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Received February 3, 1984

Two new, hindered secondary amines, 7-azadispiro[5.1.5.2]pentadecane hydrochloride (**1a**) and 6-azadispiro[4.1.5.2]tetradecane hydrochloride (**1b**), have been prepared in four steps from 1-ethynylcyclohexylamine (**2**). The final thermal cyclization of 1-(2-(1-aminocyclohexyl)ethyl)cyclohexyl chloride (**5a**) produces 1-(2-(1-aminocyclohexyl)ethyl)cyclohexene hydrochloride (**6a**) and an unsaturated hydrocarbon **7** in addition to **1a**.

J. Heterocyclic Chem., **21**, 1289 (1984).

Because bulky secondary amines were of interest to us for biological studies, 7-azadispiro[5.1.5.2]pentadecane (**1a**) became the target of our synthetic efforts. A number of patents have mentioned the 7-azadispiro[5.1.5.2]pentadecane ring system generically [1a-e], but in no case has the preparation of the compound been described. Members of the isomeric 14-azadispiro[5.1.5.2]pentadecane system have been prepared, but only as oxygen-containing analogs [2a-d].

We have now prepared **1a** in four steps from 1-ethynylcyclohexylamine (**2**) and cyclohexanone, as shown in Scheme 1. The related compound, 6-azadispiro[4.1.5.2]tetradecane (**1b**) was prepared from **2** and cyclopentanone in the same manner. Using the method (A) of Kopka *et al.* [3] to prepare tertiary acetylenic alcohols, **2** was condensed with cyclohexanone in sodium and liquid ammonia. Although pure **3a** was obtained, the yield was low (16%). An alternative method (B) using *n*-butyllithium in tetrahydrofuran afforded **3a** in 56% yield and this method proved to be simpler and more reliable.

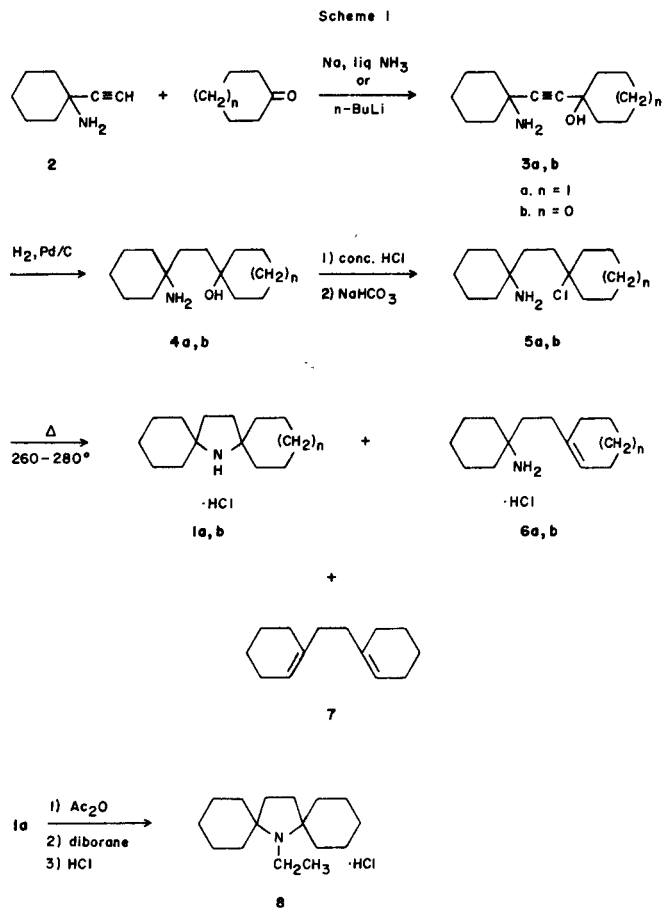
Compound **3a** was hydrogenated rapidly and nearly quantitatively with 5% palladium on carbon to give **4a**. By simply shaking **4a** in methylene chloride with concentrated hydrochloric acid and pouring the organic layer onto saturated sodium bicarbonate solution, the chloroamine **5a** was precipitated as a white solid (83%). Apparently, the solubility of **5a** in methylene chloride is low enough to give this precipitate at this point.

Although the melting point of **5a** is low (45-49°) it was observed that heating the melt above 250° caused it to resolidify. Indeed, by placing **5a** neat under a nitrogen atmosphere in an oil bath at 270-280°, the initial melt suddenly darkened and a "puff of smoke" appeared in the flask. After about one-half hour, the dark melt began to crystallize. The reaction was heated for another hour and then cooled to give a mixture of products which was readily separated.

