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Conformational Analysis of Substituted Hexahydropyrrolo [2,3-*b*]indoles and Related Systems. An Unusual Example of Hindered Rotation about Sulfonamide S-N Bonds. An X-ray Crystallographic and NMR Study

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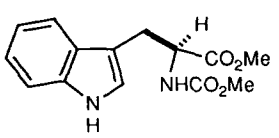
Abstract: An indepth comparison of the solution ($CDCl_3$, ^{1}H-NMR) and solid state (X-ray) conformations of the hexahydropyrrolo[2,3-*b*]indoles **4**, **5**, and **6** is made. Close parallels with the literature conformations of the aflatoxin furo[2,3-*b*]benzofuran skeleton and with the conformation of the naturally occuring hexahydropyrrolindole physostigmine are noted. In the solid state the sulfonamide N in **4** - **6** is non-planar with various degrees of rotation about the S-N bond. In solution, variable temperature ^{1}H-NMR evidence indicates hindered rotation about the N-S bond of the sulfonamide group in **4** - **6**, possibly coupled to inversion of the pyramidal sulfonamide N atom. Reaction of **5** with LDA followed by quenching with methyl iodide resulted in alkylation with clean inversion of configuration.

The acid mediated tautomerization of *N*-methoxycarbonyl tryptophan methyl ester (**1**) results in an equilibrium mixture of the two hexahydropyrrolo[2,3-*b*]indoles (**2**) and (**3**) in which the *endo*-2-methoxycarbonyl isomer (**2**) predominates very significantly.[1] After sulfonylation the sulfonamides **4** may be isolated in high yield as single diastereomers. These sulfonamides have proven especially useful in the synthesis of enantiomerically pure α- and β-substituted tryptophan derivatives,[2] as well as in the synthesis of pyrrolo[2,3-*b*]indole alkaloids,[3] owing to their extreme propensity for reaction on the less hindered, *exo*-face of the diazabicyclo[3.3.0]octane framework. With a view ultimately to biasing the equilibrium ratio of **2** and **3** toward the *exo*-isomer **3**, we have been interested in probing the factors determining the stability of **2** vis à vis **3**.[4] Below we describe the conformational analysis of **2** and **3**, based on an X-ray crystallographic analysis of the sulfonamide derivatives **4** and **5**, from which we draw the conclusion that subtle conformational effects within the bicyclo[3.3.0]octane nucleus itself are responsible for the observed difference in energies. We also present evidence for hindered rotation about the S-N bond in **4**. Furthermore, we demonstrate that alkylation of **5** occurs with inversion of configuration at C2.



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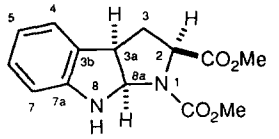

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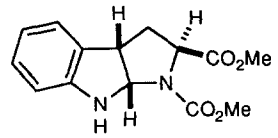

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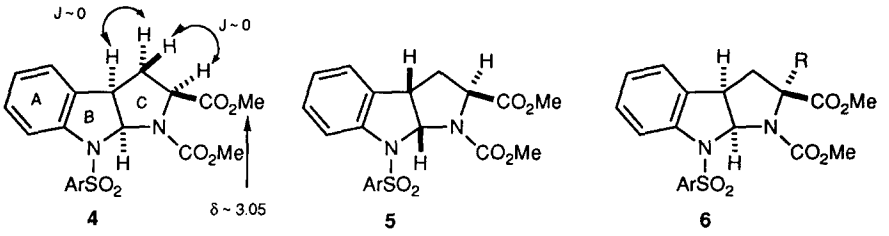
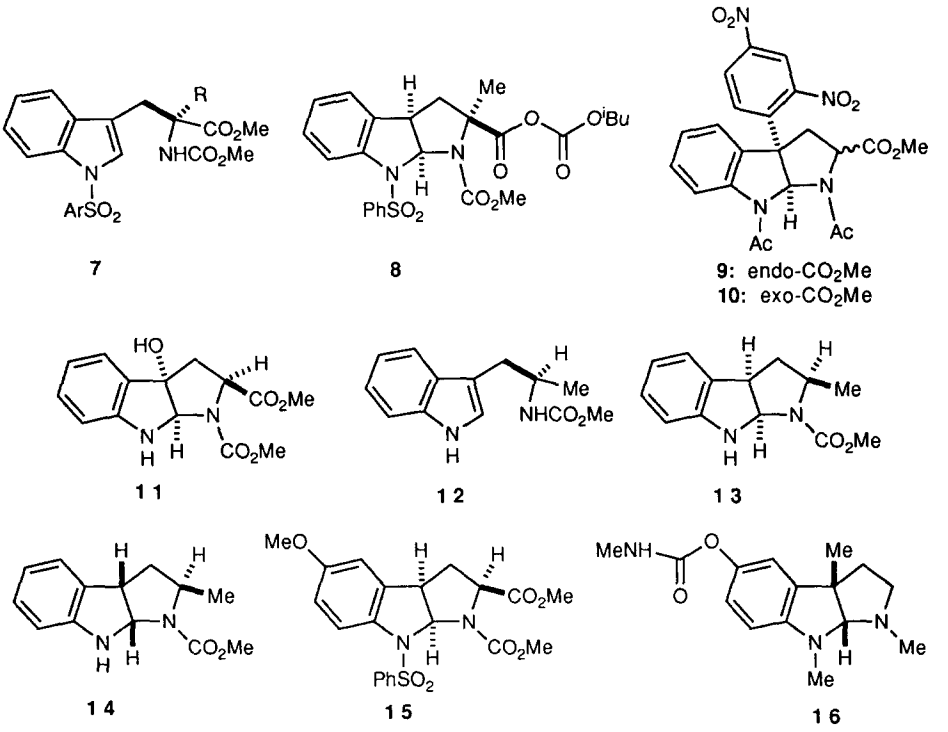


