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STEREOCONTROLLED SYNTHESIS OF DIAMINES FROM IODOLACTAMS

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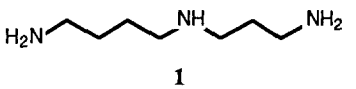
Summary: Displacement of iodide from iodolactams by azide occurs with retention of configuration if a catalytic amount of NaH is added, due to the intervention of an N-acyl-aziridine. Several diamine equivalents and a spermidine analogue are prepared in this way.

Diamines are of general interest as components of biologically active compounds[1] and as ligands.[2] One such compound, the naturally occurring polyamine spermidine (**1**), has been implicated in a variety of cellular processes.[3] We became attracted to the synthesis of analogues of **1** for use as inhibitors of polyamine metabolism,[4] and to this end have examined the reaction of iodolactams[5] with nitrogen nucleophiles. We report here the synthesis of the cyclic spermidine homologue **2** from 5-iodomethyl-2-pyrrolidinone (**3**), and the conversion of iodolactams **4**-**6** to vicinal diamine equivalents using a device for control of stereochemistry.[6,7]



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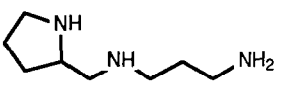

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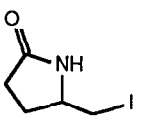

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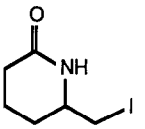

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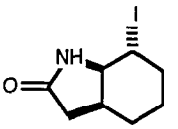

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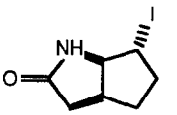

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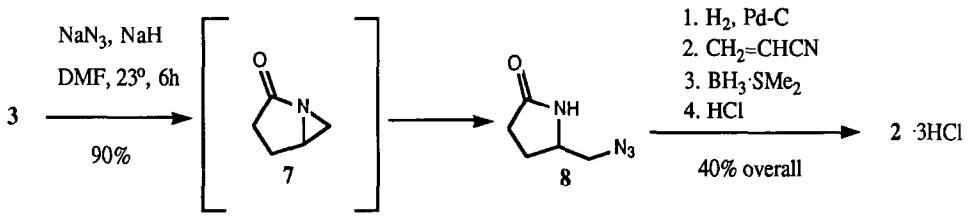
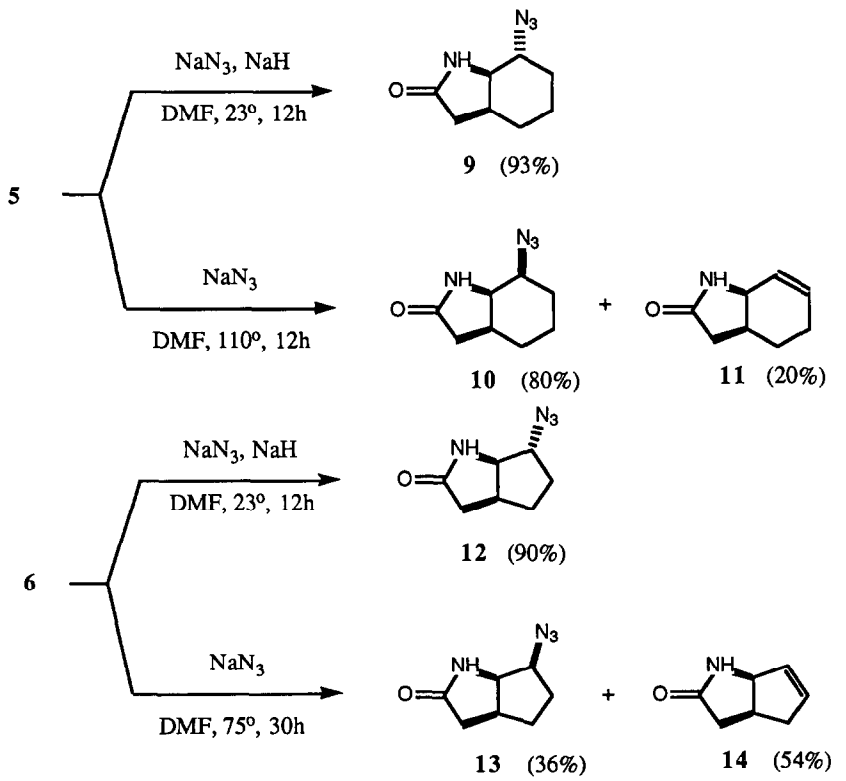
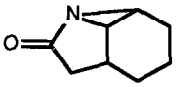
The iodolactams **3**-**6** are each prepared by iodocyclization of the N,O-bis(trimethylsilyl) derivative of the corresponding unsaturated amide.[5] Reaction of **3** with 1,3-diaminopropane did not give the simple S_N2 reaction, but rather led to a complex mixture that contained very little lactam. Sodium azide, in contrast, reacted slowly but cleanly with **3** at 60° in DMF solution to give azidolactam **8**. The reaction was greatly accelerated by the addition of a catalytic amount (0.1 equiv) of sodium hydride. From this latter observation we infer that base promoted ring closure to the N-acyl-aziridine **7** is taking place prior to attack by azide. The synthesis of **2** was completed by hydrogenation, cyanoethylation, reduction, and HCl treatment.



