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Interconvertions between δ-Lactam and δ-Lactone Derivatives Initiated by Unique Transannular Interactions of the Rigid Cyclohexane Boat Structure in Pentacycloundecane

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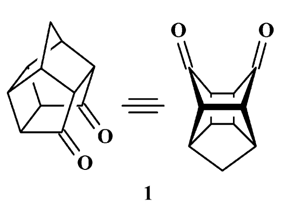
Abstract: The pentacycloundecane (PCU) cage structure resembles a perfect boat conformation, and for the first time unique lactam/lactone interconversions on the flagpole carbons of a cyclohexane boat structure are reported. The syntheses of a novel dihydroxy-PCU-δ-lactone and two novel N-substituted PCU-δ-lactams are reported. Hydrolysis of some of the PCU-δ-lactam compounds produced δ-lactones, and reaction of the lactones with ammonia or primary amines again produced δ-lactams. Reaction mechanisms to account for the unusual interconversion reactions induced by transannular interactions are proposed.

As part of a program to investigate the synthesis and chemistry of amino acids with cage structures, the dione **1** was utilized as a substrate in Strecker reactions. The dione (**1**) is easily obtained from the Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone by intramolecular photocyclization.[1,2] As treatment of the dione with Strecker reagents normally leads to cyanohydrin and/or amino nitrile products,[3] the one-pot conversion of the dione to the three novel δ-lactams **2**−**4** is quite unique.[3,4] The role of the rigid cyclohexane boat structure of the pentacycloundecane skeleton (see alternative view of the dione **1** below) with respect to transannular interactions was highlighted in the proposed mechanisms.[3,4]



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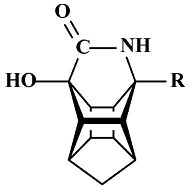
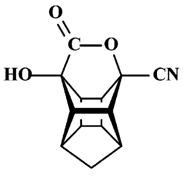


2, **R = OH**
3, **R = CN**
4, **R = NH_2**

A literature search revealed a vast number of publications about the separate synthesis of lactam and lactone derivatives with a cyclohexane boat basis, but very little is known about the interconversion between these lactam and lactone derivatives. A number of studies focused on the transannular interactions of cyclohexane boat structures as well as transition states involving a boat conformation.[5,6] The cyclohexane boat structure is a transition state.[7−9] Therefore, performing reactions on the two flagpole carbons is therefore difficult to envisage, except if this conformation is conveniently rigidified as in the pentacyloundecane skeleton or in alternative structures.[10]

The effect of transannular interactions on the pentacycloundecane skeleton has been throroughly studied.[1,4,11] However, the interconversions between the PCU-lactam and lactone derivatives have not been investigated.

Certain lactams can be hydrolyzed to their corresponding amino acids,[12] and our initial aim was to convert the different lactam compounds (**2**−**4**) to their corresponding amino acids. Substituent groups on the ring[13−15] as well as ring strain[16−18] play an important role on the ease of hydrolysis. An amino group on the ring carbon atom adjacent to the nitrogen atom in the β-lactam ring greatly increases the rate of hydrolysis.[16] These type of β-amino lactams are all moisture sensitive. Hydrolysis of lactam compounds does not always produce the corresponding amino acid,[19,20] as was the case with the cyano lactam **3**.[4] The cyano lactam was selectively hydrolyzed to three different novel lactone compounds (**5**−**7**).[4]



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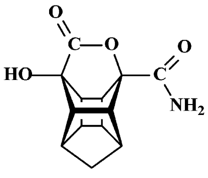

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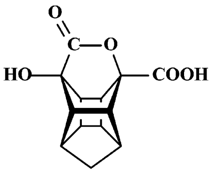

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The cyanolactam **3** is very susceptible to ring cleavage in acidic media and is hydrolyzed to the corresponding

