Ring-Opening and a Novel Ring Expansion in the Reactions of 1-Alkyl-2-carbomethoxyazetidine with Hydrazine. (1)

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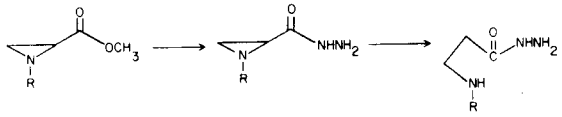
The mechanism of the reactions of 1-*t*-butyl-2-carbomethoxyazetidine and 1-benzyl-2-carbomethoxyazetidine with hydrazine hydrate was investigated. Treatment of 1-alkyl-2-carbomethoxyazetidine with hydrazine hydrate in cold ethanol yielded 1-alkylazetidine-2-carbohydrazide. Depending on the steric bulkiness of the alkyl group of the amino functionality, reactions of 1-alkylazetidine-2-carbohydrazides in methanol gave the appropriate aminoester, or the appropriate pyrrolidone, or a mixture of both. The intermediacy of the diimide in these transformations was confirmed by the concurrent reduction of azobenzene to hydrazobenzene.

J. Heterocyclic Chem., 13, 247 (1976).

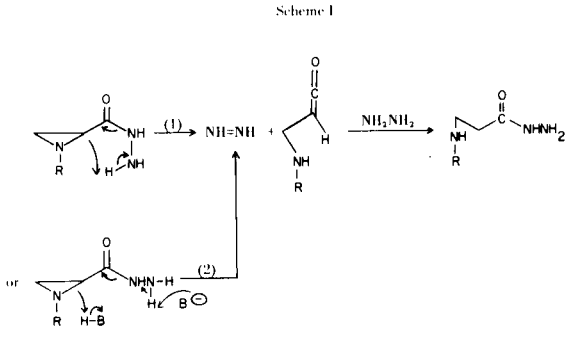
Deyrup and Clough (4) have reported that 1-*t*-butyl-2-carbomethoxyaziridine underwent ring opening when treated with hydrazine hydrate at reflux or at room temperature to give **3** as the only isolable product. Intermediate **2** was observed by pmr spectroscopy as the first product. For the *N*-benzyl analog, intermediate **2** was



1 2 3

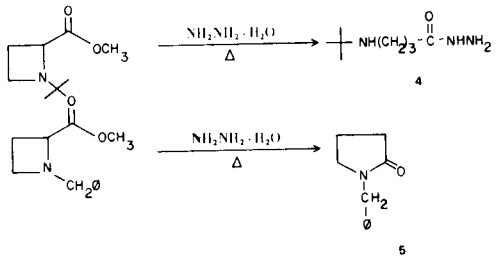
isolated. When 1-benzylaziridine-2-carbohydrazide (**2**) was refluxed in methanol in the presence of azobenzene, methyl γ-benzylaminopropionate (**3**) and hydrazobenzene were observed to form. These observations were interpreted in terms of the mechanism in Scheme I. It was undecided as to whether the reaction proceeded through path 1 or 2.

Scheme I



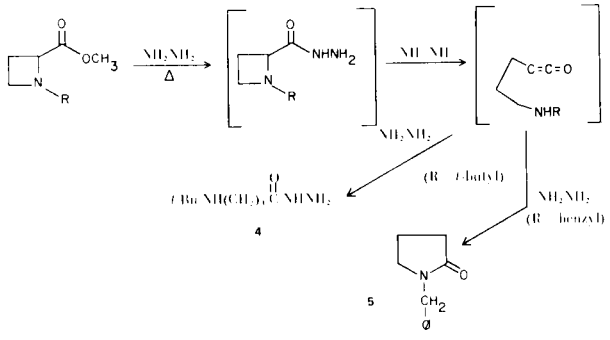
Cromwell and Rodenbaugh (5) have reported the reaction of *N*-*t*-butyl-, and *N*-benzyl-2-carbomethoxyazetidine with excess hydrazine hydrate at reflux temperature. The open chain carbohydrazide **4** and pyrrolidone **5** were isolated, respectively.

Scheme II



The mechanism of these reactions was postulated as proceeding by way of an azetidinecarbohydrazide which decomposes via a ketene intermediate as shown in Scheme III.

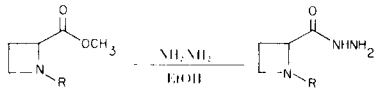
Scheme III



In the case of *N*-*t*-butyl-2-carbomethoxyazetidine, the ketene intermediate is attacked by another mole of hydrazine to give the open chain carbohydrazide **4**, and in the case of the *N*-benzylanalog, the ketene intermediate reacts intramolecularly to give the pyrrolidone **5**. This was explained by the small steric requirement of the benzyl group, allowing intramolecular attack, whereas the sterically large *t*-butyl group favored an intermolecular reaction.

