

A Novel Isomeric Analog of DL-Proline

David S. Soriano, Kenneth F. Podraza and Norman H. Cromwell

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588

Received November 11, 1979

L-Azetidine-2-carboxylic acid is a naturally occurring azetidine currently used in the synthesis of abnormally high molecular weight polypeptides. The synthesis of 2-carboxy-4-methylazetidine is now reported which is a novel isomeric analog of DL-proline. Reaction of α,γ -dibromo carbonyl ester with three molar equivalents of benzylamine yields 1-benzyl-2-carbomethoxy-4-methylazetidine. Hydrolysis of the latter compound with barium hydroxide yields 1-benzyl-2-carboxyl-4-methylazetidine which, if subjected to catalytic hydrogenation, yields the title compound in practical yield. The *cis* configuration is tentatively assigned to the title compound on the basis of previously published arguments.

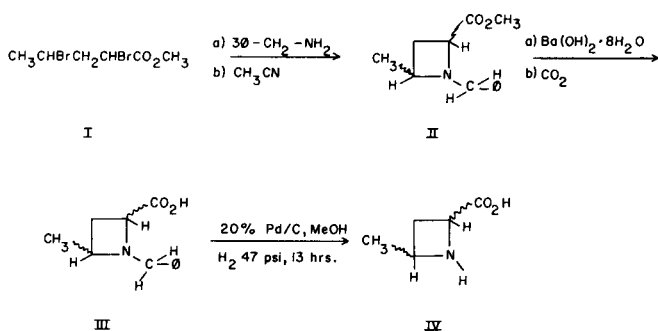
J. Heterocyclic Chem., **17**, 623 (1980).

Sir:

L-Azetidine-2-carboxylic acid is a known naturally occurring azetidine which was first isolated (and subsequently synthesized) by Fowden from the leaves of *Convallaria Majalis* (Lily-of-the-Valley) (2). In 1969, a preliminary communication (3) from this laboratory reported an economical procedure for the preparation of DL-azetidine-2-carboxylic acid and its subsequent resolution to the D and L forms. This imino acid (L antipode) has been found to be a specific antagonist of L-proline and is currently being used in the synthesis of abnormally high molecular weight polypeptides (4,5).

Primarily because of these above factors, we would now like to report the synthesis of 2-carboxy-4-methylazetidine (IV) which is an isomer of DL-proline. We have found that the sequence of reactions shown in Scheme I affords the title compound in practical yield.

Scheme I



A 55.0 g. (0.2 mole) sample of α,γ -dibromocarbonyl ester (I), prepared according to the published procedure of Rodebaugh and Cromwell (6), was refluxed in 600 ml. of acetonitrile with 0.6 mole of benzylamine for 24 hours. The solvent was then evaporated under reduced pressure, and to the oily residue was added anhydrous ethyl ether.

Filtration to remove benzylamine hydrobromide followed by exposure of the filtrate to a stream of hydrogen chloride gas yielded a syrupy precipitate from which the ether was decanted. The precipitate was dissolved in chloroform and then treated with three molar equivalents of triethylamine. The chloroform was evaporated under reduced pressure and the residue extracted with ether. Filtration of the ethereal extract and evaporation of the solvent yielded a brown residue which, by vacuum distillation, gave 24.3 g. of a light yellow oil (II), (57% yield), b.p. 105-107°/5.0 mm Hg; ν (carbon tetrachloride): 1745 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.1 (3H, d, $J = 6.5$ Hz, CH_3 *cis* isomer).

0.9 (3H, d, partially masked by *cis* isomer doublet, $J = 6.0$ Hz), 3.5 (3H, s, CO_2CH_3 *cis* isomer), 3.7 (3H, s, CO_2CH_3 *trans* isomer), 3.45-2.9 (5H, m, C_3 ring protons, CH_2-CHCO *cis*, *trans*, and CHCO *cis* isomers), 3.9 (2H, s, benzyl protons), 4.0 (1H, apparent quartet, $J_{\text{trans}} = 3.0$ Hz, CHCO *trans* isomer), 7.35 (5H, s, aromatic protons); exact mass measurement: Calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{N}$: 219.1259. Found: 219.1256 (± 0.0002).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{N}$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.41; H, 7.78; N, 6.27.

As with structurally similar azetidines reported from this laboratory previously, the cyclization reaction yields a mixture of geometric isomers which are inseparable by normal distillation or chromatographic means. Nmr integration of the carbomethoxy singlets indicates a ratio of 60:40 with the larger quantity being tentatively assigned the *cis* structure, based on discussions presented in previous publications (7-9).

