spinning-band column at reduced pressure to give 38.9 g (0.138 mole, 96.5%) of trimethylsilyl *o*-trimethylsiloxybenzoate, bp 106° (2 mm), 95° (0.5 mm), lit.[1] bp 77.5° (1.1 mm).

Anal. Calcd for $C_{13}H_{22}O_3Si_2$: C, 55.28; H, 7.85; Si, 19.87. Found: C, 55.33; H, 7.80; Si, 19.59.

Trimethylsilyl Salicylate.—A mixture of 20.7 g (0.15 mole) of salicylic acid and 12.1 g (0.075 mole) of hexamethyldisilazane was maintained at 145° until refluxing stopped (4.3 hr). The supernatant liquid was separated from the solid remaining in the reaction flask by decantation and distilled to give 19.2 g of material, bp 85–92° (2 mm). Gas chromatography of this distillate showed it to contain 91.3% of trimethylsilyl salicylate. Fractionation of the distillate afforded 12.5 g of trimethylsilyl salicylate, bp 89.5° (2 mm), lit. bp 105–107° (1.5 mm),[1] 62° (0.95 mm).[2]

Anal. Calcd for $C_{10}H_{14}O_3Si$: C, 57.12; H, 6.71; Si, 13.35. Found: C, 57.50; H, 6.75; Si, 12.97.

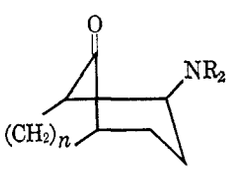
Stereoisomeric Amino Lactams from 2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.1]nonan-9-one

JANIS PLOSTNIEKS

McNeil Laboratories, Inc., Fort Washington, Pennsylvania

Received April 23, 1965

The facile synthesis of bicycloamino ketones of structure 1[1] has resulted in their use as synthetic intermediates.[2] The interest in our laboratories in



1a, $n=3$; $NR_2=N$

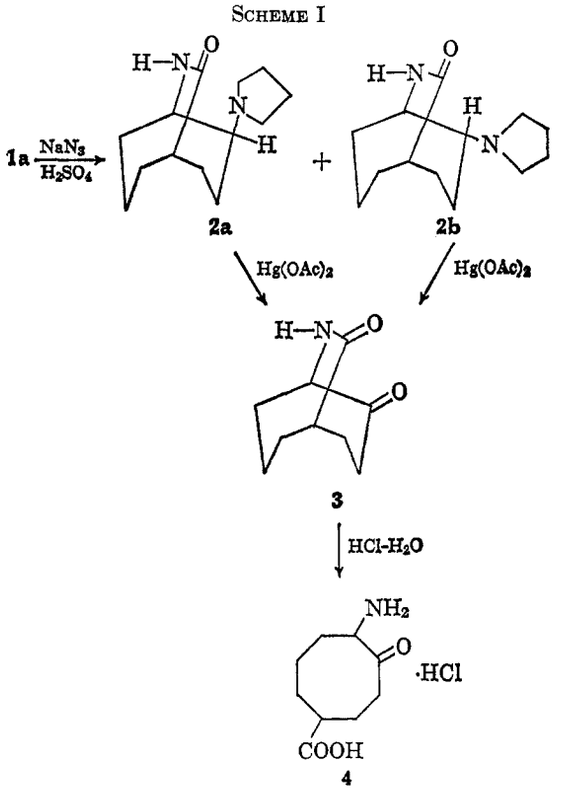
basically substituted bicyclic molecules[2d] led us to examine the Schmidt reaction on 2-(1-pyrrolidinyl)-bicyclo[3.3.1]nonan-9-one (**1a**).

The reaction was performed by treating **1a** with sodium azide in chloroform solution in the presence of an excess of sulfuric acid.[3] The major product isolated (48%) was an amino lactam, melting at 145.5–148°. Another amino lactam (8%) melting at 117–118.5° was isolated from the mother liquors. The higher-melting isomer (to be called isomer A) could be crystallized from an *n*-hexane solution of the crude reaction product; the lower-melting isomer (isomer B) was isolated as its fumaric acid salt.

In order to determine the course of the Schmidt reaction, each pure isomer was subjected to an hydrolytic oxidation with mercuric acetate in aqueous acetic acid.[4] In both cases a single keto lactam (**3**) was obtained. The two samples of the keto lactams were found to be identical by infrared and nmr spectroscopy and mixture melting point. This result clearly shows that the two amino lactams are stereoisomers around C-2 and not the two possible structural isomers that could be expected from a Schmidt reaction.

