

Azetidine-2-carboxylic Acid Derivatives

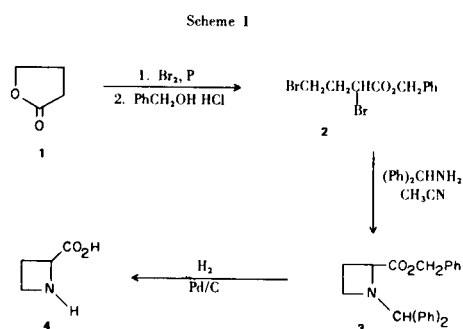
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An improved method for the preparation of DL-azetidine-2-carboxylic acid is reported. The reaction of thionyl chloride with azetidine-2-carboxylic acid in methanol gave rise to 2-carbomethoxyazetidine hydrochloride, which upon treatment with triethylamine yielded 2-carbomethoxyazetidine. 2-Carbomethoxyazetidine proved to be unstable and upon standing formed azetidine-2-carboxylic acid anhydride. The nmr and ir spectra of 2-carbomethoxyazetidine are discussed in terms of its conformation. The conversion of azetidine-2-carboxylic acid to azetidine-2-carboxamide is also described.

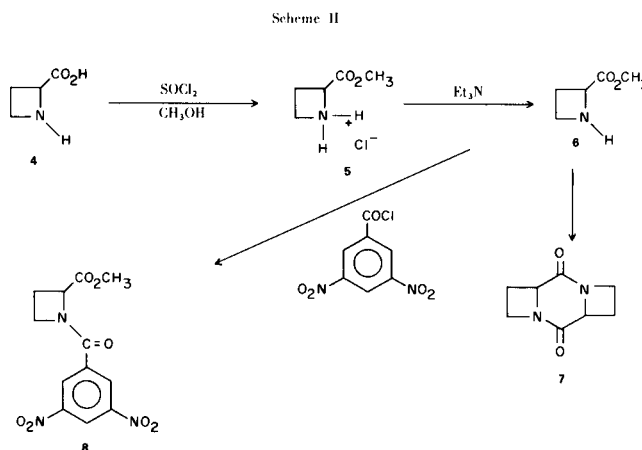
L-Azetidine-2-carboxylic acid was first found in nature by L. Fowden in 1956 (2). It was isolated from the leaves of *convallaria majalis* and shown to be the major soluble nitrogenous constituent of the plants in the Liliaceae and Agavaceae families. Fowden also synthesized the racemic and D form of azetidine-2-carboxylic acid (2), however, his method of synthesis is tedious and since the yield is relatively low the method is not readily applicable to the production of large amounts of the acid. In 1969 a preliminary communication (3) from this laboratory reported an economical procedure for the preparation of DL-azetidine-2-carboxylic acid (4) and its subsequent resolution to the D and L forms (4). Since that time we have made further simplifications in the procedure that now enable us to prepare the imino acid in an overall yield of 54.6% (Scheme I).



Benzyl α,γ -dibromobutyrate (2) was prepared from γ -butyrolactone (1) by a modification of the method used by Wladislaw for methyl α,γ -dibromobutyrate (5). The reaction of the dibromo ester 2 with benzhydrylamine to give 1-benzhydryl-2-carbomethoxyazetidine (3) was found to proceed best when the reactants were allowed to reflux

in spectral grade acetonitrile for 24 hours. The crude azetidyl ester 3 can be purified by column chromatography (3). However, this lengthy purification step is not necessary for the preparation of imino acid 4. Crude 1-benzhydryl-2-carbomethoxyazetidine can be directly hydrogenolyzed over Pearlman catalyst (6) to provide azetidine-2-carboxylic acid in 73.1% yield (from benzyl α,γ -dibromobutyrate).

The solid state ir spectra of DL-azetidine-2-carboxylic acid and the optically active L form are reproduced in Figure 1. The D and L form show identical spectra except for the position of the carboxylate band. The D form shows the carboxylate absorption centered at 1580 cm^{-1} while the L isomer absorbs at 1594 cm^{-1} . As can be seen from Figure 1 the spectrum of racemic azetidine-2-carboxylic acid is significantly different from either of the optically active forms (2). Differences in the ir spectra of other active and racemic amino acids have previously been observed (7).



