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ASYMMETRIC INDUCTION IN THE SULFENE–ENAMINE CONDENSATION REACTION

THE TRANSITION STATE GEOMETRY OF SUCH (2 + 2) CYCLOADDITIONS[1,2]

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Abstract—The extent of asymmetric induction arising from cycloaddition of sulfene to two optically active enamines, one with an acyclic tertiary amine residue and the other a cyclic amine, has been determined to be 6% and 25%, respectively. Most notably, stereospecificity is seen to increase as the rotational degrees of freedom are reduced. Degradation of initially formed aminothietane dioxides to 4-methylthiete 1,1-dioxide has permitted evaluation of the induced absolute configuration at C-4. The results are discussed in terms of transition state conformations and an asymmetric induction model is proposed.

THE STRUCTURAL and energetic features comprising the reaction profile of olefin-heterocumulene cycloaddition reactions clearly have a direct bearing on the mechanism of four-membered ring formation and on the applicability of symmetry correlations to such processes. In an effort to probe the detailed nature of such (2 + 2) cycloaddition reactions, we have examined the possibility of asymmetric induction in the addition of sulfene to enamines. As such, this study represents a continuation of our investigations into the chemical and physical properties of sulfenes.[3] A search of the existing voluminous literature on asymmetric synthesis[4] revealed that this phenomenon had never been applied to the synthesis of four-membered rings, whether carbocyclic or heterocyclic.[5] Also, at the time that this work was initiated, asymmetric induction studies with optically active enamines had not yet been described. Since then, three reports on the use of this approach for the preparation of optically active ketones have come to our attention.[6,7]

Acyclic amine studies

(*R*)-(+)-Methyl-α-phenethylamine (**1**), of established absolute configuration, was prepared by the reaction of (*R*)-(+)-α-phenethylamine[8] with formyl acetic anhydride and reduction of the resulting formamide with lithium aluminum hydride.[9] Enamine **2** was obtained in 68% yield by condensation of **1** with propionaldehyde in THF containing anhydrous K_2CO_3 (Scheme I). The NMR spectrum of **2** displayed two vinyl protons spin coupled by 13·2 Hz, thus revealing the *trans* geometry of the double bond in this enamine. When treated with sulfene, generated from methanesulfonyl chloride and triethylamine in anhydrous ether at −5°, **2** afforded an oily mixture of diastereoisomers of **3**, which was directly heated with excess MeI in

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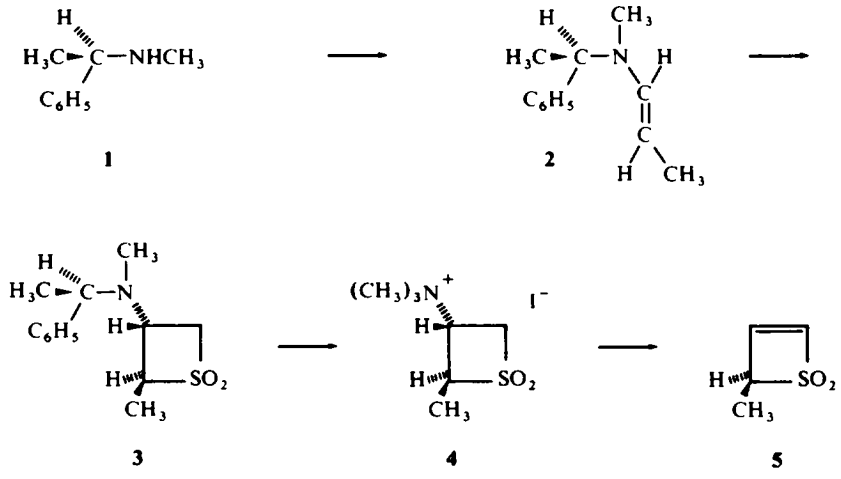
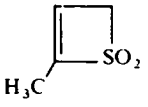
acetone at 67° for 20 hr. This reaction sequence led to the ready removal of the original asymmetric carbon atom by debenzylation. Methiodide **4** was produced in 36% overall yield from **2**. Despite the complexity of the NMR spectra of **3** and **4**, the