Hydrolysis of the keto lactam **3** in boiling 7 *N* hydrochloric acid yielded an amino keto acid **4** which could not be decarboxylated upon further vigorous acid treatment. This inability to decarboxylate rules out a β-keto acid structure and indicates a δ relationship as shown in structure **4**. Consequently, the amino lactams and the keto lactam must have structures **2** and **3**, respectively. (See Scheme I.)

SCHEME I



The two Schmidt products exhibited an unexpectedly high water solubility; two water extractions of an ether solution left virtually no material in the organic phase. Isomer A crystallized in two isomorphic forms depending upon the solvent and the rate of crystallization. Both isomorphs exhibited wide melting ranges (138–145° and 145.5–148°) and most likely were never obtained free from one another.

Chemically, the two amino lactams showed the expected behavior. Reduction with lithium aluminum hydride in tetrahydrofuran yielded the corresponding diamines (**6**). The appearance of a secondary amine function in the reduction products was demonstrated in acylation experiments with several acid chlorides. In this way the amides (**8**) of phenylacetic, diphenylacetic, 3,4,5-trimethoxybenzoic, and ethylcarbonic acids were prepared. Hydrolysis of the amino lactams in 7 *N* hydrochloric acid proceeded smoothly, giving the expected amino acid hydrochlorides (**7**). Alcoholysis of the lactams with isopropyl alcohol containing dry hydrogen chloride led to the isopropyl esters (**5**) (peaks at 1728 and 1180 cm^{-1} in the infrared spectrum of a potassium bromide pellet). These esters, however, proved to be rather unstable and reverted back to **2** during purification.

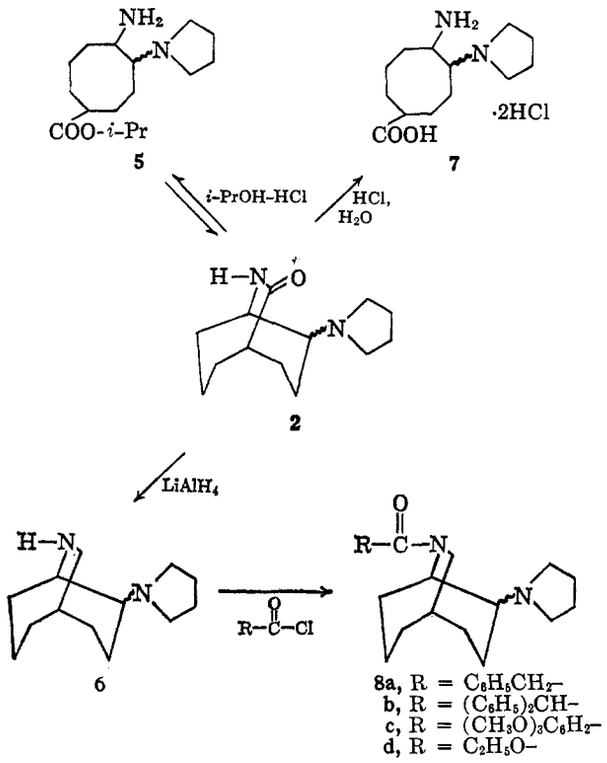
(1) (a) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956); (b) K. G. Untch, Ph.D. Thesis, Columbia University, 1959.

(2) (a) N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964); (b) C. S. Foote and R. B. Woodward, *ibid.*, **20**, 687 (1964); (c) N. A. LeBel and L. A. Spurlock, *J. Org. Chem.*, **29**, 1337 (1964); (d) G. I. Poos, U. S. Patent 3,108,998 (1963).

(3) R. J. Michaels and H. E. Zaugg, *J. Org. Chem.*, **25**, 637 (1960).

(4) For a leading reference on mercuric acetate oxidations, see N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

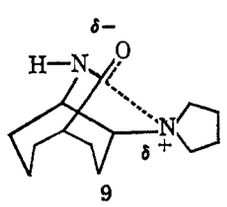
SCHEME II



Both amino lactams formed normal quaternary ammonium salts with methyl iodide. (See Scheme II.)