The postulated mechanism was further supported by the fact that 1-*t*-butylazetidine-2-carboxamide was recovered unchanged after refluxing for several hours in methanolic hydrazine hydrate (5). This implies that azetidine ring cleavage by hydrazine does not involve a simple reductive cleavage.

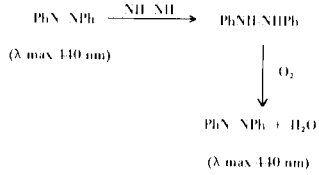
Treatment of the 1-alkyl-2-carbomethoxyazetidines with 90% hydrazine hydrate in ethanol at room temperature gave 1-alkylazetidine-2-carbohydrazides in good yield.



6. R = *t*-butyl
7. R = benzyl
8. R = benzhydryl
9. R = cyclohexyl

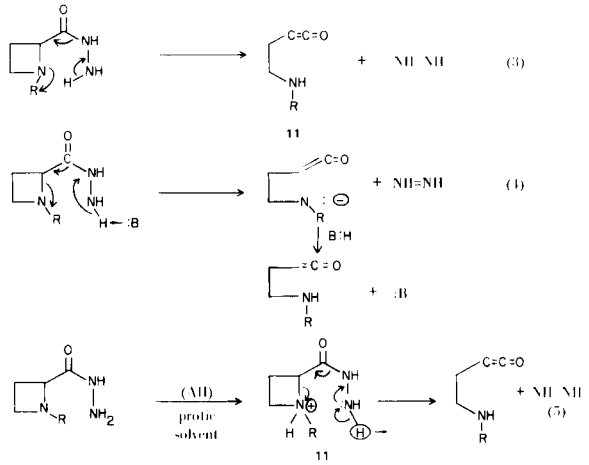
Refluxing **7** respectively in water, methanol, and 90% hydrazine hydrate yielded *N*-benzyl-2-pyrrolidone (**5**). Refluxing of **6** in 90% hydrazine hydrate yielded γ-*t*-butylaminobutyrohydrazide, quantitatively. Similar treatment of **6** in water or methanol yielded, respectively, γ-*t*-butylaminobutanoic acid and methyl γ-*t*-butylaminobutyrate. These results strongly suggest that 1-alkylazetidine-2-carbohydrazide is the first intermediate formed in the reactions between hydrazine and different 1-alkyl-2-carbomethoxyazetidines.

According to the postulated mechanism, diimide, a very strong reducing agent, is formed during the decomposition of the initially formed carbohydrazide. Confirmatory evidence for the intermediacy of the diimide was obtained by the observation of concurrent reduction of azobenzene to hydrazobenzene in the conversion of, respectively, **6** and **7** to **10**, and **5**. The same result was observed when this latter reaction was carried out in an oxygen free condition. The existence of the hydrazobenzene was demonstrated by the disappearance of an absorption peak (440 nm) in the visible region, which was characteristic for azobenzene, and the reappearance of that absorption peak when the reaction mixture was subjected to air oxidation.



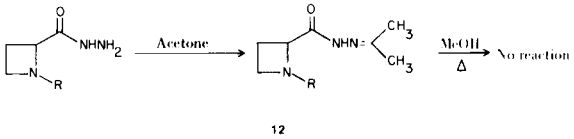
There are at least three ways that the decomposition of the initially formed 1-alkylazetidine-2-carbohydrazide can occur: see Scheme IV. We can consider in pathways 3

Scheme IV



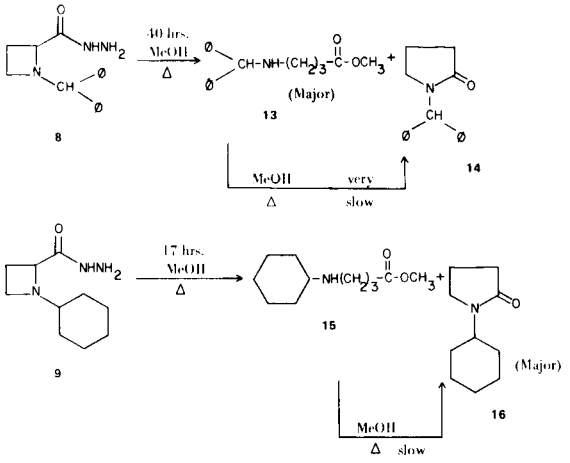
(intramolecular) and 4 (intermolecular), that the decomposition is base induced, while in pathway 5, the decomposition is acid induced. Pathways 3 and 4 were eliminated by the fact that when refluxed in aprotic solvents like benzene, toluene, and acetonitrile, **6** was recovered unchanged after several hours. Thus we consider pathway 5, which involves a prior protonation at the basic center (azetidine ring nitrogen) of the compound, followed by the elimination of diimide molecule, to be the best description of the reaction. Kinetic studies of these reactions appear necessary to establish this point.

