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Azetidines. V. Preparation and Deamination of Azetidinylpropylamines[1]

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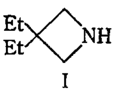
The addition of 3,3-diethylazetidine to acrylonitrile and crotononitrile, followed by reduction, gave the corresponding azetidinylpropylamines. The deamination products of the amines were identical with the alcohols prepared by the addition of diethylazetidine to methyl acrylate and crotonate, followed by reduction with lithium aluminum hydride.

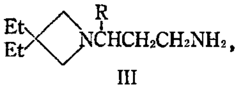
In Part I[3] of this series, it has been reported that azetidine gave addition products readily with active unsaturated compounds. The addition product with acrylonitrile is of particular interest since it may be converted to the corresponding amine, which then gives a cationic intermediate on deamination. It seemed to be of interest to see if the cation so generated can be attacked by the nitrogen atom in the molecule to give the spiro-azetidinium cation. The formation of such a spiro-azetidinium cations as intermediates has been suggested from time to time, and they have actually been isolated in some cases.[4]

A relatively readily accessible 3,3-diethylazetidine[5] (I) was used as the starting meterial, because the NMR spectra of its derivatives can be easily analyzed. The reaction of I with acrylonitrile proceeded readily to give β-(3,3-diethylazetidinyl-1)propionitrile (IIa), which was then reduced with lithium aluminum hydride to the corresponding amine IIIa in a good yield. The alcohol isolated after the deamination of the amine IIIa with nitrous acid was homogeneous, as judged by v.p.c., and its NMR spectrum was completely consistent with the structure IVa. It shows two triplets, at τ 6.47 and 7.43, corrresponding to the two protons on the methylene groups adjacent to the hydroxyl group and to those two adjacent to the nitrogen atom respectively (See Experimental Section). Conclusive evidence in support of the structure IVa could be obtained by the preparation of IVa by the addition of I to methyl acrylate to give Va, followed by its reduction with lithium aluminum hydride to IVa. This product was identical with the deamination product of IIIa.



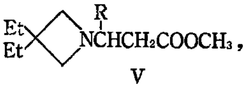
I

II

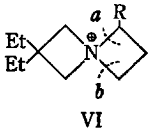


III

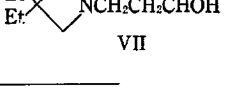
IV



V



VI



VII

a, R = H
b, R = Me

These results may be explained by considering the direct attack of an hydroxyl anion on the cation, but it does not rigorously exclude an alternative path *via* the spiro-azetidinium intermediate VIa, since it has been known that the less-heavily-substituted azetidine rings are in general more unstable than those which are more heavily substituted.[4] Hence, even if the spiro-azetidinium intermediate VIa may be formed as the intermediate, it will invariably give the alcohol IVa by the cleavage of the unsubstituted ring (at *a* or *b*).

In order to check this possibility, 3-(3,3-diethylazetidinyl-1)butylamine (IIIb) was prepared from I and crotononitrile by the method described above; it was then subjected to the deamination reaction. It was expected that if the spiro intermediate VIb was formed, it would give the product VII, resulting mainly from the cleavage of the ring at *a*.

The structure and purity of the nitrile IIb and the reduction product, amine IIIb, were determined by correct analyses, infrared spectra, and v.p.c.,

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[1] Part IV: T. Chen, H. Kato and M. Ohta, This Bulletin, **41**, 712 (1968).

[2] Present address: National Tsing Hua University, Taiwan, The Republic of China.

[3] Part I: T. Chen, H. Kato and M. Ohta, This Bulletin, **40**, 1964 (1967).

[4] J. A. Moore "Heterocyclic Compounds with Three- and Four-membered Rings," Part Two, ed. by A. Weissberger, Interscience Publishers, New York, N. Y. (1964), p. 885; E. Testa, A. Wittgens, G. Maffii and G. Bianchi, *Research Progress in Organic, Biological and Med. Chem.*, **1**, 477 (1964).

