National Library of Canada
Bibliothèque nationale du Canada

Canadian Theses Service
Service des thèses canadiennes

Ottawa, Canada
K1A 0N4

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, tests publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30.

NL-339 (r. 88/04)

Canada

ISBN 0-315-46746-0

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

ABSTRACT

The role of 1,3-dihydrothieno[3,4-b]pyridine-2,2-dioxide **31** as a synthetic intermediate in the synthesis of *Sceletium* alkaloid A-4 was investigated. Attempts were made to prepare **31** by several new routes: photolysis of 2-methylpyridine-3-carboxaldehyde **18** in the presence of SO_2, trapping of SO_2 by an *o*-quinodimethane generated by fluoride-catalyzed 1,4-elimination, and cyclization of the 4-thioderivative **47** were attempted. None of these approaches were successful. Cyclization of sulfide **56** by thermal elimination of iosobutene and tosic acid and sodium sulfide 1,4-elimination of chloride, both followed by *m*-CPBA oxidation, afforded **31** in moderate yields.

The monoanion and dianion of **31** generated by treating **31** with 1 and 2 equivalents of LDA respectively were found to be efficient nucleophiles, trapping various electrophiles in high yield. Generally, reaction of the monoanion and the dianion with 1 equivalent of electrophile introduced substitution mainly at C-3 and C-1 respectively.

The thermolysis of **31** and some of its derivatives were briefly investigated.

ACKNOWLEDGEMENTS

The support and guidance provided by Dr. Tony Durst in the preparation of this thesis are gratefully acknowledged.

As well the author would like to thank Raj Capoor for the many nmr spectra he recorded, and Dr. Klem Kazakoff for recording the mass spectra.

A very special thanks to Bill Ogilvie and Bill Brown, whose help and insight made this project worthwhile and the preparation of this thesis more enjoyable.

Finally, the author would like to thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for its financial support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIBN	azobisisobutyronitrile
aq	aqueous
°C	degrees Celcius
C.I.	chemical ionization
cm.	centimeter
DA	Diels Alder
E.I.	electron impact
eq	equivalent(s)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	Hertz
I.R.	infrared
L	leaving group

LDA	lithium diisopropylamine
M^+	parent molecular ion
m-CPBA	meta-chloroperbenzoic acid
M	molar
m.p.	melting point
M.S.	mass spectrum
mm	millimole
n-BuLi	n-Butyllithium
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
o-QDM	ortho-quinodimethane
pmr	proton magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
ppm	parts per million
R.T.	room temperature
TBDMS-otf	tert-butyldimethylsilyl- trifluoromethane sulfonate

TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS-Cl	trimethylsilyl chloride
TsCl	*p*-toluenesulfonyl chloride

INTRODUCTION

The mesembrine alkaloids, a group of alkaloids named after the most important member, mesembrine **1**, have been studied only recently in great detail[1-5]. The discovery of several new bases found in various *Sceletium* species has renewed interest in this particular class of alkaloids. The mesembrine alkaloids were discovered in a drug preparation that was named Channa or Koegoed by the bushman of Namaqualand [6]. The drug is obtained by fermentation of *Sceletium ficodacea* growing in the southwest Cape province. Channa, a favorite stimulant of the natives of South-West Africa, is said to have a narcotic, even cocaine-like, effect when chewed.

The content of alkaloids in the Channa drug ranges from 1.0 to 1.5%. The hydrochloride of mesembrine **1** was isolated in 0.7% from the drug. Therefore, since nearly all of the alkaloids from these plants which have been isolated thus far are not available in sufficient quantity for biological evaluation, various synthetic

---

[1] -R.R. Arndt and P.E. Kruger, *Tetrahedron Lett.*, 3237 (1970).

[2] -P.W. Jeffs, G. Ahmann, H.F. Campbell, D.S. Farrier, G. Gangull, and R.L. Hawks, *J.Org. Chem.*, 35, 3512 (1972).

