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## Azetidines. IV. The Reaction of 1-*t*-Butylazetidiny-3 Tosylate with Amines and Mercaptans<sup>1)</sup>

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3-Amino and 3-mercapto-azetidine derivatives were prepared by the reaction of 1-*t*-butylazetidiny-3 tosylate with ammonia, primary and secondary amines, and mercaptans. Ring cleavage was observed when the tosylate was reacted with compounds of higher acidity, such as thiobenzoic acid.

In a previous communication,<sup>1)</sup> we reported that a nitrile group could be introduced onto the azetidine ring by the reaction of 1-*t*-butylazetidiny-3 tosylate (I) and potassium cyanide; the nitrile was then hydrolyzed to 1-*t*-butylazetidine-3-carboxylic acid in fairly good yield.

This result suggests that tosylate I is a promising starting material for the preparation of a wide variety of azetidine derivatives. In this communication we report the preparation of amino and mercapto derivatives of azetidine by the reaction of I with amines and mercaptans.

When 1-*t*-butylazetidiny-3 tosylate (I) was allowed to react with dimethylamine, 1-*t*-butyl-3-

dimethylaminoazetidine (IIa) was obtained in 40% yield. The NMR spectrum of IIa (Fig. 1) exhibits two singlets at  $\tau$  9.01 (9H) and 7.90 (6H) and a complex multiplet between 6.5—7.3 (5H), corresponding to the *t*-butyl group, the dimethylamino group and the ring protons respectively. The treatment of I with piperidine and morpholine likewise afforded the corresponding amino derivatives, 1-*t*-butyl-3-(1-piperidino)-azetidine (IIb) and 1-*t*-butyl-3-(1-morpholino)-azetidine (IIc). The reaction of I with methanolic ammonia also gave the expected derivative, 1-*t*-butyl-3-aminoazetidine (IIId), but in lower yield. The infrared spectrum of IIId shows a characteristic bands of a primary amino group at 3360 and 3280  $\text{cm}^{-1}$  and a NH bending band at 1610  $\text{cm}^{-1}$ . The NMR spectrum of IIId (Fig. 1) which consists of a nine-proton singlet at  $\tau$  9.05 for the *t*-butyl

1) Part III: T. Chen, T. Sanjiki, H. Kato and M. Ohta, *This Bulletin*, **40**, 2401 (1967).

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group, a two-proton broad singlet at 8.19 for the amino group and two complex multiplets at 7.05–7.35 (2H) and at 6.40–6.75 (3H) for the *cis* and *trans* protons of the methylene group plus the methine proton, agrees with the assigned structure (IIId), if not prove it.

The reaction of I and cyclohexylamine, a pri-

mary amine, gave directly the disubstituted derivative, di-(1-*t*-butylazetidiny-3)-cyclohexylamine (III) as an oil, which was purified by conversion to its trihydrochloride monohydrate. The hydrochloride shows bands of an OH and N<sup>+</sup>H groupings at 3500–3280 and 2800–2400 cm<sup>-1</sup>. When I was treated with a large excess of cyclohexylamine,

