labeled to permit more sensitivity in detection of cross-linking in the present bilayer systems as well as those containing other lipid types. Cross-linking to specific integral or peripheral membrane proteins could also be studied; peptide segments residing near the membrane surface could be identified.[32] In fact, protein amino or thiol functional groups may be reactive enough relative to OH[33] to compete effectively with water, a possibility that needs to be tested in model studies analogous to those already reported.[11]

Conclusion

We were particularly interested in synthesizing and determining the properties of a membrane photolabeling reagent which has a diazo group *within* a fatty acid chain analogue, and we chose initially to place the diazo group near the highly organized polar–nonpolar interface region of lipid bilayers. Our initial experiments with the galactocerebroside photolabeling reagent we have synthesized showed (a) that the bilayer systems so far studied did not exclude water from the photogenerated carbene, so that water insertion was predominant, and (b) that the OH groups of cholesterol or phosphatidylglycerol incorporated into bilayers still did not compete with water. Water would not necessarily be capable of penetrating a bilayer membrane in sufficient quantity or at a sufficient rate to give such a predominance of water insertion. Though further proof is needed, the present results suggest that water may actually be incorporated in the membrane structure to the depth of the photogenerated carbene.

(32) (a) Wisnieski, B. J.; Bramhall, J. S. *Nature (London)* **1981**, *289*, 319. (b) Hu, V. W.; Wisnieski, B. J. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5460. (c) Montecucco, C.; Bisson, R.; Dabbeni-Sala, F.; Pitotti, A.; Gutweniger, H. *J. Biol. Chem.* **1980**, *255*, 10040. (d) Bisson, R.; Montecucco, C.; Capaldi, R. A. *FEBS Lett.* **1979**, *106*, 317.

(33) Reference 29a, pp 409–412, 437–441.

Acknowledgment. Support of this work by the National Institutes of Health and the National Science Foundation and assistance in the purchase of the NMR spectrometers by National Science Foundation Departmental Instrument Grants are gratefully acknowledged. We also thank Dr. G. Furst for his technical assistance in operating the NMR spectrometers and Dr. T. Terwilliger for his help in obtaining the DCI mass spectrum. Finally we thank K. Carduner, J. Suhadolnik, and S. Goodman for their experimental assistance and H. Brachowski for preparing this manuscript.

Registry No. 1, 88035-97-6; 3, 88035-94-3; 4, 88035-95-4; 5, 88035-96-5; 7, 2238-90-6; (*R*)-8, 88035-98-7; (*S*)-8, 88082-54-6.

Cyclization of 2-[*N*-(Methylsulfonyl)anilino]acetaldehyde Diethyl Acetals to Indoles. Evidence for Stereoelectronic Effects in Intramolecular Electrophilic Aromatic Substitution

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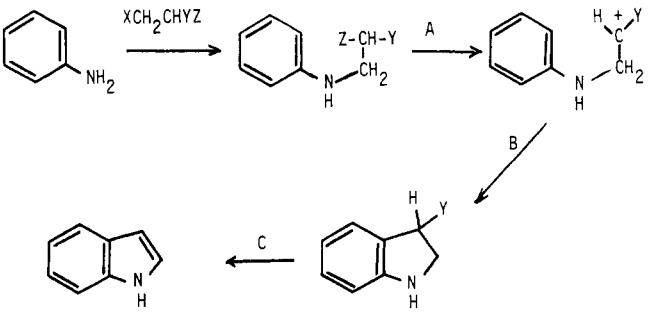
Methanesulfonamides of *N*-(2,2-diethoxyethyl)anilines can be cyclized to indoles in aromatic solvents by reaction with titanium tetrachloride. The temperature of the cyclization is substituent dependent, occurring at 0 °C for the *m*-methoxy derivative but requiring 130 °C for the *p*-bromo compound. Yields are good for various alkoxy-, alkyl-, and haloindoles, ranging from 60% to 90%. Meta-substituted reactants give rise to mixtures of 4- and 6-substituted indoles in which the 6-substituted product dominates by 2–4:1. The cyclization fails for ortho-substituted reactants. The major reaction process is N-dealkylation in the case of ortho-substituted compounds. An analogous cyclization occurs with the methanesulfonamides of *N*-(3,3-diethoxypropyl)anilines to give 1-(methylsulfonyl)-4-chloro-1,2,3,4-tetrahydroquinolines. This cyclization is much more rapid than for the five-membered ring closure leading to indoles and indicates a substantial rate retardation due to stereoelectronic effects in the indole cyclization. Ortho substitution also prevents cyclization in the six-membered-ring case.

The efficient conversion of anilines to indoles is a useful synthetic objective. The classical Fischer synthesis via the diazonium ion and aryl hydrazones is quite general but is usually not applicable for 2,3-unsubstituted indoles.[1] Gassman developed a method for conversion of substituted anilines to indoles that has good generality for 2,3-unsubstituted indoles and is based on the Sommelet rearrangement of anilinosulfonium ions.[2] Both of these methods depend on a sigmatropic rearrangement to effect the crucial ortho substitution. Most other syntheses of 2,3-unsubstituted indoles depend upon having appropriate ortho disubstitution built in to the reactant.[3]

Scheme I



(1) For reviews of the Fischer indole cyclization see: Brown, R. K. In "Indoles, Part I, Chemistry of Heterocyclic Compounds"; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, pp 232–317. Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1970; pp 142–163.

