a colorless oil (bp 112-115 °C, 0.1 Torr): IR (film) 3343, 3285, 3203 (NH) 1253, 1019 (NSO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ .94 (t, 6 H), 1.33 (m, 4 H), 1.55 (m, 4 H), 2.05 (br, 1 H), 2.85 (s, 3 H), 3.18 (m, 4 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.66, 19.93, 31.19, 38.71, 48.48. Anal. Calcd for $C_9H_{22}N_2OS$: C, 52.39; H, 10.75. Found: C, 52.51; H, 10.85.

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## Concerning the Pathway of Xylyl Rotation in 9-(2,6-Xylyl)-9,10-dihydroanthracenes

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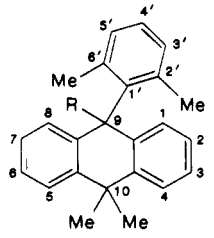
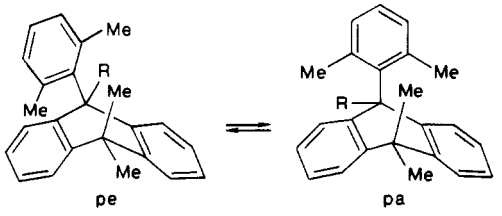
Nakamura and Oki[1] have examined the proton NMR behavior of 9-aryl-9,10-dihydroanthracenes (as well as 9-arylxanthenes) in a study directed towards the measurement of the $C(sp^2)$–$C(sp^3)$ rotational barrier of the aryl substituent. At elevated temperatures, the methyl groups of the xylyl substituent in **1** and **2** coalesce, and inversion




1: R = H ($\Delta G^{\ddagger}$ = 19.6 kcal/mol)
2: R = OH ($\Delta G^{\ddagger}$ = 15.4 kcal/mol)

barriers of 19.6 and 15.4 kcal/mol, respectively, were determined.[1a] In formulating their proposed pathway for this rotation, the authors made two assumptions: (1) the 9,10-dihydroanthracene ring in **1** and **2** undergoes rapid boat-to-boat ring inversion and (2) the xylyl substituent occupies the pseudoequatorial (pe) rather than the pseudoaxial (pa) position in the most stable conformation. On




this basis, they reasoned that xylyl rotation could not take place from the pe conformation due to a prohibitive barrier between the xylyl methyls and peri hydrogens on the aromatic rings of the dihydroanthracene. Hence they suggested that xylyl rotation must first involve an inversion to the pa form whereupon the rotation actually takes place. As noted above, a lower inversion barrier was observed for **2**, and this was attributed to a destabilization of the ground-state geometry by the interaction of the xylyl methyl(s) with the OH substituent. More recently, the traditional concept of boat-to-boat inversion for 9,10-dihydroanthracene (DHA) and many of its derivatives has been challenged by molecular mechanics calculations.[2-5] In fact, MM2 predicts a planar conformation for DHA itself[2] but with very little energy required to reach the fully puckered state (i.e., 145° angle between the planes of the benzene rings), and so one might expect a broad range of geometries on a time average. Calculations suggest a much greater tendency toward planarity for symmetrically disubstituted trans derivatives as well as gem disubstituted compounds.[3] Monosubstituted DHA's, on the other hand, show a parabolic potential well with the minima indicating some degree of ring puckering proportional to the size of the substituent (which is always pa).[4] Most importantly, the conformational description of these systems provided by theory has been supported by carbon-13 NMR studies.[5] In view of these results, we thought it worthwhile to further examine the question of aryl rotation in **1** and **2** by molecular mechanics.

In contrast to the previous suggestions of puckered DHA rings and pe xylyl substituents for **1** and **2**, *the MM2 global minima are nearly planar in each case*! DHA puckering is minor, 4° and 10° respectively, with the xylyl ring perpendicular and very slightly pe (see Figure 1a).