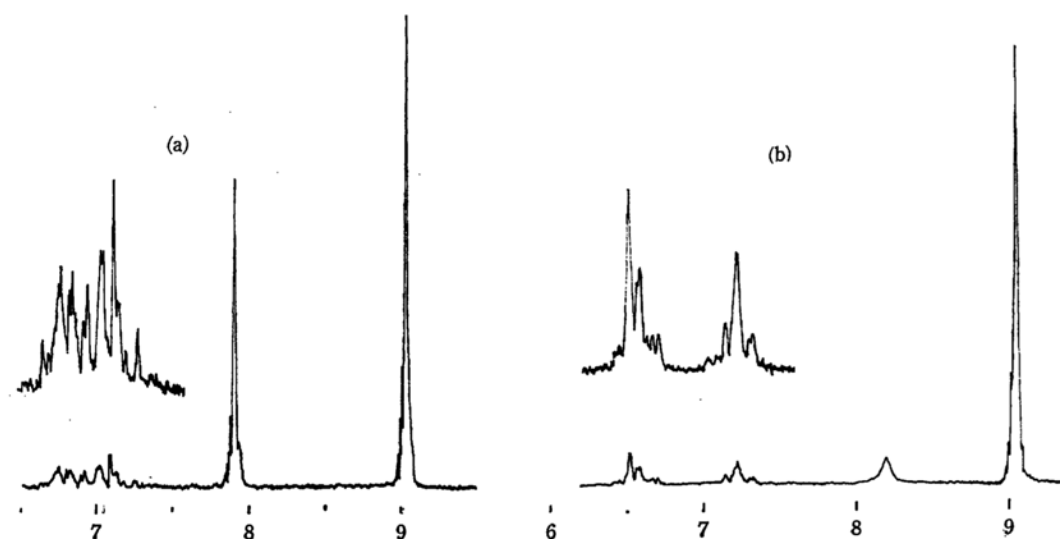
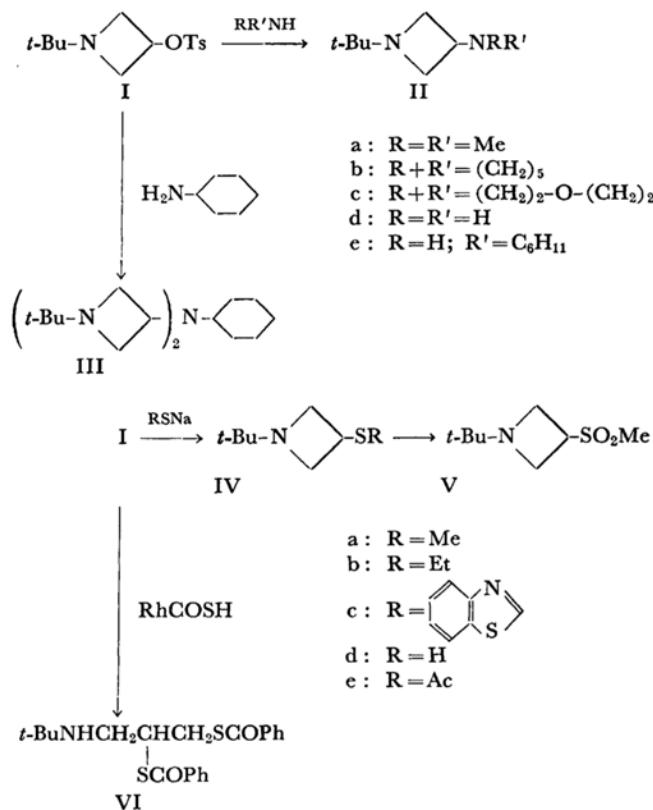


Fig. 1. The NMR spectrum of 1-*t*-butyl-3-dimethylaminoazetidine (a) and 1-*t*-butyl-3-aminoazetidine (b).

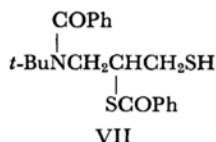


however, mono-substituted derivative IIe was obtained. Compound IIe was also a liquid but it could be crystallized in the form of its monohydrate. The infrared spectrum of IIe monohydrate shows a broad band of an OH group between 3500—3200  $\text{cm}^{-1}$  and a band of an NH group at 3260  $\text{cm}^{-1}$ .

The reaction of I with methyl mercaptan, ethyl mercaptan, and 2-mercaptobenzothiazole in ethanol in the presence of sodium ethoxide proceeded smoothly to give the corresponding sulfide, 1-*t*-butyl-3-methylthioazetidine (IVa), 1-*t*-butyl-3-ethylthioazetidine (IVb) and 1-*t*-butyl-3-(2-benzothiazolylthio)azetidine (IVc) respectively in good yields. Permanganate oxidation of IVa gave the corresponding sulfone V as a solid. The NMR spectrum of IVa consists of two sharp singlets at  $\tau$  9.12 (9H) corresponding to the *t*-butyl group and 8.00 (3H) corresponding to the methyl group, and a complex multiplet between 6.50 and 7.10 (5H) for the ring protons.