(2) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

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Table I. Cyclization Conditions and Product Yields

reactant	substituent	ring size	% yield of alkylation	cyclization conditions	cyclization yields,[a] %	other products, % dealkylation[b]	other products, % aldehyde
1a	H	5	83	$C_6H_5CH_3$, 110 °C	62	<10	0
1b	p-CH_3	5	79	$C_6H_5CH_3$, 110 °C	83 (57)	<10	0
				CH_2Cl_2, 0 °C	33[c]	0	25
1c	p-OCH_3	5	94	$C_6H_5CH_3$, 110 °C	70 (67)	<10	0
				CH_2Cl_2, 0 °C	0	0	86
1d	p-Br	5	75	C_6H_5Cl, 132 °C	68 (8)[d]	<10	0
1e	m-CH_3	5	74	$C_6H_5CH_3$, 110 °C	88	<10	0
				CH_2Cl_2, 0 °C	30	<10	43
1f	m-OCH_3	5		$C_6H_5CH_3$, 110 °C	84	<10	0
				CH_2Cl_2, 0 °C	84	<10	0
1g	m-Cl	5	62	$C_6H_5CH_3$, 110 °C	94 (82)	<10	0
1h	2-CH_3-3-OCH_3	5	93	$C_6H_5CH_3$, 110 °C	0	67	0
1i	o-OCH_3	5	78	$C_6H_5CH_3$, 110 °C	0	63	0
1j	o-F	5	82	$C_6H_5CH_3$, 110 °C	0	25	20
				C_6H_5Cl, 132 °C	0	40	0
1k	o-CH_3	5	72	$C_6H_5CH_3$, 110 °C	0	0	0
7a	H	6	61	$C_6H_5CH_3$, 0 °C	97	<10	0
7b	p-CH_3	6	80	$C_6H_5CH_3$, 0 °C	88	<10	trace
7c	p-OCH_3	6	61	$C_6H_5CH_3$, 0 °C	94	<10	0
7d	o-CH_3	6	62	$C_6H_5CH_3$, 25 °C	0	<10	84
				$C_6H_5CH_3$, 110 °C	0	84	trace
7e	o-OCH_3	6	69	$C_6H_5CH_3$, 25 °C	0	<10	88

[a] Yields given are for chromatographically and spectroscopically (NMR) pure oils isolated by chromatography from runs on a 0.2–0.5-mmol scale. Yields in parentheses are for solids isolated from runs on a 0.25–7.0-g scale. [b] Yields given as <10% indicate that the compound was not detected in the crude product or isolated by chromatography. Unlike the indoles and aldehydes which are readily detected by TLC and characteristic NMR peaks, the dealkylated sulfonamides are less readily detected, and the limit of detection in the crude reaction mixtures is estimated to be 5–10%. [c] No pure 3b is found. The 33% yield refers to a mixture of 6 and a second substance which on the basis of spectroscopic data appears to be 3-[1-ethoxy-2-[*N*-(methylsulfonyl)-4′-methylanilino]ethyl]-1-(methylsulfonyl)-5-methylindole. [d] A better yield of 5-bromo-1-(methylsulfonyl)indole (49% oil, 21% solid) was isolated by cyclizing the dioxolane derivative at 180 °C in *o*-dichlorobenzene.

A conceptually attractive route from aniline to indole would involve intramolecular electrophilic aromatic substitution as outlined by the generalized equation shown in Scheme I. An obvious possibility for the two-carbon fragment is an α-haloacetaldehyde equivalent, and α-anilinoacetaldehyde derivatives have been examined as substrates for cyclization on several occasions.[4] Some limited success was achieved for *N*-alkylindoles, but until the recent work of Nordlander and co-workers[5] no route appropriate for 1-unsubstituted indoles had been developed.

In connection with an ongoing synthetic problem we undertook an investigation aimed at exploring this cyclization pattern in the hope of achieving a smooth aniline → indole transformation. An analysis of the problem revealed at least four factors which might detract from the efficiency of such cyclizations. (1) Under protonic or Lewis acid catalysis, step B is likely to be disfavored by protonation or coordination at nitrogen, which would retard the desired electrophilic substitution. (2) Unsubstituted indoles are sensitive to protonic and Lewis acids so that subsequent reactions of the product might be a serious complication. (3) It was suspected that there might be a stereoelectronic restriction on step B since the electrophile must presumably approach the aromatic ring in such a way as to interact with the π electrons. (4) The initial carbocation intermediate might be inherently unstable to a pinacol-type hydride shift, because of the high carbocation-stabilizing capacity of a nitrogen atom. The successful cyclization conditions developed by Nordlander,[5] which involve heating *N*-(2,2-diethoxyethyl)trifluoroacetanilides in trifluoroacetic acid–trifluoroacetic anhydride, specifically address factors 1 and 2 since the trifluoroacetyl group both decreases the basicity of the aniline nitrogen and stabilizes the product indole.

