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Azetidines. III. The Tosylation and Acylation of 1-Substituted 3-Azetidinols. The Preparation of 1-*t*-Butylazetidine-3-carboxylic Acid[1]

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The tosylation of 1-*t*-butyl-3-azetidinol in pyridine gave 1-*t*-butylazetidinyl-3 tosylate, but 1-cyclohexyl-3-azetidinol gave mainly *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol. The reaction of both the azetidinols with *p*-nitrobenzoyl chloride in pyridine gave the 3-nitrobenzoates, while in acetone 1-cyclohexyl-3-azetidinol gave a ring cleavage product. The preparation of 1-*t*-butylazetidine-3-carboxylic acid is described.

In the preceding paper of this series,[1] we reported the preparation of some functional derivatives of azetidines. Some of these methods, however, seem to be limited by the availability of the starting materials required, and the methods themselves cannot claim a wide applicability. Recently, an elegant method of preparing 3-azetidinol derivatives has been described[3]; these derivatives seem to be ideally suited as the starting materials for the preparation of a wide variety of azetidine derivatives. The present communication is concerned with the effects of the substituents on the ring-nitrogen atom of 3-azetidinols towards tosyl and *p*-nitrobenzoyl chloride, and with the successful synthesis of an azetidinecarboxylic acid.

When 1-*t*-butyl-3-azetidinol (I) was allowed to react with tosyl chloride in pyridine, a 73% yield of 1-*t*-butylazetidinyl-3 tosylate (III) was obtained, plus a small amount (1.6% yield) of 1-tosylazetidinyl-3 tosylate (IV); 1-cyclohexyl-3-azetidinol (II) did not give the corresponding tosylate (V) under the same reaction conditions, but the ring opened to produce *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol (VI; 66% yield) and *N*-tosyl-1-cyclohexylamino-3-chloropropyl-2 tosylate (VII; 3% yield).

The NMR spectrum of the ditosylate IV shows a one-proton multiplet at τ 4.7—5.1 for the hydrogen on the 3-position of the ring; a four-proton multiplet between 5.6—6.3 for the ring methylene; a six-proton singlet at 7.41 for the two methyl groups, and a benzene-ring multiplet between 1.5—2.2, thus lending support to the structure IV. The tosylation of 1-cyclohexylamino-3-chloro-2-propanol with tosyl chloride afforded VI; this on further tosylation, gave VII, both substances being identical with the products isolated from II.

From the yields of VI and VII, it is evident that the main reaction of II with tosyl chloride in pyridine is ring cleavage, but we can not exclude the possibility that a small amount of the azetidinyl-3 tosylate V may also have been formed. This view may be supported by the fact that the reduction of the crude reaction mixture with lithium aluminum hydride gave, as distillable products, 1-cyclohexylamino-2-propanol (VIII) and a small amount of 1-cyclohexylazetidine (IX), the latter perhaps arising from 1-cyclohexylazetidinyl-3 tosylate (V). The structure of VIII was proved by an examination of the spectroscopic data (see Experimental Section) and by comparison with the sample of VIII prepared by the reaction of cyclohexylamine and propylene oxide. The picrate of IX gave correct analysis, and the NMR spectrum of IX (Fig. 3) exhibits a four-proton

1) Part II: T. Chen, T. Sanjiki, H. Kato and M. Ohta, This Bulletin, **40**, 2398 (1967).

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3) V. R. Gaertner, *Tetrahedron Letters*, **1966**, 4691; R. A. Clasen and S. Searles, Jr., *Chem. Commun.*, **1966**, 289.

triplet at τ 6.8 for the azetidine methylene group adjacent to nitrogen, besides the multiplets of the hydrogens on the 3 position of azetidine and the methine hydrogen of the cyclohexane ring around 8.0, with the multiplet of the remaining methylenes at 8—9 superimposed.

The tosylation of II with tosyl chloride in acetone also gave the ring-cleavage product, but I gave a viscous substance from which no pure substance could be isolated.