[5] E. Testa and L. Fontanella, *Ann.*, **625**, 95 (1959); E. Testa, L. Fontanella and G. F. Cristiani, *ibid.*, **626**, 114 (1959).

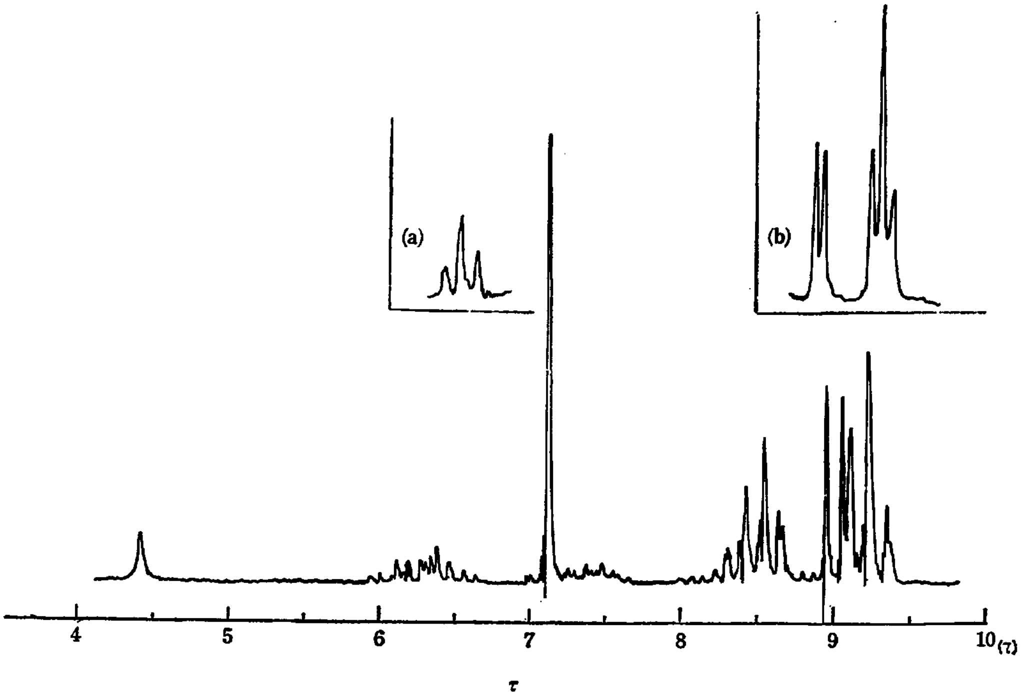

Fig. 1. The NMR spectrum of the deamination product of 3-(3,3-diethylazetidinyl)butylamine in CDCl$_3$. (a) Partial NMR spectrum of the same compound in DMSO; (b) Partial NMR spectrum of the HCl salt of the same compound in D$_2$O.

and were confirmed by means of a study of the NMR spectra.

The alcohol isolated after the deamination of the amine IIIb was homogeneous, as judged by v.p.c., and gave a correct analysis. The NMR spectrum shown in the figure contains ABX-pattern multiplets at τ 6.98—7.68 and 7.95—8.9 because of the asymmetric carbon adjacent to the ring nitrogen. The resonance peak of the methylene adjacent to the hydroxyl group appears at τ5.8—6.65 as complex multiplets, and the chemical shift of the hydroxyl proton appears at τ 4.41 as a singlet. The remaining part of the NMR spectrum is essentially similar to that of the amine IIIb (See Experimental Section). The integrated areas of the peaks agree well with the structure IVb. The NMR spectrum is not changed by changing the temperature of measurement. The purest sample isolated by v.p.c. also shows the same NMR spectrum as the distilled sample. However, the possibility of the formation of the alcohol VII through the nitrogen spiro intermediate VIb can not be precluded on the basis of the appearance of the NMR spectrum alone.