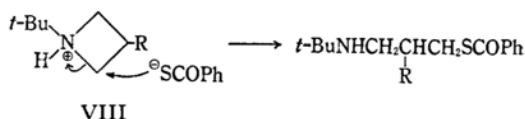
The reaction of I and potassium hydrogen sulfide in methanol was also tried with a hope of obtaining 1-*t*-butylazetidine-3-thiol (IVd). The crude reaction product was treated with acetic anhydride and distilled to give two components. The minor, lower boiling fraction shows a carbonyl absorption band at 1695  $\text{cm}^{-1}$  and the elemental analysis was in agreement with the composition of 1-*t*-butyl-3-acetylthioazetidine (IVe). The major component, a highly viscous higher boiling liquid shows two carbonyl absorption bands at 1695 (acetylthio) and 1640 (amide)  $\text{cm}^{-1}$ , suggesting this component to be a ring cleavage product, but attempts of its purification failed. The ring cleavage reaction may have taken place at the stage of treatment with acetic anhydride rather than at the stage of treatment with potassium hydrogen sulfide.

The reaction of I with an excess of thiobenzoic acid in the presence of potassium carbonate also provided a ring cleavage product as a highly viscous oily substance which was purified by conversion to its hydrochloride. The infrared spectrum of the base shows a weak band at 3320  $\text{cm}^{-1}$  (NH), a strong band of a carbonyl group at 1660  $\text{cm}^{-1}$  and no absorption due to an SH group was found around 2600  $\text{cm}^{-1}$ . The infrared spectrum of its hydrochloride shows a group of bands between 2800—2500  $\text{cm}^{-1}$  besides the carbonyl band at 1660  $\text{cm}^{-1}$ . These spectral data, as well as the results of elemental analyses suggest its structure to be VI rather than VII.



This ring cleavage reaction may be considered to proceed through a protonated azetidinium salt

(VIII; R=TsO or PhCOS) followed by an attack of an thiobenzoate anion to the ring, as is shown as follows:



There have been ample examples<sup>3)</sup> of such a mode of ring cleavage of azetidine ring.

The reaction of I with thioacetic acid also gave a highly viscous intractable substance. The infrared absorption spectrum of this crude substance was almost identical with that of the high boiling product obtained by acetic anhydride treatment of the reaction product of I and potassium hydrogen sulfide, but trials of its purification failed.

From the results described above, it may be concluded that amino and mercapto groups can be introduced to the 3 position of azetidine ring by the reaction of an azetidiny-3 tosylate with an appropriate amine or mercaptan, but the reaction of the tosylate with compounds of higher acidity such as thiobenzoic acid leads to ring cleavage product.

### Experimental<sup>4)</sup>

**1-*t*-Butyl-3-dimethylaminoazetidine (IIa).** To a solution of 6 ml (0.07 mol) of dimethylamine in 20 ml of methanol were added 5 g (0.017 mol) of I and 2.7 g (0.02 mol) of potassium carbonate successively with cooling and stirring. After stirring for five hours at room temperature, the mixture was allowed to stand overnight. After removal of the precipitate by filtration, the filtrate was concentrated under reduced pressure, and was diluted with 40 ml of water and filtered again to remove unchanged I. The filtrate, after being saturated with potassium carbonate, was extracted with ether, and the ether extract was dried over sodium sulfate. Distillation under reduced pressure afforded 1 g (40% yield) of colorless liquid boiling at 60—64.5°C/20 mmHg.  $n_D^{25}$  1.4232, IR: 2960—2780, 1460, 1360 and 1240  $\text{cm}^{-1}$ . The NMR spectrum is shown in Fig. 1 (a).

Found: C, 68.99; H, 12.69; N, 17.57%. Calcd for  $\text{C}_9\text{H}_{20}\text{N}_2$ : C, 69.17; H, 12.90; N, 17.93%.

Picrate of IIa melted once at 133—135°C, then solidified and melted again at 220—251°C with decomposition.