Exposure of **5** to the same combination of sodium azide and sodium hydride gave a single azido-lactam to which we assign structure **9**. Similarly, **6** gave the azido-lactam **12**. Both of these reactions proceed under conditions which are remarkably mild for S_N2 displacement of cycloalkyl halide.[8] Without sodium hydride, the reactions of **5** and **6** gave azido-lactams (**10** and **13**) which are epimeric with **9** and **12**, respectively, and which were accompanied by the products of dehydroiodination, **11** and **14**.[9] Thus, by choice of conditions, any of the four azido-lactams could be prepared in stereocontrolled fashion, depending upon whether the N-acyl-aziridine (**15** or **16**) intervened as an intermediate. Each is also an obvious precursor to a vicinal diamine.[10]





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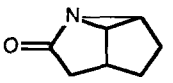

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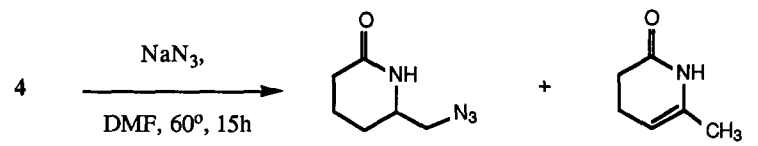
Additional evidence for the formation of **15** was obtained by omitting the sodium azide in the reaction of **5** with sodium hydride in DMF. After 2 h at 23° a new product was observed by tlc at higher R_f than starting material. IR analysis of the crude reaction mixture revealed a carbonyl absorption at 1750 cm^{-1}, indicative of the presence of **15**.[11] The same transformation occurred when the reaction was run in THF solution using potassium hydride as the base. In this case pure **15** (mp 112-114°) was isolated by chromatography on silica gel using 1:1 ether - petroleum ether as the eluant.

The reaction of **4** with sodium azide was also successful, although not improved by the addition of sodium hydride, and the resulting azido-lactam **17** was always accompanied by the product of dehydroiodination, 6-methyl-3,4-dihydro-2(1H)-pyridone (**18**). Treatment of **4** with DBU in toluene at reflux gave **18** directly in 89% yield. N-Acyl-enamines such as **18** are useful as nucleophiles for conjugate addition, and **18** itself was used by Schumann and Naumann in their concise synthesis of *alpha*-obscurine.[12]



17 (50%) **18** (50%)

We are continuing our study of the reactions of iodolactams and N-acyl-aziridines with a view toward C-C bond formation.

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References and Notes

1. Knirel, Y. A. et al. *Carbohydr. Res.* **1983**, *122*, 181. Olsen, R. K.; Hennen, W. J.; Wardle, R. B.*J. Org. Chem.* **1982**,*47*, 4605. Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266. Szmuszkovicz, J.; Von Voigtlander, P. F.; Kane, M. P. *J. Med. Chem.* **1981**, *24*, 1230.

2. Tsubomura, T.; Yano, S.; Kobayashi, K.; Sakurai, T.; Yoshikawa, S. *J. Chem. Soc., Chem. Commun.* **1986**, 459. Fraenkel, G.; Pramanik, P. *J. Org. Chem.* **1984**, *49*, 1316.

3. Bachrach, U.; Kaye, A.; Chayen, R.; Eds. *Advances in Polyamine Research* ; Raven: New York, 1983; Vol. 4. Morris, D. R.; Marton, L. J.; Eds. *Polyamines in Biology and Medicine* ; Marcel Dekker: New York, 1981.

4. Leading references: Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1986**, *51*, 4856. Bergeron, R. J. *Acc. Chem. Res.* **1986**, *19*, 105. Bey, P.; Bolkenius, F. N.; Seiler, N.; Casara, P. *J. Med. Chem.* **1985**, *28*, 1.

5. Knapp. S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803.

6. Early formalization of stereoselective diamine synthesis using azide as nucleophile: Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511. Recent stereocontrolled diamine synthesis: Oriek, B. S. *Tetrahedron Lett.* **1986**, *27*, 1699. Egli, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 1442. Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Amer. Chem. Soc.* **1984**, *106*, 7867. Jung, S.-H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399. Kohn, H.; Jung, S.-H. *J. Amer. Chem. Soc.* **1983**, *105*, 4106. Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787.

7. Characterization of new compounds (mp, selected IR in cm^{-1}): **8**, oil, 3230, 2095, 1700; **9**, 69-70°, 3200, 2090, 1685; **10**, 91-92°, 3200, 2100, 1690; **11**, oil, 3200, 1690, 1645; **12**, 67-68°, 3200, 2100, 1695; **13** (see ref. 10), 3200, 2100, 1697; **14**, oil, 3230, 1695, 1620; **17**, 93-94°, 3250, 2090, 1660; **2**·3HCl, 121-123°. The structure assignments are all consistent with decoupled 400 MHz ^{1}H NMR spectra. Iodolactam/azido-lactam pairs with the otherwise identical structure (**3/8**, **4/17**, **5/9**, **6/12**) show very similar coupling patterns. Yields shown are isolated yields of pure compounds (except for **13**) following column chromatography.

8. Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Amer. Chem. Soc.* **1975**, *97*, 5936.

9. Compounds **11** and **14** were independently synthesized from **5** (92% yield) and **6** (100% yield), respectively, by treatment with DBU in toluene at reflux.

10. Although **9**, **10**, **12**, **13**, and **17** were not taken on to diamines *per se*, as was done with **8**, azido-lactams **12** and **13** were hydrogenated to the corresponding amino-lactams, which were characterized as their hydrochloride salts, mps 164-166° and 183-185°, respectively. In the case of **13**, this served to remove some contamination by **14**.

11. Brown, I.; Edwards, O. E.; McIntosh, J. M.; Vocelle, D. *Can. J. Chem.* **1969**, *47*, 2751.

12. Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1983**, 220.

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