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The Preparation and Deamination of 1-*t*-Butyl-3-amino-, 1-*t*-Butyl-3-aminomethyl-, and 1-*t*-Butyl-2-aminomethylazetidine

Teng-Yueh CHEN, Mu-Huang HUNG, Po-Tau CHEN, and Masaki OHTA*

Institute of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, China

**Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo*

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1-*t*-Butyl-3-amino-, 1-*t*-butyl-3-aminomethyl-, and 1-*t*-butyl-2-aminomethylazetidine were prepared by the ammonolysis of 1-*t*-butyl-3-azetidinyl tosylate, and by the reduction of 1-*t*-butyl-3-cyano, and 1-*t*-butyl-2-cyano-azetidine respectively. In the deamination, both of the first two azetidines gave only the corresponding alcohols, 1-*t*-butyl-3-azetidinol and 1-*t*-butyl-3-hydroxymethylazetidine, while the last one was found to afford two products, 1-*t*-butyl-2-hydroxymethylazetidine and 1-*t*-butyl-3-hydroxypyrrolidine. The deamination products were identified as the corresponding acetates.

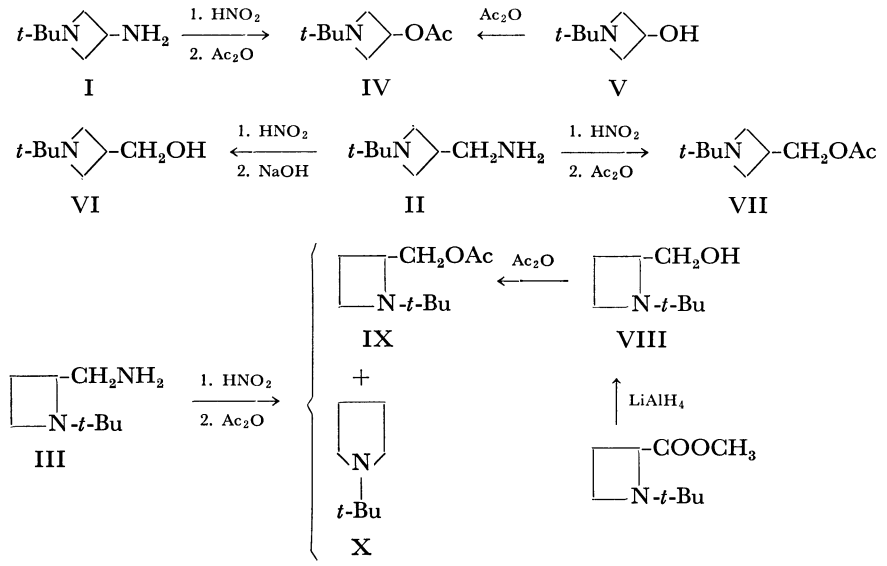
Rearrangements involving carbonium ions in small-ring compounds[1] or involving the nucleophilic participation of the amino group in strainless alicyclic amines[2] are already known. With regard to the highly strained azetidines, reactions which closely resemble the above rearrangements have also been reported very recently by Gaertner,[3] Deyrup and Moyer,[4]

1) Review: R. Breslow, in "Molecular Rearrangements," ed. by P. de Mayo, Part One, Interscience Publishers, New York, N. Y. (1963), pp. 233—294.

2) R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, **70**, 2760 (1948); R. H. Reitsema, *ibid.*, **71**, 2041 (1949); E. G. Brain, E. P. Doyl, and M. D. Mehta, *J. Chem. Soc.*, **1961**, 633.

3) V. R. Gaertner, *Tetrahedron Lett.*, **1968**, 5919; V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).

4) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, **1968**, 6179.



and Masuda *et al.*[5] Here, we will present the results of the deamination of the title compounds.[6] It is of interest to see if the cation so generated can be attacked by the nitrogen atom in the ring to give ring-contraction or ring-expansion products.