Treatment of 1-alkylazetidine-2-carbohydrazide with acetone gave quantitatively the carboxylic hydrazone derivative of acetone **12**, which was found to be stable in refluxing methanol. This piece of evidence also supports



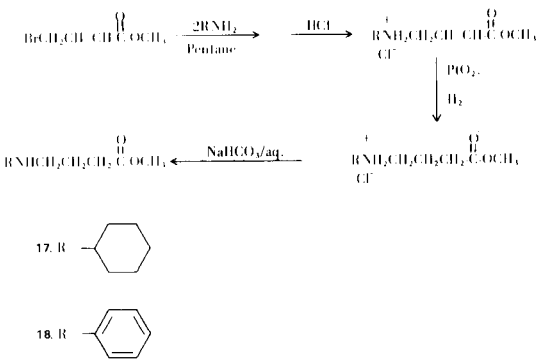
our argument for the most probable reaction pathway.

As mentioned earlier, refluxing **6** or **7** in methanol gave respectively **10** or **5** as the exclusive products. However, when similar treatment was applied to **8** and **9**, coexistence of both the cyclized and open-chain products was observed. The open-chain products were observed to change very slowly to the cyclized products.



In order to study the cyclization reaction, the open chain aminoesters were synthesized by an independent route (5) (Scheme V). Treatment of the methyl γ-bromo-

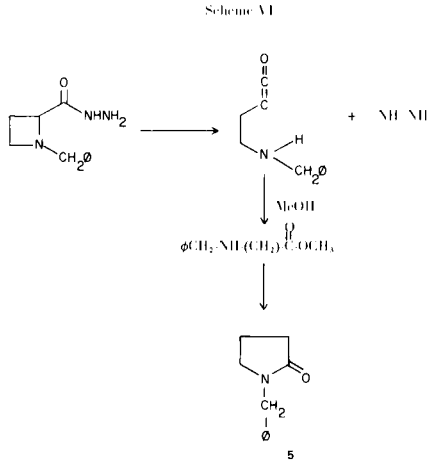
Scheme V



crotonate with an amine yielded the appropriate methyl γ-aminocrotonate. The compound was isolated as its hydrochloride salt. Hydrogenation of the hydrochloride salt of the methyl γ-aminocrotonate in the presence of Adam's catalyst yielded the appropriate amine salt of the aminobutyrate.

Both **17** and **18** gave pyrrolidone on prolonged standing in refluxing methanol, hydrazine hydrate, and benzene. This seems to suggest that, in the original reaction of hydrazine hydrate with 1-benzylazetidine-2-carbohydrazide, *N*-benzyl-2-pyrrolidone could also be formed by intermolecular attack of the methanol at the ketene intermediate, forming an open-chain ester, followed by the cyclization of the γ-aminoester, see Scheme VI.

Scheme VI



However, judging from the fact that the cyclization of the ester is a relatively slow reaction, and that not a trace of the open chain ester has ever been observed by interrupting the reaction of 1-benzylazetidine-2-carbohydrazide, we believe that intramolecular reaction of the ketene intermediate, giving directly the 1-benzyl-2-pyrrolidone (**5**) is the major pathway responsible for the formation of the final product.

EXPERIMENTAL

Melting points were determined from a Mel-Temp. apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Models 237, and 621 spectrometers. The visible spectra were obtained from a Cary 14 recording spectrophotometer. The pmr spectra were determined by Varian Model A-60 Spectrometer utilizing tetramethylsilane as an internal standard. The mass spectra were determined on a Hitachi RMU-60 Spectrometer at 70 ev. Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

The preparative details for the 1-alkyl-2-carbomethoxyazetidine have been reported previously (5,6,7).

General Procedure of Preparing 1-Alkylazetidine-2-carbohydrazide.

1-Alkyl-2-carbomethoxyazetidine was stirred with 3 molar equivalents of 98% hydrazine hydrate in 100 ml. of absolute ethanol for 2 days. The solvent and excess hydrazine were evaporated at room temperature either under reduced pressure or by blowing nitrogen through it. The crude product obtained was purified by recrystallization.