In 85% H_3PO_4 **1** undergoes clean tautomerization to **2** and **3** in an approximate ratio of 9:1. After work-up, sulfonylation of the crude reaction mixture in pyridine enables isolation of the sulfonamides **4** as single, mostly crystalline, diastereomers. Deprotonation of **4** with LDA followed by reaction with alkyl halides results in clean alkylation at C2 with retention of configuration, as in **6**. Treatment of this alkylated product with trifluoroacetic acid then brings about ring opening to the tryptophan **7**. Overall, after deprotection, this sequence permits alkylation of tryptophan with retention of configuration, without recourse to a chiral auxiliary. In principle, application of the same deprotonation, alkylation, ring opening sequence to a sulfonamide **5** derived from **3** would enable α-alkylation of tryptophan with inversion of configuration and so the use of inexpensive L-tryptophan in the formation of α-alkyl-D-tryptophan derivatives. In practice we have been unable to realize this highly desirable protocol owing to our inability to manipulate the equilibrium of **1** with **2** and **3** so as to permit the isolation of **3**, or its derived sulfonamide, in workable quantities. Recently however, we succeeded in the isolation of a minor amount of **5**. The structure of **5** has been determined by single crystal X-ray analysis which, together with that of **4**, enables us to conduct an informed comparison of the two isomers and so to comment on the enhanced stability of **2** with respect to **3**.

As previously described, ^{1}H NMR analysis of **4** shows that the C-ring adopts a half-chair conformation in which C2 is puckered in toward the *endo*-surface of the bicyclic system.[2b,4] This solution conformation is indicated by the combination of the highly shielded nature of the ester Me group (typically δ 3.05 ppm) resulting from its location directly under the A-ring and by the zero values of the ^{3}J couplings between H2 and H3endo as well as between H3endo and H3a. This analysis is nicely confirmed by the crystal structure depicted in Fig 1. A parallel conformation is adopted in solution and in the crystal (Fig. 2) by the α-alkylated derivatives, as for example by **6**, by the crystalline mixed anhydride **8**,[2f] by the 3a-aryl derivative **9**,[5] and by the 3a-hydroxy derivative **11**.[6] The close proximity of the ester group to the face of the aromatic A-ring initially suggested that **4** (and hence **2**) was stabilized by an attractive, through space, interaction between the two moities. An experiment in which the α-methyltryptamine **12** was subjected to treatment with TFA/$CDCl_3$ leading to the formation of **13** and **14** in the ratio 3.25:1 effectively eliminated this hydpothesis.[4] This experiment also served to invalidate the hypothesis that the preferential formation of **2** rather than **3** is due to H-bonding between the indole-N and the ester group. Additional evidence against a stabilizing, through space, interaction between the electron deficient C7a and the OMe oxygen of the ester group in **4** is provided by the 5-MeO analogue **15** which adopts the same solution conformation.[7] Somei has demonstrated that the 2exo-carbomethoxy derivative **10** undergoes inversion at C2 on treatment with ^{t}BuO$^-$ K$^+$ to give the endo-isomer **9**, clearly indicating that the preference for the 2endo over the 2exo configuration holds under basic as well as acidic conditions.[5]



^{1,3}A strain[8,9] between the endo-ester group and the N1^{+}=C(O^{-})OMe double bond is efficiently minimized in **4** (Fig. 1) and presumably therefore in **2**. However, the possibility that this minimization of ^{1,3}A strain is solely responsible for the observed energy difference between **2** and **3** appears unlikely as an inspection of molecular models reveals that, by inversion of the C-ring, **3** is also capable of reducing ^{1,3}A strain to a strict minimum.

The X-ray crystal structures of sulfonamide **4** and of **6** are presented in Figs 1 and 2. Salient torsion angles of all the various structures presented here are grouped in Table 1 for comparison. The conformations of the ring systems of **4** and **6** are closely related. Both C-rings are imperfect half-chairs. Both molecules have essentially planar carbamate nitrogens and short N1-C9 bonds indicating strong double bond character. In both systems this double bond has the *E*-geometry with the carbonyl oxygen trans to the B-ring. In both systems the ester group is disposed so as to minimize ^{1,3}A-strain with this exocyclic double bond. In both systems the C8a-N8 bond is similarly placed so as to reduce ^{1,3}A-strain. The major difference between the two structures lies in the orientation of the ester group. In **4** it is the C(O)-OMe bond that essentially eclipses the N1-C2 bond whilst in **6** it is the C=O bond. Both of these diametrically opposite conformations can be understood in terms of electrostatic attraction between the positively charged carbamate nitrogen N1 and one or other of the relatively electron rich ester oxygen atoms.

