The Preparation of 2,5-Diazabicyclo[2.2.2]octane: A Bridged Piperazine

Howard Newman

Infectious Disease Therapy Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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In connection with other studies in our laboratory, we required the bicyclic heterocycle, 2,5-diazabicyclo[2.2.2]-octane (**1**), a two carbon bridged congener of piperazine. The latter moiety is present in a great number and variety of pharmacologically active and clinically useful compounds (1).

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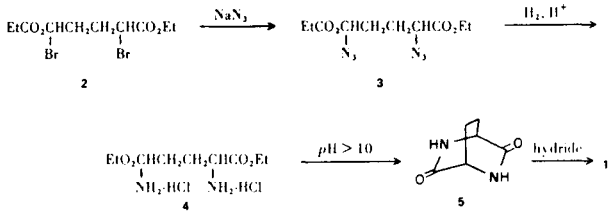
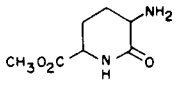
A search of the literature revealed this compound was reported once previously in a patent (2) in which its synthesis was sketchily described.



The preparative route we employed is outlined in the following equations.

Crystalline *meso* ethyl 2,5-dibromoadipate (**2**), readily obtained by fractional crystallization of the bromination product of adipoyl chloride from ethanol, was converted to the bisazide **3** with sodium azide in refluxing ethanol and the latter catalytically reduced over platinum in the presence of acid to furnish the diamine dihydrochloride **4**. Bicyclization of **4** to **5** was effected in methanolic methoxide at *p*H 10 or greater and the latter reduced to **1** with sodium bis(2-methoxyethoxy) aluminum hydride in benzene (Vitride^{TM}, Eastman).

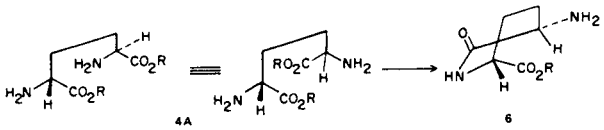
The interesting and crucial observation was made regarding the bicyclization conditions, that at lower basic *p*H, only the monocyclic product **6** was formed. Similarly, **6** was the only product obtained from the treatment of **4** in methanol with basic Dowex resin.



6

By contrast, the monocyclic product of gross structure **6** obtained from **5** by treatment with methanolic hydrogen chloride did, in fact, close back to **5** under the same resin treatment. (See Experimental for details). The products of gross structure **6** obtained from **4** and **5** must therefore differ with respect to stereochemistry; that obtained from **4** being the *trans* isomer and that from **5**, the *cis*. (This difference in stereochemistry suggested by the difference in chemical behavior could not be unequivocally demonstrated spectrally; and the fact that **6** obtained from both sources was non-crystalline also precluded melting points as a means of establishing non-identity).

A *trans* stereochemistry for **6** obtained from **4** requires that the precursor **4** be the *meso* stereoisomer 4A.



4A **6**

This stereoisomer would, in fact, be the one that might be expected to obtain by analogy with previously reported related work (3). Thus, reaction with sodium azide should be a bimolecular one and proceed with inversion of each center with no net overall stereochemical change and the assymetric center is not directly involved in the subsequent hydrogenation of **3** to **4**.

The relatively high *p*H required to effect further cyclization of **6** obtained from **4** would be understandable in terms of a prerequisite isomerization to the *cis* isomer which apparently requires the relatively stronger basic conditions.

Our scheme differs from that previously reported (2) in the use of sodium azide in place of potassium phthalimide to introduce nitrogen.

EXPERIMENTAL (4)

Meso-Diethyl 2,5-Dibromoadipate (**2**).

A combination of the procedure described in Organic Synthesis (5) and that described by Le Sueur (6), was used. Thus, a suspension of 1 kg. (6.85 moles) of adipic acid was heated under reflux in 1.2 l. (16.8 moles) of thionyl chloride for *ca.* 3 hours

and the excess thionyl chloride was removed by low pressure distillation from the resulting solution. The residual bis acid chloride was then treated with 805 ml. (15.6 moles) of bromine while irradiating with a photoflood lamp and heating on the steam bath over *ca.* a 12 hour period (the rate of addition was adjusted to the rate of reaction of the bromine with the bis acid chloride). After heating for an additional 2 hours, the reaction mixture was cautiously added to about twice its volume of absolute ethanol and the resulting solution allowed to stand at room temperature overnight. The solid *meso* dibromide which separated was collected by filtration; yield 719 g. (29%), m.p. 65-67° (lit. (6) 67°).

Diethyl 2,5-Bisazidoadipate (**3**).

As previously described by Bertho and Maier (7), a mixture of 150 g. (0.42 mole) of *meso* dibromide **2** and 75 g. (1.15 moles) of sodium azide in 500 ml. of absolute ethanol was heated under reflux for 18 hours, then poured into ice-water. Extraction with ether, drying and evaporating left 112 g. (94%) of the liquid bisazide suitable for further transformation.

Diethyl 2,5-Diaminoadipate Dihydrochloride (**4**).