[3] -P.W. Jeffs, P.A. Luhan, A.T. McPhail, and N.H. Martin, *Chem. Commun.*, 1466 (1971).

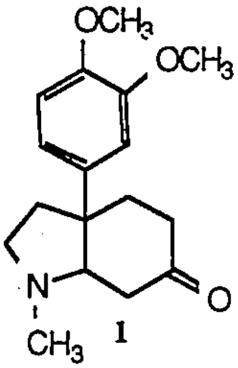
[4] -P.W. Jeffs, T. Capps, D.B. Johnson, J.M. Karle, N.H. Martin, and B. Rauckman, *J. Org. Chem.*, 39, 2703 (1974).

[5] -F.O. Synckers, F. Strelow, and A. Wieckers, *Chem. Commun.*, 1467 (1974).

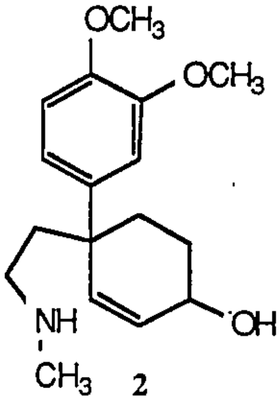
[6] -A. Popelak and G. Lettenbauer, "The Alkaloids", Vol. IX, R.H.F. Manske, Ed. Academic Press, New York, N.Y., 1967, p467.

pathways have been investigated for the total synthesis of mesembrine alkaloids.

Previous studies[6] have led to the isolation of two basic structure-types of the alkaloids from *Sceletium* species. The mesembrine group, based on the 3a-aryl-octahydroindole ring system being the most common, is exemplified by mesembrine **1** itself. The second type, represented by joubertinamine **2**, has been recently reported[2] .

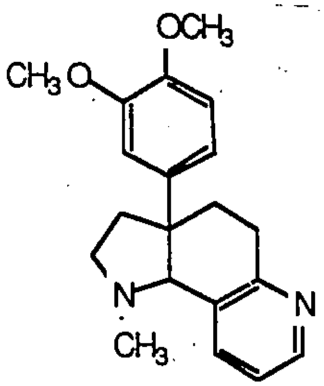


1

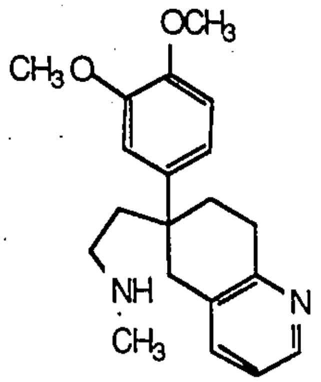


2

Of particular interest are the pyridine alkaloids *Sceletium* A-4 3 and its seco analog tortuosamine 4[4,5]. The structures of these two compounds differ from the more common mesembrine alkaloids aforementioned, by the interesting addition of a fused pyridine ring.



