ether was cooled to 0–5° under a nitrogen atmosphere. To this solution was added 45 mmol of phenylmagnesium bromide in 50 ml of ether with stirring. After 1 hr the solution was quenched with water. The ether layer was separated and dried over anhydrous potassium carbonate and then evaporated in vacuo. The liquid residue was identical with starting material.

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Registry No.—**4,** 54193-54-3; **4** HCl, 54193-55-4; **5,** 54193-56-5; **6,** 54193-57-6; **7,** 54193-58-7; **7** HCl, 54193-59-8; **8,** 54193-60-1; **8** HCl, 54193-61-2; **9,** 54193-62-3; **9** HCl, 54193-63-4; **10,** 54193-64-5; DMNA, 62-75-9; DENA, 55-18-5; PipNA, 100-75-4; PyrNA, 930-55-2; PhBr, 108-86-1; $PhCH_2Cl$, 100-44-7; *t*-BuBr, 507-19-7; $C_6H_{11}Br$, 108-85-0; 1-cyclohexyl-2-ethyl-3-methyldiaziridine, 54193-65-6; acetaldehydecyclohexylimine, 1193-93-7; cyclohexylamine, 108-91-8; *N*-chloroethylamine, 24948-82-1.

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Reductive Cyclization of Aminobenzoic Acids

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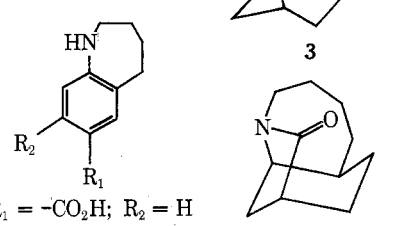
Hydrogenation of 3- and 4-aminobenzoic acids over a ruthenium catalyst at 150° under 1600 psig of hydrogen gave fair yields of the bicyclic lactams **8** and **6,** respectively. Cyclization also occurs on hydrogenation of 3-methyl-4-aminobenzoic acid, but on hydrogenation of the 3,4-diaminobenzoic acid one of the amine groups is lost. The 4-amine is lost twice as readily as is the 3-amine. With the 3-hydroxy-4-aminobenzoic acid complete hydrogenolysis of the amine group occurs.

It was previously found that on hydrogenation of the carboxybenzazepines **1**[1] and **2**[2] good yields were obtained of the cyclic lactams **3** and **4,** respectively. Since this reaction was of general synthetic interest, the hydrogenation of other aminobenzoic acids was also run to determine whether the simpler bicyclic lactams would be formed.



1, $R_1 = -CO_2H$; $R_2 = H$
2, $R_1 = H$; $R_2 = -CO_2H$

3

4

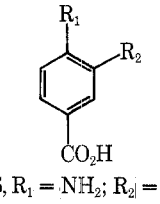
Hydrogenation of 4-aminobenzoic acid (**5**) occurred readily in methanol over a ruthenium on charcoal catalyst at 160° and 1600 psig to give a 40–50% yield of isoquinuclidone (**6**). 3-Aminobenzoic acid (**7**), on hydrogenation under these same conditions, afforded a 35–45% yield of the bicyclo[3.2.1]lactam, **8,** along with a small amount of another material.

The mass spectrum of **6** was analogous to that of 2-piperidone[3] with fragmentation occurring by the successive loss of the two C_2H_4 bridges giving a base peak at mass 69 ($M - C_4H_8$) and a strong peak at mass 97 ($M - C_2H_4$). Fragmentation of **8** followed the pattern observed in the mass spectrum of ε-caprolactam[4] with a base peak at mass 83 ($M - C_2H_4N$) and no other large peaks present. The minor component obtained on hydrogenation of **7** had a mass spectrum which was unlike that of **8** but similar to that of *N*-methylcaprolactam,[4] a base peak at mass 97 ($M - C_2H_4N$) and strong peaks at mass 110 ($M - CH_3N$) and 96 ($M - C_2H_5N$). On this basis, this material was tentatively identified as the *N*-methyllactam, **9.**

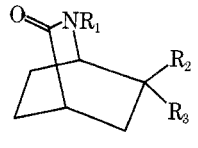
Hydrogenation of 3-methyl-4-aminobenzoic acid (**10**) gave four compounds in 8.5, 5, 65, and 10% yields, respectively, as determined by gas chromatographic analysis