SCHEME 1



data agree with the *trans* stereochemical assignment which, additionally, follows from earlier precedent.[10]

Unpurified **4**, which was noted to be optically active, was treated directly with dry silver oxide in anhydrous THF to which had been added some $CaSO_4$. This modification of the Hofmann elimination procedure gave in 62% yield the desired 4-methylthiete 1,1-dioxide (**5**) containing no more than 7 ± 1% (NMR analysis) of the more stable, but optically inactive 2-methylthiete 1,1-dioxide (**6**). In contrast, the silver oxide-induced Hofmann elimination of such quaternary salts in water gives



6

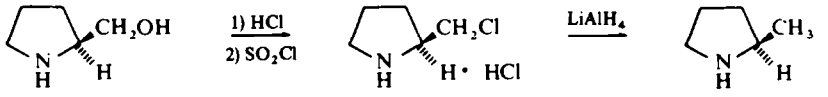
rise chiefly to **6**.[11] Allowing for the slight contamination of **5** by **6**, the thiete dioxide was found to exhibit an optical rotation of $[\alpha]_D^{19}$ +1·32 ± 0·51° (*c* 6·065, $CHCl_3$). This level of optical rotation could be readily duplicated, provided that great care was exercised at each step to avoid accidental separation of diastereomers. When such conditions were not met, the optical purity of **5** was seen to increase approximately tenfold.

The maximum rotation of (*R*)-(−)-4-methylthiete 1,1-dioxide has previously been realized to be $[\alpha]_D^{21·5}$ −21·2 ± 0·4° (*c* 5·995, $CHCl_3$).[13] The absolute configuration of **5** was established by chemical correlation with (*S*)-(+)-3-acetoxybutyric acid.[13]

On the basis of these data, the asymmetric induction experiments are seen to produce **5** which is 6% enriched in the amount of (*S*)-(+)-isomer (as depicted).

Cyclic amine studies

(*R*)-(−)-2-Methylpyrrolidine (**9**) was selected as the starting secondary amine for the synthetic scheme under consideration. Treatment of *L*-proline with $LiAlH_4$ afforded the known *L*-prolinol (**7**). This amino alcohol, as its hydrochloride salt, was converted to the crystalline 2-chloromethyl pyrrolidine hydrochloride (**8**) with

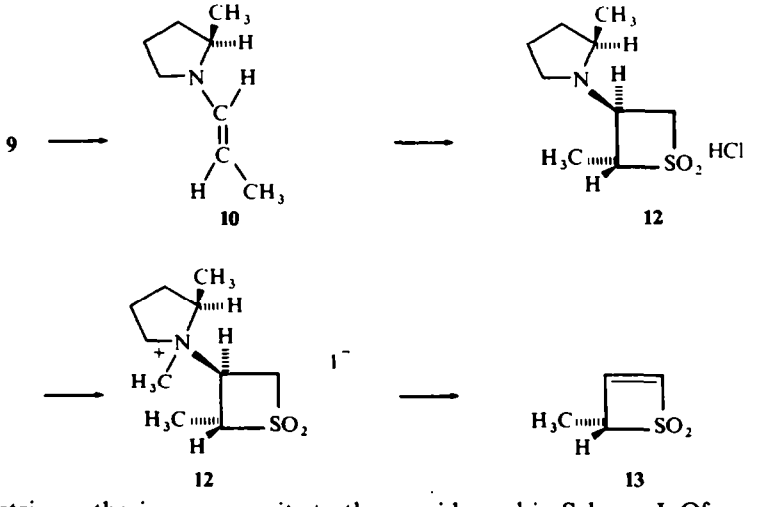


7 **8** **9**

$SOCl_2$; subsequent reduction to the desired amine (**9**) was achieved with $LiAlH_4$. The conversion of **8** to **9** occurred with approximately 95% retention of configuration.[12]

