2-Carboazetidine Derivatives (1)

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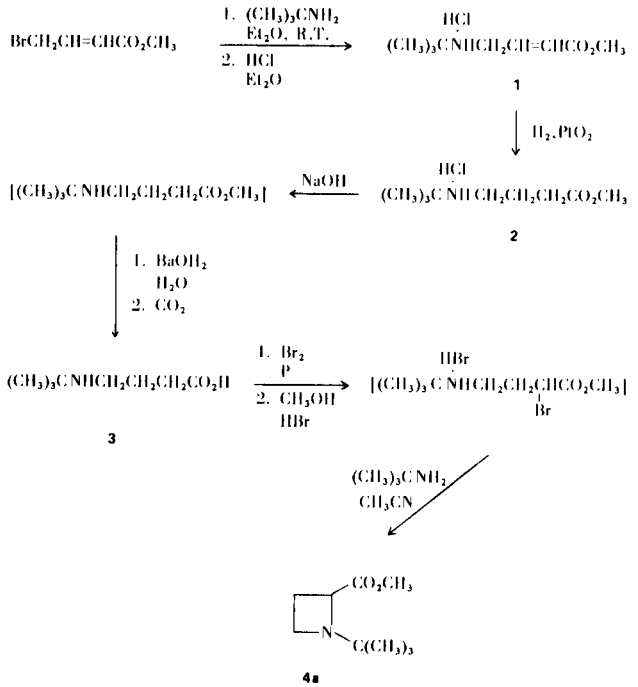
A reaction sequence is reported for converting methyl γ-bromocrotonate to 1-alkyl-2-carbomethoxyazetidines thus confirming our earlier structural assignments of these compounds obtained by a more direct route. Methods are described for obtaining azetidinyl alcohols, acids, amides, amines and ketones. 1-*t*-Butyl-2-carbomethoxyazetidine was observed to undergo ring opening to an acyclic γ-aminohydrazide derivative when treated with hydrazine hydrate. On the other hand, the corresponding *N*-benzylazetidine under similar conditions rearranged to 1-benzyl-2-pyrrolidinone.

In a preliminary communication we reported (4) that methyl α,γ-dibromobutyrate reacts with a number of primary amines to give 1-alkyl-2-carbomethoxyazetidines thus providing a convenient, one-step procedure for obtaining these and related compounds in useful yields.

Previously we had approached the problem of azetidine synthesis from a more classical standpoint and had considered the conversion of various crotonic acid derivatives into the corresponding γ-bromopropylamines followed by cyclization. A related method had been developed in this laboratory (5) which led to 1-alkyl-2-aryl-3-aroylazetidines in high yields. These conversions have now been effected for the 2-carboazetidine series thus providing further confirmation of the structures originally assigned (4) on the basis of spectral evidence. Methyl γ-bromocrotonate was found to react (Scheme I) with two molar equivalents of *t*-butylamine at room temperature forming the corresponding γ-*t*-butylaminocrotonic ester which was isolated as the hydrochloride salt **1**. Catalytic reduction of ester **1** provided the corresponding saturated amino ester hydrochloride **2**, which when neutralized and hydrolyzed under alkaline conditions gave γ-*t*-butylaminobutyric acid (**3**). Phosphorus-catalyzed bromination of amino acid **3** followed by esterification with acidified methanol gave methyl α-bromo-γ-*t*-butylaminobutyrate hydrobromide as an intermediate which was not isolated but was treated with *t*-butylamine in refluxing acetonitrile producing a product which was spectrally and chromatographically identical to 1-*t*-butyl-2-carbomethoxyazetidine (**4a**) (4).

