Synthesis of Azetidines

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Abstract □ The synthesis of 3-amino-2-phenylazetidine and the *p*-chloro analog is reported. The reduction of azetidinones with diborane was investigated and found successful with *N*-unsubstituted systems. 3-Amino-2-phenylazetidine was found active *in vitro* against monoamine oxidase.

Keyphrases □ Azetidines (3-amino-2-phenylazetidine, *p*-chloro analog)—synthesis, monoamine oxidase inhibitory activity evaluated *in vitro* □ Monoamine oxidase inhibitors—azetidines, synthesized, evaluated *in vitro* □ IR spectrophotometry—structure, identification □ NMR spectroscopy—structure, identification

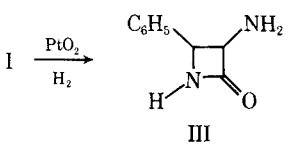
It has been postulated that the potent monoamine oxidase (MAO) inhibitory activity exhibited by 2-phenylcyclopropylamine might be explained in terms of the electronic and steric properties of the cyclopropane ring system (1, 2). Larger cycloalkyl analogs including 2-phenylcyclobutylamine are much less active MAO inhibitors, presumably for steric reasons and because of a change of electronic properties of the ring system. Relative to 2-phenylcyclopropylamine, 2-phenylcyclobutylamine is only $^1/_{1000}$ times as active by *in vitro* testing for MAO inhibition (3). Since the geometrical factors are approximately constant, this difference in activity is presumably due to the loss of electronic delocalization.

To investigate this theory, it appeared that heterocyclic analogs of 2-phenylcyclobutylamine, in which the hetero atom could provide the electron density, would merit study for MAO inhibitory activity.

As a continuation of a study of small ring heterocycles (4–6) as potential MAO inhibitors, several azetidines were prepared by reductive methods. This article reports the use of lithium aluminum hydride to reduce 3-amino-4-phenyl-2-azetidinone to the azetidine without ring cleavage. It also reports the first use of diborane to reduce 2-azetidinones to the corresponding azetidines.

As previously reported (4), *cis*-3-azido-4-phenyl-2-azetidinone (I) may be prepared from azidoacetyl chloride and hydrobenzamide. When treated with lithium aluminum hydride, I gave rise to a mixture of 3-amino-2-phenylazetidine (II, Scheme I) and *N*-benzylethylenediamine.

Scheme I



Scheme II

Catalytic reduction converted I into 3-amino-4-phenyl-2-azetidinone (III, Scheme II) in good yield.

Reaction of III with lithium aluminum hydride in ether gave 3-amino-2-phenylazetidine (II) in 84% yield. No evidence of *N*-benzylethylenediamine was found in the reaction mixture. The NMR spectrum of II showed a five-proton aromatic signal at δ 7.32, a one-proton doublet at 5.0 (methine), a two-proton doublet at 3.98 (NH—C$\underline{H}_2$), a one-proton doublet at 3.20 (C$\underline{H}$NH$_2$), and a three-proton singlet at 1.88 (NH and NH$_2$) which was exchangeable with D_2O. This spectrum is in agreement with the deduced spectrum of II in a mixture with *N*-benzylethylenediamine (4).

Only *N*-benzylethylenediamine was isolated when tetrahydrofuran (THF) was used in the hydride reduction. The downfield doublet at δ 5.0, characteristic of II, was absent in the NMR of the crude reaction mixture. The only apparent difference in these two systems is that III is soluble in THF and relatively insoluble in ether.

Diborane has been used to reduce various primary, secondary, and tertiary amides (7), pyrrolidinones (8), and azides (9); thus it seemed germane to attempt the reduction of both III and I with diborane. When III was reacted with excess diborane in THF, followed by hydrolysis with dilute hydrochloric acid, a 66.5% yield of II was obtained. When I was reacted with excess diborane, a 65% yield of II was obtained, both the azido and the carbonyl functions being reduced in one step. The NMR spectrum of the product of each of these diborane reductions was identical with that of II produced by lithium aluminum hydride reduction of III. The mass spectrum showed a parent peak at *m/e* 148 and a fragmentation pattern consistent with 2-phenylazetidines (10). This reaction also proved successful in the preparation of 3-amino-2-(*p*-chlorophenyl)-azetidine.