A solution of 10 g. (0.035 mole) of bisazide in 200 ml. of ethanol containing 15 ml. of concentrated hydrochloric acid was hydrogenated in a Parr apparatus over 3 g. of reduced platinum oxide for 2 hours. (The net pressure drop in this reduction is zero. To achieve complete reduction in this fairly large scale run, it was necessary to evacuate the system [done after *ca.* 1 hour] and refill with hydrogen). The catalyst was separated by filtering through Celite, the filtrate concentrated to a small volume, the suspension chilled and the solid collected and washed with a small amount of ethanol; yield 5 g. (47%), m.p. 207-210° dec. (The dimethyl ester analog of **4** was previously reported (8) m.p. 206-207° dec.).

2,5-Diaza-3,6-dioxobicyclo[2.2.2]octane (**5**).

To 35 g. (0.11 mole) of diamine dihydrochloride **4** in 3.5 l. of absolute methanol was added 13.5 g. (0.25 mole) of solid sodium methoxide giving a solution with a *p*H of 10 or somewhat higher. (It is important that the *p*H not be lower if the reaction is to take place at an appreciable rate. The desired reaction takes place extremely slowly at *p*H 9). The solution was heated under reflux for 3 hours, evaporated to dryness *in vacuo* and the solid residue extracted with boiling ethanol (one 200 ml. and 3 x 100 ml. portions). Evaporation of the combined ethanolic extracts left 14.8 g. (96%) (9) of essentially colorless solid, m.p. 250-257° dec. (with some prior darkening); λ max (potassium bromide): *ca.* 3.1 (broad) (NH) and 5.9 μ (somewhat broadened) (C=O); R_f on tlc (chloroform:methanol:water 40:20:4) *ca.* 0.85. The analytical sample was obtained by recrystallization from ethanol, m.p. 264-267° dec. The compound is very water soluble and only sparingly soluble in chloroform and methylene chloride. Its nmr spectrum in deuterium oxide shows a somewhat broadened 2-proton singlet at 4.44 δ (bridgehead protons) and a 4-proton multiplet centered about 2.34 δ (-CH_2CH_2-bridge); its mass spectrum showed a fairly strong M^+ at m/e 140.

Anal. Calcd. for $C_6H_8N_2O_2$ (140.14): C, 51.42; H, 5.75; N, 19.99. Found: C, 51.50; H, 5.92; N, 19.84.

3-Amino-6-carbomethoxy-2-piperidone (**6**) from Diamine Dihydrochloride **4**.

Twelve g. of Dowex 2-X8 resin was converted to its basic form by treating with 2*N* sodium hydroxide, washing with water until washings were neutral and than washings with methanol. A solution of 1.2 g. of the diamine dihydrochloride **4** in 40 ml. of methanol was slurried with the resin for *ca.* 5 minutes and the resin separated by filtration; *p*H of the methanolic filtrate *ca.* 9. After standing at room temperature for 25 hours, the methanolic solution was acidified by brief treatment with gaseous hydrogen chloride and evaporated to leave a yellow syrup which transformed into a hard colorless opaque gum on standing under acetone (*ca.* 50 ml.) overnight, but did not crystallize. The acetone was decanted and the residual gum dried *in vacuo* at *ca.* 56° for 5 hours giving a glassy foam. Its identification as the piperidone **6** follows from the following spectra data: λ max (potassium bromide): 5.78 (ester) and 5.98 μ (6-membered lactam); nmr: 4.7-4.28 δ (multiplet, C-3 and C-6 protons), 4.03 δ (sharp singlet, CO_2CH_3) 2.48 δ (sharp singlet with a weak lower field shoulder multiplet, C-4 and C-5 protons); MS: m/e 172, 140 (M^+ **6** = 172; M-MeOH = 140).

The product showed one major spot at R_f *ca.* 0.55 on tlc (chloroform:methanol:water 20:40:4) along with a minor impurity running close to the origin.

3-Amino-6-carbomethoxy-2-piperidone (**6**) from Bicyclic Lactam **5**.

A suspension of 91 mg. (0.65 mmole) of 2,5-diaza-3,6-dioxobicyclo[2.2.2]octane (**5**) in *ca.* 2 ml. of absolute methanol was acidified with gaseous hydrogen chloride and kept at room temperature for 1 hour. (After 0.75 hour, the system was completely homogeneous). The solution was evaporated *in vacuo* with minimal heating during ≤ 5 minutes and the syrupy residue triturated with acetone (*ca.* 10 ml.). After 15 minutes, the acetone was decanted and the residual opaque colorless gum was triturated with a fresh portion of acetone for another 15 minutes. Decantation followed by high vacuum pumping gave 115 mg. (81%) of a glassy foam whose ir, nmr, and ms spectra were grossly the same as those obtained for **6** from **4** (previous experiment) but with differences in fine detail.

(Extending the reaction time to 21 hours converted **5** to the known (8) dimethyl 1,4-diaminoadipic acid dihydrochloride).

Behavior of **6** Obtained from **4** in Refluxing Methanolic Solutions of *p*H 9 and 10.

