Synthesis and Epimerization of 1-Alkyl-2-carbomethoxy-4-methyl (or phenyl)azetidines

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A number of 1-alkyl-2-carbomethoxyazetidines have been prepared from the reaction of primary amines with α,γ-dibromocarbonyl compounds. A series of base catalyzed reactions performed on selected *cis*, *trans*-1-alkyl-2-carbomethoxy-4-alkyl(aryl)azetidines reveal the *cis* isomer to be of greater thermodynamic stability. Furthermore, base catalyzed deuterium exchange studies suggest this to be the case.

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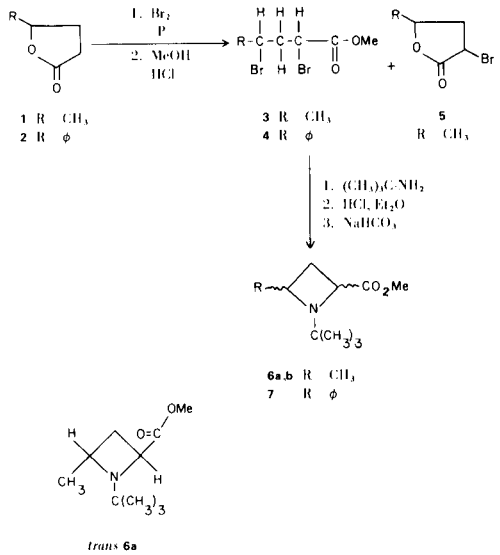
Results and Discussion

In previous publications (2) we reported that several primary amines react with α,γ-dibromocarbonyl compounds to afford, in useful yields, various 2-carboazetidines.

Chart I



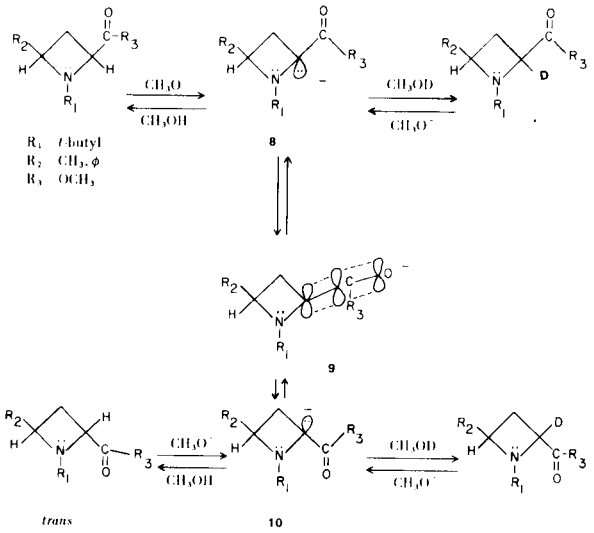
The epimeric pair of azetidinylesters **6a,b** was obtained by condensation of methyl α,γ-dibromovalerate with *t*-butylamine, the isomers being separated by preparative vpc (3). In the earlier publication (3) the preparation of **6a,b** was described but it now appears that the tentative configurations of these geometrical isomers which were assigned now need to be reversed.

β-Benzoylpropionic acid was reduced by sodium borohydride and lactonized by vacuum distillation to γ-phenyl-γ-butyrolacetone (**2**). Lactone **2** was converted to methyl 2,4-dibromo-4-phenylbutyrate (**4**) by treatment of the former with bromine and a catalytic amount of phosphorus. The azetidinylester **7** was obtained by condensation of **4** with *t*-butylamine (Chart I).

Bottini and Roberts (4) have suggested that attachment of substituents to aziridine ring carbons leads to greater nitrogen inversion rates, but that such groups if affixed in a *cis* orientation to one another tend to make the molecules assume preferred conformations with the *N*-substituent *anti* to the other ring substituents. It has been found in this laboratory (5) that the *cis* compounds do assume the preferred conformation as suggested above. If a similar situation is assumed to apply in the azetidines **6a,b** then, the *cis* azetidine **6b** should exist in the preferred conformation with the carbomethoxy and *t*-butyl gorups *trans* to each other. It has been observed by Nagel and Cromwell (5) that in the case of *trans*-1-alkyl-2-aryl-3-carboaziridines, the preferred conformation is the one with the *N*-alkyl group and the benzoyl occupying a *syn* relationship.