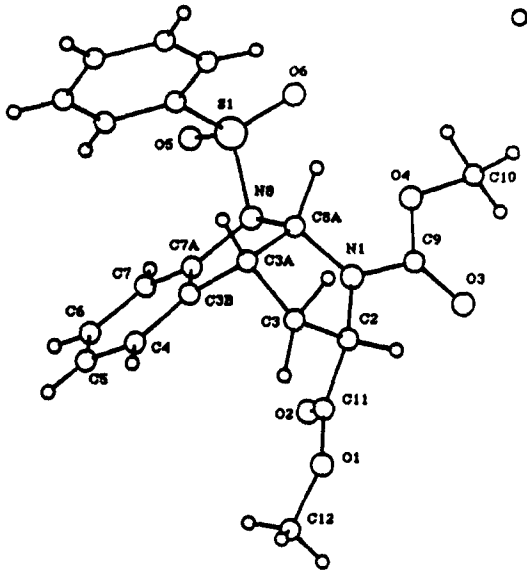


Fig. 1. X-ray Crystal Structure of 4 (Ar = Ph)

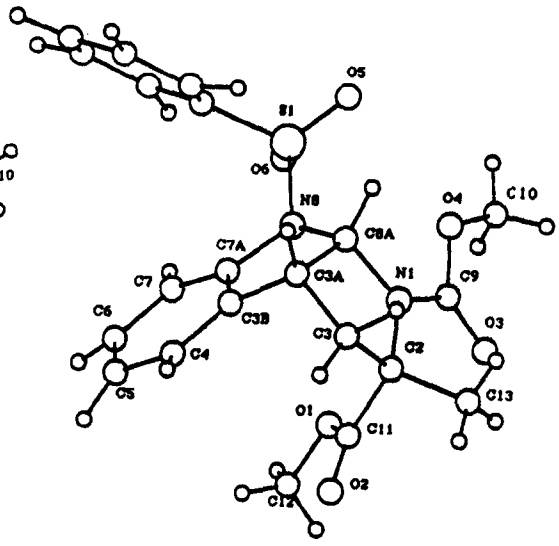


Fig. 2. X-ray Crystal Structure of 6 (Ar = Ph, R = Me)

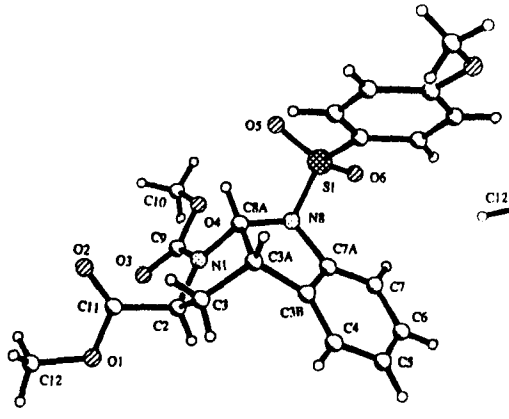


Fig. 3. X-ray Crystal Structure of 5 (Ar = p-$MeOC_6H_4$), Conformer 5A

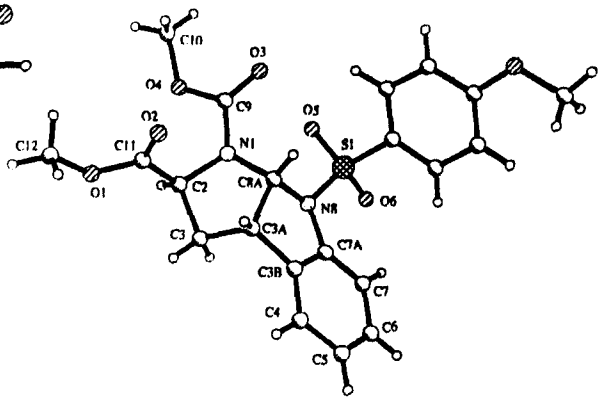
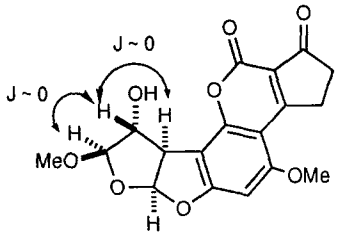


Fig. 4. X-ray Crystal Structure of 5 (Ar = p-$MeOC_6H_4$), Conformer 5B

Table 1. Important Torsion Angles (°) for Hexahydropyrrolidoles **4**, **5A**, **5B**, **6** and **11**

	C9-N1-C2-C11	C9-N1-C8a-N8	C9-N1-C8a-C3a	N8-C8a-C3a-C3b	O1-C11-C2-N1
4	-89.66	77.10	-167.78	19.60	178.98
5A	-46.4	-65.2	-177.2	21.5	-136.7
5B	-46.9	-108.2	140.2	-24.5	-155.9
6	-76.22	61.25	173.23	20.01	5.00
11	81.3			19.0	

Comparison of the conformation of **4** with that adopted in the crystal by the acetylcholinesterase inhibitor physostigmine **16**[10] reveals that, despite the differences in hybridization of N1 between **4** (sp^2) and **16** (sp^3), the two molecules adopt essentially the same conformation with C2 being puckered in toward the endo-face of the molecule. Similarly, comparison can be made with the furo[2,3-*b*]benzofuran skeleton common to the aflatoxins. Thus, it was recently reported[11] that methanolysis of aflatoxin B_1 epoxides gave, *inter alia*, the hydroxy ether **17** in which the ^3J coupling of H2 to H3endo and of H3endo to H3a was approximately zero, indicating a conformation for **17** very similar to that found for **4**. The same effect was noted by Rapoport for **18** in the course of a recent synthetic study.[12] Equally relevant is the observation, supported by semiempirical calculations, by Messeguer, whereby the endo-hydroxy alfatoxin model **19** is favored by a factor of 2:1 over its exo-isomer **20** under equilibrating conditions.[13] Hence, both the hexahydropyrrolo[2,3-*b*]indoles and their furano[2,3-*b*]benzofurans show a preference for a conformation in which C2, in the C-ring, is puckered under the endo-surface of the bicyclic system. Moreover, under equilibrating conditions, substituents at C2 prefer to occupy the endo-site, in both series of compounds.