(GC). GC–MS analysis of this reaction mixture showed that the first two components each had a molecular ion at mass 153, a base peak at mass 83 (69 + 14) and a strong peak at mass 111 (97 + 14). Thus, these materials were considered to be the *exo-* and *endo-N*-methyllactams, **11** and **12.** The second two compounds each had a molecular ion at mass 139, a base peak at mass 69 and a strong peak at mass 97 as expected for the fragmentation of the [2.2.2] bicyclic lactams **13** and **14.** Since there was only a small peak at mass 111 in the spectra of these compounds, the loss of the substituted bridge must occur more readily than the cleavage of the unsubstituted one. As it is known that hydrogenation of polysubstituted benzenes over ruthenium gives predominantly the all cis product,[5] the major component in this reaction mixture was assigned the exo configuration, **13.**

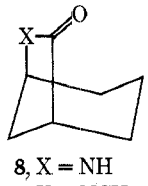
This obtaining of an exo:endo isomer mixture was contrary to a recent report[6] in which it was found that only the exo isomer was obtained from the reductive cyclization of substituted aminobenzoic esters. To clarify this discrepancy, **10** was hydrogenated under the conditions used in this latter study (RuO_2, ethanol, 125°, and 1900 psig).[6] The product from this reaction was shown by GC analysis to be composed of a single compound, presumably the exo isomer,[5] in an 80% yield. Further NMR and mass spectral analysis showed this material to be the *N*-ethyllactam, **15.** Thus, at the lower temperature endo isomer formation does not take place.



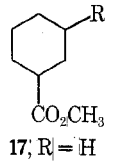
5, $R_1 = NH_2$; $R_2 = H$
7, $R_1 = H$; $R_2 = NH_2$
10, $R_1 = NH_2$; $R_2 = CH_3$
16, $R_1 = R_2 = NH_2$
18, $R_1 = NH_2$; $R_2 = OH$



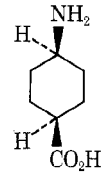
6, $R_1 = R_2 = R_3 = H$
11, $R_1 = R_2 = CH_3$; $R_3 = H$
12, $R_1 = R_3 = CH_3$; $R_2 = H$
13, $R_1 = R_3 = H$; $R_2 = CH_3$
14, $R_1 = R_2 = H$; $R_3 = CH_3$
15, $R_1 = C_2H_5$; $R_2 = CH_3$; $R_3 = H$



8, X = NH
9, $X = NCH_3$
19, X = O



17, R = H
20, R = OH



21

Attention was then shifted to the hydrogenation of 3,4-diaminobenzoic acid (**16**) to determine which of the two possible lactams would be formed preferentially. From this reaction an 80% yield of a clear viscous oil was obtained. This oil was shown by GC–MS analysis to be composed of 8% of **9**, 56% of **8**, and 32% of **6**, along with a small amount of methyl cyclohexanecarboxylate (**17**). The complete absence of amine substituents on the bicyclic lactams was unexpected since hydrogenolysis of aromatic amines does not normally occur over ruthenium catalysts.[7,8] About the only exception to this generalization is the reported cleavage of the dialkylamine group on hydrogenation of *p*-dialkylaminoanilines over ruthenium.[9]

There were present in **16** some factors which could have facilitated this amine hydrogenolysis. The para carboxy group was probably influential since twice as much of the 4-amine was lost than was the 3 substituent. This cannot be the only influence, though, since more 4-amine cleavage occurred with **16** than was observed on hydrogenation of **5** or **10.** The only difference between **16** and **5** or **10** is the presence in **16** of a substituent ortho to the amine group which is capable of hydrogen bonding with it. The importance of this factor was further illustrated in the hydrogenation of 4-amino-3-hydroxybenzoic acid (**18**).