It has been previously proved (6) that protons lying in conical regions, extending above and below the plane of the trigonal carbon atom of a carbonyl group, will be shielded by this function, while those lying elsewhere, and particularly those in the plane of the trigonal atom, will be deshielded. The careful examination of molecular models reveals that the C_4-methine proton comes in the carbonyl deshielding zone and, therefore, it appears at a comparatively lower field. The C_4-methine proton of **6a** appears at a lower field (at 252 Hz) than that of **6b** (at 190-213

Chart 2



Hz). Therefore, compound **6a** is the *trans* isomer and **6b** is the *cis* isomer.

The nmr spectrum of the product **6** indicated the mixture to consist of *ca.* 57% of the *cis* epimer and 43% of the *trans* isomer. Refluxing this mixed product with sodium methoxide in methanol for 48 hours increased the *cis/trans* percentage ratio to 74%/26% with no destruction of product, indicating that the *cis* isomer is thermodynamically more stable than the *trans* isomer. When this mixed product was stirred for 72 hours with sodium methoxide in deuterated methanol, 60% deuterium incorporation was observed and the *cis/trans* percentage ratio increased to 74%/26%.

The nmr spectrum of compound **7** indicated the product to be only one isomer. Refluxing this product **7** with sodium methoxide in methanol for 48 hours did not effect epimerization to another isomer. When compound **7** was stirred for 72 hours with potassium *t*-butoxide in deuterated methanol 50% deuterium incorporation was observed; however, no epimerization was detected.

An examination of molecular models for these *cis* and *trans* pairs suggest less lone pair-lone pair interaction is to be expected in the carbanion of the *cis* isomer **8** than that of the *trans* carbanion **10** and is consistent with Gillespie-Nyholm VSEPR theory (8). Also 1,2-non-bonded interactions can be minimized in the *cis* isomers owing to the *anti*-position of the group on nitrogen relative to those at C-2 and C-4 (see Chart 2). The *cis* carbanion would be expected to rapidly take up either hydrogen or deuterium and retain its configuration. On the otherhand, the *trans* carbanion can be expected to stereomutate, *via* the enolate intermediate **9** to the more stable *cis* carbanion which then again acquires a proton or deuteron to form the *cis* isomer.

The fact that the *N*-alkyl group is oriented mainly *syn* to the carbonyl group in the *trans* isomer (5) further destabilizes the *trans* isomer and slows formation of its carbanion.

In principle, the *cis* isomer stability appears greater than that of the *trans* analog when these systems tend toward equilibrium. Hence the *cis* azetidinylester skeleton is of greater thermodynamic stability than that of the more highly conjugated *trans* compound. Therefore, *cis* configuration is assigned to the 1-*t*-butyl-2-carbomethoxy-4-phenylazetidine (**7**). This result was in agreement with the behavior of the related 1-alkyl-2-methyl-3-aroylaziridines for which the *cis* isomer was shown to be thermodynamically more stable than the *trans* isomer (9). A comparable discussion of the relative stabilities of the *cis*- and *trans*-1-alkyl-2-aryl-3-aroylaziridines and their carbanions has recently been published by Tarburton and Cromwell (10). Results similar to ours appear to have been obtained by Robert Carrie and his co-workers (7) in the case of 1,4-diphenyl-2-carbomethoxyazetidine.

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 analysis were performed by Micro Tech Laboratories, Skokie, Illinois. The infrared spectra were recorded on a Perkin-Elmer Model 621 Grating Infrared Spectrophotometer using carbon tetrachloride solutions. The nmr spectra were recorded on a Varian A-60 spectrometer and the chemical shifts are reported in Hertz, with tetramethylsilane as an internal standard. The mass spectra were determined on a Hitachi RMU-6D spectrometer.

The preparation of compounds **1**, **3**, **5** have been reported previously (3).

1-*t*-Butyl-2-carbomethoxy-4-methylazetidines (**6a,b**).

The preparation of compounds **6a,b** have been reported previously (3), and their nmr and ir spectra were described. A modified interpretation of these nmr and ir spectra is given below.

Cis Isomer **6b**.