As before, **9** was treated with propionaldehyde in the presence of anhydrous K_2CO_3 to give enamine **10** (Scheme II). When this labile substance was exposed to the action of sulfene in ether at − 5°, the sole product isolated upon acidification with HCl was the thietane dioxide **11**. Conversion of the free base of **11** to methiodide **12**, followed by controlled Hofmann elimination as previously described, led to (*R*)-(−)-4-methylthiete 1,1-dioxide (**13**) with an average rotation of $[\alpha]_D^{22}$ −5·38 ± 0·55°. It can therefore be seen that the stereochemical consequences of this

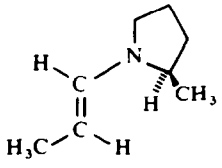
SCHEME II



asymmetric synthesis are opposite to those evidenced in Scheme I. Of equal importance was the observation that the degree of asymmetric induction was enhanced more than fourfold to an optical purity level of 25%.

DISCUSSION

An initial premise necessary to the understanding of the observed stereoselectivity is founded on the realization that in the transition state for cycloaddition, considerable buildup of negative charge is required at the β-carbon atom of the enamine. As a result, significant double bond character is produced at that stage of reaction between the nitrogen atom and the α-carbon, such that the asymmetric carbon and all substituents on the double bond become coplanar. From a consideration of molecular models, two coplanar conformations for the enamines seem most reasonable, one (**14**) which may be termed cisoid, and a transoid form (**15**). Approach of sulfene to the frontside of **14**, whether stepwise or concerted (the $\pi^2s + \pi^2a$ process), is sub-



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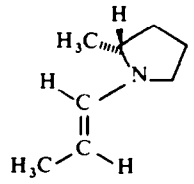
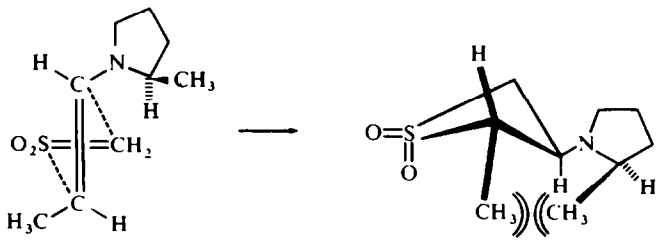


15

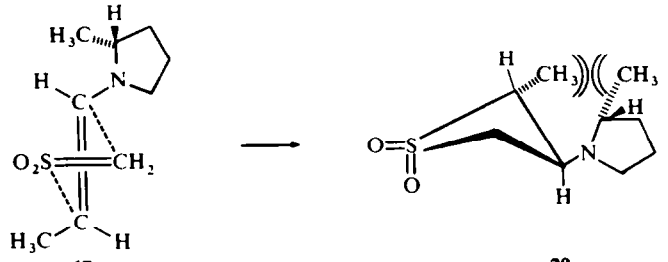
stantially encumbered by the bulk of the 2-Me group on the pyrrolidine ring, and therefore represents a relatively high energy mechanistic alternative. Related compression effects do not come into play as the sulfene approaches the rearside of **15** because of the increased distance from the β-carbon atom to the sphere of steric influence. As a result, the first possibility appears less likely at present than the three remaining options which involve ultimate bonding of sulfene to the rearside of **14** or to either surface of **15**.

The experimental fact that the resulting 4-methylthiete 1,1-dioxide is significantly enriched in the proportion of (R)-(−)-isomer **13** indicates that transition state **17** is characterized by a somewhat higher energy of activation relative to **16** and **18** since it gives rise to the enantiomeric structure. Yet, a cursory analysis of group interactions associated with the mutual approach of the two reacting molecules would not give anticipation of such a result.