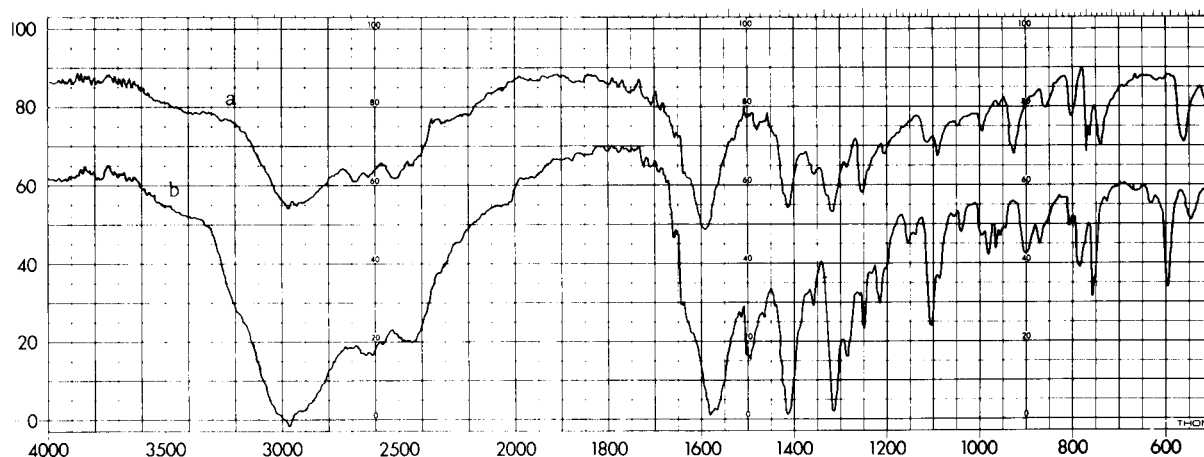



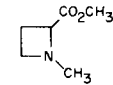
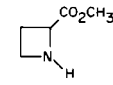
Figure 1. Infrared spectra of (a) L-azetidine-2-carboxylic acid and (b) DL-azetidine-2-carboxylic acid taken as potassium bromide pellets.

A method for the synthesis of 1-alkylazetidines bearing different functional groups at the 2-position has been developed in this laboratory (8); however, no N-H derivatives of azetidine-2-carboxylic acid (4) have been reported previously. Azetidine-2-carboxylic acid was found to react with thionyl chloride in methanol to give 2-carbomethoxyazetidine hydrochloride (5) as a noncrystalline oil (Scheme II). Treatment of the hydrochloride 5 with triethylamine led to the isolation of 2-carbomethoxyazetidine in 76% yield. The acetidinyl ester 6 proved, however, to be unstable. Attempted distillation at reduced pressure led to the formation of azetidine-2-carboxylic acid anhydride (7) as well as straight chain condensation polymerization products. Also, upon standing at room temperature 2-carbomethoxyazetidine loses two molecules of methanol and cyclizes to form the diketopiperazine 7. The cyclization can be readily followed by nmr and ir and is approximately 70% complete after one day. 2-Carbomethoxyazetidine can be conveniently stored as its hydrochloride 5 and used immediately upon liberation. The reaction of 3,5-dinitrobenzoyl chloride with freshly liberated amino acid ester 6 gave the dinitrobenzoyl derivative 8. However, formation of the diketopiperazine 7 is a competitive reaction. The ir spectrum of 2-carbomethoxyazetidine indicates that no significant hydrogen bonding is present. Table I shows that the position of the N-H and ester carbonyl stretching frequency of the azetidyl ester 6 is not significantly different from that of the model compounds, 1-methyl-2-carbomethoxyazetidine (9) and 2-methylazetidine (10). In a previous paper (9), the conformation of 1-alkyl-2-carbomethoxyazetidines

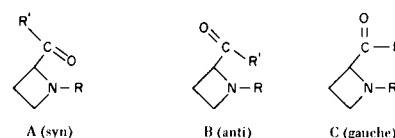
was discussed in terms of the double infrared absorption of the ester carbonyl. The three conformations A, B, and C were considered. Analogous to 1-methyl-2-carbomethoxyazetidine (9), 2-carbomethoxyazetidine (6) shows only one carbonyl absorption, the position of which (1740 cm^{-1}) indicates a marked preference for the gauche conformer C.