3) See for example: a) G. F. Gibbs and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 1137 (1935); b) C. Mannich, and G. Baumgarten, *Ber.*, **70**, 210 (1937); c) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949); d) R. C. Elderfield and C. Ressler, *J. Am. Chem. Soc.*, **72**, 4059 (1950); e) W. B. Wheatley and L. C. Cheney, *ibid.*, **74**, 1359 (1952); f) A. Müller, E. Funder-Fritzchse, W. Konar and E. Rintersbacher-Wlasak, *Monatsh.*, **84**, 1206 (1953); g) V. R. Gaertner, *Tetrahedron Letters*, **1967**, 343.

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

Found: C, 47.06; H, 6.20; N, 18.19%. Calcd for  $C_{15}H_{23}N_3O_7$ : C, 46.75; H, 6.02; N, 18.17%.

The following compounds were obtained by a similar method as described above.

**1-*t*-Butyl-3-(1-piperidino)azetidide (IIb).** (55% yield) Bp 64–67°C/1.5 mmHg,  $n_D^{25}$  1.4678. IR: 2980–2660, 1460, 1360 and 1240  $cm^{-1}$ .

Found: C, 73.27; H, 12.48; N, 14.38%. Calcd for  $C_{12}H_{24}N_2$ : C, 73.41; H, 12.32; N, 14.27%.

Picrate of IIb: partially melted at 150°C, then solidified and melted again at 202–225°C with decomposition.

Found: C, 50.55; H, 6.56; N, 15.96%. Calcd for  $C_{15}H_{27}N_3O_7$ : C, 50.81; H, 6.40; N, 16.46%.

**1-*t*-Butyl-3-(1-morpholino)azetidide (IIc).** (90% yield—crude). Very hygroscopic colorless prisms, mp 43–45°C (from petroleum ether). IR: 2980–2800, 1480, 1360, 1240 and 1120  $cm^{-1}$ .

Found: C, 66.30; H, 11.20; N, 13.76%. Calcd for  $C_{11}H_{22}N_2O$ : C, 66.62; H, 11.18; N, 14.13%.

Dipicrate of IIc: mp 223–230°C (decomp.).

Found: C, 42.54; H, 4.30; N, 17.30%. Calcd for  $C_{23}H_{25}O_{13}N_8$ : C, 42.07; H, 4.29; N, 17.06%.

**1-*t*-Butyl-3-aminoazetidide (IId).** This was prepared in 35% yield by treatment of 10 g of I with 40 ml of saturated methanolic solution of ammonia for a week at room temperature. Colorless liquid, bp 55–61°C/13.5 mmHg,  $n_D^{25}$  1.4545, IR: 3360, 2380, 1610, 1480, 1360 and 1240  $cm^{-1}$ . The NMR spectrum is shown in Fig. 1 (b).

Found: C, 64.72; H, 12.65; N, 21.93%. Calcd for  $C_7H_{16}N_2$ : C, 65.57; H, 12.58; N, 21.85%.

*p*-Nitrobenzamide of IId: mp 163.5–165°C.

Found: C, 60.49; H, 6.58; N, 15.42%. Calcd for  $C_{14}H_{19}O_3N_3$ : C, 60.63; H, 6.91; N, 15.15%.

Monopicrate of IId: mp 245–250°C (decomp.).

Found: C, 43.95; H, 5.50; N, 19.26%. Calcd for  $C_{13}H_{19}N_3O_7$ : C, 43.69; H, 5.36; N, 19.60%.

Dipicrate of IId: mp 224–228°C (decomp.).

Found: C, 38.49; H, 3.80; N, 19.28%. Calcd for  $C_{19}H_{22}N_8O_{14}$ : C, 38.91; H, 3.78; N, 19.10%.

***N,N*-Di-(1-*t*-butylazetidiny-3)cyclohexylamine (III).** This was obtained in ca. 60% yield by the reaction of 0.02 mol of I and 0.04 mol of cyclohexylamine.