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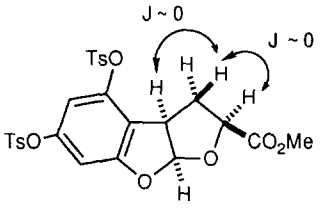

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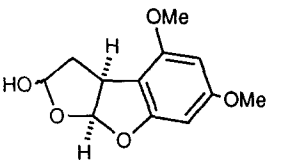
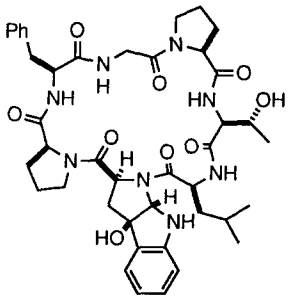


19: endo-OH
20: exo-OH

Careful chromatography of the mother liquers obtained on crystallization of a crude reaction mixture from the sulfonylation of an equilibrium mixture of the cyclic tryptophan tautomers **2** and **3** resulted in the isolation, for the first time, of a crystalline sample of an exo-isomer **5**. X-ray crystal structure determination revealed the presence of two equally populated conformations **5A** and **5B** in the crystal. These are presented in Figs 3 and 4 respectively. The most obvious difference between conformers **5A** and **5B** is the orientation of the carbamate rotamers. In effect in **5A** this is the same (E) as in **4** and **6** whilst in **5B** it is reversed. In conformation **5A** the C-ring is a half-chair closely related to **4** and **6** but with the ester group on the exo-face (Fig 3). Conformation **5B** is also a half chair (Fig 4) but inverted with respect to **5A**. In neither conformation is ^{1,3}A-strain effectively minimized with the torsion angle C9-N1-C2-C11 equal to -46° in both cases. The

recently isolated isophakellistatin 3 (**21**) contains a 2-exo substituted hexahydropyrroloindole framework and whose conformation, as determined crystallographically, is closely related to that of **5B** with the exception that the opposite rotamer of the carbamate is found.[14]



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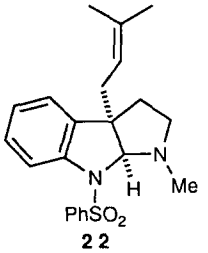
Three of the four structures (**4**, **6** and **5A**) adopt essentially the same conformation for the tricyclic ring system with the same orientation (E) of the carbamate rotamer.[15] The fundamental difference between **4**, with its endo-ester, and **5A**, with its exo-ester, which reflects directly on the difference between **2** and **3** and so on the preferential formation of **2**, is that ^{1,3}A-strain is better minimized in **4** than in **5A**. Why does **5A** adopt this conformation of the C-ring and not an inverted chair which would better minimize ^{1,3}A strain ? It effectively attempts to do so in conformer **5B**. Close inspection of **5B** reveals that, in addition to the opposite geometry of the carbamate rotamer, the carbamate nitrogen is no longer planar with the sum of its bond angles 352.1°. Thus, in **5B** the carbamate nitrogen is somewhat pyramidalized with its CO_2Me group disposed toward exo-surface of the bicyclic system. This pyramidalization nullifies any advantage gained by placing the C2 ester pseudoaxial by reducing the torsion angle between the two CO_2Me groups. In **4**, **6** and **5A** the sulfonamide nitrogen (N8) is pseudoequatorially disposed toward the half-chair C-ring whilst C3b is pseudoaxial. In **5B** the inverse is true, as is to be expected from the inverted half-chair conformation of the C-ring. This has the effect of imposing a different conformation on the B-ring. In **4**, **6** and **5A** the B-ring may be considered as an envelop conformation in which C8a is the flap, and toward which the carbamate nitrogen (N1) is pseudoaxial. In **5B** the B-ring is likewise an envelope with N8a as the flap but now N1 is pseudoequatorial. Physostigmine (**16**), and the aflatoxins **17** and **18**, adopt the same B-ring conformation, evident from the X-ray structure of the former and the ^{1}H-NMR parameters of the latter, as **4**, **6** and **5A**. The close conformational homgeneity between **4**, **5A**, **6**, **9**, **11**, **16**, **17** and **18** leads to the notion that this particular conformation is the one that confers minimum strain on the complete tricyclic system. In **4** and **6** the preference for this conformation is enhanced through through minimization of ^{1,3}A strain between the 2-endo substituent and the N1 carbamate. In **5A** imperfectly minimized ^{1,3}A strain between the 2-exo substituent and the N1 carbamate detracts from the stability of the "standard" tricyclic core conformation. In going to conformation **5B**, in which ^{1,3}A strain would be minimized were it not for the pyramidalization of N1, a higher energy conformation is imposed on the tricyclic core. In **17** the preference for the standard tricyclic conformation is presumably enhanced by a favorable anomeric effect. The strong parallels between the conformations of **4**, **6**, **5A**, **8**, **9**, **11**, **17** and **18** also indicate that the sulfonamide group in **4** - **6** does not have a major influence on the overall conformation and hence that the conclusions drawn for **4** - **6** can be transposed to **2** and **3**. *The observed preference for the*