3

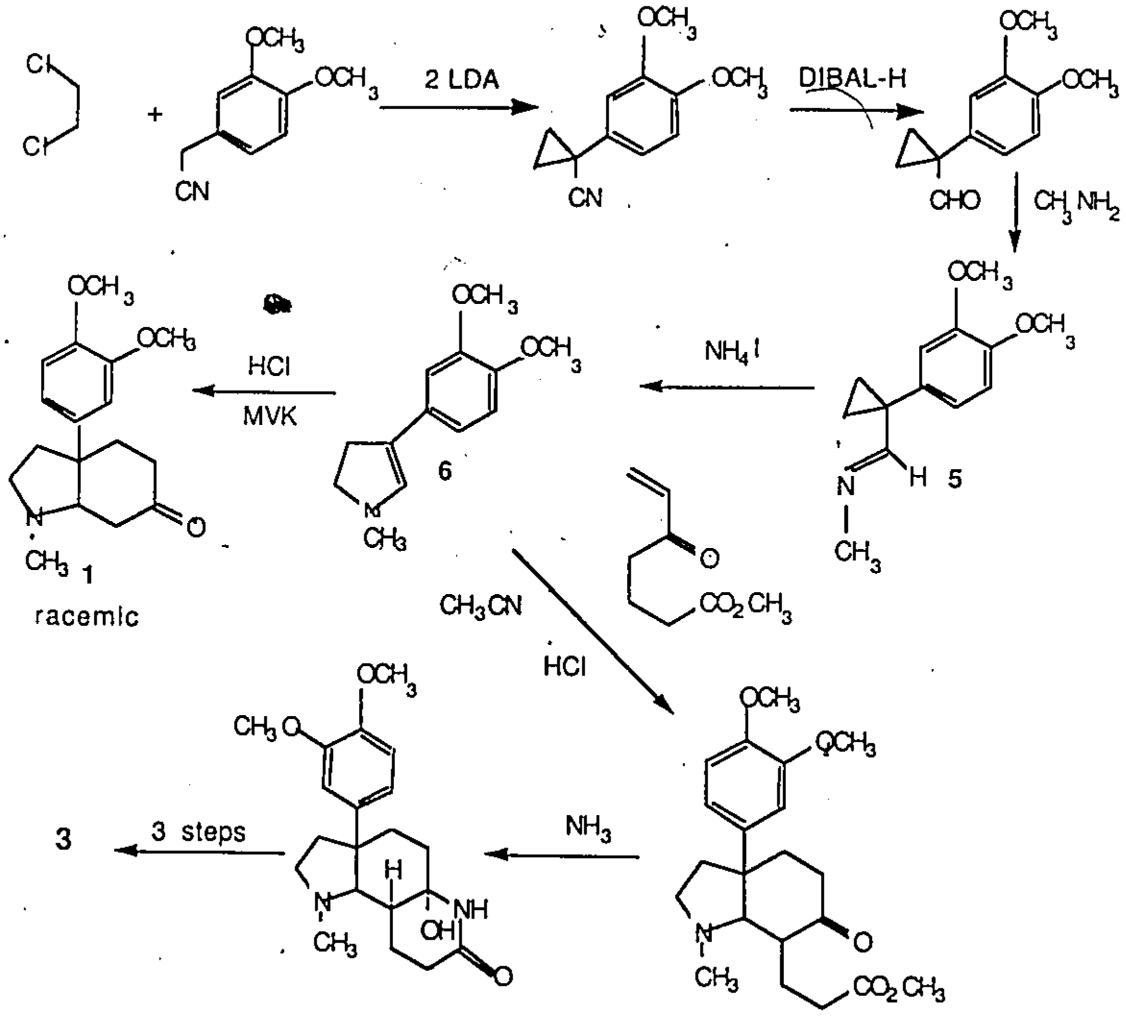


4

An efficient total synthesis of alkaloid *Sceletium* A-4 and improved synthesis of mesembrine was achieved by Stevens[7] and coworkers in 1975. The key steps in the synthesis involved the utilization of the acid-promoted rearrangement of cyclopropylimine **5** to 2-pyrroline **6** and acid-catalyzed annelation of this intermediate with methyl vinyl ketone (MVK) or methyl 5-oxohept-6-enoate. The sequence of reactions is illustrated in scheme 1.