TABLE I

Infrared N-H and Ester C=O Stretching Frequencies of Some Azetidine Derivatives (a)

| |  |  |  |
|--------------------------------|---|---|---|
| γ C=O, cm^{-1} | ----- | 1745 | 1740 |
| γ N-H, cm^{-1} | 3290 | ----- | 3300 |

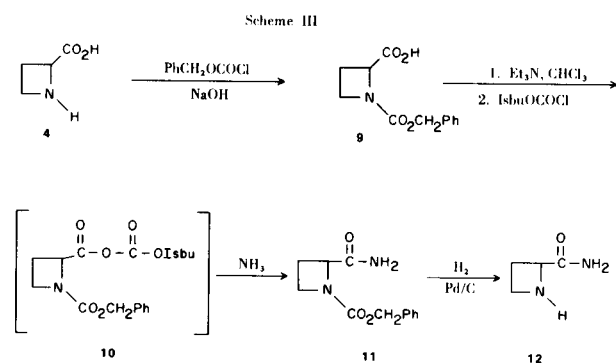
(a) All spectra were obtained in carbon tetrachloride solution, terms of the double infrared absorption of the ester carbonyl. The three conformations A, B, and C were considered. Analogous to 1-methyl-2-carbomethoxyazetidine (9), 2-carbomethoxyazetidine (6) shows only one carbonyl.



The nmr spectrum of 2-carbomethoxyazetidine suggests, however, that the conformation of the azetidine ring is different than that of previously reported 1-alkyl-2-carbomethoxyazetidines (9). The C-2 proton of known

1-alkylazetidyl methyl esters (9,11) appears as a triplet (collapsed quartet, average $J = 8.2$ Hz) whereas it appears as a quartet ($J_{cis} = 8.3$ Hz, $J_{trans} = 5.5$ Hz) in 2-carbomethoxyazetidine. The larger coupling constant is assigned to the *cis* vicinal proton by analogy with other small ring compounds (12) and in agreement with the Karplus relationship (13). The observed difference in the nmr signal of the C-2 proton is rationalized in terms of the azetidine ring of 2-carbomethoxyazetidine being more puckered than the *N*-alkylated analogs. A similar decrease in *cis* and *trans* vicinal coupling constants was also noticed for one set of protons (C₃-C₄) in the 2-aryl-3-arylazetidines. As the amount of ring puckering increased both the *cis* and *trans* vicinal coupling constants decreased (14). In addition the C-2 proton of *cis*-1-*t*-butyl-2-carbomethoxy-4-methylazetidine appears as a quartet ($J_{cis} = 7.6$ Hz, $J_{trans} = 5.0$ Hz) whereas the *trans* isomer appears as a triplet ($J = 8.2$ Hz). This has also been attributed to the azetidine ring being more puckered in the *cis* derivative than in the *trans* (9). The nmr spectrum of 2-carbomethoxyazetidine also supports the previous observation that the conformation of the azetidine ring is a function of the steric requirement of the *N*-substituent, and that the azetidine bearing the smaller *N*-substituents are puckered to a greater extent (14).