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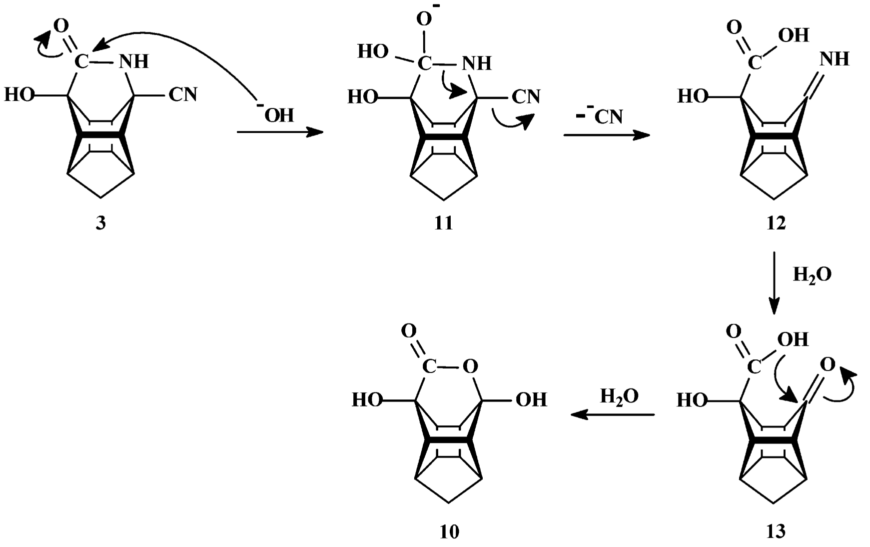
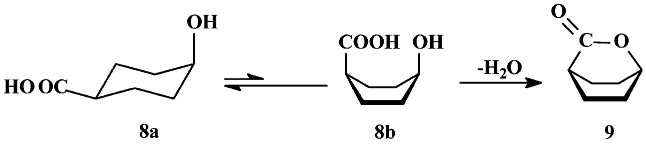
SCHEME 1. Conversion of the Cyano Lactam 3 to the Dihydroxylactone 10



novel lactone **5** at room temperature.[4] Under different reaction conditions the other novel lactones **6** and **7** were obtained.[4]

The δ-lactone **9**[21] with a cyclohexane boat skeleton as the basis was reported in 1929. *cis*-4-Hydroxycyclohexanecarboxylic acid **8** is converted to the corresponding cyclohexane boat δ-lactone **9**, while the trans form of **8** does not lactonize.[5,22]



The corresponding lactam of **9** was also reported,[12,23] but interconversion between these lactam and lactone derivatives have not been investigated.

In view of the discussion above, it was decided to investigate the hydrolysis of the polycyclic δ-lactam derivatives **2**−**4** as well as the interconversion of the lactam and lactone derivatives. These interconversions on a cyclohexane boat structure had not been reported before.

The dihydroxylactam **2** could not be converted to the corresponding lactone in acidic media. Similarly, the amino hydroxylactam **4** is surprisingly stable under acidic reaction conditions. The obvious difference between the lactams **2** and **4** with respect to the cyano lactam **3** is the ability of the cyano group to stabilize[4,24,25] an intermediate cation required for ease of hydrolysis. The mechanism proposed for the hydrolysis of **3** in acidic media to produce the lactone **5** was reported previously.[4]

Alkaline hydrolysis of the cyano hydroxylactam **3** unexpectedly led to cyano group substitution. Treatment of **3** with 30% sodium hydroxide under reflux conditions produced the novel dihydroxylactone **10**. A possible explanation for the formation of the lactone **10** from alkaline catalyzed hydrolysis of the lactam **3** is provided in Scheme 1.

Nucleophilic attack from hydroxyl anions on the carbonyl carbon atom of the lactam **3**, to displace the cyanide group in **11**, is probably energetically a more likely process than nitrile group hydrolysis. The highly reactive imine group in **12** is easily hydrolyzed to the keto acid **13** which spontaneously converts to the lactone **10**. The infrared spectrum, FAB mass spectrum, and NMR data all support the structure of **10**. The product tests negative for nitrogen. The NMR data of **10** is provided in the Experimental Section. A diacetate was obtained when the lactone **10** was acetylated, confirming the presence of two hydroxyl groups.