Ir (carbon tetrachloride): 1751/70 (ester ν_1, C=O% abs.) and 1725 cm^{-1}/63 (ester ν_2, C=O% abs.); nmr (deuteriochloroform): 227 (t, 1H, J = 8.2 Hz C_2 proton), 223 (s, 3H, methoxy), 190-213 (m, 1H, C_4 methine proton), 96-153 (m, 2H, C_3 protons), 75 (d, 3H, J = 5.9 Hz, C_4 methyl) and 59 Hz (s, 9H, *t*-butyl).

Trans Isomer **6a**.

Ir (carbon tetrachloride): 1751/57 (shoulder-ester ν_1, C=O% abs.) and 1738 cm^{-1}/82 (ester ν_2, C=O% abs.); nmr (deuteriochloroform): 252 (q, 1H, J *cis* = 7.6 Hz, J *trans* = 5.0 Hz, C_2 protons), 252 (m-partially masked by C_2H quartet, 1H, C_4 methine proton), 223 (s, 3H, methoxy), 87-152 (m, 2H, C_3 protons), 77 (d, 3H, J = 6.1 Hz, C_4 methyl), and 63 Hz (s, 9H, *t*-butyl).

Partial Epimerization of 1-*t*-Butyl-2-carbomethoxy-4-methylazetidine (**6a,b**).

A 0.25 g. sample of **6a,b** (57% *cis* and 43% *trans*) was refluxed in 2 ml. of absolute methanol with 0.04 g. of sodium methoxide

for 48 hours. The methanol was evaporated, ether added, and the suspension filtered. Removal of the ether followed by a double evaporation with 2 ml. portions of carbon tetrachloride gave a yellow oil, the nmr spectrum of which indicated by electronic integration the presence of 74% of the *cis* isomer **6b** and 26% of the *trans* isomer **6a**.

Reaction of Compound **6a,b** with Deuterated Methanol and Sodium Methoxide.

A 0.350 g. sample of **6a,b** (57% *cis* and 43% *trans*) was stirred in 5 ml. of deuterated methanol with 0.065 g. of sodium methoxide for 72 hours. The methanol was evaporated, ether added and the suspension filtered. Removal of the ether followed by a double evaporation with 3-ml. portions of carbon tetrachloride gave a yellow oil, the nmr spectrum of which indicated 60% of deuterium incorporation, and by electronic integration, the presence of 74% of the *cis* isomer **6b** and 26% of the *trans* isomer **6a**.

Synthesis of γ-Phenyl-γ-butyrolactone (**2**).

A 8.91 g. sample of β-benzoylpropionic acid was dissolved in 20% sodium hydroxide solution. The solution was stirred and 1.01 g. of sodium borohydride was added slowly. This reaction mixture was further stirred for 2 hours at room temperature and 8.0 ml. of concentrated hydrochloric acid was added slowly for strong acidity. The water layer was then extracted with 200 ml. of ether and 100 ml. of chloroform. The ether and chloroform extract was dried over magnesium sulfate, filtered and solvent evaporated to give 7.99 g. of crude product. This was distilled under vacuum to give 7.02 g. of colourless oil, b.p. 114° at 0.1 mm Hg. This colourless oil solidified on cooling, m.p. 38° (Lit. m.p. 38°) (11).

Synthesis of Methyl 2,4-Dibromo-4-phenylbutyrate (**4**).