Attempted preparation of an amide derivative directly from 2-carbomethoxyazetidine hydrochloride (5) or the free base 6 thus far has been unsuccessful. Upon treatment of 5 or 6 with excess amine the only isolable product is the diketopiperazine 7. It was, therefore, necessary to protect the amino function of azetidine-2-carboxylic acid with the carbobenzyloxy group (Scheme III). The reaction of imino acid 4 with benzyl chloroformate in



the presence of aqueous sodium hydroxide gave an essentially quantitative yield of the *N*-carbobenzyloxy derivative 9 as a viscous oil (4). Treatment of azetidyl acid 9 with triethylamine in chloroform at 0° followed by the addition of isobutyl chloroformate gave the corresponding mixed ester anhydride intermediate 10 (not isolated) which, when treated with excess anhydrous ammonia, afforded

the crystalline primary amide 11 in good yield. Hydrogenolysis of 11 over 5% palladium on carbon gave azetidine-2-carboxamide (12) in 97.2% yield. This represents an overall yield of 71.5% starting from azetidine-2-carboxylic acid.

EXPERIMENTAL

Melting points were determined with a Mel-temp capillary tube melting point apparatus and are uncorrected. Boiling points were determined at pressures recorded on a standard McCleod gauge and are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Illinois. The ir spectra were determined on a Perkin-Elmer Model 237 or 621 spectrophotometer. The nmr spectra were recorded on a Varian A-60-D spectrometer and the chemical shifts are reported with tetramethylsilane as an internal standard unless otherwise noted. The mass spectra were determined on a Hitachi RMU-60 spectrometer at 70 ev.

Benzyl α,γ -Dibromobutyrate (2).

α -Butyrolactone (26.7 g., 0.31 mole) and a catalytic amount of red phosphorus (ca. 0.2 g.) were stirred magnetically and heated to 115°. Bromine (49.6 g., 0.31 mole) was added dropwise at a rate such that the reaction temperature was maintained at 115-120°. When the rate of bromine uptake decreased, as evidenced by a decrease in temperature, an additional portion of red phosphorus was added and the remaining bromine was added with the reaction temperature being maintained by some heating. After the bromine addition was completed, the reaction mixture was stirred for 1 hour at 115°. The reaction mixture was then allowed to cool to room temperature and was subsequently cooled to 0° in an ice bath. Benzyl alcohol (37.8 g., 0.35 mole) was cooled to 0° and added to the original reaction mixture. The cold solution was saturated with dry hydrogen chloride gas (passed through for 15 minutes), stoppered tightly and stirred at room temperature for 60 hours. The mixture was diluted with an equal volume of ethyl ether and washed with 300 ml. of 3% aqueous sodium bicarbonate solution (3 x 100 ml.) and then with 100 ml. of water (2 x 50 ml.). The ether solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give crude benzyl α,γ -dibromobutyrate as a light yellow oil (occasionally the crude product was brown). Vacuum distillation of this crude product afforded 74.6 g. (74%) of benzyl α,γ -dibromobutyrate (3) as a colorless oil, b.p. 126-128° (0.2 mm); ir (carbon tetrachloride): 1740 cm^{-1} (ester C=O) nmr (carbon tetrachloride): δ 7.29 (s, 5H, aromatic), 5.14 (s, 2H, $\text{CH}_2\text{C}_6\text{H}_5$), 4.46 (t, $J = 7.4$ Hz, 1H, CHBr), 3.44 (t, $J = 6.5$ Hz, 2H, CH_2Br), 2.45 (q, $J = 6.7$ Hz, 2H, BrCH_2CH_2).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{Br}_2\text{O}_2$: C, 39.32; H, 3.61; Br, 47.56. Found: C, 39.31; H, 3.81; Br, 47.56.

1-Benzhydryl-2-carbomethoxyazetidine (3).

A mixture of benzyl α,γ -dibromobutyrate (49.6 g., 0.148 mole) and benzhydrylamine (81.0 g., 0.444 mole), both freshly distilled, was refluxed in spectral grade acetonitrile (680 ml.) for 24 hours. Upon cooling, the reaction mixture was evaporated to dryness. Anhydrous ether (150 ml.) was then added to the residue and the precipitated benzhydrylamine hydrobromide (68.3 g., 87.5%) was filtered. The ether solution was dried over anhydrous magnesium sulfate and evaporated to give 52.9 g. (100%) of crude 1-benzhydryl-2-carbomethoxyazetidine (3) as a light yellow oil (3). A portion of the crude product (13.5 g.) was chromato-

