22.87; H, 5.12. Found: C, 23.00; H, 5.30.

The ethereal filtrate from which **11** was separated, was evaporated under reduced pressure and the residue was recrystallized from methanol to give 22.1 g (86%) of methyl trityl ether (**12**) which was identical to reported **12** [55].

Azetidine Hydrogen Perchlorate (**11**) From **2** In One Step (Scheme IIIB).

To a vigorously stirred mixture of 28.0 g (93.6 mmoles) of **2** and 600 ml of dry and pure methanol in an ice bath and under argon was added dropwise, 29.3 ml (93.6 mmoles) of 3.2 *M* perchloric acid in acetic acid [54]. After addition, the reaction mixture was stirred at 0° for 10 minutes, at room temperature for 30 minutes and then refluxed for 60 hours. The clear solution was allowed to cool to room temperature and it was condensed to a volume of about 300 ml under reduced pressure. The mixture, from which methyl trityl ether (**12**) started to precipitate, was kept in a refrigerator for 1 day. The white crystals were filtered and recrystallized from methanol to give 21.5 g (84%) of **12**. The methanolic filtrate was evaporated under good vacuum (bath temperature was kept below 25°) and the residue was stirred vigorously with 400 ml of dry and pure ether under argon for 1 hour. The white precipitate was filtered, dried and recrystallized from 2-butanone to give 7.65 g (52%) of **11** which was identical to **11** above.

Trityl Chloride (**4**) From Methyl Trityl Ether (**12**) (Scheme IIIC).

To a stirred mixture of 16.0 g (58.3 mmoles) of **12** and 80 ml of heptane at room temperature and under argon, was added dropwise, 6.4 ml (10.4 g, 87.7 mmoles) of thionyl chloride. After addition, the reaction mixture was stirred at room temperature for 10 minutes then refluxed for 1 day. The reaction mixture was kept at room temperature for 6 hours and in a refrigerator 2 days. The crystals were filtered and dried in a vacuum desiccator over potassium hydroxide pellets to give 14.4 g of **4**. The mother liquor was condensed to 30 ml and treated as above to give 1.2 g of **4** as a second crop. The combined yield as 15.6 g (96%). Compound **4** obtained this way was identical to reported **4** [56].

Azetidine Hydrogen Perchlorate (**11**) From **3** (Scheme IIID).

To a vigorously stirred solution of 55.1 g (0.15 mole) of **3** in 1030 ml of tetrahydrofuran at 0°, was added dropwise, an ice cold solution of 22 g (0.15 mole) of 70% aqueous perchloric acid in 232 ml of water. The resulting orange-red solution was stirred at 0° for 10 minutes then it was stirred at room temperature for 1 day. The solvent was evaporated under reduced pressure at a temperature below 30° and the residue was dissolved in a mixture of 500 ml of ice water and 1000 ml of ether. The phases were shaken well and separated. The aqueous phase was shaken twice with 200 ml portions of ether. The aqueous phase was stirred with 5 g of charcoal at room temperature for 2 hours, filtered and the solvent was removed in good vacuum (0.5 mm). Crude **11** was dried in a vacuum oven at 40° over phosphorus pentoxide for 1 day then recrystallized from 2-butanone to give 20.7 g (86%) of **11** which was identical to **11** above. The combined ethereal phase was shaken first with 200 ml of 10% aqueous sodium hydroxide then with 500 ml of saturated brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to give 48.5 g (99%) of **13** which according to its tlc and ^1H nmr spectrum was pure so it was used to the next step without purification; Rf (tlc): 0.2 (tetrahydrofuran/hexane = 1/10); ^1H nmr: δ 2.89 (s, broad, 1H, disappeared in deuterium oxide), 3.75 (s, 6 H), 6.80 (d, 4 H, J = 10 Hz), 7.16 (d, 4 H, J = 10 Hz), 7.28 (s, 5 H).

4,4'-Dimethoxytrityl Chloride (**5**) From **13** (Scheme IIIE).

To a stirred mixture of 48.5 g (0.15 mole) of **13** and 1220 ml of heptane in an ice bath and under argon, was added dropwise, 21.8 ml (35.6 g, 0.3 mole) of thionyl chloride. The reaction mixture was stirred at 0° for 10 minutes, at room temperature for 10 minutes and then it was refluxed for 1 hour. The hot solution was filtered, kept at room temperature for 8 hours and then in a refrigerator for 2 days. The slightly pink crystals were filtered and dried in a vacuum desiccator over potassium hydroxide pellets to give 46.5 g (91%) of **5** which was identical to reported **5** [53].

Azetidine (**14**) (Scheme IVA).