To examine the diborane reduction of other azetidinones, 4-phenyl-2-azetidinone (11) was reacted with diborane. 2-Phenylazetidine was isolated in 81% yield. The IR spectrum of the concentrated reaction mixture showed absence of the carbonyl, indicating that the reduction was complete.

Examination of the literature reveals that there is no method available for reduction of *N*-substituted azetidinones to the corresponding azetidines. Reduction of *N*-substituted azetidinones with lithium aluminum hydride, Raney nickel, lithium aluminum hydride–aluminum chloride, and sodium borohydride–aluminum chloride all result in cleavage of the 1–2 bond to give the substituted 3-aminopropanols (12). It was hoped that diborane could be used to reduce *N*-substituted

azetidinones to the azetidine without ring cleavage. Thus, 1,4-diphenyl-2-azetidinone (13) was reacted with diborane to give a 53% yield of 3-anilino-3-phenylpropanol. Authentic 3-anilino-3-phenylpropanol was prepared (14). Mixed melting point showed no depression, and the IR and NMR spectra were identical. The diborane reduction of 1,4-diphenyl-2-azetidinone was repeated and hydrolyzed with water to avoid the acidic workup. This system also gave rise to 3-anilino-3-phenylpropanol as the only isolated product.

Inhibition of MAO *in vitro* was assessed by the method of Wurtman and Axelrod (15). The potential MAO inhibitor and the substrate (2-^{14}C-tryptamine) were incubated with rat liver homogenate. After a suitable time, the deaminated product (^{14}C-indolacetic acid) was extracted and counted for its radioactive content. This preliminary evaluation showed 3-amino-2-phenylazetidine to be 62% as active as iproniazid which was used as a standard in this screen.

EXPERIMENTAL[1]

3-Amino-4-phenyl-2-azetidinone (III)—3-Azido-4-phenyl-2-azetidinone (I) (6.0 g., 32.3 mmoles) was dissolved in 300 ml. 95% ethyl alcohol and catalytically reduced over platinum at 50 p.s.i. for 72 hr. at room temperature. The catalyst was removed by filtration, and the solvent was removed *in vacuo*. Recrystallization from methylene chloride–petroleum ether gave 4.13 g. (80% yield) of white crystalline solid, m.p. 128–130°; NMR ($CDCl_3$), δ 7.30 (s, 5, Ar), 7.2–6.9 (bs, 1, NH), 4.82 (d, 1, methine), 4.42 (d, 1, CH-CHNH$_2$), and 2.01 (s, 2, NH$_2$); signals at 7.2–6.9 and 2.01 were exchangeable with D_2O; IR ($CHCl_3$), 5.65 (C=O), and complete absence of azide.

Anal.—Calcd. for $C_9H_{10}N_2O$: C, 66.59; H, 6.21. Found: C, 66.34; H, 6.36.

3-Amino-2-phenylazetidine (II) by Lithium Aluminum Hydride Reduction of III—III (780 mg., 4.81 mmoles) was stirred in 150 ml. absolute ether at 0° under nitrogen, while lithium aluminum hydride (910 mg., 24 mmoles) was added through Gooch tubing over a 1-hr. period. After the addition was complete, the ice bath was removed and the reaction was allowed to warm to room temperature and then was refluxed for 12 hr. The reaction mixture was cooled to 0° and hydrolyzed with 1.75 ml. of water. The solid was removed by filtration and washed several times with ether. The ether extracts were combined and dried. The ether was removed *in vacuo* to give 600 mg. (84% yield) of liquid. The IR showed complete absence of carbonyl. The dihydrochloride was formed and recrystallized from absolute ethanol, m.p. 154–156°.

3-Amino-2-phenylazetidine (II) by Diborane Reduction of III—To 50 ml. of THF was added 95 ml. of 1 *M* diborane in THF. To this solution was added (at 0° under nitrogen) 3.0 g. (18.5 mmoles) of III dissolved in 150 ml. THF over a 2-hr. period. After the addition was complete, the reaction was allowed to warm to room temperature and then was refluxed for 16 hr. The reaction mixture then cooled to room temperature and was hydrolyzed with 100 ml. of water followed by 50 ml. of 3 *N* HCl. The mixture was stirred for 1–2 hr., and then most of the THF was distilled off at atmospheric pressure and the remainder removed *in vacuo*. The aqueous phase was made basic with aqueous sodium hydroxide and extracted with chloroform. Removal of the dried chloroform *in vacuo* gave 1.8 g. (66.5%) of II; the NMR was identical to II produced by lithium aluminum hydride reduction of III. Recrystallization of the dihydrochloride from absolute ethyl alcohol gave a white solid, m.p. 155–158°.