Trihydrochloride monohydrate of III: mp 194–196°C (white needles from ethanol). IR: 3480, 3440, 3300, a group of absorption between 2800–2400, 1470, 1430 and 1380  $cm^{-1}$ .

Found: C, 53.02; H, 10.41; N, 9.53%. Calcd for  $C_{20}H_{44}N_3OCl_3$ : C, 53.50; H, 9.80; N, 9.36%.

**1-*t*-Butyl-3-cyclohexylaminoazetidide (IIe).** This was prepared in ca. 22% yield by the reaction of 5.8 g (0.02 mol) of I and 30 ml of cyclohexylamine.

Monohydrate of IIe: Colorless plates, mp 37–39°C (from hexane), IR: a broad peak between 3500–3200, 3260, 1448, 1360 and 1240  $cm^{-1}$ . This substance melted to a liquid when kept in a desiccator, which resolidified to give the monohydrate when allowed to stand in the open air.

Found: C, 68.67; H, 12.16; N, 12.54%. Calcd for  $C_{19}H_{28}N_2O$ : C, 68.37; H, 12.36; N, 12.27%.

Dipicrate of IIe: mp 199.5–202°C (decomp.).

Found: C, 44.92; H, 4.98; N, 16.24%. Calcd for  $C_{25}H_{32}N_6O_{14}$ : C, 44.90; H, 4.82; N, 16.76%.

**1-*t*-Butyl-3-methylthioazetidide (IVa).** To a solution of ca. 0.1 mol of sodium methylmercaptide in 50

ml of ethanol was added 11.5 g (0.04 mol) of I and the mixture was stirred for a day at room temperature and was allowed to stand overnight. It was then treated in the same way as in the reaction of I and secondary amines. 4.7 g (74% yield) of colorless liquid was obtained. Bp 80–83°C/13 mmHg,  $n_D^{25}$  1.4741. IR: 2980–2820, 1480, 1430, 1360, 1250 and 1080  $cm^{-1}$ . NMR( $\tau$ ): 9.12 (singlet, 9H); 8.00 (singlet, 3H); 6.50–7.10 (multiplet, 5H).

Found: C, 60.46; H, 11.00; N, 8.34%. Calcd for  $C_8H_{17}NS$ : C, 60.34; H, 10.76; N, 8.80%.

Picrate of IVa: mp 165–167.5°C.

Found: C, 43.39; H, 5.12; N, 14.60%. Calcd for  $C_{14}H_{20}N_4O_7S$ : C, 43.30; H, 5.19; N, 14.43%.

The following sulfides were prepared by the same method as described above:

**1-*t*-Butyl-3-ethylthioazetidide (IVb).** (63% yield) Bp 95–102°C/22 mmHg,  $n_D^{25}$  1.4705, IR: 3000–2820, 1480, 1450, 1360, 1250 and 1080  $cm^{-1}$ .

Found: C, 61.91; H, 11.05; N, 8.00%. Calcd for  $C_9H_{19}NS$ : C, 62.39; H, 11.05; N, 8.09%.

Picrate of IVb: mp 134–135°C.

Found: C, 44.60; H, 5.29; N, 14.14%. Calcd for  $C_{15}H_{22}O_7N_4S$ : C, 44.77; H, 5.51; N, 13.93%.

**1-*t*-Butyl-3-(2-benzothiazolylthio)azetidide (IVc).** (41% yield). White fine crystals (from petroleum ether), mp 48–49°C. IR: 3053, 2900, 2834, 1450, 1366, 1240 1000 and 765  $cm^{-1}$ .

Found: C, 60.62; H, 6.66; N, 10.42%. Calcd for  $C_{14}H_{18}N_2S_2$ : C, 60.42; H, 6.52; N, 10.07%.

Picrate of IVc: mp 144.5–145.5°C.

Found: C, 46.99; H, 4.27; N, 14.01%. Calcd for  $C_{20}H_{21}N_5O_7S_2$ : C, 47.33; H, 4.17; N, 13.80%.