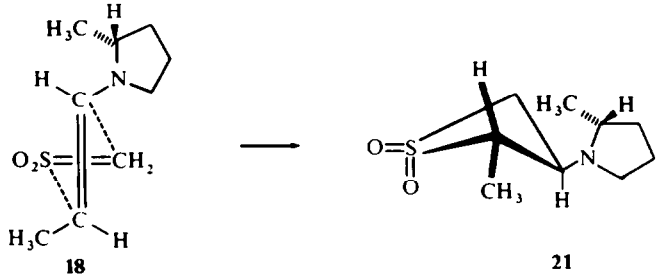
If, as anticipated, the rate-determining transition state for thietane dioxide ring formation is more product-like than reactant-like, a marked sensitivity to steric (and polar) interactions in the product will be encountered.[13] In view of this consideration and the realization that the cycloadduct (**20**) formed directly from reactive complex **17** must accommodate a serious methyl–methyl compression, one might argue that product development control would raise the activation energy for this path relative to **18**. Since the methyl–methyl interactions in **19** are analogous to those in **20**, transition state **16** would likewise be disfavoured. Only **18** is unique in producing directly a cycloadduct relatively free of non-bonded interactions. This model suggests that sulfene attacks preferentially from the rear of conformation **15** in the asymmetric synthesis step (*cf.* **18**). The inherent assumption is that attack from the formally more sterically shielded surface of the enamine is more than compensated at the transition state by the minimization of compressive methyl–methyl interactions in the develop-



16 19

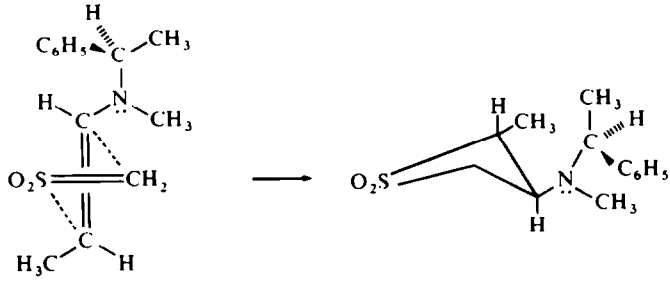


17 20



18 21

ing four-membered ring. The identical physical model can be employed to rationalize the preferred formation of **3** from enamine **2** (*cf* **22**).

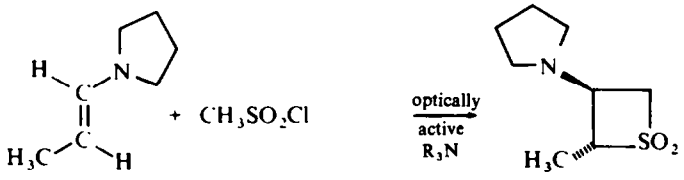


22 23

The high level of optical activity induced in the cycloaddition of sulfene to enamine **10** would appear to indicate that there is a substantial degree of concertedness to the cycloaddition, although it does not prove this point. According to current theory, the geometry of approach required for the concerted $\pi^2s + \pi^2a$ process is the orthogonal orientation of one unsaturated system relative to the other (*cf* **16–18**).[14] This novel feature is accommodated by the data.

Despite the fact that the transition state model proposed herein suffers from the usual limitations of empiricism and theoretical ingenuousness,[15] it is anticipated that it will prove to be a useful conceptual device for correlating and predicting the stereochemical consequences of (2 + 2) heterocumulene–olefin cycloadditions.

Lastly, it should be mentioned that all attempts in this laboratory to effect asymmetric induction by condensation of *trans*-1-pyrrolidino-1-propene (**24**) with sulfene generated from methanesulfonyl chloride and an optically active tertiary amine have



24 (optically inactive)

not met with success. This result is in accordance with the formation only of optically inactive product from the cycloaddition of cyclopentadiene with dimethylketene generated *in situ* from isobutyryl chloride and an optically active tertiary amine.[16] However, Borrmann and Wegler report, to the contrary, that optically active β-lactones can be synthesized from the reaction of appropriate carbonyl compounds and ketenes under analogous conditions.[17]