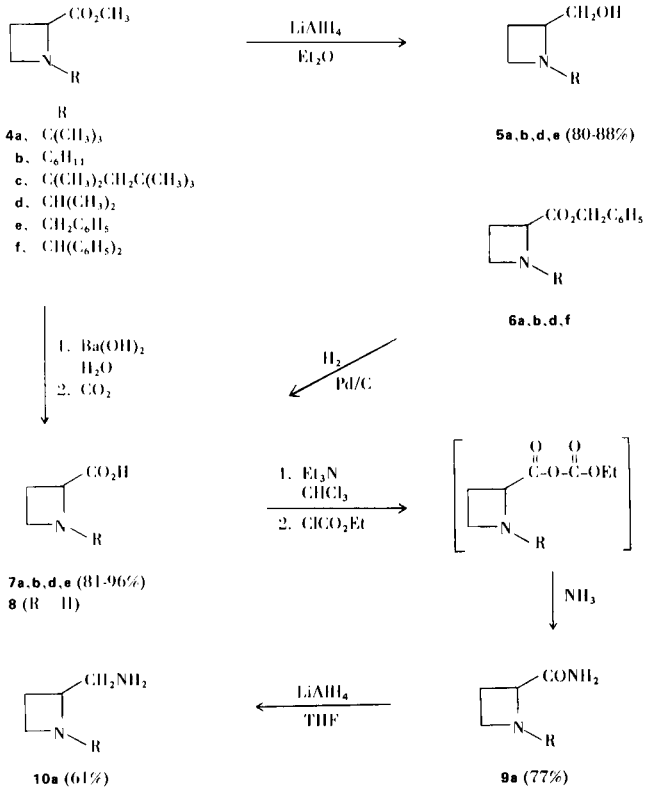
SCHEME I



By application of a few simple and well known synthetic transformations these 1-alkyl-2-carbomethoxyazetidines (**4**) could be converted into a number of azetidines bearing different functional groups at the 2-position which may be of further synthetic utility as well as of potential biological importance. The conversions shown (Scheme II) are illustrative of a few of the possible reaction conditions which the azetidine ring might be expected to withstand.

Reduction with lithium aluminum hydride proceeded with ease giving *N*-substituted azetidine-2-carbinols (**5**) in high yields. As reported previously (4), treatment of the azetidinyl esters **4** with hot aqueous barium hydroxide solution followed by acidification with carbon dioxide led

SCHEME II



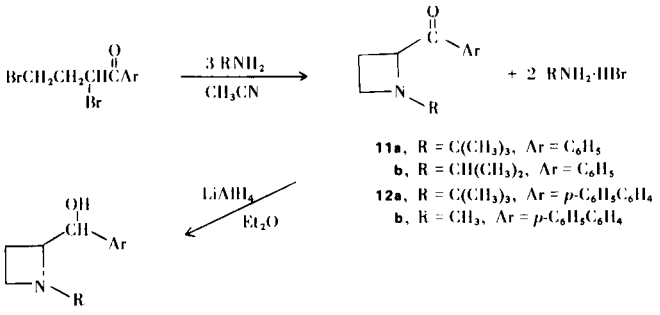
4a, $C(CH_3)_3$
b, C_6H_{11}
c, $C(CH_3)_2CH_2C(CH_3)_3$
d, $CH(CH_3)_2$
e, $CH_2C_6H_5$
f, $CH(C_6H_5)_2$

to the novel zwitterionic imino acids **7**. Alternatively, these compounds were also obtainable by hydrogenolysis of 2-carbobenzoxyazetidines (**6**). The value of this particular method is exemplified in the case of ester **4f** which could not be hydrolyzed to the corresponding acid. However, the naturally occurring imino acid, L-azetidine-2-carboxylic acid (**8**) (6) could be obtained in good yield *via* the hydrogenolytic route from ester **6f** (7).

Treatment of azetidinyl acid **7a** with triethylamine in chloroform at 0° followed by addition of ethyl chloroformate gave the corresponding mixed ester anhydride intermediate (not isolated) which, when treated with anhydrous ammonia, afforded the crystalline primary amide **9a** in good yield. Other 1-alkylazetidine-2-carboxylic acids when allowed to react under similar conditions, however, gave oily products which appeared to be mixtures and were not further characterized. Reduction of amide **9a** with lithium aluminum hydride in refluxing tetrahydrofuran provided 1-*t*-butyl-2-aminomethyl-azetidine (**10a**) as a colorless liquid.

Obtainment of 1-alkyl-2-aroylazetidines (**11** and **12**) was accomplished by preparing as precursors α,γ-dibromobutyrophenones (8) and allowing these compounds to react (Scheme III) with three molar equivalents of a primary amine in acetonitrile at room temperature. Hydride reduction gave the corresponding secondary alcohols (**13** and **14**).