1-*t*-Butyl-3-aminoazetidine (I) was prepared according to a method reported before.[7] 1-*t*-Butyl-3-aminomethylazetidine (II) was prepared by the lithium aluminum hydride reduction of 1-*t*-butyl-3-cyanoazetidine.[8] The reduction of 1-*t*-butyl-2-cyanoazetidine[9] with lithium aluminum hydride offered a third amine, 1-*t*-butyl-2-aminomethylazetidine (III).[10] The infrared spectrum of the undistilled amine, II, shows the characteristic bands of a primary amino group at 3360 and 3290 cm^{-1} and an NH bending band at 1590 cm^{-1}, while that of the product III shows bands at 3360, 3280, and 1590 cm^{-1}. The results of the elemental analyses and spectroscopic studies of the dipicrates and phenylthioureas derived from the amines were completely consistent with the structures I, II, and III respectively (see Experimental). The homogeneity of the amines was also examined by vpc before deamination.

The amine I was allowed to react with sodium nitrite in aqueous acetic acid; the reaction mixture was then acetylated with acetic anhydride and analyzed by tlc and vpc. Only one product, 1-*t*-butyl-3-acetoxyazetidine (IV), was detected. The product, IV, isolated by vpc was found to be identical (IR, tlc, and vpc) with the authentic sample synthesized independently from the reaction of 1-*t*-butyl-3-azetidinol (V) and acetic anhydride.[6,11] The results of the elemental analysis were in agreement with the structure.

The deamination of the amine II was carried out in the same way, and the reaction mixture was analyzed before being treated with acetic anhydride. The mixture, which contained nearly equal amounts of 1-*t*-butyl-3-hydroxymethylazetidine (VI) and its acetate (VII) (detected by vpc), was then hydrolyzed to give VI as its only product. The infrared spectrum shows a broad absorption between 3500—3100 cm^{-1} for the hydroxyl group; the results of elemental analysis also coincided with the structure VI. For the purpose of confirmation, the deamination of II was performed again, and the reaction product was identified after acetylation. This time, only 1-*t*-butyl-3-acetoxymethylazetidine (VII) was obtained. The infrared spectrum of the product shows a strong ester carbonyl absorption at 1745 cm^{-1}. The NMR spectrum (CCl_4) exhibits a singlet at τ 9.10 (9H, *t*-Bu), a singlet at 8.03 (3H, CH_3CO), a multiplet between 7.67 and 7.25 (1H, ring methine), a triplet at 7.09 (2H, ring methylene), a triplet at 6.79 (2H, with the center split, ring methylene) and a doublet at 5.90 (2H, J= 6.8 Hz, methylene adjacent to ester oxygen). The results of the elemental analysis of the product and its picrate also agreed with the proposed structure, VII.

According to the same procedure, the amine III, in the deamination, was found to produce 1-*t*-butyl-2-acetoxymethylazetidine (IX) and the ring-expansion product, 1-*t*-butyl-3-acetoxypyrrolidine (X), in a vpc ratio of 45.6 : 54.6. The component with the shorter vpc retention time was spectrally (IR and NMR: Fig. 1) identical with the authentic sample of 1-*t*-butyl-2-acetoxymethylazetidine IX (see Experimental) prepared by the acetylation of the 1-*t*-butyl-2-hydroxymethylazetidine (VIII) which had been

5) T. Masuda, A. Chinone, and M. Ohta, This Bulletin, **43**, 3287 (1970).

6) Some of the results have been taken from the Ph. D. thesis of T. Chen, Tokyo Institute of Technology, March (1968).

7) T. Chen, H. Kato, and M. Ohta, This Bulletin, **41**, 712 (1968).

8) T. Chen, T. Sanjiki, H. Kato, and M. Ohta, *ibid.*, **40**, 2401 (1967).

9) T. Masuda, A. Chinone, and M. Ohta, *ibid.*, **43**, 3281 (1970).