#### Reaction of I and Potassium Hydrogen Sulfide.

Hydrogen sulfide was saturated to a solution of 5 g of potassium hydroxide in 50 ml of methanol. To the above solution, 11.5 g (0.04 mol) of I was added and the mixture was processed according to the method described above. To the residue obtained by removal of the solvent was added with cooling 12 ml of acetic anhydride and the solution was warmed on a water bath for three hours. After setting aside at room temperature overnight, the reaction mixture was poured into water, made alkaline with potassium carbonate and was extracted with ether. The extract was concentrated and the residual oil was distilled to give 0.8 g of a colorless liquid, bp 44–56°C/1.5 mmHg, and 2 g of a light yellow viscous liquid, bp 142–152°C/1.5 mmHg.

Low boiling fraction:  $n_D^{25}$  1.4805, IR: 3000–2820, 1695, 1480, 1360, 1240, 1120  $cm^{-1}$ .

Found: C, 58.02; H, 9.65; N, 7.52%. Calcd for  $C_9H_{17}NOS$ : C, 57.73; H, 9.15; N, 7.48%.

Picrate of low boiling fraction: mp 168–170°C.

Found: C, 43.11; H, 4.78; N, 14.46%. Calcd for  $C_{15}H_{20}N_4O_8S$ : C, 43.27; H, 4.84; N, 13.46%.

High boiling fraction:  $n_D^{25}$  1.4850, IR: 3000–2800, 1695, 1640, 1480, 1390, 1360, 1230 and 1130  $cm^{-1}$ .

**Methyl 1-*t*-Butylazetidiny-3 Sulfone (V).** To a solution of 2 g (0.0125 mol) of IVa in 20 ml of glacial acetic acid was added dropwise with stirring a solution of 2.5 g (0.016 mol) of potassium permanganate in 25 ml of water. The mixture was stirred for half an hour at room temperature and then for another half an hour at 40–50°C. The precipitate was filtered off and the filtrate was treated with an aqueous sodium bisulfite.

Extraction with ether and removal of the solvent afforded 1.9 g of crude solid, which was recrystallized from ether to give 0.7 g (29% yield) of colorless plates, mp 46–48.5°C. IR: a group of absorption between 1330–1200 and 1140  $\text{cm}^{-1}$ .

Found: C, 50.18; H, 9.15; N, 7.11%. Calcd for  $\text{C}_8\text{H}_{17}\text{NO}_2\text{S}$ : C, 50.25; H, 8.96; N, 7.33%.

Picrate of V: Mp 188–190.5°C.

Found: C, 40.27; H, 4.91; N, 13.31%. Calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_9\text{S}$ : C, 40.00; H, 4.79; N, 13.33%.

**Reaction of I and Thiobenzoic Acid.** To a solution of 10 g (0.07 mol) of thiobenzoic acid in 9 ml of dimethylformamide was added successively 1.6 g (0.01 mol) of potassium carbonate and 5.8 g (0.02 mol) of I and the mixture was stirred for six hours and was set aside overnight. The reaction mixture was then diluted with 30 ml of water, made strongly alkaline with potassium carbonate and was extracted with ether.

A reddish brown viscous oil remained after removal of the solvent. The oil was dissolved again in ether and treated with dilute hydrochloric acid. A light colored precipitate (3.9 g) was obtained, which was recrystallized from ethanol-hexane to give white needles, mp 160–166°C. IR: 3060, 2800–2500, 2420, 1660  $\text{cm}^{-1}$ .

Found: C, 59.45; H, 6.35; N, 3.22%. Calcd for  $\text{C}_{21}\text{H}_{26}\text{NO}_2\text{S}_2\text{Cl}$ : C, 59.50; H, 6.18; N, 3.30%.

A light-colored viscous oil was recovered by neutralization and extraction of the above hydrochloride. IR: 3320, 3060, 1660  $\text{cm}^{-1}$ . (No absorption due to SH was observed.)

Found: C, 65.58; H, 6.63; N, 3.83%. Calcd for  $\text{C}_{21}\text{H}_{25}\text{NO}_2\text{S}_2$  (VI): C, 65.10; H, 6.50; N, 3.83%.

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

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