An attractive hypothesis for the formation of a small but consistent amount of the ditosylate IV would be the formation of an intermediate, X (R=*t*-Bu), followed by the removal of the *t*-butyl cation to give IV. No such hypothesis is possible, however, since no increase in the formation of IV was observed upon an increase in the amount of tosyl chloride, nor did the treatment of III with tosyl chloride give the ditosyl derivative IV. IV may be formed by the reaction of tosyl chloride with 3-azetidinol, which may in turn be formed by the reaction of epichlorohydrin and ammonia; the latter may have been present as an impurity in the commercial *t*-butylamine. This result suggests that the general synthesis of azetidinols, so far applied only to those azetidinols substituted

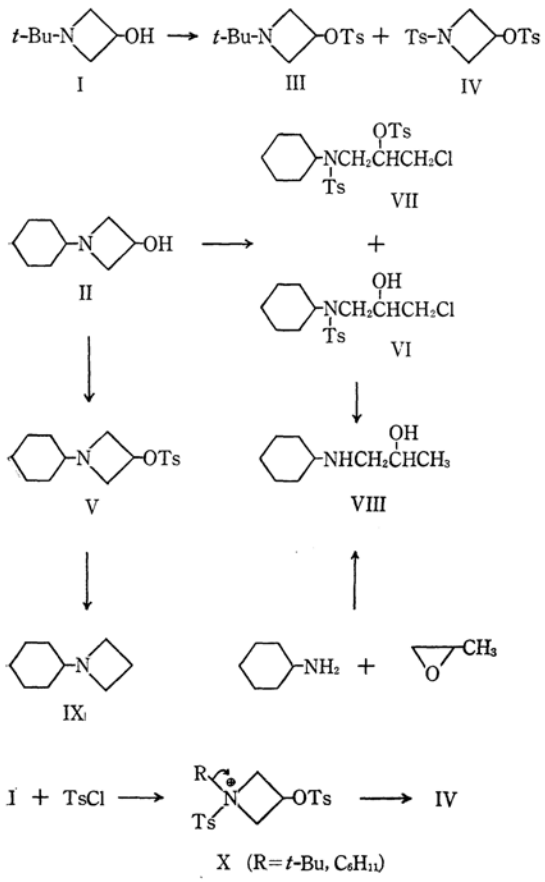

Fig. 1

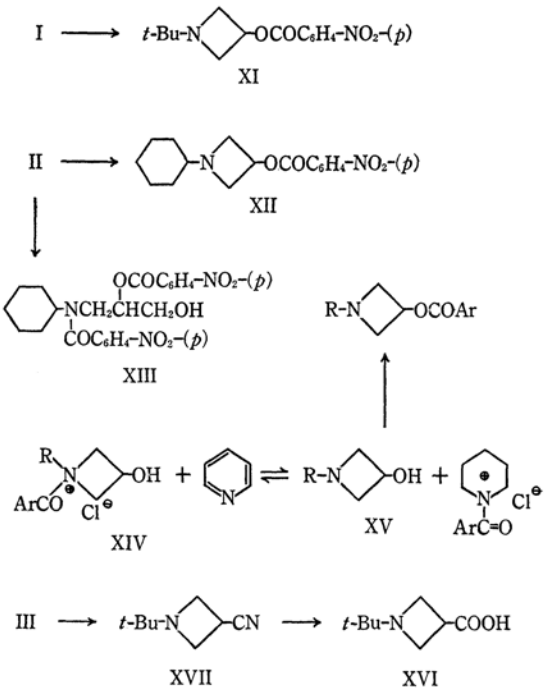

Fig. 2

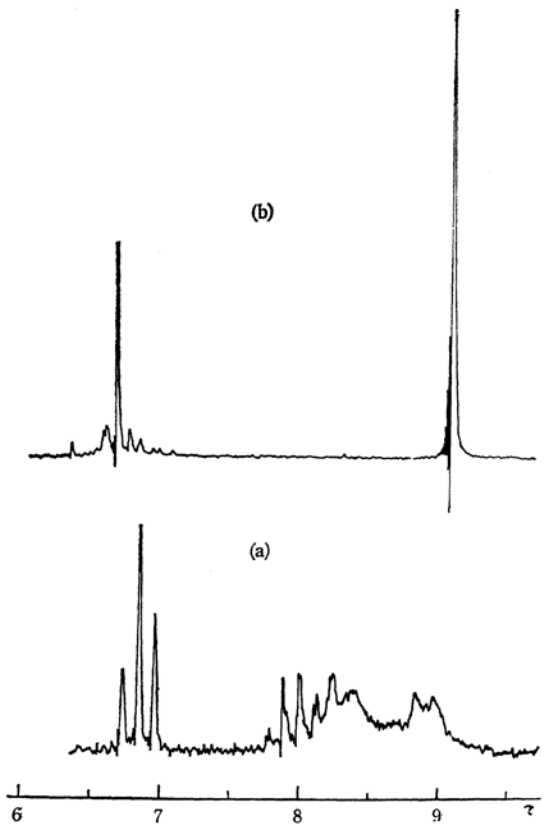

Fig. 3. The NMR spectra of 1-cyclohexylazetidine (a) and 1-*t*-butyl-3-cyanoazetidine (b).