EXPERIMENTAL

R-(+)-Methyl-α-phenethylamine **1**. Acetic anhydride (56·2 ml, 60·8 g, 0·595 mole) and HCOOH (28·2 g, 0·613 mole) was heated at 58° with stirring for 2 hr to form the mixed anhydride. After the solution cooled to room temperature, (*R*)-(+)-α-methylbenzylamine* 48·0 g (0·395 mole) was added dropwise with stirring such that the temperature remained below 40°. Ether (100 ml) was added and the mixture stirred for 4 hr at room temperature. diluted with more ether (400 ml) and washed twice with H_2O. The combined water layers were extracted with ether and these ether extracts were combined with the main organic fraction. Solid Na_2CO_3 and saturated $NaHCO_3$ were then added until CO_2 evolution ceased and the ether solution was neutral. The solution was then washed with 5% HCl, twice with small portions of water, and finally with saturated NaCl. Drying and concentration of this solution gave crude formamide (56·8 g, 96%).

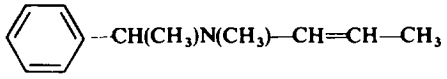
Into a 1-l 3-necked flask containing $LiAlH_4$ (28·9 g, 0·762 mole) in THF (240 ml) a solution of the above material was added dropwise in THF (117 ml) such that a gentle reflux was maintained. The reaction mixture was maintained at reflux with stirring for an additional 7 hr and then cooled to room temperature. The excess hydride was decomposed by the cautious addition of H_2O (58 ml), 12% NaOH (58 ml), and more H_2O (87 ml). The hydrated salts were removed by filtration through Celite, and the filtrate was dried and concentrated. The residue was vacuum distilled to give 41·9 g (75% based on starting amine) of **1**, b.p. 73–80°/11 mm, n_D^{26} 1·5080; $[\alpha]_D^{22}$ +62·7 ± 0·5° (EtOH, c = 3·989) [lit. for optically inactive form,[11] b.p. 87°/18 mm]; $\nu_{max}^{CCl_4}$ 2924, 2770, 1447 and 1135cm^{-1}; $\delta_{max}^{CDCl_3}$ 7·27 (m, 5H, aromatic), 3·59 (q, 1H, J = 6·8 Hz, H—C—CH_3), 2·27 (s, 3H, N—CH_3), and 1·31 ppm (d, 3H, J = 6·8 Hz, CCH_3).

The hydrochloride was prepared; m.p. 207·5–210°, from THF–EtOH.

R-(+)-trans-N-Methyl-N-(α-phenethyl)-N-(1-propenyl)amine **2**. A mixture of **1** (20·0 g, 0·148 mole), anhydrous potassium carbonate (20·5 g, 0·148 mole), and of THF (30 ml) was cooled to below 0° with stirring under nitrogen. Propionaldehyde (8·60 g, 0·148 mole) THF (43 ml) was added at such a rate that

* "Puriss" grade of the Aldrich Chemical Co. $[\alpha]_D^{21}$ +29·2 ± 0·2° (C_2H_5OH, c = 12·56); $[\alpha]_D^{21}$ +38·9° (neat). See reference 10

the temperature never exceeded 0°. The cold bath was then removed and stirring continued for 5 hr at room temperature. The solids were removed by filtration, washed twice with fresh THF, and most of the solvent removed from the combined filtrates. The liquid aminal residue was distilled to give recovered **1** [10·94 g, b.p. 35–52°/0·03 mm] and 8·77 g (68%) of **2**, b.p. 42–60°/0·03 mm, n_D^{26} 1·5088; $[\alpha]_D^{20}$ +43·5 ± 0·5° (*c* = 1·932, $CHCl_3$); $\nu_{max}^{CCl_4}$ 2941, 2849 and 1449 (C—H), 1653 (C=C) and 937 cm^{-1}; the NMR spectrum of an optically inactive sample of this enamine prepared by the same procedure: $\delta_{TMS}^{CCl_4}$ 7·40 (s, 5H, H_a), 6·23 (dq, J_{bc} = 14·0 Hz, J_{bg} = 1·4 Hz, H_b), 4·21 (sextet, J_{bc} = 14·0 Hz, J_{cg} = 6·7 Hz, H_c), 4·27 (q, *J* = 7·3 Hz, impurity), 3·68 (q, J_{eh} = 6· Hz, H_e), 2·39 and 2·30 (singlets, 3H, H_f), 1·70 (dd, J_{cg} = 6·7 Hz, J_{bg} = 1·4 Hz, H_g), 1·50 (s, impurity), and 1·32 ppm (d, J_{eh} = 6·9 Hz, H_h).



