Resolution of DL-Azetidine-2-carboxylic Acid

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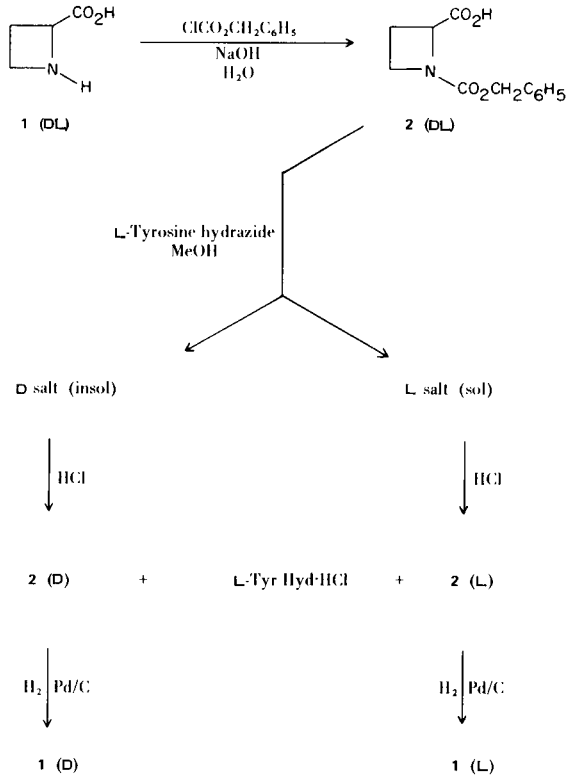
Sir:

Recently we reported (2) the development of a facile and economical method of synthesizing the DL-form of the naturally occurring imino acid, L-azetidine-2-carboxylic acid, from γ-butyrolactone in 53.5% overall yield. In view of the increasing interest (3) in the biological potentialities of the natural isomer it seemed desirable to resolve the DL-form of this acid into its optical enantiomers.

The structural similarities between azetidine-2-carboxylic acid and proline suggested that methods which have been employed successfully to resolve DL-proline might also be applicable to the lower homolog. Recently Vogler and Lanz (4) reported L-tyrosine hydrazide to be a useful resolving agent for proline as well as for several other amino acids. We have found that this particular base can be utilized with a high degree of success in resolving azetidine-2-carboxylic acid.



Treatment by standard procedures (5) of the DL-imino acid (1) with benzyl chloroformate in the presence of aqueous sodium hydroxide followed by extraction with ethyl acetate, drying and evaporation of the solvent provided a quantitative yield of the *N*-carbobenzoxy derivative (2) as a viscous, noncrystallizable oil which exhibited infrared absorption (carbon tetrachloride) at 1720 cm^{-1} (carboxyl and carbamate ν C=O). The nmr spectrum (deuteriochloroform) contained a singlet (1H) at 666 Hz (CO_2H), a singlet (5H) at 433 Hz (aromatic protons), a singlet (2H) at 303 Hz ($CH_2C_6H_5$), a quartet (1H) at 280 Hz (J_{trans} = 6.1 Hz, J_{cis} = 8.6 Hz, CH_2CHCO), a multiplet (2H) at 214-247 Hz (CH_2N), and a multiplet (2H) at 120-161 Hz (CH_2CHCO). Compound 2 was analyzed as its L-tyrosine hydrazide salt, m.p. 205-206.5°.

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.31; H, 6.14; N, 12.84.

A solution of 2 (3.0 g., 0.013 mole) in methanol (60 ml.) was treated with L-tyrosine hydrazide (2.49 g., 0.013 mole) and the suspension was boiled for ten minutes and filtered giving a white crystalline solid. The filtrate was stirred for twenty hours at 25° and the small amount of solid which separated was combined with the original precipitate giving 2.70 g. (98%) of the D salt, m.p. 205-206.5°. Evaporation of the solvent from the mother liquor provided 2.53 g. (92%) of the L salt as a semisolid.

Dissolution of the D salt in 12 ml. of water, addition of 3 ml. of concentrated hydrochloric acid and extraction with ethyl acetate followed by drying (magnesium sulfate) and evaporation of the solvent gave 1.40 g. (95%) of the pure D-form of the *N*-carbobenzoxy derivative (2) as an oil, $[\alpha]_D^{20}$ = +98.5° (*c* = 3.9 in chloroform) (6). Treatment of the L salt in a similar manner provided 1.23 g. (89%) of 2 (L) as an oil, $[\alpha]_D^{20}$ = 99.0° (*c* = 3.9 in chloroform) (6).

Catalytic hydrogenolysis of compound 2 (D) in methanol over 10% palladium on charcoal at 4 atmospheres gave 0.35 g. (59%, 55% overall yield) of D-azetidine-2-carboxylic acid, $[\alpha]_D^{20}$ = +107.5° (*c* = 3.5 in water). Similar hydrogenolysis of 2 (L) afforded 0.39 g. (74%, 61% overall yield) of L-azetitine-2-carboxylic acid, $[\alpha]_D^{20}$ = -109° (*c* = 3.6 in water), literature value (7), $[\alpha]_D^{20}$ = -108°.

Previously we had attempted to utilize several of the more common resolving bases such as brucine, strychnine, etc.; however, admixtures of these bases with several different *N*-acyl derivatives of DL-azetidine-2-carboxylic acid gave only noncrystallizable oils.

The procedure described above constitutes an exceedingly facile method of chemical resolution and it is practical as well since the yields are good and most of the resolving agent can be recovered (4). This resolution completes the first reported synthesis of the natural product, L-azetidine-2-carboxylic acid.

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(6) The specific rotation values for **2** (D and L) are only approximate due to the possibility of unremoved solvent.

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