Attempts have been made to determine the relative stereochemistry of the two isomers. A study of hydrogen bonding in the diamines (6) gave no conclusive results, indicating intermolecular bonding in both instances. Likewise, no significant differences could be observed in the nmr spectra of the isomer pairs (amino lactams, diamines, and methiodides).

An examination of Dreiding models of the two amino lactams indicates that in one, namely the *exo* isomer, an interaction between the tertiary amino function and the amide carbonyl may be possible as represented by **9**. In analogy with the well-known



transannular interaction between ketones and tertiary amines in medium-sized rings,[5] a shift of the carbonyl absorption in the infrared spectrum to lower frequencies may be expected. No significant difference was found in the carbonyl stretching frequencies of the two isomers in chloroform solution. However, in the solid-state spectrum of the higher-melting isomorph of isomer A, besides the normal 1667-cm^{-1} band, a strong band at 1612 cm^{-1} was observed. This is considered to be too high a frequency for a secondary amide II band.[6] Furthermore, no absorption is observed in this region for isomer B. This absorption may be due to an interaction such as represented by **9** in the solid state.

The pK_a' values of the amino lactam hydrochlorides were measured in an aqueous solution. Values of 8.25 ± 0.17 and 9.15 ± 0.19 were obtained for isomers A and B, respectively. The apparently decreased basicity of isomer A with respect to isomer B may be due to the proposed interaction. On the basis of the above evidence, isomer A is tentatively assigned the *exo*, and isomer B the *endo* configuration.

The production of two stereoisomeric amino lactams by the Schmidt reaction may be explained by assuming either (1) an epimerization during the Schmidt reaction, or (2) the presence of two stereoisomers in the starting ketone **1a**. Attempts to examine the latter possibility by the use of various separation techniques have not yielded conclusive results.

Experimental Section[7]

2-(1-Pyrrolidinyl)bicyclo[3.3.1]nonan-9-one (1a) was prepared in a 72% yield by the method of Stork and Landesman,[1] bp 104–110° (0.4 mm).

2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (2).—2-(1-Pyrrolidinyl)bicyclo[3.3.1]nonan-9-one (91.0 g, 0.44 mole) was dissolved in 450 ml of chloroform. The solution was cooled to 0° and 165 ml (3.1 moles) of concentrated sulfuric acid was added dropwise, keeping the reaction temperature below 20°. The resulting suspension was cooled to 0° and sodium azide (57.2 g, 0.88 mole) was added in small portions over a period of 30 min. The reaction mixture was slowly heated to 50°, at which point an exothermic reaction took place. After the reaction had subsided, the mixture was heated at 55° for 45 min.

The reaction mixture was cooled in an ice bath and 248 g (6.2 moles) of sodium hydroxide in 500 ml of water was added cautiously. The sodium sulfate thus formed was removed by filtration. The layers were separated and the water layer was extracted three times with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated, leaving a dark brown oil. This oil was dissolved in a mixture of ether and water. The layers were separated and the ether layer, containing largely starting material, was extracted with water and discarded. The water layers were combined and extracted with methylene chloride. Evaporation of the methylene chloride solution yielded 98 g of a dark brown semisolid which could be crystallized from *n*-hexane to give 60 g of a brown oily solid. Evaporation of mother liquors gave 33 g of a brown oil. (For the work-up of the oil, see below.)

The brown solid was purified by passing it in methylene chloride solution through an alumina–charcoal column. Evaporation of the solvent gave 47 g (0.21 mole, 48%) of a yellowish solid, mp 135–142°. Recrystallization from dioxane raised the melting point to 145.5–148° (isomer A). The analytical sample was purified by sublimation, mp 145.5–148°.

The mother liquor residue (see above) was purified by passing it in methylene chloride solution through an alumina–charcoal column, giving 30 g of a light brown oil. This oil was allowed to react with 15 g of fumaric acid in isopropyl alcohol solution, yielding 17 g of a fumarate, mp 140–145°. Recrystallization from isopropyl alcohol raised its melting point to 148–150°. Upon base treatment the fumarate gave 10.5 g of a solid base. Recrystallization from ethyl acetate yielded 8.1 g (0.036 mole, 8%) of a white solid, mp 113–117° (isomer B). Sublimation raised the melting point to 117–118.5°.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found (isomer A): C, 70.36; H, 10.08; N, 12.80. Found (isomer B): C, 69.97; H, 10.02; N, 12.67.