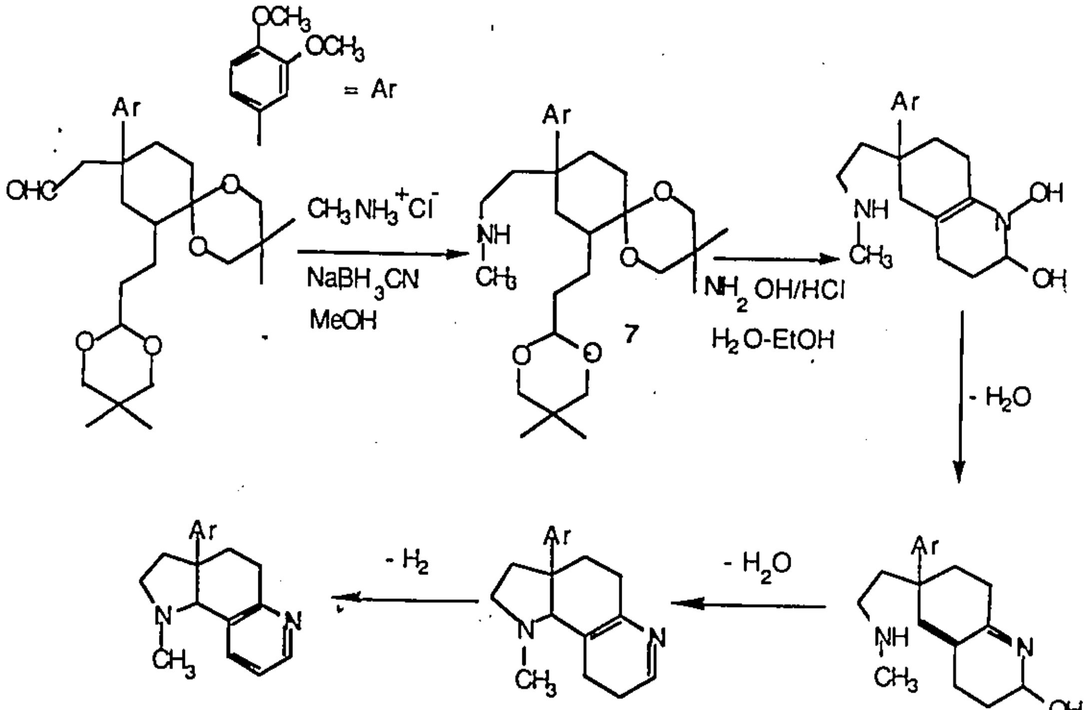
---

[7] R.V. Stevens, P.M. Lesko, and R. Lapalme, *J. Org. Chem.*, **40**, 3495 (1975).



scheme 1

Although substituted arylacetaldehydes like the one used in the synthesis just mentioned are useful precursors to mesembrine alkaloids, it has also been shown[8] that the judicious selection of the substituents present on the precursor to seco-mesembrine alkaloids can also lead to *Sceletium* alkaloid A-4. In this particular synthesis, the key step involves the formation of the [3,2-c] quinoline ring system of **1** from the amino-substituted diprotected 1,5-dioxo-system 7. This transformation involves two dehydrative ring closures followed by dehydrogenation of the resulting dihydropyridine. This reaction sequence is depicted in scheme 2.