Results

Previous experience with indoles protected as 1-phenylsulfonyl derivatives and the effectiveness of Lewis acids, especially $TiCl_4$, in promoting electrophilic cyclizations of acetals directed our attention to *N*-(2,2-diethoxyethyl)-*N*-methylsulfonyl derivatives of anilines.[6] These were readily prepared by base-catalyzed alkylation of the methanesulfonanilides. Table I gives the yields, which were generally quite good. These compounds were usually oils with only moderate stability to storage. They were best purified by flash chromatography and identified by the NMR spectra (see Table II in the supplementary material for details).

After some exploration of alternative reaction conditions, satisfactory results in the cyclization step were achieved by using aromatic solvents such as toluene or chlorobenzene and effecting cyclization by addition of titanium tetrachloride. In reactions run above the millimolar scale better yields were obtained by slow simultaneous addition of the acetal and a titanium tetrachloride solution to the reaction solvent held at an appropriate temperature. The temperature at which cyclization occurred depended on the substituents on the aromatic ring. Strongly activated

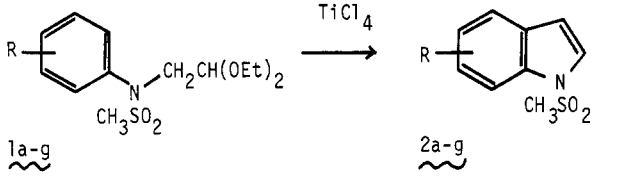
(3) Another recent example of an aniline to indole conversion has been described involving ortho acylation by chloroacetyl chloride which involves a chelated intermediate. Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578.

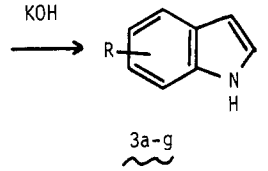
(4) A review of earlier work is provided by: Chastrette, M. *Ann. Chim. (Paris)* **1962**, 543. Bevis, M. J.; Forbes, E. J.; Naik, N. N.; Uff, B. C. *Tetrahedron* **1971**, *27*, 1253. Jackson, A. H.; Jenkins, P. R.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1698.

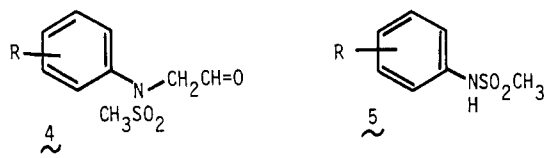
(5) Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778.

(6) Cyclization of the *p*-toluenesulfonyl derivative of 2-(3,4,5-trimethoxyanilino)acetaldehyde to 5,6,7-trimethoxyindole in HCl–dioxane has been reported: Hewlins, M. J. E.; Jackson, A. H.; Oliveira-Campos, A. M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2906.

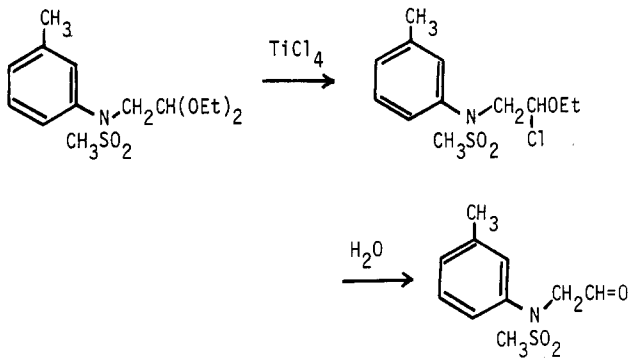
compounds (e.g., **1f**, R = *m*-OCH_3) reacted at 0 °C, whereas those with mildly deactivating groups (*m*-Cl, *p*-Br) required 110–130 °C. The products from para-substituted substrates were identified as 5-substituted 1-(methylsulfonyl)indoles, whereas meta-substituted reactants gave mixtures of the 4- and 6-substituted 1-(methylsulfonyl)indoles. Ortho-substituted compounds failed to give indoles. The yields of the 1-(methylsulfonyl)indoles obtained in this way are given in Table I.



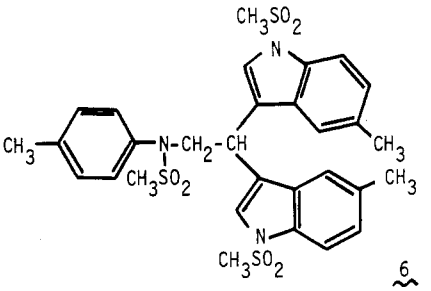




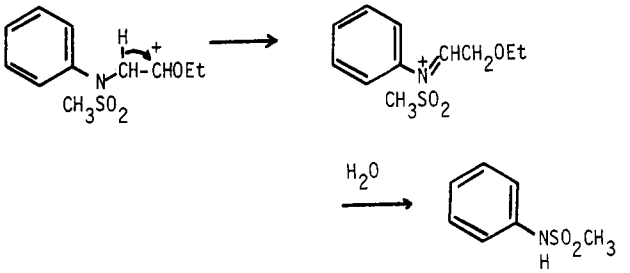
Those reactions in which the substrates failed to cyclize usually led to one of two alternative compounds as the major product. At temperatures below those required for successful cyclization, the aldehyde **4** was usually observed in the product mixture obtained after hydrolysis. From NMR studies it appears that the acetals are rapidly converted to α-chloro ethers which are hydrolyzed to the aldehydes on aqueous workup. Addition of titanium tetrachloride to solutions of **1e** in $CDCl_3$ led to a shift of the