C2 endo substituted system **2** *over the exo-isomer* **3** *is therefore the result of a combination of a minimum energy conformation for the tricyclic core and of minimization of* ^{1,3}*A strain.*[16,17]

In the course of our studies of **4**, **5**, **6** and related substances we have consistently noticed exchange broadening of ^{1}H-NMR signals for spectra ran in $CDCl_3$ solution at room temperature, which was overcome by heating to 50 °C. We previously attributed this phenomenon to slow rotation about the N1-C9 carbamate bond, however inspection of the various crystal structures above prompted us to consider alternate explanations. In particular we were struck by the non-planar nature of the sulfonamide nitrogen (Σ bond angles at N8: 338, 347, 349 and 352° respectively for **4**, **5A**, **5B** and **6**) and hence by the possibility of its slow inversion in solution. We also noted the unusal conformation about the N-S bond in **6** and so the possibility of hindered rotation about the N8-S1 bond. Our suspicions, as to the origin of exchange process were further heightened in the course of a synthesis of the marine alkaloid debromoflustramine B when the same dynamic NMR phenomenon was observed in the intermediate **22**, devoid of the carbamate group.[3]



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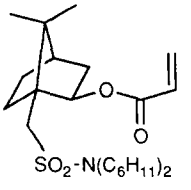

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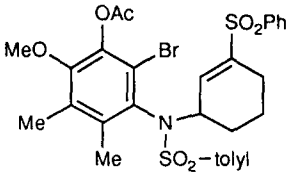

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Examination of several literature X-ray crystal structures of *N,N*-disubstituted sulfonamides reveals the sulfonamide nitrogen to be planar, sp^2-hybridized, even in very sterically hindered situations. A good example is the Oppolzer *N,N*-dicyclohexyl-camphorsulfonamide **23**,[18] while a more recent one is taken from the work of Clive in which X-ray analysis of **24** revealed a planar nitrogen atom.[19] The X-ray crystal structure of *N,N*-dimethyl-*o*-nitrobenzenesulfonamide reveals the N-atom to be essentially planar,[20] but that of *N,N*-dimethylbenzenesulfonamide itself reveals substantial pyramidalization at nitrogen,[21] perhaps due to crystal packing.[22] In each of these literature structures the sulfonamide adopts the conformation about the N-S bond depicted in Fig. 5 in which the p-orbital on nitrogen bisects the OSO angle.[23] Interestingly, in the sulfonamide **25**, where the nitrogen is constrained within a five-membered ring closely related to that in **4** - **6**, substantial deviation from planarity is observed (Σ of bond angles at N = 352.01°).[24] The barrier to rotation about the S-N bond in sulfonamides due to p_π-d_π bonding has previously been considered to be small due to the multiple degeneracy of d orbitals at S.[25] However, exchange broadening in hindered sulfonamides has previously been observed by Speckamp and co-workers for a series of *N*-sulfonyl tetrahydroquinolines.[26,27] Non-equivalence of the methylene protons Hα in **26** was observed and attributed to slow inversion of pyramidalized nitrogen rather than to slow rotation about N-S owing to the observation of only one signal for the peri-proton Hβ. Earlier, Adams had studied the $t_{1/2}$ for racemization of resolved atropisomers of **27** and reached the conclusion that a planar quinonoid transition state was stabilized by electron withdrawing groups X, which accelerated racemization.[28]

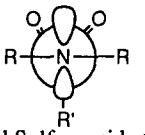
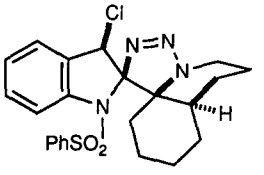


Fig. 5. Standard Sulfonamide Conformation



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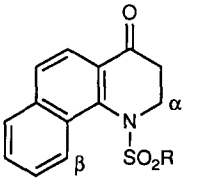

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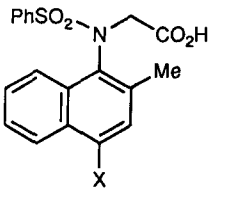

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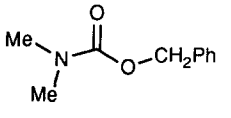
In the present study, despite the unequal population of the two dynamic conformers (~3:1), the barrier ($\Delta G^{\ddagger}$) for the rotation/inversion process observed in the sulfonamides **4** - **6** was estimated by measuring the coalsecene temperature in $CDCl_3$ by VT ^{1}H-NMR spectroscopy and application of the equation:[29]

$$\Delta G_c^{\ddagger} = 4.575 \times 10^{-3} T_c[9.972 + \log(T_c/\Delta\upsilon)] \text{ kcal.mol}^{-1}.$$

The various experimental parameters and estimated barriers are given in Table 2 together with literature values for the barrier to rotation in the carbamates **28** and **29**[30,31,32,33] and for the carbamate **30**, prepared because of its resemblence to the C-ring of **4** - **6**.