We also calculated the barriers to xylyl rotation and found values of 20.1 and 17.0 kcal/mol for **1** and **2** respectively, in good agreement with the experimental values of 19.6 and 15.4 kcal/mol; however, the pathway for this rotation is quite complex. As shown in Figure 2, the initial rotation of the xylyl group in **1** is accompanied by a slight increase in DHA ring pucker (Figure 2b) with the xylyl group becoming slightly more pe. However, after a rotation of ca. 40°, there is an abrupt change in the DHA ring with the xylyl group "flipping" into the pa position. Continued rotation passes through a maximum of about 60° and then on to the 90° position, which represents a local minimum whereupon the DHA ring is highly puckered (132°) (see Figure 1b). At this point, of course, the nonbonded interactions between the xylyl methyls and the pa 10-methyl is at a minimum. Further rotation regenerates this unfavorable interaction between the xylyl methyl and pa 10-methyl and the xylyl "flips" back down to the very slightly pe state (i.e., nearly planar) where the rotation is completed. Hence the overall process must be viewed as a "geared" rotation involving a combination of xylyl movement and DHA ring puckering.

A rather similar curve was obtained for the rotation of **2** except that the beginning geometry (i.e., the global minimum) starts out at higher energy. Hence calculations support the suggestion that the lower barrier to rotation in **2** is due to a destabilization of the ground state:[1a] the transition-state energies in both **1** and **2** are of comparable energy.

Finally, we examined rotational barriers with the DHA ring constrained to (a) the nearly planar conformation with the xylyl group slightly pseudoequatorial and (b) the

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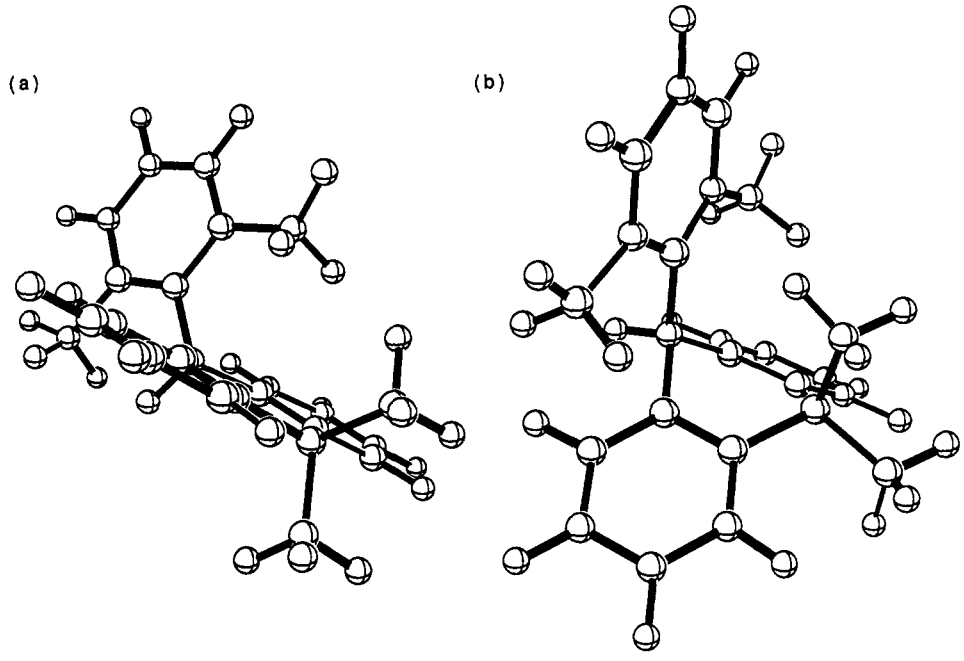


**Figure 1.** MM2 calculated geometries for compound 1: (a) global minimum (pseudoequatorial form) and (b) local minimum (pseudoaxial form).

puckered (132°) geometry with a pseudoaxial xylyl group. The first case, as suggested by Oki and co-workers,[1] does represent an unlikely path for xylyl rotation with barriers in the range of 45–60 kcal/mol. The second case indicates a much more facile process requiring only 13–14 kcal/mol for the actual rotation, although it must be realized that our starting geometry in this case is ca. 13 kcal/mol above the global minimum.