It is expected that the lactams **2** and **4** should follow the same reaction route with alkaline hydrolysis at reflux temperature. Treatment of the amino hydroxylactam **4** with 30% sodium hydroxide under reflux conditions produced the expected conversion to the dihydroxylactone **10**. However, a similar conversion of the dihydroxylactam **2** to **10** could not be achieved even after the same treatment for 48 h. Treatment of the amino hydroxylactam **4** under elevated temperature and pressure (170 °C in a pressurized reaction vessel) in the presence of water and a catalytic amount of either acetic acid or diethylamine produced the hydrate of **2**.[26] When amino hydroxylactam **4** is refluxed in concentrated hydrochloric acid for 48h the dihydroxylactone **10** was obtained in

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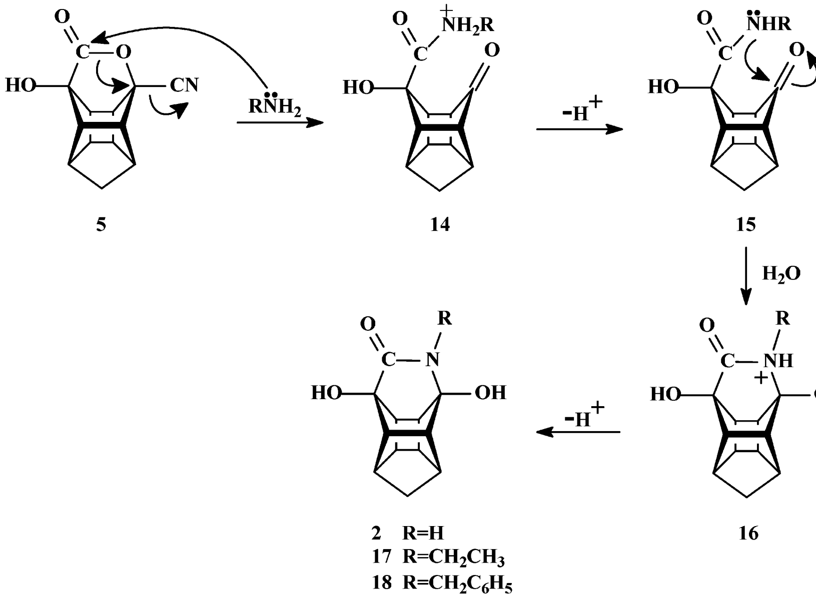
SCHEME 2. Conversion of the Cyano Lactone 10 to N-Substituted Lactam Derivatives



reasonable yield. The reaction proceeded much faster in a medium-pressure reaction vessel containing 10% hydrochloric acid.

Ammonolysis of lactones can yield lactams.[27−29] As anticipated, the dihydroxylactam **2** was obtained upon treatment of the cyano hydroxylactone **5** (1 g) with 25% ammonia (10 or 100 mL). Nucleophilic attack of ammonia on the carbonyl carbon atom of **5** will probably lead to carbon−oxygen bond cleavage with simultaneous nitrile group elimination. A possible mechanism is suggested in Scheme 2. Attack of the electron pair on the nearby nitrogen atom of the carbonyl carbon atom in **15** should lead to the formation of the dihydroxylactam **2**.

Similar conversions of the cyano hydroxylactone **5** to lactam derivatives were achieved by treatment of **5** with ethylamine or benzylamine, which afforded the novel N-substituted lactam compounds **17** and **18**, respectively. The structures of the lactams **17** and **18** were elucidated from ^{13}C and ^{1}H NMR studies and the data is provided in the Experimental Section.

Confirmative evidence for the structure of **17** was obtained from a ^{13}C NMR spectrum recorded in $(CD_3)_2SO$, which was treated with two drops of a mixture of 60% D_2O and 40% H_2O to impose partial exchange of protons. Double signals were observed for both quaternary carbon signals indicating that both bear groups with only one deuterium-exchangeable proton. MS and IR spectra also support the proposed structure of **17**.

The absorption bands in the infrared spectrum of the *N*-benzyl-substituted lactam **18** are very similar to that of **17**. The EI mass spectrum of **18** exhibits a molecular ion at *m*/*z* 309, which corresponds with a molecular formula of $C_{19}H_{19}NO_3$. As in the case of **17** partial exchange of protons influenced only the quaternary carbon atom resonances in the ^{13}C NMR spectrum (δ_C 90, 99 and δ_C 79, 95 are registered as double signals).

It is expected that ammonolysis of the dihydroxylactone **10** should proceed via the same route as proposed for the ammonolysis of the cyano hydroxylactone **5** (see Scheme 2). Surprisingly, treatment of **10** (1 g) with 25% ammonia (10 mL) led to the formation of the amino hydroxylactam **4** instead of the expected dihydroxylactam **2**. When the reaction was repeated with 10 times more ammonia (100 mL), the dihydroxylactam **2** was obtained. [Note that only the dihydroxylactam **2** was obtained when the cyano hydroxylactone **5** (1 g) was treated with 25% ammonia (10 or 100 mL)]. However, treatment of the dihydroxylactone **10** with ethylamine or benzylamine produced the expected N-substituted δ-lactams **17** and **18**, respectively, in a similar way as for the ammonolysis of the cyano hydroxylactone **5**.