SCHEME III

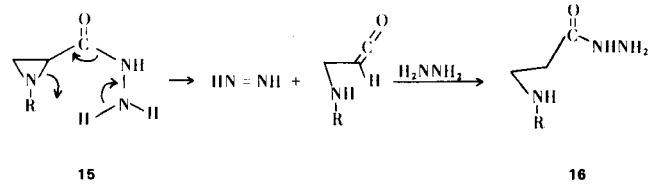


11a, R = $C(CH_3)_3$, Ar = C_6H_5
b, R = $CH(CH_3)_2$, Ar = C_6H_5
12a, R = $C(CH_3)_3$, Ar = *p*-$C_6H_5C_6H_4$
b, R = CH_3, Ar = *p*-$C_6H_5C_6H_4$

13, R = $C(CH_3)_3$, Ar = C_6H_5
14, R = CH_3, Ar = *p*-$C_6H_5C_6H_4$

Deyrup and Clough recently reported (9) that 1-*t*-butyl-2-carbomethoxyaziridine undergoes ring opening when treated with excess hydrazine hydrate at reflux or at room temperature to give **16** as the only isolable product. Intermediate **15** was observed by nmr spectrometry as the first formed product in the reaction. The *N*-benzyl analog of **15** could be isolated as a crystalline solid but when it was heated in methanol in the presence of azobenzene, methyl 3-benzylaminopropionate and hydrazobenzene were isolated. These observations were interpreted in terms of the mechanism shown in Scheme IV (10). The authors (9) suggested that electronegativity of the heteroatom and steric factors are among the variables which might be expected to influence the direction and ease of rearrangement.

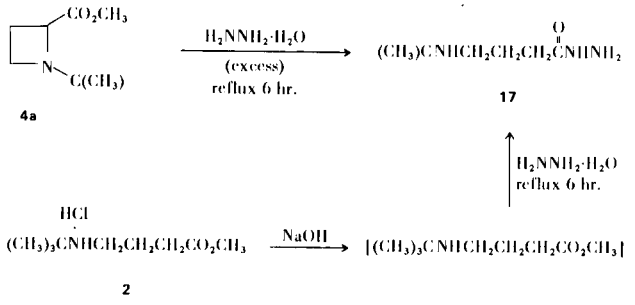
SCHEME IV



15 **16**

Since comparison of reactivity of aziridines and azetidines is of continuing interest, the reactions of some representative azetidines with hydrazine hydrate were studied. When 1-*t*-butyl-2-carbomethoxyazetidine (**4a**) was treated with excess hydrazine hydrate at reflux for six hours a viscous, colorless oil resulted. The azetidine ring proton absorption pattern of **4a** was absent from the nmr spectrum of the oil indicating it to be the acyclic hydrazide **17**. This structural assignment was confirmed by additional spectral and analytical evidence as well as by an independent synthesis of the compound from methyl γ-*t*-butylaminobutyr-

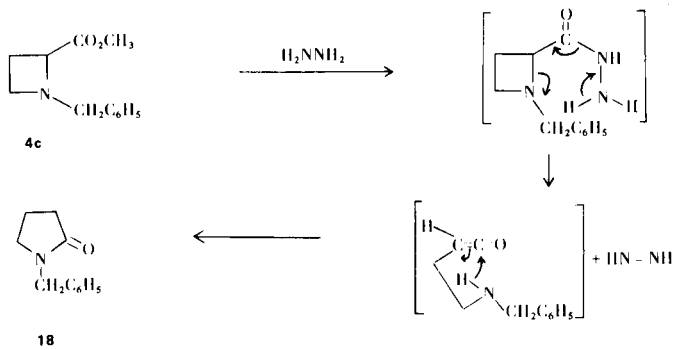
ate hydrochloride (**2**). The nmr spectra of the two products were superimposable and a mixed melting point of the corresponding picrates further confirmed their identity.



The ease of this reaction suggests that the basicity of the ring nitrogen atom may well be one of the most important factors in promoting these rearrangements. The greater basicity of the azetidine ring nitrogen compared to that of the aziridine nitrogen atom apparently overcomes the relatively greater stability of the azetidine ring making cleavage possible.

A functional group which closely approximates the hydrazide moiety in terms of electronic properties is the amide group. The fact that 1-*t*-butylazetidine-2-carboxamide (**9a**) was recovered unchanged after refluxing for several hours in methanolic hydrazine hydrate tends to confirm the suggestion of Deyrup and Clough (9) that direct reductive ring scission by hydrazine is not occurring in these systems.

Unlike the *N*-benzyl analog of **15**, however, the corresponding azetidine analog was found to undergo an anomalous reaction. When 1-benzyl-2-carbomethoxy-azetidine (**4e**) was refluxed with excess hydrazine hydrate no hydrazide derivative was isolated but rather a distillable oil was obtained which was identified by spectral and analytical methods as 1-benzyl-2-pyrrolidinone (**18**) (11). This unexpected occurrence can be rationalized in terms of a mechanism similar to that of Deyrup and Clough (9) involving a ketene-type intermediate.