by bulky alkyl groups at the 1 position, may be extended to even the preparation of *N*-unsubstituted azetidinol.

The acylation of I and II with *p*-nitrobenzoyl chloride in pyridine is in strong contrast with the tosylation; both I and II gave only the 3-*p*-nitrobenzoate XI and XII, with the ring unaffected. The reaction of II with *p*-nitrobenzoyl chloride in acetone, on the other hand, gave the ring-cleavage product, *N*-*p*-nitrobenzoyl-1-cyclohexylamino-3-hydroxypropyl-2 *p*-nitrobenzoate (XIII), while I gave XI under the same reaction conditions.

The different behavior of I and II towards tosyl chloride may be explained by considering the degree of bulkiness of the substitution group on the ring-nitrogen atom. In order to explain the behavior of II towards *p*-nitrobenzoyl chloride, one should consider an equilibrium between the azetidinium and the pyridinium salts, XIV and XV. In the acetone solvent, such an equilibrium cannot take place and the ring-cleavage product will be the exclusive product. In the reaction of II in pyridine with the more strongly nucleophilic tosyl chloride, the intermediate azetidinium cation (X, R=C_6H_{11}) does not permit such an equilibrium to take place and gives the ring cleavage product, VI, by the fission of the N-C bond rather than the N-S bond.

The *O*-tosylate III would provide a convenient route to many functional derivatives of azetidine. We will describe here the preparation of 1-*t*-butylazetidine-3-carboxylic acid (XVI). The tosylate III gave a 52% yield of 1-*t*-butyl-3-cyanoazetidine (XVII) when reacted with potassium cyanide in methanol. The NMR spectrum (Fig. 3) of XVII is rather complex for a complete analysis, but it is similar to those of the 3-acylazetidines, which have recently been reported.[4] The nitrile XVII was hydrolyzed with barium hydroxide to produce 1-*t*-butylazetidine-3-carboxylic acid (XVI) in a good yield.

Experimental[5]

1-Substituted 3-Azetidinols (I and II). They were prepared according to the method described by Gaertner.[3]

Tosylation of 1-*t*-Butyl-3-azetidinol (I) in Pyridine. To a solution of 3 g (0.024 mol) of 1-*t*-butyl-3-azetidinol in 40 m*l* of anhydrous pyridine, there were added, with stirring and cooling, 13.5 g (0.072 mol) of tosyl chloride; thereafter stirring was continued for another three hours. The reaction mixture, after having been set aside in a refrigerator overnight, was poured into 400 m*l* of ice water, and the precipitate was collected by filtration. About 10 g of potassium carbonate was added to the filtrate to precipitate 1-*t*-butylazetidinyl-3 tosylate (III), which was then filtered and washed with water to give 5 g (73%) of a practically pure product, melting at 69—71°C. Recrystallization from *n*-hexane gave colorless prisms, melting at 70—71°C. IR: 1365, 1355, 1190, 1175 cm^{-1}.

Found: C, 58.96; H, 7.44; N, 5.12%. Calcd for $C_{14}H_{21}NO_3S$: C, 59.35; H, 7.47; N, 4.94%.

The precipitate obtained by the first filtration was washed with alcohol to give 0.15 g (1.6% yield) of 1-tosylazetidinyl-3 tosylate (IV), which was then recrystallized from ethanol to give colorless needles, melting at 138—139°C. IR: 1380, 1368, 1340, 1180, 1170 cm^{-1}.

Found: C, 53.27; H, 4.88; N, 3.81%. Calcd for $C_{17}H_{19}NO_5S_2$: C, 53.54; H, 5.02; N, 3.67%.

The relation between the amount of tosyl chloride and the yield of IV is summarized in Table 1.