Preparation of 1-*t*-Butylazetidine-2-carbohydrazide (**6**).

From 11.3 g. (0.0414 mole) of 1-*t*-butyl-2-carbomethoxyazetidine, 11.2 g. (quantitative) of solid was obtained. Recrystallization from ether yielded 1-*t*-butylazetidine-2-carbohydrazide as white platelets, m.p. 83-85°; ir (sodium chloride), ν max (carbon tetrachloride): 1665, 1622 cm^{-1}; pmr, δ TMS (deuteriochloroform): 3.92 (1H, triplet, J_{HH}, 8.4 Hz, -*CH*CO-), 3.15 (2H, multiplet, -*CH*$_2$N), 2.10, (2H, multiplet, remaining methylene protons), 0.98 (9H, singlet, *t*-butyl), 8.5, 3.88 (3H, exchangeable with deuterium oxide, hydrazine protons); Mass Spectrum: M^+ 171.

Anal. Calcd. for $C_8H_{17}N_3O$: C, 56.11; H, 10.01; N, 24.54. Found: C, 56.10; H, 10.00; N, 24.70.

Preparation of 1-Benzhydrylazetidine-2-carbohydrazide (**8**).

From 9.7 g. (0.035 mole) of 1-benzhydryl-2-carbomethoxyazetidine, a light yellow oil was obtained after evaporation of the solvent and excess hydrazine. The oil was dissolved in benzene and a small amount of anhydrous ether was added. Scratching the saturated solution with a glass rod resulted in crystallization. The solid was removed by filtration and the filtrate evaporated to dryness. Ether was added again and the scratching technique repeated. After repeating this technique three times, 7 g. (72%) of product was obtained. Recrystallization from ether yielded 1-benzhydrylazetidine-2-carbohydrazide as a white crystalline solid, m.p. 150-152°; ir (sodium chloride) ν max (carbon tetrachloride): 1665, 1622 cm^{-1}; pmr, δ TMS (deuteriochloroform): 7.31 (12H, multiplet, aromatic protons), 4.50 (1H, singlet, -C*H*-Ph_2), 3.82 (1H, triplet, J_{HH} 9 Hz, C*H*-CO-), 2.91 (2H, multiplet, -C*H*$_2$N), 2.25 (2H, multiplet, remaining methylene protons), 7.78, 3.48 (3H, deuterium oxide exchangeable, hydrazine protons); Mass Spectrum: M^+ 281.

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93; Found: C, 72.39; H, 6.93; N, 14.83.

Preparation of 1-cyclohexylazetidine-2-carbohydrazide (**9**).

From 3 g. (0.015 mole) of 1-cyclohexyl-2-carbomethoxyazetidine, 3.0 g. (quantitative) of white solid was obtained after evaporation of the solvent and excess hydrazine. An ethereal solution of the crude product was dried over anhydrous magnesium sulfate. Recrystallization from ether gave 1-cyclohexylazetidine-2-carbohydrazide as white platelets, m.p. 88°; ir (sodium chloride) ν max (nujol): 3310, 1670 cm^{-1}; pmr, δ TMS (deuteriochloroform): 3.63 (1H, triplet, J_{HH} 8 Hz, -C*H*-CO-), 2.50-3.45 (3H, multiplet, -C*H*$_2$-N, and C_1 cyclohexyl proton), 1.85-2.50 (2H, multiplet, remaining methylene protons in the azetidine ring), 0.90-1.80 (10H, broad multiplet, cyclohexyl protons), 3.88, 8.32 (3H, exchangeable with deuterium oxide, hydrazine protons).

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.91; H, 9.6; N, 21.32. Found: C, 60.53; H, 9.82; N, 21.37.

Preparation of 1-Benzylazetidine-2-carbohydrazide (**7**).

From 3.73 g. (0.0182 mole) of 1-benzyl-2-carbomethoxyazetidine, 4 g. of a yellow oil was obtained, which was identified to be 1-benzylazetidine-2-carbohydrazide, ir (sodium chloride) ν max: 3300, 1670 cm^{-1}; pmr, δ TMS (deuteriochloroform): 7.30 (5H, singlet, aromatic), 3.50 (1H, triplet, J_{HH} 7 Hz, -C*H*-CO-), 3.62 (2H, doublet, nonequivalent benzyl protons), 2.50-3.50 (2H, multiplet, -C*H*$_2$-N), 1.85-2.50 (2H, multiplet, remaining methylene protons in the azetidine ring). An analytically pure sample could not be isolated, and the compound was analyzed as its hydrazone derivative of acetone.