acetal proton from 4.55 to 5.55 ppm. Preparative experiments were carried out for **1b,c,e** by adding titanium tetrachloride at 0 °C. The transformation to the aldehyde was nearly quantitative in the case of **1c**. With **1b** and **1e** both cyclized and uncyclized products were observed. One product isolated from **1b** under these conditions has been identified as structure **6** on the basis of NMR and MS data (see the Experimental Section). The mechanistic path to such a structure involves competing alkylation of the indole product by an uncyclized intermediate, presumably the α-chloro ether. The improved yields obtained in the preparative-scale experiments by simultaneous addition of the acetal and titanium tetrachloride at an elevated temperature are evidently due in part to suppression of this intermolecular alkylation.



The other competing reaction path led to dealkylation of the sulfonamides. The ortho-substituted compounds usually underwent dealkylation rather than cyclization. The yields of the dealkylated products which were isolated are shown in Table I. We postulate that dealkylation is the result of a hydride shift in the cationic intermediate (see below). Dealkylation of 2-aminoacetaldehyde acetals



has been observed before under acidic cyclization conditions, but a different mechanism was suggested.[6,7]

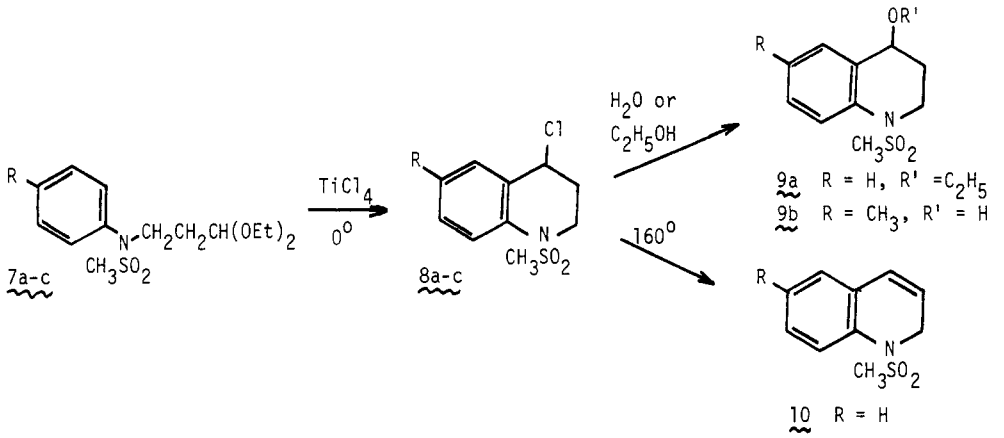
In terms of being a practical indole synthesis, this route appears to compare favorably with other methods which start from substituted anilines and is particularly suitable for 5-substituted indoles with electron-donor substituents. The Fischer cyclization is difficult in the absence of 2- or 3-substituents.[1] The Gassman method is similar in the number of steps, although it can be carried out more quickly than can our method.[2] The present method is closely analogous to that of Nordlander[5] but avoids the use of the trifluoroacetic acid–trifluoroacetic anhydride solvent system. The 1-(methylsulfonyl)indoles can be purified by chromatography or short-path vacuum distillation. The mixtures of 4- and 6-substituted isomers obtained from **1e–g** were difficult to separate, but small samples could be obtained by careful chromatography. Alkaline hydrolysis of the 1-(methylsulfonyl)indoles gave the corresponding indoles. The samples of **3a–c,e,f** had physical and spectral properties in agreement with literature values.

We also briefly examined the use of 2-(bromomethyl)-1,3-dioxolane in place of the bromoacetaldehyde diethyl acetal. Both methanesulfonanilide and the *p*-bromo derivative gave somewhat cleaner and faster alkylations with this reagent (<20 h vs. 48–60 h for complete alkylation of methanesulfonanilide). The cyclization yields for the resulting dioxolanes were similar to those obtained with the diethyl acetals. Additional improvements might be possible by optimization of the cyclization temperature.

In order to assess the importance of the postulated stereoelectronic resistance to cyclization resulting from five-membered ring formation, several *N*-(3,3-diethoxypropyl)-*N*-(methylsulfonyl)anilines were prepared. The

(7) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185. At least in our hands, fragmentation also appears to be occurring under the Nordlander reaction conditions. We have isolated as much as a 30% yield of trifluoroacetanilde, along with 45% of 1-(trifluoroacetyl)indole, in reactions carried out by heating *N*-(2,2-diethoxyethyl)aniline in trifluoroacetic acid–trifluoroacetic anhydride.