To 5.5 g (0.24 mole) of melted sodium metal in an oil bath kept at 130° and under argon, was added dropwise very slowly, 65 ml of pure and dry ethylene glycol. After the sodium metal dissolved, the temperature of the reaction mixture was cooled to 50° and 18.9 g (0.11 mole) of **11**, dissolved in 60 ml of ethylene glycol at 50°, was added dropwise under argon and while being stirred. After addition, the temperature of the oil bath was kept at 50° for 10 minutes then it was raised slowly to 190° and kept at this temperature until all the azetidine (**14**) distilled from the reaction mixture. The distillation head of the apparatus was wrapped in aluminum foil to keep the temperature even and the receiving flask was immersed in a 2-propanol-dry ice bath. The yield of pure azetidine was 5.2 g (81%); bp, 57° (640 mm Hg); ir (neat): 3269, 2985, 2957, 2921, 2859, 1447, 1335, 1238, 1153, 1084, 984, 901, 750, 664 cm^{-1}; ^1H nmr: δ 1.89 (s, 1 H, disappeared in deuterium oxide), 2.33 (quin, 2 H, J = 8 Hz), 3.63 (t, 4 H, J = 8 Hz).

Azetidine Hydrogen Perchlorate (**11**) From **14** (Scheme IVB).

To a vigorously stirred solution of 1.5 g (26.3 mmoles) of **14** in

20 ml of water in an ice bath, was added dropwise, a solution of 3.8 g (26.3 mmoles) of 70% perchloric acid in 20 ml of water. The addition was continued until the *p*H of the reaction mixture became 6.0. After addition, the reaction mixture was stirred at 0° for 10 minutes, then the solvent was evaporated under a good vacuum. This product was dried in a vacuum oven at 40° over phosphorus pentoxide for 1 day to give 4.1 g (99%) of **11** which was identical to **11** above.

N-Tritylazetidine (**2**) From **14** (Scheme IVC).

To a vigorously stirred solution of 1.5 g (26.3 mmoles) of **14** and 4.0 ml (2.9 g, 28.7 mmoles) of triethylamine in 30 ml of pure and dry tetrahydrofuran in an ice bath and under argon, was added dropwise, 7.32 g (26.3 mmoles) of trityl chloride dissolved in 30 ml of tetrahydrofuran. After addition, the reaction mixture was stirred at 0° for 20 minutes then at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of 150 ml of ether and 100 ml of ice water. The phases were mixed well and separated. The aqueous phase was shaken twice with 50 ml portions of ether. The combined organic phase was shaken with 100 ml of saturated brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to give 7.7 g (98%) of **2** which was identical to **2** above.

N-Tritylazetidine (**2**) From **11** (Scheme VA).

To a vigorously stirred mixture of 0.32 g (2.0 mmoles) of **11** and 0.57 g (2.0 mmoles) of trityl chloride in 3 ml of dry and pure tetrahydrofuran in an ice bath and under argon, was added dropwise, 0.85 ml (0.62 g, 6.1 mmoles) of triethylamine. After addition, the reaction mixture was stirred at 0° for 30 minutes then at room temperature for 1 hour. The reaction mixture was treated as above. The crude product was recrystallized from anhydrous ethanol to give 0.56 g (92%) of **2** which was identical to **2** above.

N-Benzoylazetidine (**15**) From **11** (Scheme VB).

To a vigorously stirred mixture of 0.32 g (2.0 mmoles) of **11** and 0.29 g (2.06 mmoles) of benzoyl chloride in 3 ml of dry and pure tetrahydrofuran in an ice bath and under argon, was added dropwise, 0.85 ml (0.62 g, 6.1 mmoles) of triethylamine. After addition, the reaction mixture was stirred at 0° for 5 minutes then at room temperature for 10 minutes. The reaction mixture was treated as above. The crude product was recrystallized from hexane to give 0.31 g (96%) of **15** as white crystals, mp 61-62°, (lit value, 61-62° [57]); ir (potassium bromide): 3061, 2952, 2878, 1624, 1600, 1576, 1492, 1455 cm^{-1}; ^1H nmr: δ 2.35 (quin, 2 H, J = 8 Hz), 4.12-4.40 (m, 4 H), 7.32-7.69 (m, 5 H).

N-Tosylazetidine (**16**) From **11** (Scheme VC).

To a vigorously stirred mixture of 0.32 g (2.0 mmoles) of **11** and 0.48 g (7.3 mmoles, 85%) of finely powdered potassium hydroxide in 3 ml of dry and pure tetrahydrofuran in an ice bath and under argon, was added dropwise, 0.42 g (2.2 mmoles) of tosyl chloride dissolved in 3 ml of tetrahydrofuran. After addition, the reaction mixture was stirred at 0° for 30 minutes then at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of 30 ml of dichloromethane and 30 ml of ice water. The phases were mixed well and separated. The aqueous phase was shaken twice with 15 ml portions of dichloromethane. The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from methanol to give 0.39 g (92%) of **16** as white crystals, mp 119.5-120°, (lit value, 119-120° [58]); ir (potassium bromide): 1345, 1161 cm^{-1}; ^1H nmr: δ 2.06 (quin, 2 H, J = 8 Hz), 2.47 (s, 3 H), 3.77 (t, 4 H, J = 8 Hz), 7.37 (d, 2 H, J = 9 Hz), 7.73 (d, 2 H, J = 9 Hz).