We must note that the driver method used herein is somewhat limited in determining transition states, and structures so derived should be regarded as approximate.[6] Moreover, "lagging" is often observed as sterically congested units pass by each other,[6] and so the sharpness of the curve in Figure 2 may be somewhat exaggerated. Nonetheless, the proposed rotational pathway is quite consistent with current knowledge about 9,10-dihydroanthracene conformational processes[2-5] and is in good agreement with experiment. Hence we can conclude that the acutal pathway is more complex than heretofore suggested and is reminiscent of the geared rotations reported for amides,[7,8] thioamides,[9,10] carbamates,[11] and thio- and selenocarbamates[11] having isopropyl substituents on adjacent atoms.

## Experimental Section

Molecular mechanics calculations were performed with the MM2 force field.[12] In establishing global minima, various bond rotations were performed to ensure the avoidance of local minima. All geometric parameters were optimized except where constraints

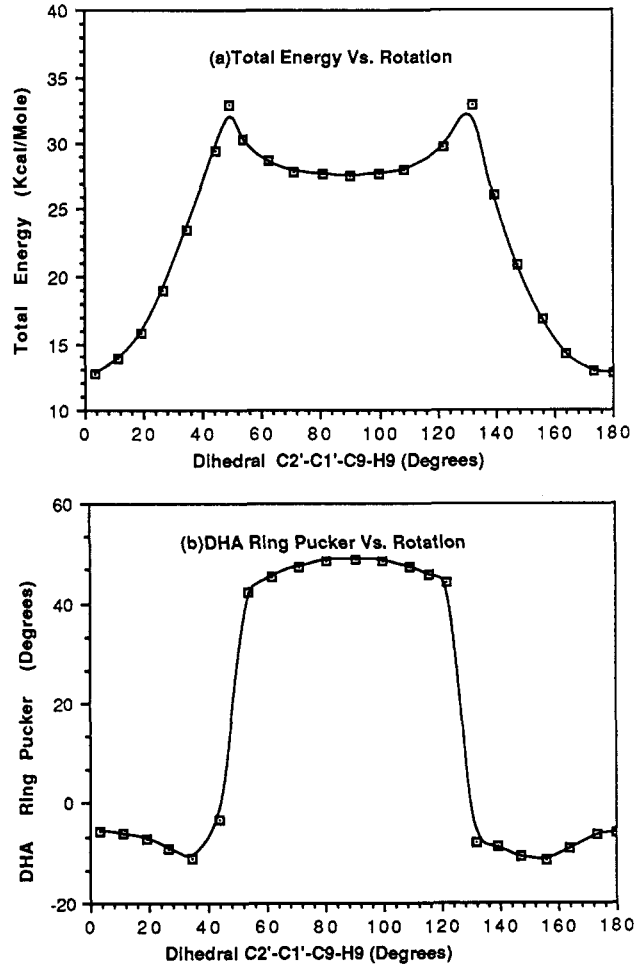


**Figure 2.** MM2 calculated energies for rotation of the xylyl substituent in 1.

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are mentioned. In those cases, all parameters were optimized except the specific constraint.

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## 1,3-Dipolar Cycloaddition Annulations to the Thieno[2,3-*d*]pyridazine, Thieno[3,2-*c*]pyridine, and Thieno[2,3-*d*]pyrimidine Ring Systems