Trituration of the crystalline mass in methylene chloride left an insoluble salt (presumably ammonium chloride). The supernate was diluted with hexane and the methylene

chloride was distilled until crystals began to appear. These turned out to be nearly pure **1a**, obtained in 46% yield. Azeotropic removal of all of the methylene chloride gave a second crystalline product, aminoalkene **6a**, in 14% yield. By evaporating the hexane and distilling the residue, diene **7** was isolated in about 22% yield.

An attempt to increase the yield of **1a** and reduce the amount of by-products **6** and **7** by conducting the cyclization at 200° gave only **6a** and some **7**, instead. Apparently, insufficient energy was available at this lower temperature to allow the S_N2 displacement of the hindered tertiary



chloride by the amino group at a rate fast enough to compete with the abstraction of the alpha proton by the amine. Presumably, **7** is formed by thermal elimination of ammonium chloride from **6a** (the "puff of smoke"?). Our structural assignment for **7** is still tentative, since the ir and nmr data did not match that reported for structure **7** by Shea and Philips [4]. However, the mass spectrum did confirm a molecular weight of 190. No effort was made to isolate the corresponding by-product from the preparation of **1b**.

7-Azadispiro[5.1.5.2]pentadecane hydrochloride **1a** is very high melting (315-316°), although the free base appears to be an oil. The infrared spectrum of hydrochloride salt **1a** showed amine hydrochloride bands and a strong NH₂ deformation band at 1580 cm⁻¹, typical of secondary amine salts [5]. In the nmr spectrum there were no vinyl protons and the mass spectrum gave a molecular ion at m/e = 207. This compound formed an acetamide which had no amide NH absorption in the infrared spectrum.

The unsaturated amine hydrochloride **6a** was characterized by combustion analysis, observance of a vinyl proton doublet in the nmr, a molecular weight of 207 by mass spectrometry, and the formation of an acetamide with a single amide NH band in the infrared spectrum.

The hydrochloride salt of 6-azadispiro[4.1.5.2]tetradecane (**1b**) is lower melting (289-290°) than its homolog **1a**. The spectral properties of **1b** were similar to those of **1a**. Caution must be observed in forming the chloride **5b** from **4b** by the method described above, because **5b** is more prone to elimination than is **5a**.

N-Alkyl derivatives of **1a,b** appear to be best prepared by acylation with the corresponding anhydride followed by reduction with diborane. Thus, as shown in Scheme 1, *N*-ethyl-7-azadispiro[5.1.5.2]pentadecane hydrochloride salt (**8**) was prepared from **1a** by acylation with acetic anhydride, followed by diborane reduction and treatment with hydrogen chloride.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer Model 727B spectrophotometer using Nujol mulls. Nuclear magnetic resonance spectra (nmr) were determined on a Varian Model EM 360A spectrometer in deuteriochloroform using tetramethylsilane (TMS) as an internal standard. Mass spectra (ms) were obtained on a Finnigan model 4023 mass spectrometer equipped with an Inco series 2000 data system. Some liquid samples were purified by short path distillation on an Aldrich Kugelrohr apparatus. All thin layer chromatographs (tlc) were run on E. Merck TLC plates coated with Silica Gel 60 R-254 (0.25 mm). Elemental analyses were performed at the Analytical Laboratories of The Dow Chemical Company, Midland, Michigan and the Analytical Laboratories of Merrell Dow Pharmaceuticals, Cincinnati, Ohio.

1-(1-Aminocyclohexyl)ethynyl)cyclohexanol (**3a**). Method A.

To 1 liter of liquid ammonia in a 2 liter flask was added 200 g (1.62

moles) of 1-ethynylcyclohexylamine (**2**) (Aldrich). Sodium metal (37 g, 1.62 moles) was added in pieces over a 90 minute period with vigorous stirring. After stirring for an additional 45 minutes, the reaction had turned dark blue. Cyclohexanone (157 g) was added dropwise over a 1 hour period. The reaction was stirred overnight while the ammonia was allowed to evaporate. The remaining traces of ammonia were evaporated under a stream of nitrogen and 1.5 liters of ice water was added. The slurry was neutralized to pH 7-8, the point where all the solid had dissolved and two clear layers separated. The organic layer was extracted into methylene chloride. The aqueous layers were washed once with methylene chloride and the combined organic layers were washed three times with water, dried over sodium sulfate and evaporated. The residual oil was distilled on the Kugelrohr (60-80°) until the unreacted starting material had been removed and the product crystallized in the pot. The crystals were suspended in hexane, and filtered, washed and dried. Recrystallization from acetonitrile gave 43.1 g of product **3a**, mp 121-123° (pure by tlc). A second crop produced another 12.0 g for a total yield of 16%; ir: NH₂ at 3300 and 3260 cm⁻¹, broad OH band; ms: m/e = 221.