9-Azabicyclo[3.3.2]decan-2,10-dione (3).—The samples of **2a** and **2b** used in this experiment were shown to be pure from one another by thin layer chromatography (methanol on silica gel) capable of detecting <1% contamination. A solution of 20 g

(5) (a) N. J. Leonard, R. C. Fox, M. Ōki, and A. Chiavarelli, *J. Am. Chem. Soc.*, **76**, 630 (1954); (b) N. J. Leonard, R. C. Fox, and M. Ōki, *ibid.*, **76**, 5708 (1954).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958.

(7) All melting points are corrected; determinations done on a Hoover melting point apparatus.

TABLE I

Compound	Isomer	% yield	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
8a hydrochloride	B	50	230–232[a]	69.49	69.22	8.61	8.59	7.72	7.63
8b	A	74	135–138	80.55	80.41	8.51	8.54	6.96	6.96
8c	A	98	123.5–126.5	68.63	68.52	8.51	8.48	6.96	7.19
8d fumarate	A	87	193–195[b]	60.58	60.50	8.14	8.09	7.07	6.96

[a] From methanol–ether. [b] From isopropyl alcohol–ether.

(0.088 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) and 112.4 g (0.35 mole) of mercuric acetate in 400 ml of 5% aqueous acetic acid was heated for 1 hr on the steam bath. The resulting suspension was cooled and filtered. The clear filtrate was saturated with hydrogen sulfide and the precipitate was removed by filtration. Methylene chloride extraction of the filtrate yielded 9.1 g of a brown solid. Sublimation of the product yielded 6.5 g (0.04 mole, 45%) of a white solid, mp 200–207° (softening at 190°).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.67; H, 7.90; N, 8.40.

Isomer B (3.0 g) was oxidized under the same conditions, giving a 4% yield of sublimed product, mp 196–206° (softening at 190°). Mixture melting point with the keto lactam obtained from isomer A was 195–206°. The infrared spectra in potassium bromide pellets and nmr spectra in deuteriochloroform of the two products were superimposable.

5-Amino-4-oxocyclooctanecarboxylic Acid Hydrochloride (4).—A solution of 0.3 g (0.0018 mole) of 9-azabicyclo[3.3.2]decane-2,10-dione in 10 ml of 6 *N* hydrochloric acid was heated under reflux for 3 hr and then kept overnight at room temperature. The hydrochloric acid was removed at the water pump, leaving a yellowish solid, mp 205–210° dec. Recrystallization from methanol–ether gave 0.15 g (0.00067 mole, 37%) of a white solid, mp 213° dec.

Anal. Calcd for $C_9H_{15}NO_3 \cdot HCl$: C, 48.79; H, 7.27; Cl, 15.99; N, 6.32. Found: C, 48.26; H, 7.30; Cl, 15.95; N, 6.16.

2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decane Dihydrochloride (6). Isomer A.—2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) (17.5 g, 0.078 mole) was dissolved in 50 ml of dry tetrahydrofuran and added to a suspension of 5.0 g of lithium aluminum hydride in 350 ml of the same solvent over a period of 15 min. The suspension was heated under reflux for 8 hr and then kept at room temperature for 16 hr.

The reaction mixture was cooled in an ice bath and 12 ml of water was added over a period of 20 min. The suspension was stirred for 1 hr and filtered. The inorganic residue was washed thoroughly with ether. The combined filtrates were evaporated, leaving 15 g (0.072 mole, 92%) of a colorless oil, bp 102–103° (0.4 mm). The product was characterized as its dihydrochloride, mp 191–194° (from methanol–ether). Consistent carbon and hydrogen analyses of the hydrochloride could not be obtained.

Anal. Calcd for $C_{13}H_{24}N_2 \cdot 2HCl$: N, 9.96. Found: N, 9.97.

Isomer B (1.0 g) was reduced under analogous conditions, giving a 96% yield of a colorless oil, bp 97° (0.3 mm), $n^{23}D$ 1.15291.

Anal. Calcd for $C_{13}H_{24}N_2$: C, 74.97; H, 11.61; N, 13.45. Found: C, 74.44; H, 11.65; N, 13.48.