3-Amino-2-phenylazetidine (II) by Diborane Reduction of 3-Azido-4-phenyl-2-azetidinone (I)—The reaction of 4.0 g. (21.4 mmoles) I in 225 ml. THF with 130 ml. 1 *M* diborane in THF, using the procedure for diborane reduction of III, gave a 63% yield of II; NMR was identical with II produced in both cases previously described. Recrystallization of the dihydrochloride gave a white solid, m.p. 158–159°.

Anal.—Calcd. for $C_9H_{14}Cl_2N_2$: C, 48.89; H, 6.38. Found: C, 48.64; H, 6.43.

3-Amino-2-(*p*-chlorophenyl)azetidine by Diborane Reduction of 3-Azido-4-(*p*-chlorophenyl)-2-azetidinone—The reaction of 2.0 g. (9.0 mmoles) 3-azido-4-(*p*-chlorophenyl)-2-azetidinone in 200 ml. THF with 80 ml. 1 *M* diborane in THF, using the procedure for diborane reduction of III, gave a 73% yield of 3-amino-2-(*p*-chlorophenyl)azetidine; NMR ($CDCl_3$), δ 7.35 (s, 4, Ar), 5.0 (d, 1, ArCH), 3.98 (d, 2, NHCH$_2$), 3.15 (d, 1, CHNH$_2$), and 2.34 (s, 3, NH and NH$_2$); exchangeable with D_2O. Recrystallization of the dihydrochloride from absolute ethyl alcohol gave a white solid, m.p. 130–133°.

Anal.—Calcd. for $C_9H_{13}Cl_3N_2$: C, 42.29; H, 5.13. Found: C, 41.99; H, 5.40.

2-Phenylazetidine—The reaction of 1.47 g. (10 mmoles) of 4-phenyl-2-azetidinone (11) in 60 ml. THF with 40 ml. 1 *M* diborane in THF gave an 81% yield of 2-phenylazetidine; NMR ($CDCl_3$), δ 7.3 (m, 5, Ar), 4.88 (t, 1, methine), 3.5 (bm, 2, NCH$_2$), 2.9 (s, 1, NH), and 2.45 (m, 2, CHCH$_2$); the signal at 2.9 exchanged with D_2O. The picrate was prepared, m.p. 122–123° [lit. (11) 128–129°]. The picrate of authentic 2-phenylazetidine was prepared (11), and mixed melting point of the two picrate derivatives showed no depression.

Diborane Reduction of 1,4-Diphenyl-2-azetidinone—The reaction of 2.27 g. (10 mmoles) 1,4-diphenyl-2-azetidinone (13) in 150 ml. THF with 40 ml. of 1 *M* diborane in THF gave a 53.8% yield of 3-anilino-3-phenylpropanol, m.p. 88.5–89.5 [lit. (14) 87–88°]. IR showed complete absence of carbonyl. NMR ($CDCl_3$), δ 7.46–6.4 (m, 10, Ar), 4.55 (t, 1, methine), 3.7 (t, 2, CH$_2$OH), 3.27 (s, 2, OH and NH), and 2.05 (q, 2, CHCH$_2$); the signal at δ 3.27 was exchangeable with D_2O.

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[1] Melting points were determined on a Buchi apparatus with open capillary tubes and are uncorrected. NMR spectra were obtained with a Varian Associates A-60-A instrument in $CDCl_3$ with tetramethylsilane as an internal standard. IR spectra were determined on Perkin-Elmer model 21 and model 237B spectrophotometers. Combustion analyses were conducted by Midwest Microlab, Inc., Indianapolis, IN 46226. The mass spectrum was determined with a Hitachi RMU-6A at 75 ev. THF was dried by distillation from lithium aluminum hydride immediately before use.