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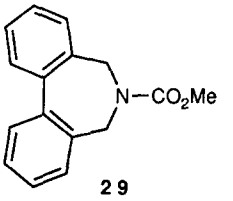

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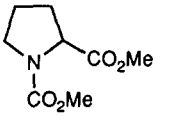

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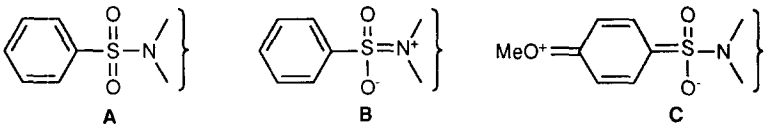
The barriers estimated for **4-6** (Table 2, entries 1 -5) are all substantially lower than the typical barriers for carbamates (Table 2, entries 6 - 7) and it is therefore most unlikely that the dynamic NMR phenomena observed for **4** - **6** results from slow rotation about the carbamate N-C bond. Indeed, for the sterically hindered carbamates **4-6** it is logical to expect a higher barrier to rotation for the N-C bond than in the simple system **30**.

Table 2. Barriers to Exchange for Sulfonamides and Carbamates.

Entry	Cmpd	Ar	T_c (K)	$\Delta\upsilon$ (Hz)	$\Delta G_c^{\ddagger}$ (kcal.mol^{-1})
1	**4**	Ph	285	33	14.2
2	**4**	4-MeOPh	258	33	12.8
3	**4**	Me	273	26	13.7
4	**6** (R = Me)	4-MeOPh	261	33	12.9
5	**5**	4-MeOPh	263	39	12.9
6	**28**	-	-	-	15.9
7	**29**	-	-	-	15.8
8	**30**	-	333	66	16.2

Inspection of Table 2 reveals that the values for the 4-methoxybenzenesulfonamides are consistently lower than those for the simple benzenesulfonamide or the methanesulfonamide. This cannot be a steric factor; the electron-donating group must be lowering the barrier to inversion/rotation. If the sulfonamide functional group is viewed as comprised of the canonical structures **A** and **B** (Fig. 6), then the inclusion of a mesomerically donating group as with the 4-methoxybenzenesulfonamides must lead to the inclusion of a further form **C** (Fig. 6). This form **C** will have the effect of reducing the overall contribution of **B** and so of reducing the barrier to rotation about the N-S bond. The data are therefore consistent with the line broadening in the spectra of **4-6**, and in that of **22**, being caused by a relatively unusual case of hindered rotation about a sulfonamide N-S bond. However, the possibility that this hindered rotation about the S-N bond is coupled to inversion at N8 cannot be ruled out. Indeed, in the X-ray structure of **6** (Fig. 2) the S-N bond is frozen in a non-standard conformation, presumably due to crystal packing, and the N8 nitrogen exhibits the least pyramidalization of the four structures presented.

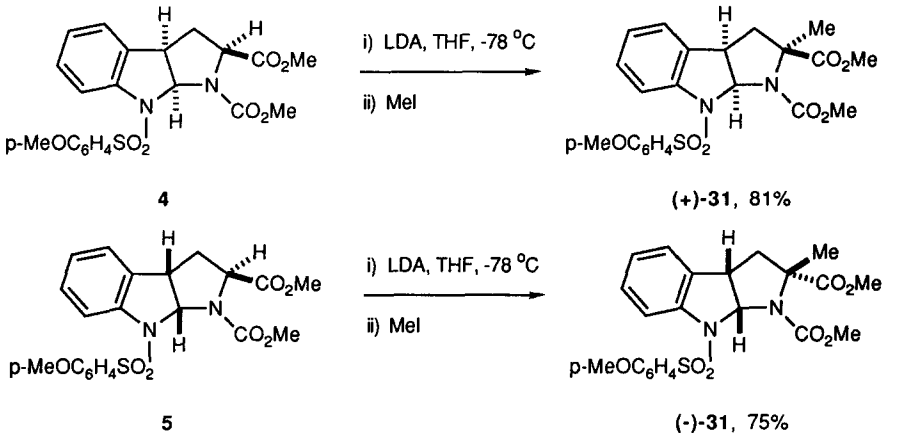


A **B** **C**

Fig. 6. Resonance Forms of Sulfonamides

Finally, with a sample of the exo-carbomethoxy compound **5** in hand, we were able to test the hypothesis that alkylation would occur with inversion of configuration at C2. Treatment of **5** with LDA in THF at -78 °C followed by addition of methyl iodide resulted in the formation of a single diastereomer of the alkylated product **(-)-31** in 75% isolated yield (Scheme 1). This alkylated product was identical in all respects, except for the sign of the optical rotation, with a sample of its enantiomer prepared by alkylation, with retention in the usual manner, from the endo-carbomethoxy isomer **4** (Ar = 4-MeOC_6H_4) (Scheme 1). Evidently, as anticipated, alkylation of the exo-ester does occur cleanly with inversion of configuration and enables the preparation of α-alkyl-D-tryptophan derivatives from readily available L-tryptophan.

Unfortunately, **5** can only be obtained in unacceptably low yields at the present time and the analysis set out above gives little grounds for optimism that this will be improved in the near future.



Scheme 1

Experimental Part

General. For general experimental details see reference 2h.