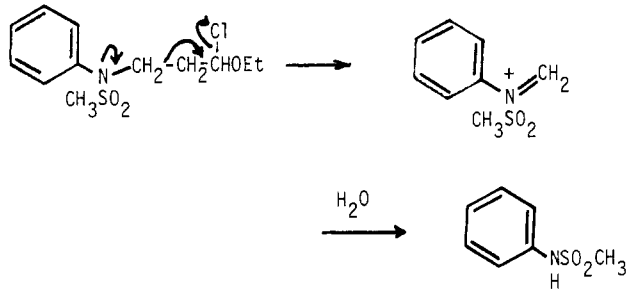
Scheme II



same alkylation procedure was used, and the results are summarized in Table I. It was found that for the unsubstituted, *p*-methyl, and *p*-methoxy compounds **7a–c** cyclization occurred readily at 0 °C, well below what is required for indole formation. The products were identified as 4-chloro-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinolines **8a–c** (Scheme II).

The halides were solvolyzed readily in ethanol or water to give the ether or alcohol. On being heated to 150 °C, **8a** eliminated HCl to give 1-(methylsulfonyl)-1,2-dihydroquinoline (**10**) which was identified by comparison with an authentic sample.[8]

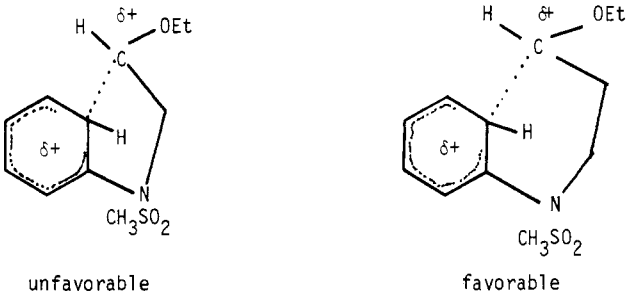
Use of the *o*-methyl compound **7d** resulted in failure of the cyclization. Some of the aldehyde (**11d**) was formed but the major product was the dealkylated sulfonanilide **5k** (84% yield). Similarly, the *o*-methoxy derivative failed to cyclize. The only product recognized after a cyclization attempt at 25 °C was the aldehyde **11e** (88% yield). Dealkylation of these materials can be accounted for by a Grob-type fragmentation reaction.



Discussion

Apart from the potential preparative value of this cyclization procedure, two mechanistic points merit discussion. The first is the fact that in cases of virtually identical electronic environment the formation of six-membered rings is much more facile than formation of the corresponding five-membered ring. The second general point is that ortho substituents have an adverse effect on both five-membered and six-membered ring closures.

The usual concept of electrophilic aromatic substitution as being an attack on the π electrons provides a rationale for the differential ease of formation of five- and six-membered rings. Examination of models shows that while the five-membered ring, when it has formed, suffers only minor strain, the transition state is significantly strained if it is assumed that the electrophilic carbon must attack from a direction more or less perpendicular to the plane of the ring (see below). The situation is similar in concept



to those analyzed by Baldwin.[9] The case of electrophilic aromatic substitution does not fit the nomenclature system employed by Baldwin, however, since the aromatic ring is neither uniquely exo nor endo to the newly formed ring.[10] The physical concept is the same, however. The geometric demands imposed by the stereoelectronic requirement for π attack lead to a strained transition state and a diminished reaction rate. The strain is significantly diminished for the six-membered ring closure, and therefore the electronically similar cyclization proceeds more rapidly. Some prior results in the literature which seem to be in general accord with our observations can be cited. In studying Friedel–Crafts-type cyclizatin of 4-phenylbutanol and 3-phenylpropanol, Khalaf and Roberts noted that while the butanol formed 1,2,3,4-tetrahydronaphthalene in 50% yield, the propanol gave no indan and formed only the dehydrated material. Similarly, substrates which are capable of structural rearrangement were found to give preferential formation of tetrahydronaphthalene derivatives when the carbocation was initially generated at a position which would lead directly to five-membered ring closure.[11]

It is also clear from the results that an ortho substituent poses an additional barrier to cyclization. This is evident from the failure of the cyclization of ortho-substituted substrates in both the 2,2-diethoxyethyl- and 3,3-dieth-

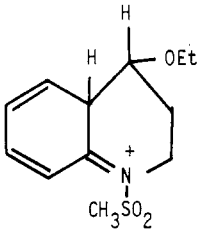
(8) Muren, J. F.; Weissman, A. *J. Med. Chem.* **1971**, *14*, 49.

(9) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

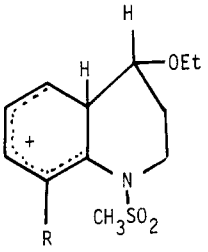
(10) Application of the "Baldwin's Rules" terminology to aromatic cyclizations is relatively rare. Sainsbury and co-workers have compared the transition-state geometry effects in indole and isoquinoline derivatives and interpreted the failure of certain five-membered ring closures as being due to the stereoelectronic factors associated with the transition state. Sainsbury, M. *Heterocycles* **1978**, *9*, 1349. Powell, M.; Sainsbury, M. *Tetrahedron Lett.* **1981**, *22*, 4751.