The large steric requirement of the *N*-*t*-butyl group may be the factor favoring a bimolecular reaction in the case of **4a** in lieu of the intramolecular reaction observed with **4e**. It is not surprising that a similar ring enlargement does not occur with the corresponding *N*-benzylaziridine since formation of a β-lactam would be much less favorable than formation of a γ-lactam.

EXPERIMENTAL (12)

The preparative details for several compounds included in the discussion have been reported previously: **4a**, **b**, **e** and **7a**, **b**, **e** (4); **6f** and **8** (7), **11a** and **13** (8a); **4c**, **d**, **f**, **6a**, **b**, **d**, **11b**, **12** and **14** (8b).

Methyl γ-Bromocrotonate (**13**).

This compound was prepared according to the method of Ziegler, *et al.* (13). From 60.00 g. (0.60 mole) of methyl crotonate and 53.50 g. (0.30 mole) of *N*-bromosuccinimide there was obtained 46.8 g. (87.3% based on NBS) of the bromo ester, b.p. 83-85° (12 mm.), lit. (13) b.p. 83-85° (13 mm.).

Methyl γ-*t*-Butylaminocrotonate Hydrochloride (**1**).

A solution of 21.10 g. (0.118 mole) of methyl γ-bromocrotonate and 17.25 g. (0.230 mole) of *t*-butylamine in 500 ml. of pentane was stirred magnetically at room temperature for 5 days while being shielded from light. The reaction mixture was cooled to 0° and the precipitated *t*-butylamine hydrobromide was removed by filtration. The cold filtrate was then exposed to a stream of dry hydrogen chloride gas for 5 minutes. The resulting white precipitate was collected and washed with dry ethyl ether. The crude product was dissolved in methanol and the solution treated with ether to a slightly turbid appearance. Cooling gave 5.0 g. of **1** as white needles, m.p. 194-195°. Concentrating the mother liquor and adding ether gave a second crop of 9.6 g., m.p. 193-195° (total yield 59.7%); ir (chloroform): 1725 cm^{-1} (ester ν C=O); nmr (deuteriomethanol): a doublet of triplets (1H) at 424 Hz ($J_{vinylic}$ = 15.5 Hz, $J_{aliphatic}$ = 6.0 Hz, C_3 vinyl proton), a doublet of triplets (1H) at 481 Hz ($J_{vinylic}$ = 15.5 Hz, $J_{allylic}$ = 1.4 Hz, C_2 vinyl proton), a singlet (2H) at 285 Hz (NH_2 exchanged with deuteriomethanol), a doublet of doublets (2H) at 234 Hz ($J_{aliphatic}$ = 6.0 Hz, $J_{allylic}$ = 1.4 Hz, HN CH_2CH), a singlet (3H) at 229 Hz (CO_2CH_3), and a singlet (9H) at 85 Hz (*t*-butyl protons).

Anal. Calcd. for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.74; N, 6.74; Cl, 17.07. Found: C, 52.29; H, 8.94; N, 6.88; Cl, 17.23.

Methyl γ-*t*-Butylaminobutyrate Hydrochloride (**2**).

To a solution of 5.00 g. (0.024 mole) of **1** in 60 ml. of methanol was added 0.064 g. of platinum dioxide (Adams catalyst). The mixture was hydrogenated in a Parr shaker at 45 psi. Within 15 minutes an uptake of 90% of the theoretical amount of hydrogen had occurred. The catalyst was removed by filtration through Celite. The filtrate was concentrated to a small volume by evaporation under reduced pressure and dry ethyl ether was added to the solution until a few crystals appeared. Cooling provided 4.00 g. (79.3%) of **2** as white platelets, m.p. 165-167.5°; ir (chloroform): 1735 cm^{-1} (ester ν C=O); nmr (deuteriochloroform): a broad flat singlet (2H) at 520-600 Hz (NH_2), a singlet (3H) at 221 Hz (CO_2CH_3), a broad triplet (2H) at 181 Hz (H_2NCH_2--sharpens upon addition of deuterium oxide), a multiplet (4H) at 123-163 Hz ($CH_2CH_2CO_2$-CH_3), and a singlet (9H) at 90 Hz (*t*-butyl protons).

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.53; H, 9.63; N, 6.68; Cl, 16.91. Found: C, 51.46; H, 9.69; N, 6.86; Cl, 17.04.

γ-*t*-Butylaminobutyric Acid (**3**).