For purposes of confirmation, the preparation of IVb by the addition of I to methyl crotonate, followed by reduction with lithium aluminum hydride, was attempted. The product so obtained was found to be identical with the deamination product. The use of a dimethyl sulfoxide solvent for the NMR determination did not cause the expected splitting of the hydroxyl group coupled by the adjacent methylene group[6,7]; instead, a broad peak at τ 5.8 was found. It is noteworthy that the NMR spectrum of the methylene group adjacent to the hydroxyl group appears as a simple triplet at τ 6.64 in this solvent (See Fig. 1(a)).

The complex multiplicity for the methylene adjacent to the hydroxyl group in CDCl$_3$ may be explained by considering that the compound forms an intramolecular hydrogen bonding between the oxygen and the ring nitrogen; thus, the chain fixes as a six-membered ring. As a result, the free rotation of the methylene group is limited and the protons are no longer equivalent. In the dimethyl sulfoxide solvent, such hydrogen bonding is broken by forming a stronger hydrogen bonding between the alcohol and the solvent; therefore, the free rotation permits the terminal methylene to split as a normal triplet.

Moreover, the doublet at τ 9.0 and the triplet at 9.22 were found to be separated further enough to permit an accurate integration when the HCl salt of the alcohol was measured in D$_2$O because of the deshielding effect of the quaternary nitrogen cation; the ratio of the two peak areas was found

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6) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

7) J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).

to be exactly 1 : 2 (See Fig. 1(b)).

From these results, it may reasonably be concluded that the alcohols obtained both from the deamination of the amine IIIb and from the reduction of the ester Vb are identical compounds, IVb, and that the alcohol arises from direct attack of the hydroxyl anion on the cation produced by the deamination rather than through the spiro-azetidinium intermediate.

Experimental[8]

β-(3,3-Diethylazetidinyl-1)propionitrile (IIa). This was prepared, by the general procedure described in Part I,[3] in an almost quantitative yield from 4 g of 3,3-diethylazetidine (I) and 2 g of acrylonitrile. Bp 65—67°C/1.5 mmHg, n_D^{25} 1.4502. IR: 2250 cm^{-1}.

Found: C, 72.35; H, 10.91; N, 16.77%. Calcd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85%.

β-(3,3-Diethylazetidinyl-1)butyronitrile (IIb). This was prepared in a 68% yield from I and crotononitrile. Bp 68—75.5°C/1.5 mmHg, n_D^{25} 1.4511. IR: 2250 cm^{-1}. NMR(τ): 7.3—8.2 (3H, multiplet); 7.18 (4H, singlet); 8.48 (4H, quartet); 9.0 (3H, doublet); 9.22 (6H, triplet). V.p.c.: Carbowax 20 M on Diasolid A, 4 mm × 150 cm, 147°C, He flow rate 50 m*l*/min, retention time 15 min; Apiezon Grease L on Diasolid A, 4 mm × 150 cm, 147°C, He flow rate 60 m*l*/min, retention time 8 min.

Found: C, 73.12; H, 10.95; N, 15.43%. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54%.

Picrate of IIb: mp 157—158°C.

Found: C, 49.94; H, 5.81; N, 17.27%. Calcd for $C_{17}H_{23}N_5O_7$: C, 49.87; H, 5.60; N, 17.11%.

Methyl β-(3,3-Diethylazetidinyl-1)propionate (Va). This was prepared in a 91% yield from 3 g of I and 2.3 g of methyl acrylate. Bp 64.5—67.5°C/1.5 mmHg, n_D^{25} 1.4430. IR: 1745 cm^{-1}.

Found: C, 65.99; H, 10.75; N, 7.20%. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03%.