(11) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1966**, *31*, 89. Khalaf, A. A.; Roberts, R. M. *Ibid.* **1972**, *37*, 4227.

oxypropyl series of compounds. Nordlander and coworkers[5] also noted the failure of ortho-substituted (N-trifluoroacetylanilino)acetaldehyde diethyl acetals to cyclize under their conditions. At least a partial cause for this effect is probably steric disruption of the π-donor component of the sulfonamido substituent effect. As a measure of the π-donor capacity of the sulfonamido group we use the Swain–Lupton $\mathcal{R}$ value which is –0.20.[12] Thus, although the total effect of the sulfonamido group as measured by σ_p (0.03) is very slightly electron attracting, this represents the balance between a π-donor and σ-acceptor contribution (Swain–Lupton $\mathcal{F}$ = +0.25). The π-donor component will be reduced by a steric prohibition of conjugation in ortho-substituted systems. The ideal geometry for stabilization of the σ-complex intermediate must retain approximate coplanarity of the sulfonamido nitrogen with the aromatic ring (see below). This factor



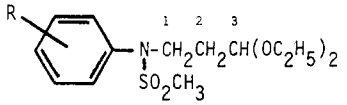
maximum π-stabilization from coplanar sulfonamide nitrogen



decreased π-stabilization from non-coplanar sulfonamide nitrogen

is clearly interrelated with the ring size effect, since rotation of the sulfonamido substituent is also required to attain the closest possible approach from above the ring. The relative importance of these two effects is unknown, but it is clear that the ortho effect increases the the barrier for both the five- and six-membered transition states.

Evidence relevant to the occurrence of steric effects in the ortho-substituted series can be seen in the NMR spectra. Comparison of compounds **7a** and **7d** is informative. Compound **7a** shows a completely "normal" spectrum, including the appearance of the ethoxy methylene group as an AB multiplet due to the anisochronic nonequivalence of the two hydrogens. In contrast, the ortho isomer **7d** shows rotational broadening of all of the peaks in the diethoxypropyl side chain, except for the C-3 acetal methine (see below), when recorded at 360 MHz. At a



probe temperature of 25 °C the C-2 methylene group appears as a broadened multiplet indicating nonequivalence of the two hydrogens. The ethoxy methyl groups are substantially broadened, and C-1 methylene peaks contribute to a series of broad multiplets between 3.4 and 3.8 ppm. At 55 °C the ethoxy methyl peak is sharp, and the C-2 methylene signals have coalesced but remain broad. The multiplet at 3.4–3.8 ppm remains broadened although somewhat sharpened compared to that at 25 °C. The temperature dependence of the spectrum is clear evidence of restricted rotational freedom of the alkyl chain in ortho-substituted compounds, which evidently affects even the rather remote ethoxy methyls.

In summary, it appears that the transition-state structure and energy in the cyclization of the sulfonanilides is influenced by the following components: (1) the necessity for a π-direction of approach; (2) the *favorable* π delocalization of the nitrogen lone pair which operates most effectively in a geometry where the nitrogen substituent can retain at least partial conjugation; (3) a steric resistence to the coplanar geometry for the nitrogen substituent when an ortho substituent is present.

Experimental Section

Preparation of N-(Methylsulfonyl)anilides. The substituted aniline (0.040 mol) was dissolved in 100 mL of dry methylene chloride, and 25 mL of freshly distilled pyridine was added. To the cooled (0 °C) solution there was added dropwise freshly distilled methanesulfonyl chloride (0.060 mol). The reaction mixture was allowed to stir at 0 °C for 1 h and at 25 °C for an additional 1 h. The solution was then poured into 150 mL of saturated $NaHCO_3$, and the product was extracted with two 50-mL portions of methylene chloride. The combined organic layers were washed with 5% HCl to remove pyridine and dried over Na_2SO_4. Evaporation of solvent afforded crude product (solid) which could be recrystallized from benzene–hexane.

Alkylation of Methanesulfonanilides by Bromoacetaldehyde Diethyl Acetal (1a–k). The N-(methylsulfonyl)anilide (0.01 mol) was dissolved in 25 mL of DMF and treated with 0.0125 mol (1.25 equiv) of NaH (60% oil dispersion). The reaction mixture was allowed to stir at room temperature for 15 min or until evolution of hydrogen stopped. Bromoacetaldehyde diethyl acetal (0.0150 mol) was added and the mixture maintained at 110 °C for 8 h. After 8 h, 0.50 equiv (0.005 mol) of the acetal and sodium hydride were added, and the mixture was kept at 110 °C overnight (16 h). Another 0.005 mol (0.50 equiv) of each reagent was then added and heating continued for an additional 12–24 h. The solution was then poured into 150 mL of saturated $NaHCO_3$ and the product extracted with three 50-mL portions of toluene. The combined organic layers were washed with three 100-mL portions of water and dried over Na_2SO_4. Evaporation of solvent afforded a crude product which was chromatographed on 230–400-mesh silica (1:1:1 ether/chloroform/hexane) to yield pure product.

Alkylation of Methanesulfonanilides by 3-Bromopropionaldehyde Diethyl Acetal (7a–e). The alkylation was carried out by using 3-bromopropionaldehyde diethyl acetal which was prepared by addition of hydrogen bromide to acrolein in ethanol.[13] The alkylation conditions were identical with those used for bromoacetaldehyde diethyl acetal.