A 19.0 g. sample (0.09 mole) of **2** was dissolved in 50 ml. of water. After the addition of 100 ml. of ether, excess solid sodium hydroxide was added. Several ether extractions of the aqueous solution were combined, dried over magnesium sulfate and the solvent evaporated under reduced pressure yielding 11.5 g. (73%) of a light yellow oil, ir (carbon tetrachloride): 1738 cm^{-1} (ester ν C=O). This crude product was added dropwise to a magnetically stirred solution of 10.15 g. (0.033 mole) of barium hydroxide octahydrate in 130 ml. of water heated to 90°. After 30 minutes, 50 ml. of water was added and carbon dioxide gas was passed through the reaction mixture until precipitation of barium carbonate ceased. The hot suspension was filtered through a sintered-glass funnel, the filter cake washed twice with 25-ml. portions of hot water and the water evaporated with heating under reduced pressure from the filtrate giving 9.0 g. of a white solid crude product. Crystallization from methanol-ethyl ether afforded 8.30 g. (78%) of **3** as a white crystalline solid, m.p. 253-155° (sublimes); ir (Nujol mull): 2670, 2475 cm^{-1} (+N-H), and 1630 cm^{-1} (ionic carboxylate ν C=O); nmr (deuterium oxide): a singlet (2H) at 282 Hz (NH and CO_2H--exchanged with D_2O), a triplet (2H) at 168 Hz (J = 7.0 Hz, $HNCH_2$), a triplet (2H) at 126 Hz (J = 6.3 Hz, CH_2CO_2H), a quintet (2H) at 105 Hz (J = 6.8 Hz, $CH_2CH_2CH_2CO_2H$), and a singlet (9H) at 70 Hz (*t*-butyl protons).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.51; H, 11.00; N, 8.76.

1-*t*-Butyl-2-carbomethoxyazetidine (**4a**).

An intimate mixture of 1.00 g. (0.006 mole) of **3** and a catalytic amount of red phosphorus was treated cautiously with 5.0 g. of bromine and then refluxed with magnetic stirring for 8 hours. The mixture was then cooled in ice and 15 ml. of ice cold absolute methanol was added portionwise with cooling and shaking. After saturation with dry hydrogen bromide gas the reaction mixture was stirred for 20 hours at room temperature. The methanol was partially evaporated and ether was added precipitating a dark red oil, ir (chloroform): 1738 cm^{-1} (ester ν C=O). A solution containing the red oil in 50 ml. of acetonitrile was treated with a solution of 2.80 g. (0.038 mole) of *t*-butylamine in 10 ml. of acetonitrile and the mixture was refluxed gently with magnetic stirring for 12 hours. Ether (50 ml.) was added, the suspension filtered and the solvent evaporated leaving a dark-colored residue. Extraction with ether and evaporation of the solvent gave 0.65 g. of a dark red oil shown by its ir spectrum to be the desired material plus some by-product(s) (ν C=O 1687 cm^{-1}). The crude product was chromatographed on 25 g. of silica gel. Elution with hexane followed by ether gave 0.45 g. (41.5%) of an oil which was spectrally (ir and nmr) and chromatographically (silica gel tlc-several solvent systems) identical to 1-*t*-butyl-2-carbomethoxyazetidine (**4a**) (4, 8b).

General Procedure for the Preparation of 1-Alkyl-2-hydroxymethylazetidines (**5**).

To a stirred suspension containing 2.0 molar equivalents of lithium aluminum hydride in sodium dried ethyl ether was added dropwise a solution of 1.0 molar equivalent of a 1-alkyl-2-carbomethoxyazetidine (**4**) in ether. After the deopwise addition was completed the reaction mixture was refluxed with magnetic stirring for 8 hours and was then allowed to cool. Hydrolysis was effected by the careful dropwise addition of a slight excess of water. After 30 minutes a quantity of magnesium sulfate was added and stirring continued for an additional 30 minutes. The suspension was then filtered, the filter cake being washed several times with ether. Evaporation of the ether from the filtrate left colorless or light yellow oils which after drying over a few crystals of Drierite were purified by vacuum distillation.

1-*t*-Butyl-2-hydroxymethylazetidine (**5a**) (14).

A solution of 4.85 g. (0.028 mole) of **4a** in 30 ml. of ethyl ether was added as described above in the general procedure to a suspension of 2.13 g. (0.056 mole) of lithium aluminum hydride in 150 ml. of ether. At the completion of the reflux period (8 hours), the reaction mixture was hydrolyzed by the addition of 11 ml. of water. Drying over magnesium sulfate, filtration and evaporation of the solvent followed by vacuum distillation of the residual oil provided 3.41 g. (85%) of **5a** as a colorless oil, b.p. 54-55° (2.4 mm.); ir (carbon tetrachloride): 3400 cm^{-1} (OH); nmr (deuteriochloroform): a broad singlet (1H) at 248 Hz (O*H*), an apparent doublet (2H) at 208 Hz (J = *ca.* 1.5 Hz, $CHCH_2OH$), a complex series of overlapping multiplets (3H) at 176-229 Hz ($CHCH_2OH$ and CH_2N), a multiplet (2H) at 100-135 Hz (CH_2CHCH_2OH), and a singlet (9H) at 59 Hz (*t*-butyl protons).