10) The amines II and III were not purified by distillation because, unexpectedly, both of them bubble over the distillation flask by heating up to 80—90°C/19 mmHg and were confirmed by spectra and their derivatives (see Experimental).

11) V. R. Gaertner, *Tetrahedron Lett.*, **1966**, 4691; V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967).

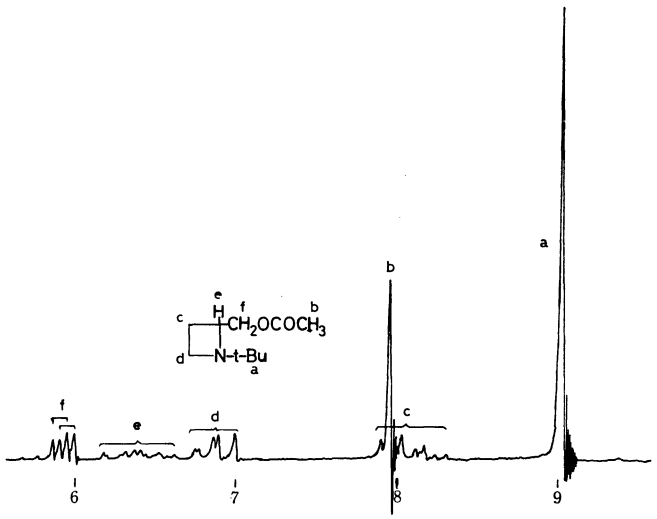


Fig. 1. The NMR spectrum of 1-*t*-butyl-2-acetoxymethylazetidine.

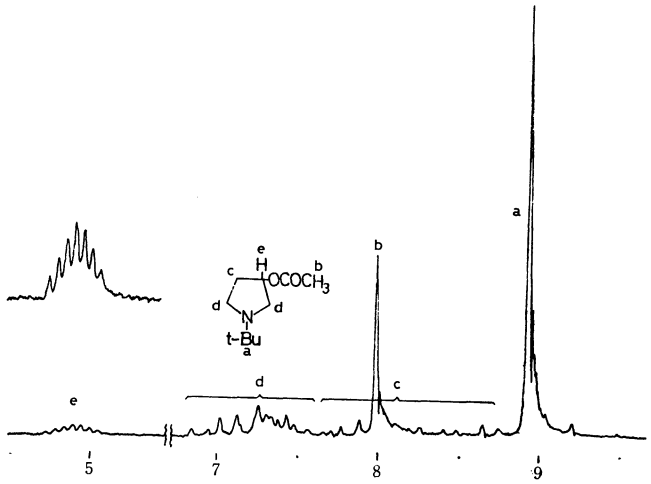
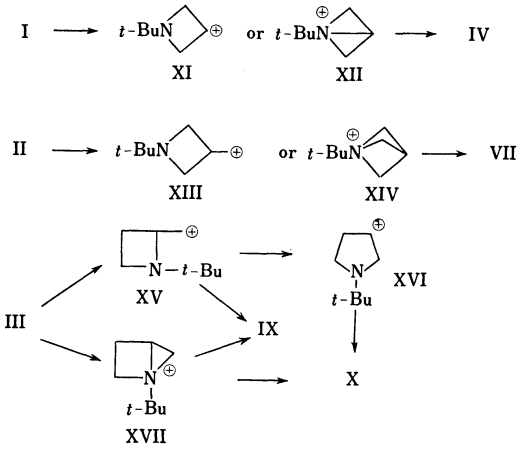


Fig. 2. The NMR spectrum of 1-*t*-butyl-3-acetoxypyrrolidine.