(a) (e) (h) (f) (b) (c) (g)

Condensation of **2** *with sulfene.* A stirred solution of **2** (8·22 g, 0·047 mole) and triethylamine (4·75 g, 0·047 mole) in dry ether (180 ml) cooled to −5° under nitrogen was treated with a solution of methanesulfonyl chloride (5·38 g, 0·047 mole) in ether (40 ml) at such a rate that the temperature remained below −5°. Stirring was continued for 1 hr after reaching room temperature. The precipitated hydrochloride was filtered and the filtrate evaporated to afford a crude yellow oil (14·79 g) which was used directly to prepare the methiodide.

Chromatography of this material on alumina furnished crystalline adduct with spectral properties identical with that of the mixture of racemic diastereoisomers.

Racemic 2-methyl-3-[N-methyl-N-(α-phenethyl)amino]thietane 1,1-dioxide was obtained as a difficult crystallizable solid, m.p. 70–85°; $\delta_{TMS}^{CDCl_3}$ 7·21 (s, 5, aryl), 2·8–4·5 (br m, 5, α-sulfonyl and benzylic protons), 2·16 and 2·12 (s and s, 3, N-methyl), 1·36 (m, 6, C-methyls). Calcd for $C_{13}H_{19}NO_2S$: C, 61·63; H, 7·56; N, 5·53%. Found: C, 61·68; H, 7·55; N, 5·48%.

(−)-2-*Methyl*-3-(*dimethylamino*)*thietane* 1,1-*dioxide methiodide* **4**. The crude oil (14·79 g) containing **3** was dissolved in dry acetone (15 ml) and methyl iodide (47 g, 7-fold excess) and heated in a thick-walled Pyrex tube at 67° for 20 hr. The white crystalline solid was filtered free of dark oil, washed with fresh acetone, and dried to give **4** (5·61 g, 36%). This product was employed without further purification in the Hofmann elimination. Its infrared spectrum was identical to that of a racemic sample.

Racemic **4** was prepared in 52% yield as a white solid, m.p. 196–197° dec (from EtOH–H_2O); ν_{max}^{Nujol} 1332 and 1145 cm^{-1}. Calcd for $C_7H_{16}INO_2S$: C, 27·55; H, 5·28; N, 4·59; S, 10·51%. Found: C, 27·57; H, 5·24; N, 4·42; S, 11·00%.

S-(+)-4-*Methylthiete* 1,1-*dioxide* **5** *from* **4**. Treatment (5·60 g, of **4** (18·4 mmoles) with dry silver oxide (19·0 mmoles) as previously described[13] afforded **5** (1·35 g, 62%), NMR analysis of which it showed it to be contaminated with 7 ± 1% of 2-methylthiete 1,1-dioxide **6**. Allowing for this optically inactive impurity, the optical rotation of **4** was calculated to be $[\alpha]_D^{21}$ +1·21 ± 0·34° (*c* = 4·53 ± 0·04, corrected; $CHCl_3$), reflecting asymmetric induction to the extent of 5·7% ± 1·8%. In a second set of reactions, the level of asymmetric synthesis was found to be 6·2% ± 2·4%.

R-(−)-2-*Methylpyrrolidine* **9**. The reduction of *L*-proline to *L*-prolinol **7** was effected with $LiAlH_4$ according to the procedure of Gassman and Fentiman.[18] Conversion of **7** to 2-chloromethylpyrrolidine hydrochloride **8** was achieved in the manner previously reported by Piper and Johnson.[19] Yields in excess of 80% were consistently realized.