graphed on florosil (400 g.). Elution with ethyl acetate-hexane (15:85) provided 11.08 g. (82.0%) of **3** as a viscous oil which was crystallized from an ether-hexane mixture as colorless crystals, m.p. 61-63°; ir (carbon tetrachloride): 1745 cm^{-1} (ester C=O); nmr (carbon tetrachloride): δ 7.60-6.90 (m, 15H, aromatic), 4.77 and 4.74 (overlapping s, 2H, $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$), 4.50 (s, 1H, $\text{CH}(\text{C}_6\text{H}_5)_2$), 3.83 (t, $J = 7.8$ Hz, 1H, CHCO), 3.60-2.60 (m, 2H, CH_2N), 2.50-1.90 (m, 2H, CH_2CHCO).

Anal. Calcd. for $\text{C}_{24}\text{H}_{23}\text{NO}_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.51; N, 3.85.

Azetidine-2-carboxylic Acid (**4**).

1-Benzhydryl-2-carbobenzyloxyazetidine (2.20 g., 0.00616 mole) was dissolved in 40 ml. of anhydrous methanol and hydrogenolyzed at a pressure of 45 psi over 0.5 g. of 5% palladium-on-carbon catalyst. After twelve hours, the catalyst was filtered and washed with methanol (15 ml.) and then water (25 ml.). The filtrate was evaporated until the methanol was removed and the remaining aqueous portion was extracted with an equal volume of ether to remove diphenylmethane and toluene. The aqueous layer was then evaporated under reduced pressure and the residual solid was washed with anhydrous methanol to afford 0.38 g. of azetidine-2-carboxylic acid. Upon standing overnight, the methanol washings provided an additional 0.15 g. of product. The combined product was recrystallized from aqueous methanol (90-95%) to give 0.50 g. (83.0%) of the imino acid **4** as white crystals which slowly darkened without melting upon heating above 200° (2); ir (potassium bromide): 1580 cm^{-1} (ionic carboxylate); nmr (deuterium oxide, acetone internal standard): δ 4.64 (t, $J = 9.7$ Hz, 1H, CHCO), 4.23-3.51 (m, 2H, CH_2N), 2.98-2.07 (m, 2H, CH_2CHCO).

Anal. Calcd. for $\text{C}_4\text{H}_7\text{NO}_2$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.36; H, 7.06; N, 13.82.

In an effort to minimize the time involved in carrying out the procedure it was found that the crude azetidyl ester **3**, obtained in quantitative yield (15) before purification by column chromatography, could be directly hydrogenolyzed to azetidine-2-carboxylic acid over Pearlman catalyst (20% palladium hydroxide-on-carbon) (**6**). A 22.4 g. sample of crude 1-benzhydryl-2-carbobenzyloxyazetidine was dissolved in 150 ml. of anhydrous methanol and hydrogenolyzed at a pressure of 45 psi over 2.0 g. of Pearlman catalyst. After twenty-four hours, the reaction mixture was worked up in the same way as described above to give 4.15 g. of azetidine-2-carboxylic acid. This represents an overall yield of 54.6% starting from γ -butyrolactone. It must be stated, however, that the yield of acid obtained is variable. The overall yield of 54.6% is maximum with the average overall yield, based on twenty runs, being 51.5%.

2-Carbomethoxyazetidine (**6**).

Azetidine-2-carboxylic acid (1.29 g., 0.0127 mole) was suspended in dry methanol (20 ml.) and cooled to 0° in an ice bath. Thionyl chloride (3.04 g., 0.0255 mole) was then added dropwise over thirty minutes, never permitting the reaction temperature to rise above 10°. The reaction mixture was then allowed to stir at room temperature for twelve hours. Evaporation of methanol and excess thionyl chloride gave 1.90 g. (100%) of crude 2-carbomethoxyazetidine hydrochloride (**5**) as a viscous colorless oil; ir (chloroform): 1740 (ester C=O). Attempts to crystallize the azetidyl ester hydrochloride **5** were unsuccessful. The hydrochloride was dissolved in the minimum amount of chloroform and triethylamine (2.60 g., 0.0255 mole) was added slowly. The reaction mixture was stirred at room temperature for one hour and then evaporated to dryness under reduced pressure at 25°.