obtained by the reduction of 1-*t*-butyl-2-methoxycarbonylazetidine[5] with lithium aluminum hydride. The second compound isolated by vpc was considered to be 1-*t*-butyl-3-acetoxypyrrolidine (X) by the use of the spectroscopic method and by elemental analysis. The general pattern of the infrared spectrum of X is markedly different from that of IX; it has a strong absorption at 1740 cm^{-1} for the ester carbonyl group. The NMR spectrum ($CDCl_3$, Fig. 2) of X exhibits a singlet at τ 8.93 (9H, *t*-Bu), a singlet at 8.01 (3H, CH_3CO), a multiplet between 8.29 and 7.65 (2H, the methylene on the 4-carbon of the ring), a multiplet between 7.50 and 6.81 (4H, the two methylenes adjacent to the ring nitrogen), and a septet centered at 4.90 (1H, J=3.1 Hz, the asymmetric methine proton on the 3-carbon of the ring). A similar splitting of the methine proton in 1-*t*-butyl-2-aminomethylazetidine has also been observed by Rodebaugh and Cromwell.[12]

The fact that the ring contraction was not observed in the deamination of the amine I is in fair agreement with most previously-reported causes of replacement reactions involving 3-azetidinium cations, XI, which have a tendency to keep the ring unchanged rather than to contract it, though there are a few exceptions.[3,7,8] In the case of the amine II, 3-acetoxymethylazetidine, VII, should be formed from either the azabicyclo[1.1.1]pentyl cation, XIV (nitrogen atom participation), or the azetidinylmethyl cation, XIII. The formation of the ring-expansion product X by the deamination of the amine III may be expansion product X by the deamination of the amine III may be explained by the participation of the nitrogen atom (*via* the azabicyclo[2.1.0]pentyl cation, XVII) or, alternatively, by a simple 1,2-sigmatropic rearrangement of the 2-azetidinylmethyl cation, XV→ XVI. The absence of a ring-enlargement product in the deamination of II lends support to the probable nitrogen atom participation.



Experimental[13]

1-t-Butyl-3-aminoazetidine (I). This compound was prepared from 1-*t*-butyl-3-azetidinyl tosylate and a saturated methanolic solution of ammonia.[7] The fraction boiling at 71°C/20 mmHg was taken for the deamination. IR: 3370, 3290, 1600, 1390, 1365 cm^{-1}. Vpc: Carbowax 20 M on Diasolid A 4 mm × 225 cm 90°C, He 60 m*l*/min, retention time, 16 min; SE30 on Varaport 30, 1/4 in × 5 ft 75°C, N_2 60 m*l*/min, retention time, 3.8 min.

Dipicrate of I: Mp 198—200°C (decomp.).

Found: C, 39.15; H, 3.85; N, 19.32%. Calcd for $C_{19}H_{22}N_8O_{14}$: C, 38.91; H, 3.78; N, 19.10%.

1-*t*-Butyl-3-phenylthioureidoazetidine: Mp 141°C.

Found: N, 16.16%. Calcd for $C_{14}H_{21}N_3S$: N, 15.95%.

1-t-Butyl-3-cyanoazetidine. This was prepared in a 73% yield (3.5 g) from 10 g of 1-*t*-butyl-3-azetidinyl tosylate and 6.8 g of potassium cyanide in 100 m*l* of methanol.[8] Bp 46—47°C/2 mmHg. IR: 2240, 1390 and 1365 cm^{-1}. Vpc: Porapak Q 1/8 in × 5.7 ft 75°C, N_2 35 m*l*/min, reten-

12) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 19 (1971).

13) All melting and boiling points are uncorrected. The melting points were measured on a micro hot state. The infrared spectra were taken on neat liquid or on KBr tablets, and the NMR spectra were determined on Varian A 60-D at 60 MHz, tetramethylsilane being used as the internal standard. The vpc were run on Shimadzu Type GC-1B Gas Chromatograph, Varian Aerograph Series 1200, Varian Aerograph Model 705, and Varian Model 90-F-3 alternatively.

tion time, 10.2 min; SE30 on Varaport 30,1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 12 min.

Found: C, 69.78; H, 10.03; N, 20.21%. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27%.

Picrate Mp 203—205°C.