Reaction of 1-*t*-Butylazetidine-2-carbohydrazide with Hydrazine Hydrate.

A 1.05 g. (0.0062 mole) sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed for three hours in excess hydrazine hydrate (98%, 10 ml.). The reaction mixture was evaporated, taken up in benzene and dried with anhydrous magnesium sulfate. Evaporation of benzene yielded an oily product (1.03 g., 96%) which was spectrally identical to an authentic sample of γ-*t*-butylaminobutyrohydrazide.

Reaction of 1-*t*-Butylazetidine-2-carbohydrazide with Water.

A 1.10 g. (0.00645 mole) sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed for six hours in 10 ml. of water. After cooling, the water was evaporated under reduced pressure to give a white solid (0.98 g.). Recrystallization from methanol-ether gave 0.91 g. (88.6%) of a white crystalline solid, m.p. 253-255°, that was proved to be spectrally identical to an authentic sample of γ-*t*-butylaminobutyric acid.

Reaction of 1-*t*-Butylazetidine-2-carbohydrazide with Methanol.

A 1.38 g. (0.0103 mole) sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed for 5 hours in excess methanol (15 ml.). Evaporation of the solvent gave 1.79 g. (quantitative) of methyl γ-*t*-butylaminobutyrate as a colorless oil. Hydrogen chloride gas was passed through an ether solution of the crude ester, resulting in the precipitation of the methyl γ-*t*-butylaminobutyrate hydrochloride, m.p. 165-167°. The product was proved tc be spectrally identical with an authentic sample.

Inertness of 1-*t*-Butylazetidine-2-carbohydrazide.

A 100 mg. sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed in 30 ml. of benzene for 10 hours. Evaporation of the solvent yielded a solid, which was spectrally identical to the starting material.

Inertness of 1-*t*-Butylazetidine-2-carbohydrazide in Acetonitrile.

A 100 mg. sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed in 30 ml. of acetonitrile for 12 hours. Evaporation of the solvent yielded a solid which was spectrally identical to the starting material.

Reaction of 1-*t*-Butylazetidine-2-carbohydrazide with Acetone.

A 500 mg. (0.0029 mole) sample of 1-*t*-butylazetidine-2-carbohydrazide was refluxed in 30 ml. of acetone for 18 hours. Removal of the solvent yielded 0.61 g. (quantitative) of yellow oil, which solidified on standing. Recrystallization from ether gave a white crystalline solid, which was shown to be the 2′-isopropylidene-1-*t*-butylazetidine-2-carbohydrazide, m.p. 45-47°; ir (sodium chloride) ν max: 3500-3250 (broad), 1680, 1640 cm^{-1}; pmr δ TMS (deuteriochloroform): 3.95 (1H, triplet, J_{HH} 8.5 Hz, -C*H*-CO-), 3.10-3.40 (2H, multiplet, -C*H*$_2$-N-), 1.80-2.50 (2H, multiplet, remaining methylene protons), 1.98 (3H, singlet, N=C-C*H*$_3$), 2.12 (3H, singlet, the other methyl group), 1.00 (9H, singlet, *t*-butyl protons).

Anal. Calcd. for $C_{11}H_{21}N_3O$: C, 62.55; H, 9.95; N, 19.90. Found: C, 62.55; H, 10.37; N, 19.87.

Inertness of 2′-Isopropylidene-1-*t*-butylazetidine-2-carbohydrazide in Methanol.

A 100 mg. sample of the above described hydrazone derivative of acetone was refluxed in methanol for 12 hours. Evaporation of the solvent yielded a yellow oil, which was found to be spectrally identical to the starting material.

Reaction of 1-Benzylazetidine-2-carbohydrazide with Acetone.

A 2.77 g. (0.014 mole) sample of 1-benzylazetidine-2-carbohydrazide was refluxed in 200 ml. of acetone for 24 hours. Removal of the solvent yielded 3.40 g. (quantitative) of white solid. Recrystallization from ether gave a white crystalline solid, identified to be 2′-isopropylidene-1-benzylazetidine-2-carbohydrazide, m.p. 82°; ir (sodium chloride) ν max (nujol): 3290, 1685, 1635 cm^{-1}; pmr δ TMS (deuteriochloroform): 7.30 (5H, singlet, aromatic), 3.87 (1H, triplet, J_{HH}, 9 Hz, -C*H*-CO-), 3.65 (2H, doublet, nonequivalent benzyl protons), 3.50-2.70 (2H, multiplet, -C*H*$_2$-N-), 3.50-2.10 (2H, multiplet, the remaining methylene protons), 2.05 (3H, singlet, -N=C-C*H*$_3$), 1.75 (3H, singlet, protons of the other methyl group).