Anal. Calcd. for $C_8H_{12}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.84; H, 12.22; N, 9.77.

1-Cyclohexyl-2-hydroxymethylazetidine (**5b**).

From a 5.00 g. sample (0.025 mole) of **4b** was obtained 3.79 g. (88.3%) of **5b** as a colorless oil, b.p. 67-68° (0.35 mm.); ir (carbon tetrachloride): 3430 cm^{-1} (OH); nmr (carbon tetrachloride): a singlet (1H) at 215 Hz (O*H*), an apparent doublet (2H) at 201 Hz ($CHCH_2OH$), a series of overlapping multiplets (2H) at 185-207 Hz ($CHCH_2OH$ and one CH_2N proton), a multiplet (1H) at 153-179 Hz (one CH_2N proton), and a series of overlapping multiplets (13H) at 44-144 Hz (CH_2CHCH_2OH and cyclohexyl protons).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.94; H, 11.08; N, 8.29.

1-Isopropyl-2-hydroxymethylazetidine (**5d**).

From a 5.62-g. sample (0.035 mole) of **4d** was obtained 3.70 g. (80%) of **5d** as a colorless oil, b.p. 47-48° (3.3 mm.); ir (carbon tetrachloride): 3450 cm^{-1} (OH); nmr (deuteriochloroform): a broad singlet (1H) at 249 Hz (O*H*), an apparent doublet (2H) at 210 Hz (J = 1.2 Hz, $CHCH_2OH$), an overlapping series of multiplets (6H) at 106-228 Hz (CH_2N, CH_2CHCH_2OH, and $CH(CH_3)_2$), and two doublets (3H each) at 54 and 57 Hz (J = 6.2 Hz, $CH(CH_3)_2$--two nonequivalent methyl groups).

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.88; H, 11.92; N, 10.82.

1-Benzyl-2-hydroxymethylazetidine (**5e**).

From a 5.22-g. sample (0.025 mole) of **4e** was obtained 3.92 g. (87.2%) of **5e** as a colorless oil, b.p. 94-95° (0.65 mm.); ir (neat): 3400 cm^{-1} (OH); nmr (carbon tetrachloride): a singlet (5H) at 429 Hz (aromatic protons), a doublet (2H) at 211 Hz (J = 4.5 Hz, $CHCH_2OH$), a singlet (1H) at 201 Hz (O*H*), a singlet (2H) at 197 Hz ($CH_2C_6H_5$), a series of overlapping complex multiplets (2H) at 183-205 Hz ($CHCH_2OH$ and one CH_2N proton), a multiplet (1H) at 153-180 Hz (one CH_2N proton), and a multiplet (2H) at 98-135 Hz (CH_2CHCH_2OH).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.74; H, 8.79; N, 7.84.

1-Isopropylazetidine-2-carboxylic Acid (**7d**) *via* Hydrolysis of **4d**.

A 12.00-g. sample (0.076 mole) of **4d** was added dropwise to a stirred solution of 12.00 g. (0.038 mole) of barium hydroxide octahydrate in 125 ml. of water heated to 90°. After stirring 30 minutes, 50 ml. of water was added and carbon dioxide was passed through the hot mixture until no further precipitation occurred.

The precipitated barium carbonate was removed by filtration of the hot suspension through a sintered-galss funnel. The water was evaporated from the filtrate under reduced pressure with heating and the resulting solid was crystallized twice from chloroform-ethyl ether providing 9.0 g. (81%) of **7d** as hygroscopic white crystals, m.p. 177-179°; ir (chloroform): 1630 cm^{-1} (ionic carboxylate ν C=O); nmr (deuterium oxide): a singlet (1H) at 282 Hz (COO*H*--exchanged with deuterium oxide), a triplet (1H) at 273 Hz (J = 9.4 Hz, C*H*CO), a multiplet (2H) at 221-242 Hz (CH_2N), a septet (1H) at 199 Hz (J = 6.5 Hz, $CH(CH_3)_2$), a multiplet (2H) at 121-164 Hz (CH_2CHCO), and two doublets (3H each) at 62.5 and 64 Hz (J = 6.5 Hz, $CH(CH_3)_2$--two nonequivalent methyl groups.).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.70; H, 9.16; N, 9.75.