1-t-Butyl-3-aminomethylazetidine (II). The reduction of 2.9 g (0.021 mol) of 1-*t*-butyl-3-cyanoazetidine with 0.9 g of lithium aluminum hydride in 80 ml of absolute ether yielded 2.2 g (74%) of a pale yellow liquid which could not be purified by distillation since it bubbled vigorously over the distillation flask when heated up to 90°C/19 mmHg. This crude product was found homogeneous by vpc and was used in the deamination. IR: 3360, 3290, 1590, 1390, and 1364 cm^{-1}. n_D^{25} 1.4645. vpc: SE30 on Varaport 30, 1/8 in × 6 ft 70°C, N_2 30 ml/min, retention time, 7.2 min.

Dipicrate of II: Mp 230°C (decomp.).

Found: C, 40.26; H, 4.20; N, 18.88%. Calcd for $C_{20}H_{24}N_8O_{14}$: C, 40.01; H, 4.03; N, 18.66%.

1-*t*-Butyl-3-phenylthioureidomethylazetidine: Mp 99—100.5°C. IR: 3470, 3150, 1600, and 1530 cm^{-1}.

Found: C, 64.72; H, 8.28; N, 15.45%. Calcd for $C_{15}H_{23}N_3S$: C, 64.94; H, 8.36; N, 15.15%.

1-t-Butyl-2-cyanoazetidine.[9] This compound was obtained by the reaction of 6.8 g of 1-*t*-butylazetidine-2-carboxamide and a solution of triphenylphosphine dibromide (prepared from 13.8 g of triphenylphosphine, 8.4 g of bromine, and 10.6 g of triethylamine) in 75 ml of acetonitrile. A colorless oil (3 g, 50% yield) was obtained. Bp 43°C/1 mmHg. $n_D^{24.5}$ 1.4482. IR: 2240, 1385, and 1355 cm^{-1}.

Picrate: Mp 150—151°C.

Found: C, 46.00; H, 4.50; N, 19.14%. Calcd for $C_{14}H_{17}N_5O_7$: C, 45.78; H, 4.69; N, 19.07%.

1-t-Butyl-2-aminomethylazetidine (III).[12] The reduction of 3 g (0.022 mol) of 1-*t*-butyl-2-cyanoazetidine with 1 g of lithium aluminum hydride in 140 ml of absolute ether gave 2.5 g (80%) of a pale yellow liquid; this liquid was not purified by distillation for the same reason as has been given above. IR: 3360, 3280, 1590, 1388, and 1362 cm^{-1}. $n_D^{24.5}$ 1.4666. Vpc: SE30 on Varaport 30, 1/8 in × 6 ft 70°C, N_2 30 ml/min, retention time, 6 min.

Dipicrate of III: Mp 196.5—197.5°C.

Found: C, 39.72; H, 4.14; N, 18.81%. Calcd for $C_{20}H_{24}N_8O_{14}$: C, 40.01; H, 4.03; N, 18.66%.

1-*t*-Butyl-2-phenylthioureidomethylazetidine: Mp 105—105.5°C. IR: 3220, 3160, 1600, 1540 cm^{-1}.

Found: C, 64.66; H, 8.19; N, 15.43%. Calcd for $C_{15}H_{23}N_3S$: C, 64.94; H, 8.35; N, 15.14%.

1-t-Butyl-3-acetoxyazetidine (IV) from 1-t-Butyl-3-azetidinol (V).[6,11] This was prepared by the acetylation of 5.6 g (0.043 mol) of V with 6 g (0.059 mol) of acetic anhydride at room temperature for 5 hr. After neutralization with sodium carbonate, by extraction with ether an subsequent distillation 6.7 g (91% yield) of a colorless liquid boiling at 30—31°C/0.5 mmHg were obtained. n_D^{24} 1.4383. IR: 1745, 1377, and 1365 cm^{-1}. NMR (CCl_4, τ): 9.08 (9H, singlet), 8.04 (3H, singlet), 7.02 (2H, triplet), 6.60 (2H, triplet), 5.35—5.07 (1H, multiplet). Tlc: Tōyō (Japan) thin-layer chromatosheet (silica gel), R_f=0.38 (acetone). Vpc: Apiezon Grease L on Diasolid A 4 mm × 300 cm 152°C, He 60 ml/min, retention time, 5.2 min; Carbowax 20 M on Diasolid A 4 mm × 300 cm 162°C, He 60 ml/min, retention time, 5 min; SE30 on Varaport 30, 1/4 in × 5 ft, 75°C, N_2 60 ml/min, retention time, 9.8 min.