On attempted reductive cyclization of **18**[10] a 92% yield of product was recovered. The infrared spectrum of this material showed no lactam carbonyl absorption but instead had a strong lactone and/or ester carbonyl band at 1725 cm^{-1}. The product was shown by GC–MS analysis to be composed primarily of two species in 15 and 65% yields, respectively. The mass spectrum of the minor component had the molecular ion peak at mass 126, a typical lactone peak[13] at M − CH_2CO_2H (mass 67) as well as a peak at M − C_3H_7 (mass 84) which is a characteristic caprolactam cleavage.[13] On the basis of this spectrum and comparison with an authentic sample[14] the minor component was assigned structure **19.** The major component in this reaction mixture was identified as methyl 3-hydroxycyclohexanecarboxylate (**20**) again by comparison with a known sample.[15] The hydrogenolysis of the amine rather than the hydroxy group on hydrogenation of **18** was contrary to previous reports concerned with the competitive cleavage of aromatic oxygen and nitrogen containing functional groups over ruthenium catalysts.[9,16] In the present instance, though, the loss of the amine is facilitated by the presence of the para carboxy group and by the ortho OH, with hydrogen bonding proably an important factor in the latter instance.

While this reaction is not of general synthetic utility, it was still of interest to determine whether the cyclization occurred by a thermal process after the ring was hydrogenated or if it took place as the substrate was being desorbed from the catalyst but before it could attain the stable boat conformation. Since the reaction conditions used for the reductive cyclization were milder than those commonly used for the thermal cyclization of aminocyclohexanecarboxylic acids,[17–19] it was felt that the latter explanation seemed more valid. To determine if this assumption were correct, samples of the known *cis*-4-aminocyclohexanecarboxylic acid (**21**) were heated under reductive cyclization conditions but in the absence of any metal catalyst. The sample which was heated at 120° was recovered unchanged while that heated at 150° was about 50% cyclized to **6.** Thus, at the lower temperature cyclization to the bicyclic lactam must occur in conjunction with ring hydrogenation while at the higher temperature no definitive conclusion can be reached. It would seem reasonable, though, that since at 120° cyclization must occur during substrate desorption, this process must also take place, at least to some extent, at 150° as well.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. Microanalyses were run either with an F & M Model 185 automated CHN analyzer or by Micro Analysis, Inc., Wilmington, Del.

Infrared spectra were recorded on a Beckman IR-10 spectrophotometer in chloroform solutions. Nuclear magnetic resonance spectra were obtained on a Varian A-60A instrument using $DCCl_3$ as solvent and Me_4Si as the internal standard. Vapor phase chromatographic analyses were run using an F & M Model 720 chromatograph with either a 6 ft × 0.25 in. 20% Carbowax 20 on Chromosorb P or a 6 ft × 0.25 in. 25% SE-30 on Gas Chrom P column. Mass spectra were run on a Perkin-Elmer 270 gas chromatograph–mass spectrometer (GC–MS) coupled to a Varian 100 MS data system using a source temperature of 200°. The spectra were run at 70 eV. The gas chromatograph was a Perkin-Elmer 900 instrument with either a 16 ft × 0.125 in. 2% Carbowax 20M on Gas Chrom P or a 16 ft × 0.125 in. 2% GE-SF-96 on Chromosorb Q column. The

hydrogenations were run in an Autoclave Engineers 300-ml Magne-stir Autoclave.

General Hydrogenation Conditions. A solution of 10 g of the aminobenzoic acid in 150 ml of methanol was hydrogenated over 10 g of 5% ruthenium on charcoal under 1600 psig of hydrogen at 160° for 24 hr. After cooling, the catalyst was removed by filtration and washed thoroughly with more methanol. Evaporation of the solvent gave the crude product.

2-Azabicyclo[2.2.2]octan-3-one (6) was obtained from the hydrogenation of 4-aminobenzoic acid (**5**) in 40–50% yield after chromatography of the reaction mixture on a silica gel column (5% MeOH in $CHCl_3$) and purification by dissolution in water, extraction with ether, and evaporation of the water (in vacuo) to give **6:** mp 192–193° after recrystallization from hexane (lit.[17] mp 197–198°); ir 3420 and 3200 (NH) and 1667 cm^{-1} (C=O); NMR δ 7.8 (s, 1, NH), 3.65 (s, 1, NCH), 2.5 (s, 1, C(=O)CH), and 1.71 (s, 8, CH_2); MS *m/e* (rel intensity) 67 (48), 68 (47), 69 (100), 82 (22), 96 (30), 97 (54), and 125 (53) molecular ion.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.16; H, 8.56; N, 10.92.