Anal. Calcd. for C₁₄H₂₃NO: C, 75.97; H, 10.47; N, 6.32. Found: C, 75.69; H, 10.39; N, 6.16.

Method B.

A stirred solution of 12.3 g (0.1 mole) of 1-ethynylcyclohexylamine (**2**) in 100 ml of tetrahydrofuran was cooled to -30°. To this was added, dropwise 40 ml of a 2.4 M solution of *n*-butyllithium in hexane with continued cooling to control the exotherm. A white precipitate formed and after stirring for 30 minutes, 9.8 g of cyclohexanone was added in one portion. After another 30 minutes the reaction was warmed to 35° for 3 hours. The reaction was poured into 1 liter of water and the resulting white solid went into solution upon acidification with concentrated sulfuric acid. The unreacted cyclohexanone was extracted into methylene chloride. Upon basification of the aqueous solution with 5*N* sodium hydroxide, a white solid separated. Collection and recrystallization from 300 ml of acetonitrile gave 12.3 g (56%) of white crystalline solid **3a**, mp 122-124°.

1-(2-(1-Aminocyclohexyl)ethyl)cyclohexanol (**4a**).

Compound **3a** (20 g) was reduced with hydrogen in 300 ml of ethanol using 4 g of 5% palladium on carbon in a Parr Shaker. Reduction appeared complete in 20 minutes, but shaking was continued for another hour. Evaporation of the ethanol, after removal of the catalyst, left an oil which was recrystallized from hexane to give 20 g (in 2 crops) of the amino alcohol **4a**, mp 59-60°; ir: NH₂ at 3300 and 3260 cm⁻¹, broad OH at 3200-3100 cm⁻¹, sharp band at 1600 cm⁻¹; nmr showed no vinyl protons; ms: m/e = 225.

Anal. Calcd. for C₁₄H₂₇NO: C, 74.61; H, 12.08; N, 6.22. Found: C, 74.49; H, 12.10; N, 6.00.

1-(2-(1-Aminocyclohexyl)ethyl)cyclohexyl Chloride (**5a**).

Amino alcohol **4a** (20 g) was dissolved in 200 ml of methylene chloride and shaken vigorously with 200 ml of concentrated hydrochloric acid for several minutes.

The methylene chloride layer was separated and the hydrochloric acid layer washed once with methylene chloride. The combined organic layers were poured into 300 ml of saturated sodium bicarbonate solution and vigorously stirred. A thick, three phase mixture resulted which could be filtered to give a white solid. The solid was washed with water and the methylene chloride layer was evaporated to give some additional solid. The combined solid was dried *in vacuo* to give 18 g of product (83%) which, when dissolved in hot acetonitrile, left a small crystalline residue (presumably sodium bicarbonate) on filtration. Crystals of **5a** from acetonitrile weighed 11.6 g, mp 47-49°. A second crop weighed 2.7 g, mp 45-49°; ms: m/e = 243. It was not necessary to recrystallize the product before using it in the next reaction.

Anal. Calcd. for C₁₄H₂₆ClN: C, 68.96; H, 10.75; N, 5.75. Found: C, 68.63; H, 10.85; N, 5.58.

7-Azadispiro[5.1.5.2]pentadecane Hydrochloride (**1a**).

Chloroamine **5a** (18 g) was placed under a nitrogen atmosphere and immersed with stirring in an oil bath maintaining at 270-280°. The initial melt suddenly darkened slightly and a puff of smoke appeared in the flask. This eventually cleared and crystals sublimed onto the cooler part of the flask. The melt began to crystallize after about 30 minutes of heating. The heating was continued for an additional hour to complete the reaction. The flask was cooled and the solid was dissolved in 200 ml of methylene chloride. After filtering the solution to remove traces of ammonium chloride, it was diluted with hexane and the methylene chloride was evaporated off under a nitrogen stream until crystals appeared (bp 50°).

After collection of the solid, the filtrate gave more crystals. When all the crystals were combined the product **1a** weighed 10.1 g (46%), mp 315-316°; ir: no NH, strong sharp band at 1580 cm⁻¹; nmr: no vinyl protons; ms: m/e = 207. The product was recrystallized for combustion analysis from methylene chloride/hexane as above.

Anal. Calcd. for C₁₄H₂₅N·HCl: C, 68.96; H, 10.75; N, 5.75. Found: C, 69.00; H, 10.70; N, 5.77.