The formation of the amino hydroxylactam **4** upon treatment of the dihydroxylactone **10** (1 g) with 25% ammonia (10 mL) can probably be attributed to the different solubility of the intermediates **15** and **19** (see Scheme 3). Note that both the reactant **10** and products **2** and **4** are relatively insoluble in aqueous media. In general structures with a carbonyl group (**15**) should be less soluble in aqueous solution compared to its corresponding imine (**19**). A possible explanation could be that when the reaction is performed in more diluted conditions (1 g of **10** in 100 mL of ammonia), enough of the intermediate **15** is dissolved to yield the kinetic product **2**. When the reaction is performed in more concentrated conditions (1 g of **10** in 10 mL of ammonia), the intermediate **15** presumably does not dissolve sufficiently and is converted to a more soluble form, namely the corresponding imine **19**. Instantaneous transannular cyclization of **19** to the amino lactam **4** follows.

Initially, it was not clear whether the dihydroxylactam **2** could serve as intermediate in the formation of the amino lactam **4** (see Scheme 3).

Treatment of the dihydroxylactam **2** with 25% ammonia at room temperature for 24 h only produced

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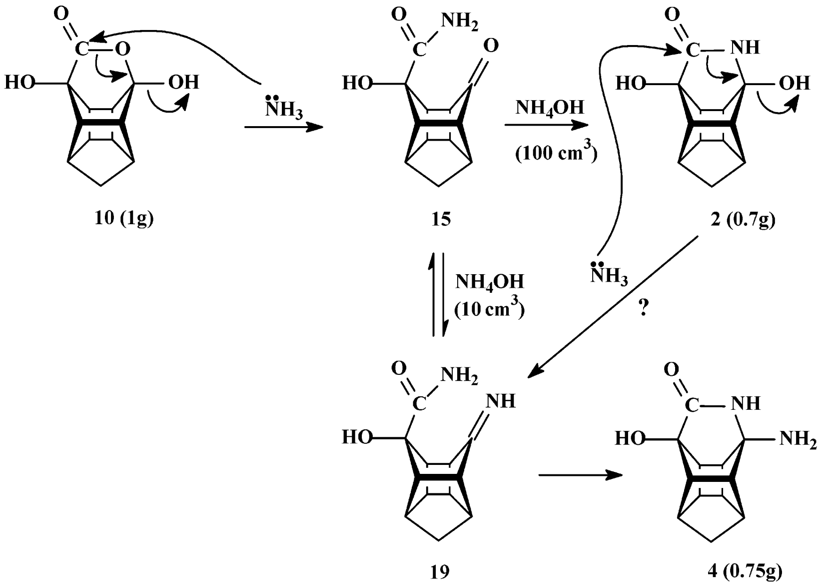
SCHEME 3. Conversion of the Dihydroxylactone 10 to the Amino Lactam 4



starting material on subsequent evaporation of the excess ammonia. Since the amino hydroxylactam **4** is less soluble than the dihydroxylactam **2** the reaction was repeated with a minimum amount of ammonia in an effort to induce precipitation of the desired product **4**. Instead the hydrate[26] of the dihydroxylactam **2** was obtained. The intermediacy of the dihydroxylactam **2** in the conversion of the dihydroxylactone **10** to **4** was confirmed by forced dissolution of **2** in ammonia (150 °C for 18 h), which indeed produced the amino hydroxylactam **4**.

Treatment of the cyano lactam **3** (1 g) with ammonia (10 or 100 mL) also produced the amino lactam **4**. A similar mechanism as proposed in Scheme 3 accounts for this transformation of the lactam **3** via intermediates **15** and **19** to the lactam **4**.

This observation explains the reason why treatment of the dione **1** with an excess of sodium cyanide and ammonia produces[4] the amino lactam **4** although the formation of the cyano lactam **3** should also occur, followed by conversion of the latter to the amino lactam **4**. This experimental observation, combined with the rate of hydrolysis of the lactam compounds **3** and **4**, implies that the amino lactam **4** is the thermodynamically determined product.

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Supporting Information Available: All experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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