Attempted Hydrolysis of 1-Benzhydryl-2-carbomethoxyazetidine (**4f**).

Following the procedure utilized with **4d**, 1.20 g. of **4f** yielded 0.6 g. of a nonmelting solid containing a large amount (42%) of ash—apparently a barium salt or complex. When hydrolysis of **4f** was attempted with ethanolic sodium hydroxide a small amount of a hygroscopic semi-solid resulted which was not further characterized.

General Procedure for Hydrogenolysis of 1-Alkyl-2-carbobenzyoxyazetidines (**6**).

A solution of the azetidinyl ester (**6a-d**) (8b) in methanol containing a small amount of 10% palladium on charcoal was hydrogenolyzed in a Parr shaker at 45 psi at room temperature for 1 hour. The catalyst was removed by filtration, the solvent evaporated from the filtrate and the residue crystallized from an appropriate solvent.

Example: Preparation of 1-Isopropylazetidine-2-carboxylic Acid (**7d**) by Hydrogenolysis of (**6d**).

A 7.00-g. sample (0.030 mole) of **6d** was hydrogenolyzed over 0.5 g. of catalyst. Crystallization of the white solid crude product from chloroform-ethyl ether afforded 4.00 g. (93%) of a white crystalline solid, m.p. 177-179°, which was identical by mixture m.p. (177-179°), ir and nmr spectra with **7d** prepared by hydrolysis of **4d**.

1-*t*-Butylazetidine-2-carboxamide (**9a**) (15).

A solution containing 10.00 g. (0.0636 mole) of **7a** and 6.42 g. (0.0636 mole) of triethylamine in 300 ml. of chloroform was cooled to 0° in an ice-salt bath and 6.90 g. (0.0636 mole) of ethyl chloroformate was added in one portion with continuous magnetic stirring. After 15 minutes, anhydrous ammonia gas was passed through the mixture for 1 hour at 0°. The suspension was then stirred for an additional hour at room temperature and allowed to stand overnight. The suspension was filtered and the chloroform evaporated. The residual oil was boiled for 15 minutes with 150 ml. of benzene and filtered while hot. The benzene was evaporated under reduced pressure and 75 ml. of petroleum ether (b.p. 60-69°) was added to the residual oil, the solution shaken and allowed to stand at room temperature. After 1 hour the mixture was cooled to 0°. Filtration yielded 7.16 g. of **9a** as colorless platelets, m.p. 77.5-79°. A second crop, 0.462 g. of slightly yellow crystals, m.p. 77-79°, was obtained from the mother liquor (total yield, 77%); ir (carbon tetrachloride): 3520, 3430 cm^{-1} (free NH_2 stretch), 3375, 3160 cm^{-1} (bonded NH_2 stretch), and 1688 cm^{-1} (amide ν C=O); nmr (deuteriochloroform): a broad, flat singlet (2H) at 430 Hz (NH_2), a triplet (1H) at 224 Hz (J = 8.0 Hz, C*H*CO), a multiplet (2H) at 181-202 Hz (CH_2N), a multiplet (2H) at 107-151 Hz (CH_2CHCO), and a singlet (9H) at 59 Hz (*t*-butyl protons).

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.34; H, 10.38; N, 18.01.

Attempted Preparation of 1-Isopropylazetidine-2-carboxamide.

Application of the procedure described for **9a** yielded a considerable amount of unreacted starting material together with an oily material shown by spectral (ir and nmr) and chromatographic (tlc) methods to be a complex mixture. No further characterization was attempted.

1-*t*-Butyl-2-aminomethylazetidine (**10a**).

To a suspension containing 1.75 g. (0.046 mole) of lithium aluminum hydride in 120 ml. of dry tetrahydrofuran (THF) was added dropwise a solution of 3.60 g. (0.023 mole) of **9a** in 30 ml. of THF. The suspension was refluxed with magnetic stirring for 8 hours. Hydrolysis of the excess hydride was accomplished by the careful addition of 12 ml. of water. After stirring for 15 minutes, magnesium sulfate was added and stirring continued for 30 minutes. The suspension was filtered and the filter cake washed several times with ether, the washes being combined with the original filtrate. Evaporation of the solvent from the filtrate followed by vacuum distillation of the resulting yellow oil from barium oxide gave 2.00 g. (61.4%) of **10a** as a colorless oil, b.p. 53-55° (3.7 mm.) (from the pot was obtained 1.0 g. of starting material after recrystallization from petroleum ether-yield of **10a** based on consumption of **9a** = 85%); ir (carbon tetrachloride): 3375, 3290 cm^{-1} (NH_2 stretch); nmr (carbon tetrachloride): a septet (1H) at 208 Hz (J = 4.2 Hz, $CH_2CHC_\alpha H_2NH_2$), a multiplet (2H) at 173-191 Hz (CH_2N_{ring}), a broad doublet (2H) at 150-164 Hz ($J_{2,\alpha} \cong 4.2$ Hz, $C_\alpha H_2NH_2$), a multiplet (4H) at 96-127 Hz ($CH_2CHC_\alpha H_2NH_2$), and a singlet (9H) at 57 Hz (*t*-butyl protons).