A solution of 91 mg. (0.42 mmole) of **6** in 1 ml. of absolute methanol was treated with 0.42 ml. of a 1*M* methanolic solution of sodium methoxide (0.42 mmole) to give a solution of *p*H 8 (alkacid test paper was the indicator paper used here and subsequently). The *p*H was raised further to *ca.* 9 with a few additional drops of the base. After refluxing this solution for 1.5 hours, a tlc (chloroform:methanol:water 40:20:4) indicated the very predominant presence of starting **6** along with only traces of the bicyclic lactam **5**.

The *p*H of the solution was raised further to 10 or somewhat more by the addition of more methanolic methoxide and refluxing continued. After 15 minutes, tlc indicated that the reaction mixture consisted of largely the bicyclic lactam **5** along with only a very small amount of starting **6**. After refluxing for 2.5 hours, tlc indicated the presence of **5** exclusively along with some origin impurity.

Behavior of **6** Obtained from **5** on Treatment with Dowex 2-X8 (OH) Resin.

Treating 10 ml. of a methanolic solution of 0.2 g. of **6** obtained from **5** with 2 g. of Dowex 2-X8 (OH) (prepared as described above under the preparation of **6** from **4**) and stirring at room temperature for 19 hours (*p*H of solution *ca.* 9 throughout) gave a product mixture indicated by tlc to be predominantly (*ca.* 70%) the bicyclic lactam **5** along with a minor amount of starting **6**. The ratio of **5** to **6** could be shifted somewhat more towards

the former (to *ca.* 85%) by refluxing for 1.5 hours. Additional refluxing (up to 3 hours) did not further alter the ratio. The minor amount of **6** which persists could be the *trans* isomer.

2,5-Diazabicyclo[2.2.2]octane (**1**).

A suspension of 14 g. (0.1 mole) of bis lactam **5** in 150 ml. of dry benzene and 120 ml. (0.39 mole) of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Vitride[TM], Eastman) was heated under reflux for 47 hours, then treated with 10 ml. of cold water to destroy the excess hydride. (A solid separated. The addition of water was strongly exothermic except for the last 1-2 ml.). The mixture was then treated with a solution of 40 g. (1 mole) of sodium hydroxide dissolved in 40 ml. of water and, after standing at room temperature for 1 hour with a large (*ca.* 400 ml.) volume of ether. (The ether dilution caused the formation of a jelly-like material; ether was added until this material no longer separated). The mixture was then filtered through a Celite pad and the clear light yellow filtrate evaporated to yield 42 g. of a moderately dark yellow clear liquid which was allowed to stand over sodium hydroxide pellets for *ca.* 2 hours (with virtually no change in their appearance). Distillation (10) (after separation from the pellets) gave 26.1 g. of colorless liquid, b.p. 25-45° (*ca.* 0.1 mm) (most of the distillate came over at 40-45°; oil bath temperature 75-90°; the receiver was cooled with dry ice). The colorless liquid was diluted with ether and treated with gaseous hydrogen chloride to precipitate 10.7 g. (58%) of colorless 2,5-diazabicyclo[2.2.2]octane (**1**) dihydrochloride; m.p. darkened extensively without melting 300-350° (at which point heating was terminated).

Anal. Calcd. for $C_6H_{14}N_2Cl_2$ (185.11): C, 38.93; H, 7.63; N, 15.14; Cl, 38.31. Found: C, 38.86; H, 7.59; N, 15.24; Cl, 37.91.

A careful redistillation (10) of the 25-45° (*ca.* 0.1 mm) distillate to separate lower boiling material (up to 35° (*ca.* 0.1 mm) left a colorless liquid still pot residue which is very largely (80-85%) the desired **1** as indicated by the conversion of a small sample to its dibenzoate, m.p. 184-186° (chilled ethanol) under Schotten-Baumann conditions.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.97; H, 6.29; N, 8.75. Found: C, 74.57; H, 6.47; N, 8.47.

Acknowledgements.

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(1) See for example W. C. Cutting, "Handbook of Pharmacology" Appleton-Century-Crofts, New York, N. Y., 1969, 4th Ed.

(2) *Chem. Abstr.*, **62**, 7761d (1965). (Netherlands Appl., 6,400,946).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York, N. Y., 1953, p. 380.

(4) Melting points are uncorrected. The nmr spectra were determined on a Varian HA-100D spectrometer, the mass spectra on an AEI ms-9 instrument. Silica gel G covered micro slides obtained from Analtech Inc., Newark, Delaware were used for thin layer chromatography and spots were visualized with Cl_2-tolidine (4a). The absolute methanol used was commercial grade. Magnesium sulfate was used for drying.

(4a) D. Waldi in "Thin Layer Chromatography", 2nd Edition, E. Stahl, Ed., Springer-Verlog, New York, N. Y., 1968, p. 488.

(5) "Organic Synthesis", Coll. Vol. 3, 623.

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(8) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, 72, 2786 (1950).

(9) This yield is somewhat high because of the additional presence of some sodium alkoxide.

(10) A short path (*ca.* 7 cm) distillation head was used.