Methyl β-(3,3-Diethylazetidinyl-1)butyrate (Vb). This was prepared in a 84% yield from I and methyl crotonate. Bp 67—68°C/1.5 mmHg, n_D^{25} 1.4445. IR; 1745 cm^{-1}. NMR in $CDCl_3$(τ): 6.38 (3H, singlet); 7.12 (4H, singlet); 7.16—8.21 (3H, multiplet); 8.42 (4H, quartet); 9.03 (3H, doublet); 9.24 (6H, triplet). V.p.c.: Silicone Grease DC550, 4 mm × 225 cm, 154°C, He flow rate 60 m*l*/min, retention time 22 min; Apiezon Grease L on Diasolid A, 4 mm × 150 cm, 150°C, He flow rate 60 m*l*/min, retention time 8 min; Carbowax 20 M on Diasolid 4 mm × 150 cm, 150°C, He flow rate 60 m*l*/min, retention time 6 min.

Found: C, 67.28; H, 10.75; N, 6.76%. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57%.

Picrate of Vb: mp 88—89°C.

Found: C, 48.97; H, 5.64; N, 12.72%. Calcd for $C_{18}H_{26}N_4O_9$: C, 48.86; H, 5.92; N, 12.66%.

3-(3,3-Diethylazetidinyl-1)propylamine (IIIa). A solution of 6 g of IIa in 20 m*l* of ether was stirred into a suspension of 1.6 g of lithium aluminum hydride in 80 m*l* of ether. After two hours, the reaction mixture was hydrolyzed by the addition of dilute aqueous sodium hydroxide. The ether layer was separated, and the residue was washed several times with a total of 200 m*l* of ether. The combined ether extract was then dried and distilled *in vacuo* to afford 4.5 g (75% yield) of a product boiling at 55—57°C/1.5 mmHg, n_D^{25} 1.4565. IR: 3360, 3290, 1590 cm^{-1}.

Found: C, 70.35; H, 12.33; N, 15.73%. Calcd for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45%.[9]

Picrate of IIIa: mp 199.5—201.5°C (decomp).

Found: C, 42.39; H, 4.40; N, 17.93%. Calcd for $C_{22}H_{28}N_8O_{14}$ (dipicrate): C, 42.04; H, 4.49; N, 17.83%.

3-(3,3-Diethylazetidinyl-1)butylamine (IIIb). This was similarly prepared, in a 88% yield, from 3.2 g of IIb and 1 g of lithium aluminum hydride. Bp 62—63°C/1.5 mmHg, n_D^{25} 1.4590, IR: 3362, 3295, 1600 cm^{-1}. NMR in $CDCl_3$ (τ): 7.16 (4H, singlet); 7.34 (2H, triplet with each peak split); 7.52—8.0 (1H, multiplet); 8.1—8.85 (2H, multiplet); 8.45 (4H, quartet) (These two peaks are superimposed); 9.11 (3H, doublet); 9.23 (6H, triplet) (These two peaks separate further when the HCl salt of IIIb is measured in D_2O and the ratio of the peak area was found to be exactly 1 : 2). V.p.c.: Carbowax 20 M on Diasolid A 4 mm × 150 cm, 150°C, He flow rate 40 m*l*/min, retention time 9 min; Apiezon Grease L on Diasolid 4 mm × 225 cm, 150°C, He flow rate 70 m*l*/min, retention time 10 min.

Found: C, 71.63; H, 12.97; N, 14.99%. Calcd for $C_{11}H_{24}N_2$: C, 71.68; H, 13.13; N, 15.20%.

Picrate of IIIb: mp 238—241°C (decomp).

Found: C, 42.73; H, 4.71; N, 17.16%. Calcd for $C_{23}H_{30}N_8O_{14}$ (dipicrate): C, 42.99; H, 4.70; N, 17.44%.

γ-(3,3-Diethylazetidinyl-1)propanol (IVa). This was prepared in a 88% yield by the reduction of 4.8 g of Va with 1 g of lithium aluminum hydride. Bp 65—69°C/1.5 mmHg, n_D^{25} 1.4575. IR: a broad peak between 3500 and 3100 cm^{-1}. V.p.c.: Carbowax 20 M on Diasolid A 4 mm × 225 cm, 150°C, He flow rate 60 m*l*/min, retention time 31.5 min.