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.60; H, 13.00; N, 19.67.

Reaction of 1-*t*-Butyl-2-carbomethoxyazetidine (**4a**) with Hydrazine Hydrate.

A 1.0-g. sample (0.0058 mole) of **4a** was refluxed with 1.5 ml. of 99% hydrazine hydrate for 6 hours. Evaporation of the excess hydrazine hydrate *in vacuo* gave 1.0 g. (98%) of a clear, viscous oil suggested to be γ-*t*-butylaminobutyrohydrazide (**17**); ir (chloroform): 3440, 3310 cm^{-1} ($NHNH_2$) and 1675 cm^{-1} (hydrazide ν C=O); nmr (deuterium oxide): a singlet (4H) at 282 Hz (N*H* and $NHNH_2$--exchanged with deuterium oxide), a triplet (2H) at 152 Hz (J = 7.0 Hz, CH_2N), a triplet (2H) at 130 Hz (J = 6.5 Hz, CH_2CO), an apparent quintet (broad) (2H) at 97 Hz ($J \cong 6.9$ Hz, CH_2CH_2CO), and a singlet (9H) at 62 Hz (*t*-butyl protons). Compound **17** was analyzed as its picrate salt, m.p. 171-172°.

Anal. Calcd. for $C_{14}H_{22}N_6O_8$: C, 41.79; H, 5.51; N, 20.89. Found: C, 42.05; H, 5.71; N, 20.73.

γ-*t*-Butylaminobutyrohydrazide (**17**) from Methyl γ-*t*-Butylaminobutyrate Hydrochloride (**2**).

A 1.0-g. sample (0.0048 mole) of **2** was converted to the corresponding free base as described in the preparation of **3**. A 0.6-g. sample of the resulting crude ester was refluxed with 1.0 ml. of hydrazine hydrate for 6 hours. Evaporation of the excess hydrazine hydrate gave a viscous, colorless oil, the ir and nmr spectra of which were identical with those of **17**. Picrate, m.p. 170-172°; mixed m.p. (with **17** prepared from **4a**) 170-172°.

Stability of 1-*t*-Butylazetidine-2-carboxamide (**9a**) with Hydrazine Hydrate.

A 0.25-g. sample of **9a** was dissolved in 1.0 ml. of methanol, 1.0 ml. of hydrazine hydrate was added and the mixture was stirred for 12 hours at 25° and then refluxed 6 hours. Evaporation of the solvent and hydrazine hydrate left a light yellow oil, the nmr spectrum of which indicated it to be unchanged **9a**.

Reaction of 1-Benzyl-2-carbomethoxyazetidine (**4e**) with Hydrazine Hydrate.

A 1.0-g. sample of **4e** was treated with hydrazine hydrate as described for (**4a**). The crude product (0.58 g., 68.3%) was distilled *in vacuo* from barium oxide yielding 0.45 g. (53%) of a colorless oil, b.p. 115-116° (0.3 mm.) (16) suggested to be 1-benzyl-2-pyrrolidinone (**18**), lit. (13) b.p. 160-170° (10-11 mm.); ir (chloroform): 1675 cm^{-1} (amide ν C=O –lit. (13) ν C=O 1670 cm^{-1}; nmr (deuteriochloroform); a singlet (5H) at 436 Hz (aromatic protons), a singlet (2H) at 276 Hz ($CH_2C_6H_5$), a triplet (2H) at 192 Hz (J = 6.8 Hz, CH_2N), an apparent triplet (2H) at 142 Hz (J ≅ 6.5 Hz, CH_2CO), and a multiplet (2H) at 102-103 Hz (CH_2CH_2CO); mass spectrum (70eV) m/e (rel. intensity): M^+ 175 (28), 150 (19), 91 (100), 84 (45), 77 (11), 71 (13), 65 (33).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.72; H, 7.56; N, 7.91.

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