Table 1

Material I g (mol)	TsCl g (mol)	Compd. III g (Y. %)	Compd. IV g (Y. %)
3 (0.024)	9 (0.048)	3.8 (55)	0.12 (1.3)
3 (0.024)	13.5 (0.072)	5 (73)	0.15 (1.6)
3 (0.024)	18 (0.096)	5 (73)	0.15 (1.6)

Tosylation of 1-Cyclohexyl-3-azetidinol (II) in Pyridine. The procedure was the same as that described above except in the latter part. After the reaction mixture was poured into ice water, a yellow oil was obtained. The oil was taken up in ether, and then the ether was removed, giving a crude product which was then extracted with methanol.

The methanol extract was concentrated to give a 66% yield of *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol (VI) as white needles after recrystallization from *n*-hexane, mp 75—77°C. IR: a broad absorption at 3500 cm^{-1}. It was positive to Beilstein's halogen test.

Found: C, 55.70; H, 7.04; N, 4.26%. Calcd for $C_{16}H_{24}NO_5SCl$: C, 55.57; H, 6.95; N, 4.05%.

The residue remaining after the methanol extraction was recrystallized from hot methanol to give a 3% yield of *N*-tosyl-1-cyclohexylamino-3-chloropropyl-2 tosylate (VII) as white needles, melting at 131—132°C.

Found: C, 55.15; H, 6.08; N, 3.15%. Calcd for $C_{23}H_{30}NO_9S_2Cl$: C, 55.26; H, 6.01; N, 2.80%.

The addition of an excess of potassium carbonate to the aqueous filtrate did not cause any precipitation.

Tosylation of II in Acetone. A solution of 2.5 g of II and 3 g of tosyl chloride in 30 m*l* of acetone in the presence of 1.3 g of potassium carbonate was refluxed for six hours. The mixture was then filtered, and the filtrate was concentrated to give 4 g (72% yield) of VI, melting at 74—76°C. This substance was identical with the sample of VI previously described. (Found: C, 55.65; H, 7.01; N, 4.28%).

***N*-Tosyl-1-cyclohexylamino-3-chloro-2-propanol (VI).** A solution of 1-cyclohexylamino-3-chloro-2-propanol[3] (1.9 g) and tosyl chloride (1.9 g) in acetone was treated as has been described above to give a 32% yield of VI; this substance was identical with the samples of VI previously obtained. (Found: C, 55.41; H, 6.89; N, 4.40%).

4) J. L. Inbach, E. Doomes, R. P. Rebman and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

5) The general conditions for the measurements of physical constants and spectra were the same as those described in Part I; T. Chen, H. Kato and M. Ohta, This Bulletin, **40**, 1964 (1967).

***N*-Tosyl-1-cyclohexylamino-3-chloropropyl-2 Tosylate (VII).** The *N*-tosyl derivative VI (0.69 g) prepared by the above method was treated with tosyl chloride (0.57 g) in pyridine with cooling to give a 30% yield of VII. It was identical with the sample of VII obtained previously. (Found: C, 55.28; H, 6.37; N, 2.94%).

Reduction of the Crude Tosylation Product of II. The crude reaction product obtained from 5 g of II and 6.7 g of tosyl chloride in pyridine was treated overnight at room temperature with 2.9 g of lithium aluminum hydride in 80 m*l* of ether. The mixture was then decomposed with dilute aqueous sodium hydroxide and extracted with ether, and the extract was dried over magnesium sulfate and distilled to give the following two substances:

1-Cyclohexylamino-2-propanol (VIII): yield 12%, bp 75—85°C/1 mmHg, mp 43—44°C. IR: 3280, 3120, 1050 cm^{-1}. NMR: τ 6.5 (1H multiplet, methine bearing the hydroxyl group); 6.91 (2H singlet, NH and OH); 7.45—7.77 (3H multiplet, methylene and methine adjacent to nitrogen); 8.92 (*ca* 3H doublet, methyl group); 7.95—9.0 (*ca*. 10 H, multiplet, ring methylene).

Found: C, 68.73; H, 11.55; N, 9.15%. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91%.

1-Cyclohexylazetidine (IX): bp 30—45°C/10 mmHg, purified by v. p. c. (10% Carbowax 20 M on Diasolid A). The NMR spectrum is shown in Fig. 3.

Picrate: mp 208—210°C.