The residual solid was washed with anhydrous ether and the triethylamine hydrochloride (1.9 g., more than theoretical) was filtered. Evaporation of ether gave 1.05 g. (71.4%) of 2-carbomethoxyazetidine as a colorless liquid; ir (carbon tetrachloride): 3300 cm^{-1} (broad, N-H), 1740 (ester C=O); nmr (carbon tetrachloride): δ 4.10 (q, $J_{trans} = 5.5$ Hz, $J_{cis} = 8.3$ Hz, 1H, CHCO), 3.73 (s, 3H, CO_2CH_3), 3.70-3.20 (m, 2H, CH_2N), 2.90-2.05 (m, 3H, NH, and CH_2CHCO); ms: m/e 115 molecular peak.

Attempted distillation of 2-carbomethoxyazetidine resulted in polymerization. Further purification of the azetidyl ester **6**, was therefore not possible; however, the structure was confirmed by preparation of the 3,5-dinitrobenzoyl derivative **8**.

1-(3,5-Dinitrobenzoyl)-2-carbomethoxyazetidine (**8**).

2-Carbomethoxyazetidine (0.30 g., 0.0026 mole) was dissolved in 10 ml. of dry benzene. Triethylamine (0.26 g., 0.0026 mole) and 3,5-dinitrobenzoyl chloride (0.59 g., 0.0026 mole) was added and the reaction mixture was stirred overnight at room temperature. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate evaporated to dryness. The crude product was recrystallized from benzene to give 0.17 g. (21%) of 1-(3,5-dinitrobenzoyl)-2-carbomethoxyazetidine, m.p. 93-95°; ir (potassium bromide): 1740 cm^{-1} (ester C=O), 1640 (amide C=O), 1535 (NO_2); nmr (deuteriochloroform): δ 9.01 (s, 1H, *para*-H or $\text{C}_6\text{H}_3(\text{NO}_2)_2$), 8.83 (s, 2H, *ortho*-H of $\text{C}_6\text{H}_3(\text{NO}_2)_2$), 5.04 (q, $J_{cis} = 8.5$ Hz, $J_{trans} = 5.5$ Hz, 1H, CHCO), 4.40 (m, 2H, CH_2N), 3.78 (s, 3H, CO_2CH_3), 3.35-2.20 (m, 2H, CH_2CHCO); ms: m/e 309 molecular peak.

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_7$: C, 46.60; H, 3.59; N, 13.59. Found: C, 46.90; H, 3.74; N, 13.86.

Azetidine-2-carboxylic Acid Anhydride (**7**).

2-Carbomethoxyazetidine (0.05 g., 0.0043 mole) was allowed to stand at room temperature for three days. Following the reaction by nmr indicated that the reaction was approximately 70% complete after one day. The solid reaction mixture was dried under vacuum for two hours and recrystallized from acetone to give 0.27 g. (67.5%) of azetidine-2-carboxylic acid anhydride. The product was further purified by sublimation at 100° and 0.4 mm/Hg, m.p. 170-172°; ir (potassium bromide): 1660 cm^{-1} (amide C=O); nmr (deuteriochloroform): δ 5.00 (t, $J = 8.0$ Hz, 2H, CHCO), 4.10 (m, 4H, CH_2N), 3.01-2.10 (m, 4H, CH_2CHCO); ms: m/e 166 molecular peak.

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.55; H, 6.13; N, 17.04.

1-Carbobenzyloxyazetidine-2-carboxylic Acid (**9**).