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.57; H, 7.76; N, 17.14. Found: C, 68.58; H, 7.83; N, 17.38.

Inertness of 2'-Isopropylidene-1-benzylazetidine-2-carbohydrazide in Methanol.

A 100 mg. sample of the above described hydrazone derivative of acetone was refluxed in methanol for 10½ hours. Evaporation of the solvent yielded a white solid, which was found to be spectrally identical to the starting material.

Reaction of 1-*t*-Butylazetidine-2-carbohydrazide with Methanol in the Presence of Azobenzene.

A 0.5941 g. (0.00347 mole) sample of 1-*t*-butylazetidine-2-carbohydrazide was dissolved in 40 ml. of methanol together with 0.0569 g. (0.00031 mole) of azobenzene. The solution was orange-red in color. The visible spectrum of the mixture showed an absorption peak at 440 nm. The solution was then refluxed for 12 hours. The solution became decolorized during the reaction, and at the end of that period, the absorption peak at 440 nm was found to be absent. Refluxing an equimolar solution of azobenzene alone in methanol did not effect such a change. Pmr spectrum of the reaction mixture showed that methyl γ-*t*-butylaminobutyrate was the only detectable product. The reaction mixture was then left in open air for 2 days. The orange-red coloration of azobenzene developed again, and the absorption peak at 440 nm reappeared in the visible spectrum.

Reaction of Crude 1-Benzylazetidine-2-carbohydrazide with Hydrazine Hydrate.

A 560 mg. (0.0027 mole) sample of crude 1-benzylazetidine-2-carbohydrazide was refluxed in 5 ml. of 95% hydrazine hydrate for 11.5 hours. Hydrazine was removed by blowing nitrogen through it. The oily product remaining was dissolved in benzene and dried over anhydrous magnesium sulfate. Removal of the solvent yielded quantitatively a light yellow oil which was spectrally equivalent to 1-benzyl-2-pyrrolidone.

Reaction of Crude 1-Benzylazetidine-2-carbohydrazide with Methanol.

A 620 mg. (0.0030 mole) sample of crude 1-benzylazetidine-2-carbohydrazide was refluxed in methanol for 14 hours. Removal of the solvent by rotary evaporation yielded quantitatively a yellow oil. Vacuum distillation gave a colorless oil spectrally equivalent to 1-benzyl-2-pyrrolidone.

Reaction of Crude 1-Benzylazetidine-2-carbohydrazide with Water.

A 100 mg. sample of crude 1-benzylazetidine-2-carbohydrazide was suspended in 10 ml. of water and the mixture heated under reflux for 6 hours. The oily product was taken up by chloroform. The chloroform solution was dried over anhydrous magnesium sulfate. Removal of the solvent yielded a colorless oil spectrally identical to 1-benzyl-2-pyrrolidone.

Reaction of Crude 1-Benzylazetidine-2-carbohydrazide with Methanol in the Presence of Azobenzene.

A 4.36 g. (0.021 mole) sample of crude 1-benzylazetidine-2-carbohydrazide and 0.45 g. (0.0025 mole) of azobenzene were dissolved in methanol. The orange-red solution showed an absorption peak at 440 nm. The solution was then refluxed for 12 hours. The solution decolorized during the reaction, and at the end of that period, the absorption peak at 440 nm had totally disappeared. Refluxing an equimolar solution of azobenzene in methanol did not effect such a change. A pmr spectrum of the reaction product showed that 1-benzyl-2-pyrrolidone was the only detectable compound. The reaction mixture was left in open air for a few days. The orange-red coloration of azobenzene reappeared again, and the absorption at 440 nm reappeared in the visible spectrum.

Reaction of 1-Cyclohexylazetidine-2-carbohydrazide with Methanol.

A 950 mg. (0.0048 mole) sample of 1-cyclohexylazetidine-2-carbohydrazide was refluxed in 40 ml. of methanol. After 12 hours, an aliquot sample was removed. Pmr spectrum of the sample was taken after evaporation of the solvent. The reaction was by no means complete, and a sharp singlet was observed at δ 3.67, corresponding to the -OMe group in the methyl γ-cyclohexylaminobutyrate. After 48 hours, 1-cyclohexyl-2-pyrrolidone was the only product isolated (quantitative): ir (sodium chloride) ν max: 1675 cm^{-1}; pmr, δ TMS (deuteriochloroform): 3.35 (2H, triplet, J_{HH}, 6.5 Hz, -CH_2-CO-), 1.00-2.50 (15H, complex multiplet, methylene protons); Mass Spectrum: M^+ 167.