6-Azabicyclo[3.2.1]octan-7-one (8) was obtained in 35–45% yield from 3-aminobenzoic acid (**7**) on recrystallization of the crude reaction mixture from hexane: mp 191–192°; ir 1690 cm^{-1} (C=O); NMR δ 7.12 (s, 1, NH), 3.77 (s, 1, NCH), 2.36 (s, 1, C(=O)CH), and 1.68 (m, 8, CH_2); MS *m/e* (rel intensity) 67 (28), 82 (28), 83 (100), 96 (27), and 125 (30) molecular ion.

Anal: Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.45; H, 9.16; N, 10.97.

GC–MS analysis of the reaction mixture showed the presence of about 4% of another material tentatively identified as the *N*-methyllactam, **9:** MS *m/e* (rel intensity) 68 (23), 83 (11), 96 (69), 97 (100), 110 (96), and 139 (58) molecular ion.

The hydrogenation of 3-methyl-4-aminobenzoic acid (10) gave a mixture of products which by GC–MS were identified as **11** (9%) [MS *m/e* (rel intensity) 55 (21), 82 (54), 83 (100), 110 (20), 111 (34), and 153 (36) molecular ion], **12** (5%) [MS 55 (23), 82 (47), 83 (100), 110 (19), 111 (33), and 153 (39) molecular ion], **13** (65%) and **14** (10%) [MS 55 (21), 68 (51), 69 (100), 96 (22), 97 (49), and 139 (22) molecular ion]. A small sample of pure **13** was isolated as a thick oil by chromatography on silica gel (2% MeOH in $CHCl_3$): NMR δ 7.95 (s, 1, NH), 3.3 (d, 1, NCH), 2.4 (s, 1, C(=O)CH), 2.1–1.8 (m, 7), and 0.92 (d, 3, CCH_3); MS 55 (27), 68 (48), 69 (48), 69 (100), 96 (26), 97 (52), and 139 (35) molecular ion.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 9.95. Found: C, 69.19; H, 9.54; N, 9.95.

In addition a fraction composed of almost equal amounts of **13** and **14** was also obtained.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 9.95. Found: C, 69.38; H, 9.36; N, 10.04.

2-Ethyl-6-methyl-2-azabicyclo[2.2.2]octan-3-one (15). A solution of 1 g of **10** in 75 ml of ethanol was hydrogenated over 1 g of RuO_2 under 1900 psig of hydrogen at 125° for 24 hr.[6] The catalyst was removed and the solvent evaporated to give 1.2 g of the crude product which was shown by gas chromatographic or GC–MS analysis to be composed of about 80% of one component which was neither **11, 12, 13** nor **14.** On distillation a pure material was obtained which was identified as the *N*-ethyllactam, **15:** bp 74–76° (0.3 mmHg); NMR δ 3.0–4.0 (m, 2, $-CH_2CH_3$), 3.3 (s, 1, NCH), 2.51 (s, 1, C(=O)CH), 1.12 (t, 3, CH_2CH_3), and 0.93 (d, 3, CCH_3); MS *m/e* (rel intensity) 55 (24), 56 (20), 96 (37), 97 (100), 124 (22), 125 (30), and 167 (34) molecular ion.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.53; H, 10.64; N, 8.08.

The hydrogenation of 3,4-diaminobenzoic acid (16) using the general conditions described above gave a mixture of products which was shown by gas chromatographic analysis to be composed of 8% of **9,** 56% of **8,** and 32% of **6.** In addition a small amount of methyl cyclohexanecarboxylate, identified by comparison with an authentic sample, was also formed.