Found: C, 48.78; H, 5.48; N, 15.91%. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21%.

1-Cyclohexylamino-2-propanol (VIII). A solution of 3.8 g of cyclohexylamine and 2.3 g of propylene oxide in 5 m*l* of water was allowed to stand overnight. From the reaction mixture, 3.1 g (50% yield) of VIII were isolated by distillation, bp 110—112°C/12 mmHg, mp 43—45°C. This substance was identical with the specimen of VIII previously obtained. (Found: C, 69.04; H, 11.99; N, 8.90%).

1-*t*-Butylazetidinyl-3 *p*-Nitrobenzoate (XI). This was prepared from I and *p*-nitrobenzoyl chloride in pyridine by the same procedure as has been described for the tosylation of I; the product was recrystallized from *n*-hexane to give a 45% yield of XI as colorless needles, mp 92—94°C, IR: 1723 cm^{-1}.

Found: C, 60.90; H, 6.41; N, 10.18%. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07%.

1-Cyclohexylazetidinyl-3 *p*-Nitrobenzoate (XII). This was prepared from 0.78 g of II and 0.93 g of *p*-nitrobenzoyl chloride in 10 m*l* of pyridine, and was recrystallized from *n*-hexane to give 0.78 g (50% yield) of yellow needles, melting at 90—91.5°C. IR: 1710 cm^{-1}.

Found: C, 62.93; H, 6.40; N, 9.33%. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21%.

Reaction of II with *p*-Nitrobenzoyl Chloride in Acetone. A solution of 0.78 g of II and 0.93 g of *p*-nitrobenzoyl chloride in 30 m*l* of acetone was refluxed for six hours in the presence of 0.41 g of potassium carbonate. The mixture was then filtered and concentrated, and the residue was recrystallized from ethanol to give 1 g (42% yield) of *N*-*p*-nitrobenzoyl-1-cyclohexylamino-3-hydroxypropyl-2 *p*-nitrobenzoate (XIII) as white plates, melting at 160—161.5°C. IR: 3380, 2940, 1730, 1520 cm^{-1}.

Found: C, 58.62; H, 5.69; N, 8.71%. Calcd for $C_{23}H_{25}N_3O_8$: C, 58.58; H, 5.35; N, 8.91%.

Reaction of I with *p*-Nitrobenzoyl Chloride in Acetone. The treatment of 0.5 g of I with 0.7 g of *p*-nitrobenzoyl chloride in acetone by the method described above gave XI in a 23% yield, and no ring-cleavage by-product was isolated.

1-*t*-Butyl-3-cyanoazetidine (XVII). A solution of 5.6 g (0.02 mol) of III and 4 g (0.06 mol) of potassium cyanide in 100 m*l* of methanol was stirred at room temperature for two days. The reaction mixture was then filtered, the filtrate was concentrated under reduced pressure, and the residue was extracted with ether. The ether extract was dried over sodium sulfate and concentrated, and the residual oil was distilled to give 1.4 g (52% yield) of colorless liquid, boiling at 39—40.5°C/1.5 mmHg, n_D^{25} 1.4485. IR: 2240 cm^{-1}. Its NMR spectrum is shown in Fig. 3.

Found: C, 69.73; H, 10.15; N, 19.64%. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27%.

Picrate: mp 208—210°C.

Found: N, 19.18%. Calcd for $C_{14}H_{17}N_5O_7$: N, 19.07%.

1-*t*-Butylazetidine-3-carboxylic Acid (XVI). One gram (0.007 mol) of XVII was added dropwise with stirring to 1.5 g (0.045 mol) of barium hydroxide octahydrate in a small amount of water with the temperature kept between 90—95°C; the resulting mixture was stirred for another forty minutes at the same temperature. About 30 m*l* of hot water was then added to the mixture, and a stream of carbon dioxide was passed through until the precipitation of barium hydroxide was complete. The precipitate was removed by filtration and washed twice with 20-m*l* portions of hot water. The combined filtrate and water washings were concentrated to dryness under reduced pressure, and the residue was recrystallized from chloroform to give 0.8 g (73% yield) of white needles, melting at 189—191°C. IR: 3480, 3420, 1600 cm^{-1}.

Found: C, 60.78; H, 9.41; N, 9.10%. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91%.

We are indebted to Miss Mizuko Yoshida for the measurement of the NMR spectra.