(-)-Dimethyl (2S, 3aS, 8aR)-8-(4-Methoxybenzenesulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (5). N_b-Methoxycarbonyltryptophan methyl ester (1.00 g, 3.6 mmol) was added to cold TFA (10 mL, between -10 and -15 °C) and the reaction mixture stirred at that temperature for 10 min before it was transfered with a canula to a vigorously stirred mixture of dichloromethane (150 mL) and 15% sodium carbonate solution (150 mL). The organic layer was run off and the aqueous layer further extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried (Na_2CO_3), filtered and evaporated to give a crude mixture of the starting material, the endo-hexahydropyrroloindole **2** and its 2-exo-isomer **3**. This mixture was taken up in pyridine (10 mL) and treated with DMAP (56 mg) before cooling to 0 °C and treatment with p-methoxybenzenesulfonyl chloride (1.872 g, 9.05 mmol). After stirring for 16 h at room temperature the reaction mixture was poured into water (80 mL), extracted with dichloromethane (3 x 30 mL), washed with saturated ammonium chloride (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude reaction mixture. Chromatography on silica gel [Eluent hexane:ethyl acetate (2:1)] gave first the recovered substrate (0.87 g, 87%) then the desired exo-carbomethoxy cmpd **5** (138 mg, 8.6%) and finally the endo-isomer **4** (R = 4-$MeOC_6H_4$)[2h] (46 mg, 2.9%). The title compound was a white crystalline solid with mp 164-165 °C (EtOH); $[\alpha]_D$ = -193.1 (c = 1.12, $CHCl_3$); δ_H: 2.23 (1 H, dt, $J_{2,3} \sim J_{3,3a}$ 7.7, J_{gem} 12.9, 1 x 3-H), 2.31 (1 H, ddd, $J_{2,3}$ 7.0, $J_{3,3a}$ 2.9, J_{gem} 12.9, 1 x 3-H), 3.45 (1 H, m, 3a-H), 3.70 (3 H, s, ArOMe), 3.75 (3 H, s, CO_2Me), 3.77 (3 H, s, CO_2Me), 3.98 (1 H, t, $J_{2,3}$ 7.7, 2-H), 6.13 (1 H, d, $J_{3a,8a}$ 6.05, 8a-H), 6.79 (2 H, d, *J* 6.97, 3', 5'-H), 7.05 (2 H, m, 4-H, 6-H), 7.23 (1 H, t, *J* 7.72, 5-H), 7.56 (3 H, d, *J* 7.0, 2', 6'-H, 7-H); υ_{max} ($CHCl_3$): 1748, 1700 cm^{-1};

m/z: 446 ($M^{+\cdot}$), 387 (M^+-CO_2Me), 275 (M^+-$MeOC_6H_4SO_2$), 243, 171, 130. (Found: C, 56.8; H, 4.9; N, 6.4; S, 7.5. $C_{21}H_{22}N_2O_7S$ requires: C, 56.49; H, 4.97; N, 6.27%).

(+)-Dimethyl (2S, 3aR, 8aS)-8-(4-Methoxybenzenesulfonyl)-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (+)-(31). A solution of **4** (R = 4-$MeOC_6H_4$)[2h] (45 mg, 0.1 mmol) in THF (1 mL) was cooled under Ar to -78 °C and treated dropwise with a solution of LDA (1M, 0.1 mL). After stirring for 20 min at that temperature methyl iodide (18.7 μL, 0.3 mmol) was added with a syringe and the reaction mixture allowed to come to room temperature before it was poured into saturated NH_4Cl solution (2 mL) and extracted with dichloromethane (2 x 3 mL). The extracts were dried ($MgSO_4$), filtered and concentrated. Preparative TLC on silica gel [eluent hexane:ethyl acetate (1:1.5)] then gave the title compound as a white foam with $[\alpha]_D$ = +102.3° (c = 2.58, $CHCl_3$); δ_H: 1.66 (3 H, s, 2-Me), 2.17 (1 H, dd, $J_{3exo,3a}$ 7.48, J_{gem} 13.3, 3exo-H), 2.71 (1 H, d, J_{gem} 13.3, 3endo-H), 3.06 (3 H, s, 2-CO_2Me), 3.39 (1 H, dd, $J_{3exo,3a}$ 7.5, $J_{3a,8a}$ 6.5, 3a-H), 3.69 (3 H, s, ArOMe), 3.79 (3 H, s, 1-CO_2Me), 6.24 (1 H, d, $J_{3a,8a}$ 6.48, 8a-H), 6.81 (2 H, d, *J* 7.0, 3', 5'-H), 6.96 (1 H, d, *J* 7.5, 4-H), 7.04 (1 H, t, *J* 7.5, 6-H), 7.20 (1 H, t, *J* 7.4, 5-H), 7.47 (1 H, d, *J* 7.5, 4-H), 7.55 (2 H, d, *J* 7.0, 2',6'-H). (Found: C, 57.3; H, 5.3; N, 6.0. $C_{22}H_{24}N_2O_7S$ requires: C, 57.38;, H, 5.25; N, 6.08%).

Alkylation of 5 with Inversion of Configuration: (-)-Dimethyl (2R, 3aR, 8aS)-8-(4-Methoxybenzenesulfonyl)-2-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (-)-(31). Treatment of **5** (98 mg, 0.219 mmol) in THF (2 mL) under Ar at -78 °C with LDA (1M, 0.28 mL) for 20 min followed by addition of methyl iodide (41 μL), work up as described for **(+)-(31)** above and chromatography on silica gel [eluent hexane:ethyl acetate (2:1)] gave the title compound (75.7 mg, 75%) as a white foam $[\alpha]_D$ = -101.3° (c = 1.06) whose spectral data were identical to those of its enantiomer.