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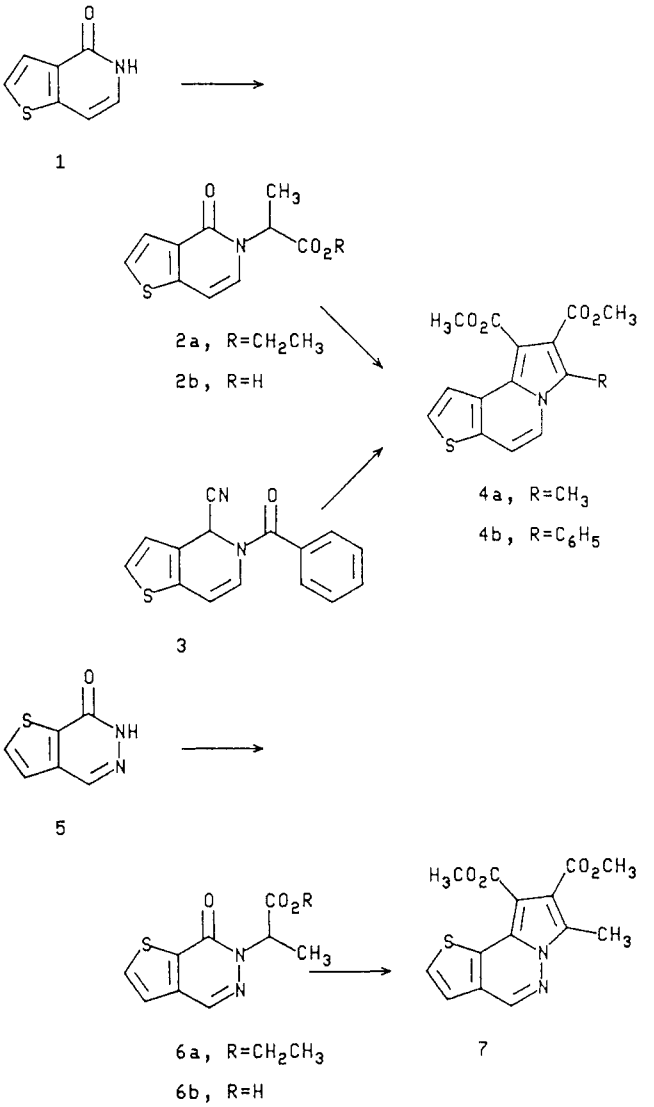
A series of recent disclosures in the literature reveal that potent affinity for the benzodiazepine receptor can be achieved in a variety of triheterocyclic molecules that do not contain the benzodiazepine ring system.[1,2] The impetus for the synthesis of such molecules is the development of antianxiety drugs that have a cleaner side-effect profile. An expedient, yet versatile, methodology to elaborate triheterocyclic compounds was found in the mesoionic cycloaddition reaction of dipolarophiles with oxazolones, or the hydrofluoroborate salts of Reissert compounds. Alkylation of thieno[3,2-*c*]pyridin-4(5*H*)-one[3] (**1**) with ethyl 2-bromopropionate generated **2** (Scheme I). The same transformation with thieno[2,3-*d*]pyridazin-7-(6*H*)-one (**5**)[4] generated the analogous product **6**. After basic hydrolysis to their free acids and treatment with acetic anhydride, **2b** and **6b** reacted with dimethyl acetylenedicarboxylate (DMAD) to give **4a** and **7**, respectively. The synthesis of the thieno[2,3-*g*]indolizine structure **4** was also realized through trifluoromethanesulfonic acid[5] treatment of **3**,[6] and subsequent reaction of the derived salt with DMAD in DMF.[7,8]

Alkylation of **8** (Scheme II) was routine,[9] as was obtention of the derived acid **9b**. Reaction of **9b** with DMAD in acetic anhydride at 90 °C for 1 h yielded a complex mixture, which was resolved into **10** (trace), **11** (15%), and **12** (29%). Compound **10** resulted from the Dakin–West[10] reaction of **9b**, but attempts to increase the sporadic yield of this product through optimized (pyridine–acetic anhydride) Dakin–West conditions were unsuccessful. The yield of the desired cycloaddition product **11** could be

**Scheme I**




increased slightly (28%) through the use of 10 equiv of DMAD rather than the 1.2 equiv normally employed. This product distribution was temperature dependent since the identical reaction time at 140 °C led to a 6.4% yield of **10** and 14.6% yield of **11**, with only trace amounts of compound **12** being formed. Compound **12** apparently results from the mesoionic species derived from **9b** adding in Michael fashion to DMAD, with subsequent attack of the intermediate anion occurring at the imine linkage rather than the carbonyl group in the pyridazinone ring. Decarboxylation and isomerization of the double bond produces compound **12**.

The formation of this major side product highlights the limitations of a 1,3-dipole possessing an electrophilic center whose reactivity is competitive with that of the dipolarophile. Earlier studies investigating the cycloaddition properties of *anhydro*-3-hydroxythiazolo[3,2-*c*]-quinazolin-4-ium hydroxides to various dipolarophiles did not report any inter- or intramolecular addition of the initial DMAD adduct to the sensitive imine bond in the quinazoline ring.[11] The feasibility of converting **12** into **11** was also explored because mechanistically this transformation appeared reasonable. The reaction of **12** with potassium carbonate in dry acetonitrile under nitrogen did

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