Azetidine-2-carboxylic acid (3.0 g., 0.03 mole) and sodium hydroxide (1.2 g., 0.03 mole) were dissolved in 20 ml. of water and cooled to 5° in an ice bath. Benzyl chloroformate (6.0 g., 0.035 mole) and sodium hydroxide (1.60 g. in 10 ml. of water, 0.04 mole) were then added alternately over 30 minutes in five equal portions to the magnetically stirred solution. After stirring for 15 minutes, excess benzyl chloroformate was extracted with 10 ml. of ethyl ether. The aqueous solution was slowly acidified to Congo Red with 5N hydrochloric acid. The product which separated was extracted into chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give 6.9 g. (98%) of 1-carbobenzyloxyazetidine-2-carboxylic acid as a oil (**4**); ir (carbon tetrachloride): 1720 cm^{-1} (carboxyl and carbamate C=O overlapping); nmr (deuteriochloroform): δ 7.34 (s, 5H, aromatic), 5.14 (s, 2H, $\text{CH}_2\text{C}_6\text{H}_5$), 4.76 (q, $J_{cis} = 9.0$ Hz, $J_{trans} = 6.5$ Hz, 1H, CHCO), 4.05 (m, 2H, CH_2N), 2.80-2.10 (m, 2H, CH_2CHCO).

1-Carbobenzoyazetidine-2-carboxamide (11).

1-Carbobenzoyazetidine-2-carboxylic acid (9.40 g., 0.040 mole) was dissolved in 100 ml. of chloroform and 4.0 g. (0.04 mole) of triethylamine was added. The reaction mixture was cooled to 0° in an ice-salt bath and isobutyl chloroformate (5.50 g., 0.040 mole) was added in one portion to the magnetically stirred solution. After 15 minutes, anhydrous ammonia gas was passed through the cooled solution for one hour. The reaction mixture was then allowed to warm to room temperature and stand overnight. The white precipitate was removed and the filtrate was evaporated under reduced pressure. The resulting crude solid was recrystallized from methylene chloride to give 7.05 g. (75%) of 1-carbobenzoyazetidine-2-carboxamide, m.p. 126-128°; ir (chloroform): 3485, 3445, 3365, and 3285 cm^{-1} (N-H), 1690 cm^{-1} (C=O amide and carbamate overlapping); nmr (deuteriochloroform): δ 7.31 (s, 5H, aromatic), 6.98-6.16 (broad peak, 2H, CONH₂), 5.10 (s, 2H, CH₂C₆H₅), 4.66 (t, J = 8.1 Hz, 1H, CHCONH₂), 4.10-3.77 (m, 2H, CH₂N), 2.65-2.20 (m, 2H, CH₂CHCONH₂).

Anal. Calcd. for C₁₂H₁₄N₂O₃: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.44; H, 6.08; N, 11.98.

Azetidine-2-carboxamide (12).

1-Carbobenzoyazetidine-2-carboxamide (1.16 g., 0.005 mole) was dissolved in 30 ml. of anhydrous methanol. After the addition of 0.5 g. of 5% palladium on carbon catalyst, the solution was hydrogenolyzed at 45 psi for 3½ hours. The catalyst was filtered and the methanol evaporated to give 0.485 g. (97.2%) of azetidine-2-carboxamide. The product was recrystallized from a chloroform-ether mixture to give the analytical sample, m.p. 109-111°; ir (potassium bromide): 3415 cm^{-1} (N-H), 3323 and 3160 (amide N-H), 1682 (amide C=O); nmr (deuteriochloroform): δ 7.60-6.70 (broad peak, 2H, amide NH₂), 4.34 (t, J = 8.5 Hz, 1H, CHCONH₂), 3.98-3.18 (m, 2H, CH₂N), 2.75 (broad s, 1H, amine N-H), 2.80-2.18 (m, 2H, CH₂CHCONH₂); ms: m/e 100 molecular peak.

Anal. Calcd. for C₄H₈N₂O: C, 47.99; H, 8.05; N, 27.98. Found: C, 47.78; H, 7.95; N, 27.82.

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- (15) Although the yield of crude 1-benzhydryl-2-carbobenzoylazetidine is designated as quantitative, the nmr spectrum and tlc indicate the presence of a small amount of benzhydrylamine and two unidentified products.