To a slurry of $LiAlH_4$ (24 g) in anhydrous ether (500 ml) was added **8** (74·6 g, 0·481 mole) through a Gooch tube during 3–4 hr. The mixture was heated at reflux for 24 hr with stirring under a dry ice condenser. The excess hydride was destroyed as before and the dried ether filtrates were combined and carefully freed of solvent by distillation through a 16-in Vigreaux column. The residue was rapidly distilled at 760 mm pressure; all material boiling up to 95° was collected.

The distillate was dissolved in ether, cooled to 0–5°, and treated with a stream of dry hydrogen chloride gas. The ether was evaporated and the semisolid residue was triturated extensively with acetone. The residual solid was discarded; the acetone extracts were evaporated to leave **9** hydrochloride (30·4 g, 52·2%). Liberation of the base was achieved by treatment with NaOH aq solution, extraction with ether, and distillation, b.p. 88–94°[lit[14] b.p. 94°/728 mm]; $[\alpha]_D^{24}$ −11·5° (*c* = 2·5, H_2O) [lit[14] $[\alpha]_D^{22}$ = −11·97° (H_2O)].

2-Methyl-3-(2-methylpyrrolidinyl)thietane 1,1-dioxide hydrochloride **11**. An ethereal solution of **9** prepared from 4·5 g (0·033 mole) of the hydrochloride was mixed with anhydrous K_2CO_3 (5 g) and propionaldehyde (2·1 g, 0·036 mole) was added dropwise at 0° under N_2. After addition, the mixture was stirred at room temperature for 12 hr, filtered, and evaporated at reduced pressure. The enamine produced was employed without further rectification because it polymerized on attempted distillation. To a solution of this enamine in ether (200 ml) was added triethylamine (2·5 g, 0·025 mole) in one portion, followed by the dropwise addition of methanesulfonyl chloride (2·74 g, 0·024 mole) as described. A stream of hydrogen chloride gas was introduced (0°) and the resulting white paste was dissolved in H_2O. The solution was extracted with ether to remove any neutral products, basified with NaOHaq, and again extracted with ether. The latter combined ethereal rextracts were dried, filtered, and evaporated to furnish thietane dioxide (2·75 g, 56%) which was used without further purification.

In another run, the initially formed hydrochloride was recrystallized several times from EtOH to give **11** as white crystals, m.p. 218–220° dec. The most notable feature of the NMR spectrum (in $CDCl_3$) are the two methyl doublets at δ 1·45 (J = 7 Hz) and 1·65 (J = 7 Hz). Calcd for $C_9H_{18}ClNO_2S$: C, 45·19; H, 7·53; N, 5·85%. Found: C, 44·88; H, 7·58; N, 5·77%.

Hofmann Elimination of 2-methyl-3-(2-methylpyrrolidinyl)thietane 1,1-dioxide. In a typical run, thietane dioxide (4·1 g, 0·02 mole) dissolved in acetone (10 ml) was treated with MeI (27 g, 0·19 mole) and the solution was heated in a sealed glass tube at 55° for 12 hr and at 61° for 16 hr. The solvent and excess MeI were evaporated and the residue was triturated with ether to give a powdery, hygroscopic solid (6·6 g, 94·7%) which was employed directly.

Treatment of this methiodide (6 g, 17·4 mmoles) with silver oxide (4·03 g, 17·4 mmoles) and calcium sulfate (5·1 g) as predescribed led to a pale yellow oil, double distillation of which [b.p. 55–60°/0·04 mm] afforded **13** (410 mg, 20%) contaminated with an average of **6** (18·4%). Allowing for this optically inactive impurity, the optical rotation of **13** from three independent runs was found to be $[\alpha]_D^{24}$ −5·30 (c = 3·77, corrected; $CHCl_3$), −4·92 (c = 3·66, corrected; $CHCl_3$), and −5·93 (c = 3·83, corrected, $CHCl_3$), reflecting an average asymmetric induction level of 25%. The NMR and IR spectra of **13** were identical with those of the authentic sample.

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