Proximate Functionality Induced Restricted Rotation of a Carbamate: 2,6-Dicarbethoxy-7-methoxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline

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The 6-carbethoxy group of 2,6-dicarbethoxy-7-methoxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline (**4**) is observed by nmr to experience an unusual steric barrier to free rotation about the N-CO bond which arises from the proximate 7-methoxy group.

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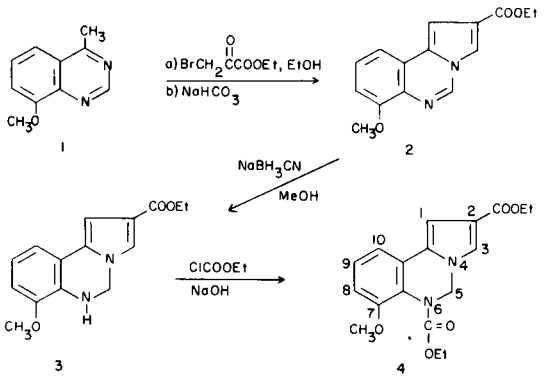
Sir:

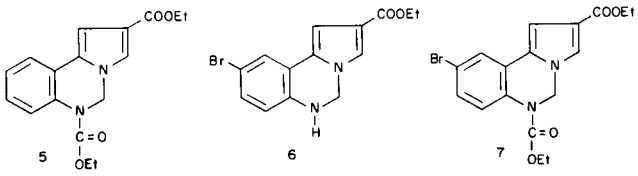
We have observed by nmr an unusual steric barrier to rotation of a carbamate about the N-CO bond. The 6-carbethoxy group of 2,6-dicarbethoxy-7-methoxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline (**4**) experiences a steric barrier to free rotation which arises from the adjacent 7-methoxy group. Carbamates are known to exist as two rotational isomers and their internal rotation has been studied by nmr (1). Our example represents the first report of this barrier to internal rotation arising from the steric bulk of a proximate function.

The carbamate **4** was synthesized from 8-methoxy-4-methylquinazoline (**1**) (2) in 33% overall yield as shown in the following scheme (3):



The C-5 methylene protons of **4** appeared in the nmr (deuteriochloroform and DMSO-d_6) as a broad signal (~40-80 Hz) at the ambient temperature of the probe (35°). This was in marked contrast to the spectrum of its precursor (**3**), in which these protons appeared as a narrow doublet (J = 2 Hz), which became a sharp singlet when coupling to the amine proton was removed by addition of deuterium oxide. The apparent equivalency of the C-5 methylene protons of **3** could be the result of a planar conformation for the dihydropyrimidine ring or most probably due to a time averaged spectrum involving rapid nitrogen inversion with concurrent ring inversion. In the related tetrahydropyrimidine system this type of rapid ring inversion-nitrogen inversion has been reported (4).

It was suspected that the 7-methoxy group was a major contributor to the time dependent phenomenon observed in the spectra of **4**, since the 7-desmethoxy compound **5** (5) did not display any anomalous behavior. The C-5 methylene protons of **5** appeared as a sharp singlet and only one carbamate isomer was observed in the nmr at ambient temperature. Either one carbamate rotomer was predominant at this temperature or we were above the coalescence temperature for the rotomers. Evidence to support the latter conclusion came from inspection of the spectra of the related compounds **6** and **7** (6). In **7**, the C-5 methylene protons or the 7-aromatic proton should appear downfield from their respective positions in the parent compound **6** depending upon the orientation of the anisotropic carbonyl of the carbamate group. This effect has been previously noted with amide rotomers (7). In **6** (deuteriochloroform) the C-5 methylene protons appeared at δ = 5.06 and the C-7 aromatic proton at δ = 6.56, while in **7** they appeared at δ = 5.60 (Δ = 0.54 ppm) and δ = 7.37 (Δ = 0.81 ppm), respectively. The protons at both positions 5 and 7 in compound **7** experienced a downfield shift. These results suggest that we are observing the time-averaged spectrum of the free rotation of the carbamate group in both **5** and **7**.



The effect of temperature on the time dependent phenomenon observed for **4** was explored (8). At ambient temperature, the C-5 methylene protons were a broad signal while the other resonances in the spectrum appeared normal in both deuteriochloroform and DMSO-d_6. When the spectrum was obtained in DMSO-d_6 at 80°, the methylene protons became a sharp singlet which experienced further narrowing when the temperature was raised to 100°. Low temperature studies of **4** were conducted in

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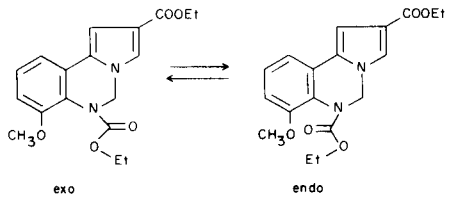
deuteriochloroform and coalescence was observed at 19°. When the temperature was lowered to −15.5°, the C-5 methylene protons appeared as one AB quartet (J = 12 Hz) centered at δ = 4.83 and δ = 6.23. No evidence for another isomer was observed.



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Two carbamate rotomers can exist for **4**, the *exo*- and the *endo*-isomers. The low temperature nmr studies suggest that one isomer predominates, which appears to be the *exo*-isomer, judging from the large chemical shift differences between the two C-5 protons. In *exo*-4 large chemical shift differences between the two methylene protons would result if the carbonyl of the carbamate did not lie in the plane bisecting these protons, while in *endo*-**4** such large chemical shift differences would not be expected. The observation of only one isomer does not rule out the possibility of the presence of another isomer at much lower concentration. The energy barrier calculated from the coalescence temperature data was 13.9 kcal/mole (9). This value is of the same order reported for barriers to rotation for both amides (10) and carbamate groups (11).

The non-planarity of the dihydropyrimidine ring or the deformation of the carbamate group from non-planarity must be considered based on the lower temperature nmr observations. The dihydropyrimidine ring may exist in more than one conformer. Inversion from one conformer to another might be restricted by the steric bulk of the 7-methoxy and 6-carbethoxy groups. Alternatively, deformation of the carbamate group at the N-CO bond to relieve the severe steric constraints in this molecule may be present, leading to a non-planar conformation of the dihydropyrimidine ring. In this case, one preferred conformation may be present with the N-CO bond of the carbamate out of the plane of the 7-methoxy group. Rotation of the carbamate from *exo*- to *endo*-isomer would involve an intermediate in which the carbamate is constrained to reside in the plane of the 7-methoxy group, resulting in an increased barrier for rotation of the carbethoxy group.

Acknowledgments.

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(3) All compounds reported had acceptable elemental analyses and mass spectra.

(4) H. Booth, *J. Chem. Soc.*, 1841 (1964).

(5) This compound was synthesized in an analogous manner to **4**, starting with 4-methylquinazoline.

(6) Compounds **6** and **7** were synthesized in an analogous manner to **4**, starting with 6-bromo-4-methylquinozoline.

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(8) Nmr studies were run on a Varian T60-A equipped with a T-6080 variable temperature accessory.

(9) This value was calculated using the equations:

$$k_c = \pi (\delta\omega^2 + 6J^2)^{1/2}/\sqrt{2}$$

$$k = k_o e^{-E_a/RT}$$

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