N-Acetylazetidine (**17**) From **11** (Scheme VD).

To a vigorously stirred mixture of 0.32 g (2.0 mmoles) of **11** and 0.48 g (7.3 mmoles, 85%) of finely powdered potassium hydroxide in 3 ml of dry and pure ether in an ice bath and under argon, was added dropwise, 0.23 ml (0.25 g, 2.4 mmoles) of acetic anhydride dissolved in 3 ml of ether. After addition, the reaction mixture was stirred at 0° for 1 hour and at room temperature for 2 hours. Then, 15 ml of ether and 1 g of anhydrous magnesium sulfate was added to the reaction mixture and it was stirred for another 30 minutes. The solid material was filtered and washed with ether. The filtrate and washings were combined and this solution was evaporated under reduced pressure to give 0.18 g (91%) of pure **17**; ir (neat): 2952, 2882, 1652, 1436 cm^{-1}, (lit values, 2950, 2880, 1645, 1430 cm^{-1} [59]); ^1H nmr: δ 1.84 (s, 3 H), 2.25 (quin, 2 H, J = 8 Hz), 4.02 (t, 2 H, J = 8 Hz), 4.13 (t, 2 H, J = 8 Hz), (lit values, 1.85 (s, 3 H), 2.26 (quin, 2 H, J = 8 Hz), 4.10 (q, 4 H, J = 8 Hz) [59]); ms: (CI) m/z 100 (M + 1).

X-ray Crystal Structure Determinations.

Suitable crystals of **11**, **10**, and **2** were prepared and used for the X-ray structural studies. Crystal and intensity data for the three crystals were obtained using a Siemens R3m/V automated diffractometer using graphite monochromated MoKα radiation, (λ = 0.71073 Å). The lattice parameters and orientation matrix for each crystal were obtained using a least-squares procedure involving angular settings of several carefully centered reflections. Crystal data for the crystals are summarized in Table 8. Intensity data were collected using a variable scan rate θ-2θ procedure. Data for **11** were collected to a 2θ limit of 55° while data for **10** and **2** were collected to a 2θ limit of 50°.

Trial structures for the three compounds were obtained using direct methods. The structure of **11** and its refinement was difficult because of the disorder in the compound. The ClO_4^- group of that compound was disordered with two orientations of the oxygens for the ion being found in the Fourier map. Both orientations of the ion were initially refined as rigid bodies with the Cl-O distances refined to 1.39 Å. Later in the refinement the oxygen atoms were allowed to ride on the chlorine maintaining the tetrahedral geometry of each ClO_4^- ion. All non-hydrogen atoms of **11** were refined anisotropically. The large thermal motion for the oxygens of the ClO_4^- indicated that the disordered model was not completely satisfactory. Also the large thermal motion of C3 suggested that there was probably some disorder in the ring but it could not be resolved. Positions for the hydrogens of **11** were calculated based on known chemical geometry and the hydrogens were allowed to ride on their neighboring heavy atoms. The isotropic thermal parameters of the hydrogens were set equal to 0.08 $Å^2$ and were not refined.

The structure of **10** contains a mirror plane which passes through C1, O1, O3, N1, C3, C4, C11 and C14 (see Figure 2). The non-hydrogen atoms of **10** and **2** were refined anisotropically. The hydrogens of **10** were located in difference maps and allowed to ride on their neighboring heavy atoms and were refined isotropically. The positions for the hydrogens of **2** were calculated and treated in the refinement in the same manner as the hydrogens of **11**. Weights based on counting statistics were applied to the intensity data of **2** and **11** and the data for **2** was also correct-

ed using an empirical extinction correction. Unit weights were used in the refinement of **10**. The resulting R values for the structures were R = 0.061 and Rw = 0.078 for **11**, R = 0.065 for **10** and R = 0.077 and Rw = 0.094 for **2**. The maximum and minimum peaks in the final difference maps were 0.34 e$Å^{-3}$ and -0.28 e$Å^{-3}$ for **11**, 0.41 e$Å^{-3}$ and -0.31 e$Å^{-3}$ for **10** and 0.29 e$Å^{-3}$ and -0.26 e$Å^{-3}$ for **2**. All programs used in solving, refining and displaying the three structures are contained in SHELXTL PLUS™ [60]. Atomic scattering factor were taken from The International Tables for X-ray Crystallography [61].

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