A 5.0 g. sample (0.024 mole) of 1-benzyl-2-carbomethoxy-4-methylazetidine was added dropwise, with stirring, to a 0.012 mole sample of barium hydroxide octahydrate in 80 ml. of water at 90°. The solution was

stirred at this temperature for thirty minutes and the barium salt of the azetidine partially precipitated. An additional 40 ml. of water was then added and carbon dioxide bubbled in for 10 minutes. Filtration of the barium salt and evaporation of the water yielded a viscous yellow oil which crystallized within 10 minutes. Recrystallization from methanol-ether yielded 4.1 g. (83%) of white solid (III), m.p. 169-171°; ir (potassium bromide): 1630 cm^{-1} (ionic carboxylate); nmr (deuterium oxide): δ 1.2 (3H, d, $J = 6.0$ Hz, CH_3 *trans* isomer), 1.55 (3H, d, $J = 7.0$ Hz, CH_3 *cis* isomer), 2.65-2.3 (1H, m, CH_3 -CH-N *cis*, *trans* isomers), 4.2 (2H, s, benzyl protons), 4.8-4.2 (4H, m, partially masked by deuterium oxide exchange, CHCO, CH_2 , CHCO), 4.7 (1H, s, CO_2H proton deuterium oxide exchange), 7.3 (5H, s, aromatic protons); the nmr integration of CH_3 doublets shows a *cis:trans* ratio of 90:10, respectively; exact mass measurement: Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{N}$: 205.11027. Found: 205.11001 (± 0.0001).

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{N}$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.05; H, 7.37; N, 6.72.

A 1.0 g. sample of (III) was dissolved in 70 ml. of anhydrous methanol and to this was added 0.5 g. of Pearlman catalyst (20% palladium on charcoal) prepared according to the previously published procedure (10). The heterogeneous mixture, at 25°, was placed in a Parr shaker and hydrogenated at 47 psi for 13 hours. At the end of the required time, the catalyst was filtered and washed with 50 ml. 95% methanol and 75 ml. of water. The filtrates were combined and evaporated under reduced pressure, to yield a yellow oil. The oil was dissolved in 10 ml. of methanol and ether was added to affect crystallization of 0.4 g. (72% yield) of a white solid (IV) which slowly darkened above 175° and decomposed at 200-201°;

ir (potassium bromide): 1600 cm^{-1} (ionic carboxylate); nmr (deuterium oxide): δ 1.5-2.8 (5H, m, CH_2 -CHCO, and d, $J = 6.5$ Hz, *cis* isomer CH_3), 4.6-4.3 (1H, m, CH_3 -CH-N), 4.8 (2H, broad s, CO_2H , NH exchange which partially masks CH_2 - CO_2H multiplet). No evidence of the *trans* isomer was observed in the nmr spectrum; exact mass measurement: Calcd. for $\text{C}_5\text{H}_9\text{O}_2\text{N}$: 115.06332. Found: 115.06324 (± 0.0001).

Anal. Calcd. for $\text{C}_5\text{H}_9\text{O}_2\text{N}$: C, 52.17; H, 7.88; N, 12.17. Found: C, 51.80; H, 7.76; N, 11.89.

REFERENCES AND NOTES

- (1) Author to whom inquiries should be addressed.
- (2) L. Fowden, *Biochem. J.*, **64**, 323 (1956).
- (3) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **6**, 435, 993 (1969).
- (4) H. F. Jacobson, J. Asso and D. Baltimore, *J. Mol. Biol.*, **49**, 657 (1970).
- (5a) P. J. Peterson and L. Fowden, *Nature*, **200**, 148 (1963);
- (b) L. Fowden and M. H. Richmond, *Biochem. Biophys. Acta*, **71**, 459 (1963).
- (6) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 421 (1971).
- (7) S. B. Kulkarni, R. M. Rodebaugh, and N. H. Cromwell, *ibid.*, **13**, 329 (1976).
- (8) N. H. Cromwell and B. Phillips, *Chem. Rev.*, **79**, 350 (1979).
- (9) D. S. Soriano, K. F. Podraza and N. H. Cromwell, (included in a recently submitted article).
- (10) W. M. Pearlman, *Tetrahedron Letters*, **17**, 1663 (1967).
- (11) The chemical shifts and coupling constants (J), reported in δ and Hertz, respectively, using a Varian A60-D nmr, with TMS as the internal standard, with the exception of spectra recorded in deuterium oxide solution, where acetone was used as the internal standard.