To a stirred suspension of a catalytic quantity of red phosphorus in 8.35 g. (0.0516 mole) of γ-phenyl-γ-butyrolactone in 34 ml. of carbon tetrachloride was added 2 ml. of bromine in 5 ml. of carbon tetrachloride. After stirring for 1 hour at room temperature, the suspension was heated to reflux and 3.5 ml. (0.066 mole) of bromine in 11 ml. of carbon tetrachloride was added dropwise through a long-stemmed dropping funnel beneath the surface of the liquid. When the rate of bromine uptake decrease as evidence by a temperature decrease, a small quantity of red phosphorus was added and the remaining bromine was added in a dropwise manner as before. After all the bromine had been added the reaction mixture was stirred for 1 hour. It was then allowed to cool slowly to room temperature, the carbon tetrachloride was evaporated under rotary evaporator, and the mixture finally cooled to 0° in an ice bath. Methanol (50 ml.) was cooled to 5° and added to the original reaction mixture. The cooled solution was saturated with dry hydrogen chloride gas, the flask was stoppered tightly and the mixture stirred magnetically at room temperature for 35 hours. The excess methanol was evaporated under reduced pressure. The residual oil was dissolved in 100 ml. of ether, washed with 3% sodium bicarbonate solution, dried over magnesium sulfate, and the ether evaporated. The product was obtained as a pink oil by column chromatography on florisil, using benzene as eluent. After standing for two days at room temperature a portion of the oily product crystallized. The crystals were separated from the oil and recrystallized from hot petroleum ether (b.p. 60-69°) colourless crystals were obtained, 12.5 g., m.p. 71-73°, yield 55%; ir (carbon tetrachloride): (ester ν C=O) 1740 cm^{-1}; nmr (deuteriochloroform): 170-213 Hz (m, 2H, C_3 methylene protons), 228 Hz (s, 3H, methoxy), 280-327 (m, 2H, C_2 and C_4-methine protons), 450 Hz (s, 5H, C_4-phenyl protons).

Anal. Calcd. for $C_{11}H_{12}Br_2O_2$: C, 39.22; H, 3.60. Found: C, 39.29; H, 3.80.

Synthesis of *cis*-1-*t*-Butyl-2-carbomethoxy-4-phenylazetidine (**7**).

A solution of 17.0 g. (0.050 mole) of methyl 2,4-dibromo-4-phenylbutyrate (**4**) and 21.9 g. (0.30 mole) of *t*-butylamine in 300 ml. of benzene was stirred for 72 hours. The mixture was diluted with ether (100 ml.), filtered, and the solvent evaporated. The residue was extracted with ether (300 ml.) and the extract exposed to a stream of hydrogen chloride gas for 5 minutes. The ether was decanted and the residual syrup was dissolved in 50 ml. of water. The aqueous solution was washed twice with ether (discarded), 200 ml. of ether added and solid sodium bicarbonate added to effect neutrality. The ether layer was separated, the aqueous layer washed with three 50 ml. portions of ether, and the combined ether extracts dried over magnesium sulfate. Evaporation of ether gave 3.5 g. of orange, oily product. This liquid was purified by column chromatography on silica gel using benzene as eluent. The product was obtained as a colourless oil, 3.2 g. (28% yield); ir (carbon tetrachloride): (ester ν_1 C=O) 1750 cm^{-1} and (ester ν_2 C=O) 1725 cm^{-1}; nmr (deuteriochloroform): 65 Hz (s, 9H, *t*-butyl), 114-173 (m, 2H, C_3 protons), 199 (t, 1H, J = 7.9 Hz, C_2 methine proton), 250 (q, 1H, J *cis* = 7.5 Hz, J *trans* = 5.2 Hz, C_4 methine proton), 222 (s, 3H, C_2 methoxy), 440-487 Hz (m, 5H, C_4 phenyl proton), m.p. picrate (ethanol) 162.5-164°.

Anal. Calcd. for $C_{21}H_{24}N_5O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.09; H, 5.12; N, 11.90.

Attempted Epimerization of 1-*t*-Butyl-2-carbomethoxy-4-phenylazetidine (**7**).

A 0.300 g. sample of **7** was refluxed in 5 ml. of absolute methanol with 0.05 g. of sodium methoxide for 48 hours. The methanol was evaporated, ether added and the suspension filtered. Removal of the ether followed by a double evaporation with 2 ml. of carbon tetrachloride gave a yellow oil, the nmr spectrum of which indicated no epimerization to the other isomer.

Reaction of **7** with Deuterated Methanol and Potassium *t*-Butoxide.

A 0.350 g. sample of 1-*t*-butyl-2-carbomethoxy-4-phenylazetidine (**7**) was stirred in 5 ml. of deuterated methanol with 0.050 g. of potassium *t*-butoxide for 72 hours. The methanol was evaporated, ether added and the suspension filtered. Removal of the ether followed by a double evaporation with 3 ml. portions of carbon tetrachloride gave a yellow oil, the nmr spectrum of which indicated 50% deuterium exchange; however, no epimerization was detected.

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(1) To whom inquiries should be addressed.

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