Reaction of 1-Benzhydrylazetidine-2-carbohydrazide with Methanol.

A 2 g. (0.0071 mole) sample of 1-benzhydrylazetidine-2-carbohydrazide was refluxed in 70 ml. of methanol. The reaction was monitored by pmr spectroscopy. After 40 hours, the reaction mixture was found to consist of 70% of the open-chain aminoester **13**, and about 30% of the pyrrolidone **14**. (The percentages were estimated from the intensity of the singlet at δ 3.55, corresponding to the -OCH_3, and the intensity of the triplet at 3.08, corresponding to -CH_2-CO-). Prolonged refluxing did not effect complete conversion of **13** to **14** although significant changes of the intensity of the two absorptions were observed. Compound **13** was observed to convert very slowly to **14** on refluxing in methanol.

General Procedure for Preparing Methyl γ-Aminobutyrate Hydrochlorides.

A solution of methyl γ-bromocrotonate and 2 molar equivalents of the appropriate amine in pentane was stirred magnetically at room temperature for five days while being shielded from light. The reaction mixture was cooled to 0° and the precipitated by-product, amine hydrobromide, was removed by filtration. The cold filtrate was then exposed to a stream of dry hydrogen chloride gas. The resulting white precipitate was collected and washed with dry ethyl ether. Recrystallization from methanol-ether mixture yielded the appropriate methyl γ-aminocrotonate hydrochloride as white needles.

To a solution of methyl γ-aminocrotonate hydrochloride in methanol was added a catalytic amount of Adam's catalyst (0.064 g.). The mixture was hydrogenated in a Parr shaker at 40 psi for 12 hours. The catalyst was removed by filtration through celite. The filtrate was concentrated to a small volume by evaporation under reduced pressure. Dry ethyl ether was added to the solution until a few crystals appeared. Cooling yielded the methyl γ-aminobutyrate hydrochloride as white crystals.

Preparation of Methyl γ-Cyclohexylaminobutyrate Hydrochloride (**17**).

From 10 g. (0.058 mole) of methyl γ-bromocrotonate and 11.90 g. (0.11 mole) of cyclohexylamine, 6.28 g. (48.4%) of methyl γ-cyclohexylaminocrotonate hydrochloride was obtained, m.p. 238°; ir (sodium chloride) ν max (nujol): 2700-2250 (broad), 1715, 1665 cm^{-1}.

Anal. Calcd. for $C_{11}H_{20}ClO_2N$: C, 56.53; H, 8.56; N, 5.99. Found: C, 56.66; H, 8.83; N, 5.89.

From 2.46 g. (0.010 mole) of methyl γ-cyclohexylaminocro-

tonate hydrochloride, 2.1 g. (89%) of methyl γ-cyclohexylaminobutyrate hydrochloride was isolated as white needles, m.p. 230°; ir (sodium chloride) ν max (nujol): 2400-2700 (broad), 1740, 1590; pmr, δ TMS (deuteriochloroform): 9.42 (broad singlet, exchangeable with deuterium oxide, amine protons), 3.68 (3H, singlet, -OC*H*$_3$), 3.02 (2H, broad singlet, becoming a triplet on addition of deuterium oxide, -N-C*H*$_2$-CH$_2$-), 1.00-2.70 (17H, complicated multiplet, methylene protons).

Anal. Calcd. for $C_{11}H_{22}ClO_2N$: C, 56.05; H, 9.34; N, 5.94. Found: C, 55.98; H, 9.62; N, 5.81.

Preparation of Methyl γ-Benzylaminobutyrate Hydrochloride (**18**).

From 5 g. (0.00279 mole) of methyl γ-bromocrotonate and 5.89 g. (0.055 mole) of benzylamine, 2.2 g. (32.6%) of methyl 4-benzylaminocrotonate hydrochloride was obtained as white crystals, m.p. 183°; ir (sodium chloride) ν max (nujol): 2500-2700 (broad), 1720, 1670 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}ClO_2N$: C, 59.63; H, 6.62; N, 5.80. Found: C, 59.51; H, 6.69; N, 5.90.

From 1.9 g. (0.0078 mole) of methyl γ-benzylaminocrotonate, 1.23 g. (64.7%) of methyl γ-benzylaminobutyrate hydrochloride was obtained, m.p. 144°; pmr δ TMS (deuteriochloroform): 7.50 (5H, broad multiplet, aromatic protons), 4.16 (2H, singlet becoming sharp after addition of deuterium oxide, benzyl protons), 3.61 (3H, singlet, -OC*H*$_3$), 2.95 (2H broad singlet, becoming a triplet after addition of deuterium oxide), 2.10-2.70 (4H, complicated multiplet, remaining methylene protons), 9.50 (broad singlet, exchangeable).