Hydrogenation of 3-Hydroxy-4-aminobenzoic Acid (18). Sublimed 3-hydroxy-4-nitrobenzoic acid[11] was hydrogenated under the general reaction conditions described above. An initial, rapid uptake of 3 equiv of hydrogen indicated that this material was converted into **18**[12] before the reactor began heating up to the temperature required for ring hydrogenation. Gas chromatographic analysis of the product showed the presence of two major components in 15 and 65% yields. GC–MS comparison with a sample of the known material[14] indicated that the smaller of these was the lactone, **19:** MS *m/e* (rel intensity) 54 (89), 55 (48), 67 (100), 70 (38), 82 (43), 83 (37), 84 (69), and 126 (2) molecular ion. The major component was identified as methyl 3-hydroxycyclohexanecarboxylate (**20**) by comparison with an authentic sample.[15] MS 53 (18), 54 (29), 55 (82), 56 (13), 57 (71), 59 (23), 67 (26), 69 (26), 70 (29), 71 (11), 74 (12), 78 (11), 79 (27), 80 (44), 81 (100), 82 (17), 83 (30), 84 (50), 87 (52), 88 (49), 97 (38), 98 (41), 99 (25), 109 (19), 116 (37), 126 (29), 127 (12), 129 (14), 140 (5), and 158 (4) molecular ion.

Methyl 3-Hydroxycyclohexanecarboxylate (20). A solution of 20 g of 3-hydroxybenzoic acid in 150 ml of methanol was hydrogenated over 5 g of 5% ruthenium on charcoal under 1700 psig of hydrogen at 140° for 18 hr. After cooling, the catalyst was removed by filtration and the solvent evaporated to give 19 g of crude product which on distillation gave 13 g of **20:** bp 95° (1.1 mmHg); $n^{25}D$ 1.4669 [lit.[15] bp 134–146° (19 mmHg); $n^{25}D$ 1.4667]; ir 3400 (OH) and 1725 cm^{-1} (C=O); NMR δ 4.0 (s, 1, HOC*H*) and 3.67 (s, 3, CO_2CH_3); MS *m/e* (rel intensity) 53 (20), 54 (45), 55 (82), 56 (12), 57 (58), 59 (25), 67 (44), 68 (14), 69 (24), 70 (33), 71 (10), 74 (10), 77 (15), 78 (16), 79 (35), 80 (46), 81 (100), 82 (23), 83 (31), 84 (46), 87 (51), 88 (34), 97 (34), 98 (49), 99 (18), 100 (13), 108 (16), 109 (11), 116 (17), 126 (20), 127 (11), 129 (10), and 140 (4).

6-Oxabicyclo[3.2.1]octan-7-one (19). A solution of 5 g of **20** in 50 ml of 10% sodium hydroxide was stirred at room temperature overnight. The resulting mixture was extracted with ether. The aqueous phase was acidified with concentrated HCl and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give about 4 g of a thick viscous oil which on heating in a short path distillation column to about 200° under vacuum (20 mm) resulted in the distillation of a waxy semisolid material identified as **19:**[14] ir 1725 cm^{-1} (C=O); nmr δ 4.83 (m, 1, OCH) and 2.63 (m, 1, O=CCH); MS *m/e* 54 (92), 55 (45), 67 (100), 70 (35), 82 (50), 83 (34), 84 (63), and 126 (2) molecular ion.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.40; H, 8.22.

Thermal Cyclization of *cis*-4-Carboxycyclohexylamine (21). A 1.09-g sample of **21,** prepared by the hydrogenation of *p*-aminobenzoic [mp 299–300° (lit.[19] mp 303°)] was heated in 75 ml of methanol at 120° under 1900 psig of hydrogen for 24 hr. On evaporation of the solvent, 1 g of residue was recovered which was shown to be only unreacted **21** by infrared spectral comparisons.

When this reaction was repeated at 150° 1 g of residue was again obtained. This was washed with chloroform and the insoluble material removed by filtration. This residue, which was the starting material, **21,** weighed 0.5 g. Evaporation of the chloroform gave 0.57 g of **6,** identified by infrared spectral comparison.

Registry No. —**5,** 150-13-0; **6,** 3306-69-2; **7,** 99-05-8; **8,** 6142-56-9; **9,** 24173-53-3; **10,** 2486-70-6; **11,** 53862-59-2; **12,** 53862-60-5; **13,** 53862-61-6; **14,** 53906-41-5; **15,** 53862-62-7; **16,** 619-05-6; **18,** 34021-72-2; **19,** 4350-83-8; **20,** 37722-82-0; **21,** 3685-23-2; 3-hydroxy-4-nitrobenzoic acid, 619-14-7; 3-hydroxybenzoic acid, 99-06-9.

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