1-(2-(1-Aminocyclohexyl)ethyl)cyclohexene Hydrochloride (**6a**).

The filtrate from the recrystallization of **1a** was distilled until all of the methylene chloride had been driven off (bp 69°) and further crystals had separated. The mixture was cooled and filtered and the crystals were washed with hexane and dried to give 3.15 g (14%) of **6a**, mp 192-196°; ir: broad but weak band at 1600-1580 cm⁻¹; nmr: vinyl doublet δ 5.5 ppm; ms: m/e = 207.

Anal. Calcd. for C₁₄H₂₅N: C, 68.96; H, 10.75; N, 5.75. Found: C, 68.91; H, 11.02; N, 5.66.

This compound formed an amide with acetic anhydride; ir: amide NH 3320 cm⁻¹, C=O 1640 cm⁻¹.

1,1'-(1,2-Ethanediy)bis(cyclohexene) (7).

The hexane layer from above was evaporated to dryness. The residual oil was distilled on the Kugelröhr at 100° to give 3.9 g (22%) of the diene **7**; ir: 1450, 1120, 970, 912 cm⁻¹; nmr: m 5-6 ppm; ms: m/e = 190.

6-Azadispiro[4.1.5.2]tetradecane (**1b**).

This compound was prepared in exactly the same manner as was **1a** except that cyclopentanone was used in the condensation with the lithium acetylide. Azadispirotetradecane **1b** was prepared in 41% overall yield from **2**, mp 289-290°; ir: strong sharp band 1580 cm⁻¹; ms: m/e = 193.

Anal. Calcd. for C₁₃H₂₃N·HCl: C, 67.95; H, 10.53; N, 6.10. Found: C, 67.97; H, 10.50; N, 5.77.

1-(2-(1-Aminocyclohexyl)ethyl)cyclopentanol (**4b**).

Saturated amino alcohol **4b** was obtained in essentially quantitative yield as above from **3b**, mp 62-63°; ir: 3300, 3260, 1600 cm⁻¹; ms: m/e = 211.

Anal. Calcd. for C₁₃H₂₅NO: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.73; H, 11.86; N, 6.44.

1-(1-Aminocyclohexyl)ethynyl)cyclopentanol (**3b**).

This material was synthesized in 34% yield from 1-ethynylcyclohexyl-

amine (**2**), mp 118-119°; ir: NH₂ at 3300 and 3260, broad stretching at 1600 cm⁻¹; ms: m/e = 207.

Anal. Calcd. for C₁₃H₂₁NO: C, 75.31; H, 10.21; N, 6.75. Found: C, 75.39; H, 10.16; N, 6.84.

N-Ethyl-7-azadispiro[5.1.5.2]pentadecane Hydrochloride (**8**).

Azadispiropentadecane hydrochloride **1a** (4.96 g) was converted to its free base (oil) by adding 1*N* sodium hydroxide to its aqueous solution and extracting the amine into methylene chloride. After drying (over sodium sulfate) and evaporation of the methylene chloride solution, 4.23 g of the free base remained as a light brown liquid. To this oil was added 15 g of acetic anhydride and the mixture was heated at 70° overnight. The initial two-phase system gradually became homogeneous over the first hour of heating. The reaction was cooled and poured into water. The crystals which formed were isolated by filtration, washed with water and dried in air to give 4.86 g of the amide, mp 117-118°; ir: no NH, amide carbonyl at 1620 cm⁻¹. This amide (2 g, 0.008 mole) was dissolved in 100 ml of tetrahydrofuran under nitrogen and 32 ml (0.032 mole) of 1 *M* diborane in tetrahydrofuran was added. The solution was stirred at room temperature overnight. Ethanol was added until effervescence stopped. Saturated ethereal hydrogen chloride was added and the solvents were removed on the rotary evaporator. The residue was recrystallized from toluene and then from ethanol/ethyl acetate to give 0.86 g of the pure *N*-ethylamine hydrochloride **8**, mp 224-225°; ir: NH⁺ 2700-2300 cm⁻¹; ms: m/e = 235. A second crop weighed 0.34 g, mp 222-223°. Another recrystallization from ethanol/ethyl acetate provided a sample of **8** for elemental analysis.

Anal. Calcd. for C₁₆H₂₉N·HCl: C, 70.68; H, 11.12; N, 5.15. Found: C, 70.39; H, 11.36; N, 4.98.

Acknowledgements.

The authors wish to thank Robert Barbuch (Merrell Dow Analytical Department) for the spectral data.

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