N-Methoxycarbonyl-proline Methyl Ester (30) L-Proline methyl ester hydrochloride (0.331 g, 2 mmol) was dissolved in H_2O (5 mL) and CH_2Cl_2 (5 mL) and treated with NaCl (0.5 g) and $NaHCO_3$ (0.422 g, 5 mmol). Methyl chloroformate (0.2 mL, 3 mmol) was then added dropwise with vigorous stirring at 0 - 5 °C. After stirring for 2 h the organic layer was separated off and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to yield N-methoxycarbonyl-proline methyl ester (**30**) as an oil (0.298 g, 80%). At room temperature this substance was an approximately 1:1 mixture of rotamers with δ_H: 1.81 - 2.03 (3H, m), 2.05 - 2.27 (1H, m), 3.34 - 3.58 (2H, m), 3.63, 3.66, 3.68, 3.70 (3H, 4 x s), 4.24 - 4.36 (1H, m); δ_C: (23.32, 24.25), (29.80, 30.84), (46.23, 46.75), (52.07, 52.43), 58.65, 59.01), (154.89, 155.38), (173.08, 173.18).

Variable Temperature Spectroscopy VT ^1H NMR was conducted on dilute solutions in $CDCl_3$ at 300 MHz. Spectra were recorded at 5 K intervals and the slow exchange limit ($\Delta\upsilon$) determined when further lowering of the temperature produced no significant change. Measurements were taken on the H2, H3a or H8a signal, as resolution permitted and are recorded in Table 2.

X-Ray Crystallographic Structure Determination of 4, 5, and 6 Crystals of **4, 5,** and **6** were grown from MeOH. Structures were solved by direct methods and developed using alternating cycles of least squares refinement and difference fourier synthesis. Non-hydrogen atoms were refined anisotropically. Hydrogens were placed in idealized positions (C-H 0.96 Å) and assigned a commom isotropic thermal parameter (U = 0.08 $Å^2$). Structures **4** and **6** were solved with SDP and structure **5** with the SHELXTL PLUS program package.[34] Important crystallographic parameters are summarized in Table 3.[35]

Table 3. X-ray Collection Data for **4**, **5**, and **6**

	4	**5**	**6**
Formula	$C_{20}H_{20}N_2O_6S$	$C_{21}H_{22}N_2O_7S$	$C_{21}H_{22}N_2O_6S$
Space Group	$P2_12_12_1$	P1	$P2_12_12_1$
Crystal Size, mm	0.10 x 0.12 x 0.08	0.52 x 0.24 x 0.20	0.12 x 0.14 x 0.10
Crystal Shape	rectangular	irregular	rectangular
Laue Symmetry	orthorhombic	triclinic	orthorhombic
a, Å	8.623(2)	8.547(2)	9.655(3)
b, Å	11.225(3)	10.839(3)	7.683(2)
c, Å	20.018(5)	12.375(3)	28.615(5)
α, deg	90	108.51(2)	90
β, deg	90	96.2692)	90
γ, deg	90	93.49(2)	90
V, Å ^{3}	1937.6	1075	2122.6
Z	4	2	4
$d_{calcd.}$ g/cm^{-3}	1.46	1.38	1.35
μ(Mo-K_α) cm^{-1}	1.98	1.86	1.83
Data Coll. Instr.	Enraf-Nonius CAD4	Nicolet R3mV	Enraf-Nonius CAD4
Radiation	Mo-K_α (λ = 0.71073 Å)	Mo-K_α (λ = 0.71073 Å)	Mo-K_α (λ = 0.71073 Å)
Orientation reflections: no;	25	30	25
range (2θ)	3<2θ<46°	5≤2θ≤52°	3<2θ<46°
Temp., K	296	293	296
Scan technique	ω/2θ	ω/2θ	ω/2θ
No./freq. of std. reflections	3/200	3/100	3/200
Unique data	927	4035	1208
Cutt-off of observed data	3σ(I)	1.5σ(I)	3σ(I)
No. of parameters	262	556	272
R_1[a]	0.050	0.0556	0.042
R_2[b]	0.052	0.0680	0.043
Weighing scheme	$w^{-1} = \sigma(F_o)^2$	$w^{-1} = \sigma^2(F) + 0.025F^2$	$w^{-1} = \sigma(F_o)^2$
Largest shift/esd, final cycle	0.05	0.012	0.05
Largest peak, e/Å^3	<1.0	0.54	<1.0

[a] $R_1 = \Sigma[\,|F_o| - |F_c|\,]/\Sigma|F_o|$

[b] $R_2 = [\Sigma w.\,|\,|F_o| - |F_c|\,|^2/\Sigma w\,|.F_o|^2]^{1/2}$

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17. It is of interest to compare the conclusion reached here for a heterocyclic system with analogous carbocycles. The most **germane** comparison is with bicyclo[3.3.0]octan-1-one derivatives, with their sp^2 C and

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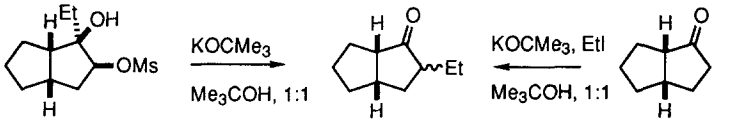

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