5-Amino-4-(1-pyrrolidinyl)cyclooctanecarboxylic Acid Dihydrochloride (7).—A solution of 5.0 g (0.022 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) in 20 ml of 7.7 *N* hydrochloric acid was heated overnight under reflux. The water was removed under aspirator pressure, the last traces being removed by azeotropic distillation with toluene. The resulting brown oil was crystallized from isopropyl alcohol: yield, 3.3 g of a white dihydrochloride; mp 212–213° dec. The mother liquors were evaporated and the residue was resubmitted to the above acid hydrolysis: total yield, 4.4 g (0.014 mole, 64%). Recrystallization from methanol–ether raised the melting point to 215–216° dec.

Anal. Calcd for $C_{13}H_{24}N_2O_2 \cdot 2HCl$: C, 49.84; H, 8.37; N, 8.94. Found: C, 49.50; H, 8.36; N, 8.86.

1-(10-Oxo-9-azabicyclo[3.3.2]decan-2-yl)-1-methylpyrrolidinium Iodide.—A solution of 8.0 g (0.036 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) and 30 ml of methyl iodide in 150 ml of dry acetone was stirred at room temperature for 3 days. The resulting suspension was filtered, yielding 13.0 g of a white solid. Recrystallization from absolute ethanol gave 12.2 g (0.034 mole, 94%), mp 241–243° dec, of a white solid.

Anal. Calcd for $C_{14}H_{25}IN_2O$: C, 46.15; H, 6.91; N, 7.69. Found: C, 45.84; H, 7.20; N, 7.52.

Acylation of 2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decanes.—For the preparation of acyl derivatives, 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decane (either isomer) was dissolved in dry acetone containing anhydrous potassium carbonate in suspension. An equimolar amount of the desired acid chloride was slowly added, the stirred reaction mixture being cooled in an ice bath. The reaction mixture was stirred at room temperature for 16 hr. The solvent was removed and the residue was dissolved in 1 *N* hydrochloric acid. The solution was washed with ether, made basic with 5% sodium hydroxide, and extracted with methylene chloride. The methylene chloride solution was dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate. The results are summarized in Table I.

Acknowledgment.—The author is indebted to Dr. G. I. Poos for many valuable discussions, and to Dr. Harold R. Almond and Mrs. M. C. Christie for analytical work.

3-Hydroxypicolinic Acid and Some of Its Derivatives

JOHN T. SHEEHAN

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received August 23, 1965

The growing number of antibiotics[1] in which 3-hydroxypicolinic acid has been found has increased the desirability of a practical preparation of this acid and, even more so, of an intermediate that could be adapted for synthetic work.[2] There are known methods for the synthesis of 3-hydroxypicolinic acid, but one[3] of these leads to isomers; others[4] require many steps or proceed in low yield.[5]

(1) T. H. Haskell, A. Maretzki, and Q. R. Bartz, *Antibiot. Ann.*, **2**, 784 (1954–1955); K. Maeda, *J. Antibiotics* (Tokyo), **A10**, 94 (1957); J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Am. Chem. Soc.*, **80**, 3349 (1958); R. B. Arnold, A. W. Johnson, and A. B. Mauger, *J. Chem. Soc.*, 4466 (1958); H. Vanderhaeghe and G. Parmentier, *Bull. Soc. Chim. Belges*, **68**, 716 (1959); F. W. Eastwood, B. K. Snell, and A. Todd, *J. Chem. Soc.*, 2286 (1960); K. Watanabe, *J. Antibiotics* (Tokyo), **A14**, 1 (1961); M. Bodanszky and M. A. Ondetti, *Antimicrobial Agents Ann.*, 360 (1963); G. Jolles, B. Terlain, and J. P. Thomas, *Nature*, **207**, 199 (1961).

(2) 3-Hydroxypicolinaldehyde has been used in a study of vitamin B_6 catalyzed reactions: D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 648 (1954).

(3) H. Bojarska-Dahlig and T. Urbanski, *Roczniki Chem.*, **26**, 158 (1952); O. Baine, G. F. Adamson, J. W. Barton, J. K. Fitch, D. R. Swayampati, and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

(4) L. R. Fibel and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 3909 (1948); W. Mathes and W. Sauermilch, *Chem. Ber.*, **90**, 758 (1957); F. W. Broekman, A. Van Veldhuizen, and H. Janssen, *Rec. Trav. Chim.*, **81**, 792 (1962).

(5) T. Urbanski, *J. Chem. Soc.*, 1104 (1946).