Found: C, 62.39; H, 9.76; N, 7.81%. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18%.

Picrate of IV: Mp 150.5—152.5°C.

Found: C, 44.71; H, 4.82; N, 14.28%. Calcd for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.04; N, 14.00%.

1-t-Butyl-2-hydroxymethylazetidine (VIII).[5] From 14.4 g (0.09 mol) of 1-*t*-butyl-2-methoxycarbonylazetidine and 2.5 g of lithium aluminum hydride in absolute ether, 8.3 g (68.8% yield) of a colorless oil, bp 38—40.5°C/0.5 mmHg, were obtained. n_D^{21} 1.4624. IR: a broad peak at 3500—3200, 1380 and 1360 cm^{-1}.

Found: C, 66.86; H, 12.11; N, 9.08%. Calcd for $C_8H_{17}NO$: C, 67.29; H, 11.95; N, 9.07%.

Picrate of VIII: Mp 190—191°C (decomp.).

Found: C, 45.09; H, 5.25; N, 15.32%. Calcd for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05%.

1-t-Butyl-2-acetoxymethylazetidine (IX) from VIII. The acetylation of 3 g (0.021 mol) of VIII with 2.3 g (0.022 mol) of acetic anhydride gave 3 g (77.3% yield) of a colorless oil. Bp 88.5—89.5°C/19 mmHg. $n_D^{25.4}$ 1.4450. IR: 1750, 1390 and 1370 cm^{-1}. NMR ($CDCl_3$, τ): (Fig. 1), 9.03 (9H, singlet), 7.96 (3H, singlet), 8.34—7.85 (2H, multiplet), 7.04—6.65 (2H, multiplet), 6.64—6.17 (1H, multiplet), 5.95 (1H, doublet, $J\simeq$5.6 Hz), 5.9 (1H, doublet, J=5.5 Hz). Vpc: SE30 on Varaport 30, 1/8 in × 6 ft 70°C, N_2 30 ml/min, retention time, 17.3 min; SE30 on Varaport 30, 1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 11.6 min.

Found: C, 64.58; H, 10.04; N, 7.46%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56%.

Picrate of IX: Mp 129—130°C (decomp.).

Found: C, 46.36; H, 5.13; N, 13.78%. Calcd for $C_{16}H_{22}N_4O_9$: C, 46.37; H, 5.35; N, 13.52%.

Deamination of 1-t-Butyl-3-aminoazetidine (I). A solution of 1.1 g (0.015 mol) of sodium mitrite in 6 ml of water was slowly stirred into a solution of 1.2 g (0.01 mol) of I in 7.2 g of 50% acetic acid cooled with ice-salt. After 5 hr, the reaction mixture was made alkaline with sodium carbonate and was extracted with ether. After the subsequent removal of the ether, 2 ml of acetic anhydride were stirred into the deamination mixture with cooling and the stirring was continued at room temperature for five hours. Then the solution was made alkaline with excess sodium carbonate, extracted with ether, and dried over magnesium sulfate overnight. The ether was removed, and the residue was analyzed by vpc and tlc. Only one component, with a R_f value of 0.38 (acetone) was detected by tlc (similar to the authentic sample, IV, under the same conditions). Vpc: SE30 on Varaport 30, 1/4 in × 5 ft 75°C, N_2 60 ml/min, retention time, a very small peak at 2.6 min and a main peak at 9.8 min, with a peak area ratio of 6 : 94. The other vpc data were identical with those of IV. The fraction corresponding to the smaller peak, isolated by vpc, did not form a picrate and may be not an amine. The IR spectrum of the main product isolated by vpc was completely identical with that of the authentic sample of IV.