Alkylation of Methanesulfonanilides with 2-(Bromomethyl)-1,3-dioxolane. A solution of the sulfonamide in DMF was treated with 1.1 equiv of sodium hydride, and then 1.1 equiv of the bromomethyldioxolane was added. The reaction mixture was stirred at 120 °C for 20 h, at which point TLC indicated the reaction had gone to completion. The products were isolated as in the proceeding alkylations.

Cyclization Conditions. (A) 1-(Methylsulfonyl)indoles (<1.0 mmol Scale). A solution of the appropriate acetal (0.35 mmol) in 25 mL of dry toluene was heated to 110 °C under

(12) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328. Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M. S. *Ibid.* **1983**, *105*, 492. Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

(13) A procedure similar to that described for β-chloropropionaldehyde diethyl acetal (Witzemann, E. J.; Evans, W. L.; Hass, H.; Shroeder, E. F. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 137) gave product with a boiling point of 36 °C (0.3 mm) in 20% yield on a 2-mol scale.

nitrogen. A solution of 1.1 equiv $TiCl_4$ in 10 mL dry toluene was added over 5 min. For compound **1f**, cyclization occurred at 0 °C. For compound **1d**, cyclization was carried out in chlorobenzene at 132 °C. The solutions were maintained at the appropriate temperature for 15–30 min after the addition was complete and then poured into 150 mL of saturated $NaHCO_3$. The product was extracted with two 50-mL portions of toluene, and the combined organic layers were washed with water and dried over $NaSO_4$. The solvent was removed by evaporation, and the crude products were purified by chromatography or distilled. Compounds **2b**, **2e** (with **2e'**), and **2f** (with **2f'**) were distillable oils. The other compounds were obtained in crystalline form: **2c**, mp 68–70 °C; **2d**, mp 84–85°C; **2g**, mp 124–125 °C. Both the crystalline and noncrystalline samples gave satisfactory analyses for C, H, and N.

(B) 1-(Methylsulfonyl)indoles (1–5 g Scale). 1-(Methylsulfonyl)-4-methylindole and 1-(Methylsulfonyl)-6-methylindole. 2-[3-Methyl-*N*-(methylsulfonyl)anilino]acetaldehyde diethyl acetal (2.2 g, 0.0074 mol), dissolved in 75 mL of dry toluene, and 1.5 equiv titanium tetrachloride (0.011 mol, 2.11 g), dissolved in 75 mL dry toluene, were added simultaneously to 200 mL of refluxing dry toluene from two separate addition funnels over a period of 15 min. The reaction mixture was allowed to stir at 110 °C for 1 h and then poured into 300 mL of saturated aqueous $NaHCO_3$. The organic layer was washed several times with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a mixture of 1-(methylsulfonyl)-4-methylindole and 1-(methylsulfonyl)-6-methylindole (1.4 g, 0.0067 mol, 91% yield) as an oil. Satisfactory separation of small of the two isomers was obtained in a Merck Lobar Size A (240–10) LiChroprep Si60 40–63-μm silica gel column with 2:1 hexane/toluene as an elution solvent.

4-Chloro-1-(methylsulfonyl)indole and 6-Chloro-1-(methylsulfonyl)indole. A solution of compound **1g** (7.0 g, 0.022 mol) was prepared in toluene (75 mL). A second solution containing 1.1 equiv (4.60 g) of titanium tetrachloride in 75 mL of toluene was prepared. These solutions were added simultaneously over about 30 min to a reaction flask containing 200 mL of toluene heated to reflux. After the addition was complete, refluxing was continued for 1 h and the reaction mixture was then poured into saturated sodium bicarbonate solution (300 mL). The toluene layer was separated, the aqueous layer was extracted with additional toluene, and the combined toluene was washed with brine and dried. Vacuum distillation [132 °C (0.005 mm)] gave 3.95 g (0.018 mol, 82%) of a white solid which is a 1:2 mixture of the 4- and 6-chloroindoles. A pure sample of the 6-chloro isomer (mp 124 °C) was obtained by several recrystallizations from ethyl acetate/hexane.

5-Bromo-1-(methylsulfonyl)indole. *p*-Bromomethanesulfonanilide was alkylated with 2-(bromomethyl)-1,3-dioxolane and the purified solid (1.3 g, 0.0039 mol) was dissolved in 50 mL of *o*-dichlorobenzene. This solution and a solution of titanium tetrachloride (1.12 g, 0.0059 mol) in 50 mL of *o*-dichlorobenzene were added simultaneously to 150 mL of *o*-dichlorobenzene which was refluxing at 180 °C. After the addition, the solution was kept at 180 °C for 1 h. The reaction mixture was cooled and processed as in the preceding experiment. The *o*-dichlorobenzene was removed under vacuum (0.1 mm), and the residual dark oil was chromatographed on silica gel 60 (E. Merck) to yield 0.52 g (49%) of an oil. This oil gave 0.22 g (21%) of solid (mp 84–85 °C) after crystallization.