Found: C, 70.00; H, 12.04; N, 8.09%. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18%.

γ-(3,3-Diethylazetidinyl-1)butanol (IVb). The reduction of 2.2 g of Vb with 0.7 g of lithium aluminum hydride afforded an alcohol fraction in a 70% yield; bp 85—90°C/1.5 mmHg, n_D^{25} 1.4615. IR: a broad peak between 3450 and 3180 cm^{-1}. NMR in $CDCl_3$ (τ): 4.41 (1H, singlet); 5.8—6.65 (2H, multiplet); 6.98—7.68 (1H, multiplet); 7.95—8.9 (2H, multiplet); 7.12 (4H, singlet); 8.48 (4H, quartet); 9.0 (3H, doublet); 9.22 (6H, triplet) (The last two peaks separate further when the HCl salt of IVb is measured in D_2O and the ratio of the peak area is exactly 1 : 2. Fig. 1 (b)). The multiplet between τ 5.8 and 6.65 appears as a simple triplet when IVb is measured in DMSO (Fig. 1(a)). V.p.c.: Apiezon Grease L on Diasolid A 4 mm × 225 cm, 160°C, He flow rate 60 m*l*/min, retention time 13 min; Carbowax 20 M on Diasolid A 4 mm × 225 cm, 160°C, He flow rate 60 m*l*/min, retention time 13.4 min;

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[8] The general conditions for the measurements of physical constants and spectra were the same as described in Part I.[3] The v.p.c. were run on a Shimadzu Type GC-1B Gas Chromatograph.

[9] Although the elemental analysis of this amine agreed only poorly with the theoretical, the picrate gave correct analysis and the v.p.c. analysis showed this compound to be homogeneous.

Silicone DC550 4 mm×225 cm, 154°C, He flow rate 60 m*l*/min, retention time 13 min.

Found: C, 71.42; H, 12.36; N, 7.87%. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56%.

Deamination of 3-(3,3-Diethylazetidinyl-1)propylamine (IIIa). A solution of 1.2 g of sodium nitrite in 7 m*l* of water was slowly stirred into a solution of 2 g of IIIa in 4.4 g of 50% acetic acid below 0°C. After five hours, the evolution of nitrogen was no longer observed; the mixture was made alkaline with potassium carbonate and extracted with ether. The combined extract was dried over sodium sulfate, and the solvent was removed by distillation. The crude product, which consisted of the alcohol IVa and its acetate, was treated with aqueous sodium hydroxide to hydrolize the acetate, and the mixture was extracted with ether, dried, and distilled *in vacuo* to give 1.3 g (65% yield) of IVa boiling at 70—78°C/1.5 mmHg. The IR spectrum and refractive index were identical with those of the product of the reduction of Va. NMR(τ): 5.64(1H, singlet); 6.47 (2H, triplet); 7.11 (4H, singlet, ring methylene); 7.43 (2H, triplet); 8.25—8.70 (2H, multiplet); 8.46 (4H, quartet); 9.19 (6H, triplet). V.p.c.: The results were similar to those described in the reduction of Va.

Found: C, 70.29; H, 12.24; N, 8.37%.

Deamination of 3-(3,3-Diethylazetidinyl-1)butylamine (IIIb). Two grams of IIIb were treated by the method described above except that the acetate by-product was treated with lithium aluminum hydride instead of sodium hydroxide. The alcohol was obtained in a 62% yield. Bp 89—96°C/1.5 mmHg, n_D^{25} 1.4615, IR: a broad peak between 3450 and 3180 cm^{-1}. The NMR spectrum (See Fig. 1) was identical with that of the product obtained by the reduction of Vb; no change in the NMR spectra was observed whether it was taken at 24, 50, or 100°C. V.p.c.: this product and the mixture with the reduction product of the Vb ester showed the same retention time under the same conditions, as has been explained in the reduction of Vb.

Found: C, 71.15; H, 12.19; N, 7.95%.

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