Picrate of the main product: Mp 150—152°C.

Found: C, 44.91; H, 4.76%. Calcd for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.04%.

Deamination of 1-t-Butyl-3-aminomethylazetidine (II). (A) The amine II (1.4 g, 0.01 mol) was deaminated with 1.5 g (0.02 mol) of sodium nitrite in 50% acetic acid in a manner similar to that described above (omitting the acetylation in this experiment). The deamination mixture, which consisted of nearly equal amounts of 1-*t*-butyl-3-hydroxymethylazetidine (VI) and its acetate (VII) (detected by vpc), was then warmed with aqueous sodium hydroxide at 55°C for 3 hr and extracted with ether. After the removal of the ether, a part of the crude product was reserved for vpc analysis, and the remainder was distilled *in vacuo* to give 0.5 g of pure VI. Bp 66—68°C/0.5 mmHg, n_D^{25} 1.4626. IR: 3500—3100(broad), 1385 and 1360 cm^{-1}.

Vpc: only one compound presented; SE30 on Varaport 30, 1/8 in ×6 ft 70°C, N_2 30 ml/min, retention time, 8.8 min; SE30 on Varaport 30, 1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 13.6 min.

Found: C, 66.81; H, 11.72; N, 9.48%. Calcd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78%.

Picrate of VI: Mp 143—144°C.

Found: N, 15.51%. Calcd for $C_{14}H_{20}N_4O_8$: 15.05%.

(B) The deamination of II was carried out again with 2 g (0.014 mol) of II and 1.5 g (0.022 mol) of sodium nitrite in 50% acetic acid; the deamination product was then allowed to react with acetic anhydride as in the deamination of I, and then it was analyzed. Both the crude product and the distilled product consist of only 1-*t*-butyl-3-acetoxymethylazetidine (VII), a colorless liquid boiling at 57—58°C/0.5 mmHg, n_D^{25} 1.4421. IR: 1745, 1390 and 1370 cm^{-1}. NMR: see the Discussion. Vpc: SE30 on Varaport 30, 1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 29.8 min.

Found: C, 64.90; H, 10.60; N, 7.85%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56%.

Picrate of VII: Mp 114°C.

Found: C, 46.10; H, 5.40; N, 13.82%. Calcd for $C_{16}H_{22}N_4O_9$: C, 46.38; H, 5.35; N, 13.52%.

Deamination of 1-t-Butyl-2-aminomethylazetidine (III). The amine III (2 g, 0.014 mol) in 10 ml of 50% acetic acid was allowed to react with 1.6 g (0.025 mol) of sodium nitrite in 10 ml of water; the products were similarly identified as their acetates. Vpc analyses showed that both the crude substance and the distilled (the fraction boiling between 40—78°C/18 mmHg was collected) substance were composed of two products in the ratio of 45.6 : 54.4 (vpc peak area).

The first product was isolated by vpc: SE30 on Varaport 30, 1/8 in × 6 ft 70°C, N_2 30 ml/min, retention time, 17.3 min; SE30 on Varaport 30, 1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 11.6 min. The IR and NMR spectra and the results of the vpc analyses showed this compound to be identical with the authentic sample of IX prepared from VIII.

Found: C, 64.61; H, 10.17; N, 7.81%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56%.

The second product (X) was also isolated by vpc: SE 30 on Varaport 30, 1/8 in × 6 ft 70°C, N_2 30 ml/min, retention time, 22.6 min; SE30 on Varaport 30, 1/4 in × 5 ft 80°C, N_2 60 ml/min, retention time, 14.7 min. IR: 1740, 1393 and 1370 cm^{-1}. NMR: see Fig. 2.

Found: C, 64.93; H, 10.07; N, 7.38%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56%.

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