(C) Reaction of Compound 1b with Titanium Tetrachloride at 0 °C. A solution of **1b** (0.50 g, 1.66 mmol) in methylene chloride (100 mL) was cooled to 0 °C. Titanium tetrachloride (1 equiv, 0.32 g, 1.7 mmol) was added, and the reaction mixture was stirred at 0 °C for 3 h. The mixture was then poured into saturated sodium bicarbonate solution, extracted, and dried. Evaporation of the extract gave a gum from which compound **6** (0.3 g) was obtained by trituration with methanol. The NMR spectrum showed four methyl peaks at 2.37, 2.40, 2.82, and 3.03 ppm, each pair being in the ratio 2:1. Other features of the spectrum were in accord with structure **6**. The mass spectrum gave a strong peak at 627, consistent with the molecular weight of **6**. After alkaline hydrolysis, the product gave M_r 471, consistent with hydrolytic removal of the two indole methylsulfonyl substituents from **6**.

(D) 4-Chloro-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinolines 8a–c. A solution of the acetal **7b** (0.100 g, 0.32 mmol) in dry toluene (60 mL) was cooled to 0 °C in a nitrogen-protected reaction flask. A solution of titanium tetrachloride (0.04 mL, 0.07 g, 0.37 mmol) in dry toluene (10 mL) was added dropwise over 5 min. The reaction mixture was allowed to stir at 0 °C for an additional 10 min and then poured into saturated aqueous sodium bicarbonate (150 mL). The product was extracted with additional toluene, dried, and evaporated. The product, 4-chloro-1-(methylsulfonyl)-6-methyl-1,2,3,4-tetrahydroquinoline was obtained as a oil (0.73 g, 88% yield), which was characterized by mass spectrometry and NMR.

Similar preparations gave **8a** (97% yield) and **8c** (94% yield). Compound **8c** was obtained as a solid in 76% yield (mp 90–92 °C) after recrystallization from ethyl acetate–hexane.

Indoles by Hydrolysis of 1-(Methylsulfonyl)indoles. 1-(Methylsulfonyl)-5-methylindole (0.30 g, 0.0014 mol) was dissolved in 25 mL of 5% methanolic potassium hydroxide and refluxed for 18 h. Dilution with water and extraction with ether gave 5-methylindole (0.16 g, 0.013 mol, 93%) which was purified by bulb-to-bulb distillation and had the expected NMR spectrum. Similarly, hydrolysis reactions were carried out for **2a** (**3a**, 92%), **2c** (**3c**, 91%), **2d** (**3d**, 85%), **2e** (**3e**, 98%), and **2g** (**3g**, 90%). NMR spectral data and physical constants were in agreement with reported values.

Chemical Transformations of 4-Chloro-1-(methylsulfonyl)tetrahydroquinolines. Thermal Dehydrohalogenation. Compound **7a** was cyclized at 0 °C in toluene according to the general procedure. The crude product was heated to 160 °C in a Kugelrohr distillation apparatus. The distilled oil (0.8 g) crystallized from ethanol–hexane to give **10**: 0.62 g (91%); mp 94–96 °C. The NMR and IR spectrum are identical with those for an authentic sample.[8]

Solvolysis in Ethanol. A solution of **8a** (0.070 g, 0.23 mmol) was refluxed in ethanol for 1 hour. TLC indicated conversion to a single material and extractive workup gave **9a** as an oil (0.045 g, 70%).

Solvolysis in Aqueous Tetrahydrofuran. 4-Chloro-1-(methylsulfonyl)-6-methyl-1,2,3,4-tetrahydroquinoline (**8b**; 0.10 g, 0.4 mmol) was dissolved in 20 mL of THF containing 1 g of KOH and 5 mL of water. This solution was allowed to stir at 80 °C for 6 h. A standard extractive workup with ether afforded 0.08 g (85% yield) of an oil which solidified upon standing. recrystallization from benzene–hexane gave **9b** [0.065 g (76%); white crystals; mp 100–102 °C] which gave a satisfactory analysis for C, H, and N.

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Registry No. **1a**, 88131-48-0; **1b**, 88131-49-1; **1c**, 88156-68-7; **1d**, 88131-50-4; **1e**, 88131-51-5; **1f**, 88156-69-8; **1g**, 88156-70-1; **1h**, 88131-52-6; **1i**, 88131-53-7; **1j**, 88131-54-8; **1k**, 88131-55-9; **2a**, 70390-93-1; **2b**, 88131-61-7; **2c**, 88131-62-8; **2d**, 88131-63-9; **2e**, 88131-64-0; **2e'**, 88131-65-1; **2f**, 88131-66-2; **2f'**, 88131-67-3; **2g**, 88131-68-4; **2g'**, 88131-69-5; **7a**, 88131-56-0; **7b**, 88131-57-1; **7c**, 88131-58-2; **7d**, 88131-59-3; **7e**, 88131-60-6; **8a**, 88131-70-8; **8b**, 88131-71-9; **8c**, 88131-72-0; **9a**, 88131-73-1; **9b**, 88131-74-2; **10**, 30831-92-6; $TiCl_4$, 7550-45-0.

Supplementary Material Available: Table II containing ^1H NMR data for the *N*-(2,2-diethoxyethyl)methanesulfonamides **1a–1e**, 1-(methylsulfonyl)indoles **2a–g**, and *N*-(3,3-diethoxypropyl)methanesulfonanilides **7a–e**, **8a–c**, **9a,b** and **10** (3 pages). Ordering information is given on any current masthead page.