Anal. Calcd. for $C_{12}H_{18}ClO_2N$: H, 7.39; N, 5.75. Found: H, 7.22; N, 5.96.

Reaction of Methyl γ-Cyclohexylaminobutyrate with Methanol.

To an aqueous solution of 500 mg. (0.0021 mole) methyl γ-cyclohexylaminobutyrate hydrochloride was added saturated sodium bicarbonate solution until the solution was alkaline. The aqueous solution was extracted several times with diethyl ether. The combined ethereal extract was dried over anhydrous magnesium sulfate. Removal of the solvent gave methyl γ-cyclohexylaminobutyrate as a yellow oil; ir (sodium chloride) ν max: 1740 cm^{-1}; pmr δ TMS (deuteriochloroform): 3.67 (3H, singlet, -OC*H*$_3$), 1.0-2.9 (6H, complex multiplet, methylene protons), 1.06 (1H, singlet, exchangeable with deuterium oxide, amine proton).

A 40 ml. amount of methanol was added to the yellow oil, and the solution refluxed for 48 hours. Ninety percent of the ester has changed to 1-cyclohexyl-2-pyrrolidone, which was spectrally identical to the product obtained by refluxing 1-cyclohexyl-2-hydrazidoazetidine.

Reaction of Methyl γ-cyclohexylaminobutyrate in Hydrazine Hydrate.

To an aqueous solution of 0.61 g. (0.0026 mole) of methyl γ-cyclohexylaminobutyrate hydrochloride was added saturated sodium bicarbonate solution. The aqueous solution was extracted several times with ether. Evaporation of the solvent yielded a yellow oil, which was spectrally identical to methyl γ-cyclohexylaminobutyrate. A 1.0 ml. sample of 95% hydrazine hydrate was added to the ester. The solution was kept at refluxing temperature for 3 hours. Removal of the hydrazine by blowing nitrogen through it yielded a yellow oil. Diethyl ether was added and a solid, which was assumed to be some derivative of hydrazine, precipitated and was removed by filtration. After being dried over anhydrous magnesium sulfate, the solution was subjected to rotary evaporation. The residue, a yellow oil was found to be spectrally identical to 1-cyclohexyl-2-pyrrolidone.

Reaction of Methyl Cyclohexylaminobutyrate in Benzene.

Methyl γ-cyclohexylaminobutyrate was prepared from its hydrochloride salt as described in the previous section. To the yellow oil was added 40 ml. of benzene, and the solution refluxed for 50 hours. Removal of the solvent yielded a light yellow oil which was spectrally identical with 1-cyclohexyl-2-pyrrolidone. High resolution mass spectrum: M^+ = 167.1313 (8) Molecular weight calcd. for $C_{10}H_{17}ON$ = 167.1310.

Reaction of Methyl γ-Benzylaminobutyrate with Methanol.

To an aqueous solution of 500 ml. (0.0020 mole) of methyl γ-benzylaminobutyrate hydrochloride was added saturated sodium bicarbonate solution until the solution was alkaline. The aqueous solution was extracted several times with diethyl ether. The combined ethereal extract was dried over anhydrous magnesium sulfate. Removal of the solvent yielded methylbenzylaminobutyrate as a slightly yellow oil; ir (sodium chloride) ν max: 1735 cm^{-1}; pmr δ TMS (deuteriochloroform): 7.27 (5H, singlet, aromatic protons), 3.72 (2H, singlet, benzyl protons), 3.60 (3H, singlet, -OC*H*$_3$), 1.4-2.8 (1H, exchangeable with deuterium oxide, amine proton).

A 40 ml. amount of methanol was added to the yellow oil, and the solution refluxed. In seven hours, 80% of the open-chained amine ester had changed to the cyclic product. After one day, evaporation of the solvent yielded a yellow oil, which was spectrally equivalent to an authentic sample of 1-benzyl-2-pyrrolidone.

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(8) The high resolution mass spectrum was determined by an AEI Mass Spectrometer equipped with a DS-30 data system. A GC inlet was used for introduction of the sample. The gas chromatographic conditions were as follows: Column: 10% OV-101 at 175°; Inject: 200°; Detector/separator: 235°; Flow rate is 30 ml./minute. The compound was found to have a retention time of ~8 minutes, and no other detectable signal has been observed from the chromatogram.