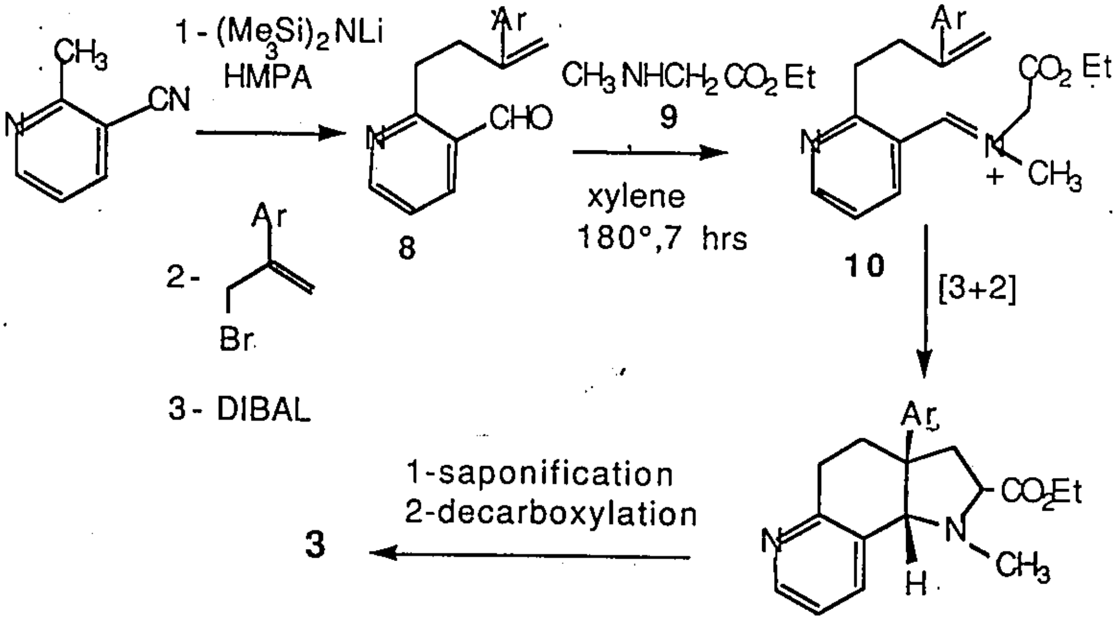


scheme 2

---

[8] C. P. Forbes and G. L. Wenteler, *J. Chem. Soc.*, Perkin Trans. I, 29 (1981).

A more recent synthesis[9] of *Sceletium* alkaloid A-4 involves an intramolecular [3+2] cycloaddition reaction which generates two carbon-carbon bonds using a stabilized iminium ylide. As shown in scheme 3, the olefin aldehyde **8** is condensed with the secondary amino acid ester **9**, generating the stabilized iminium ylide **10** in situ which undergoes a [3+2] cycloaddition. The amino acid obtained by saponification of **11** was then decarboxylated to give (±)-Sceletium alkaloid A-4 in 87% yield. This five - step synthesis, is the shortest to date and the most convergent.

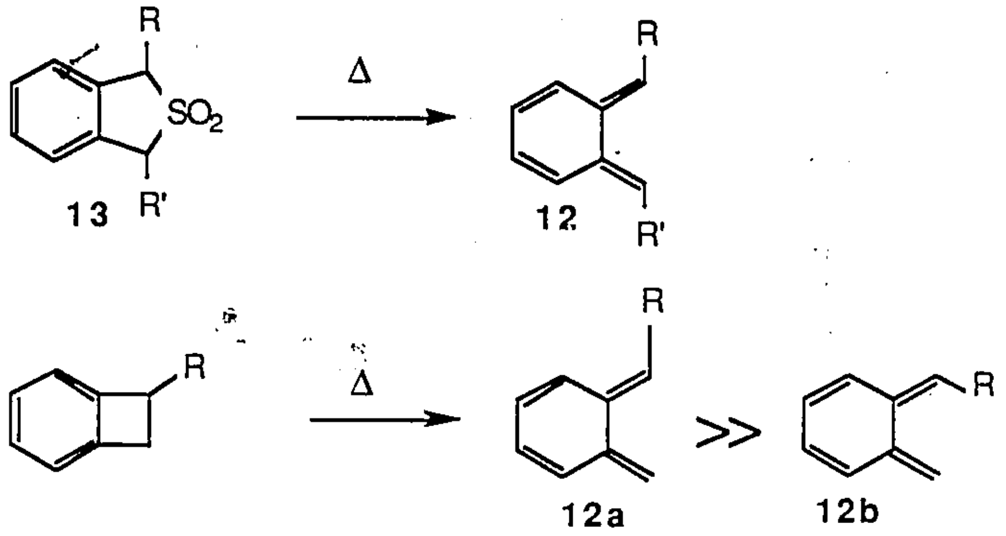


scheme 3

---

[9] P. N. Confalone and E.M. Huie, *J. Am. Chem. Soc.*, **106**, 7175, (1984).

A more novel approach to the synthesis of this particular alkaloid would make use of the well known methodology initially developped for the synthesis of steroid frameworks based on intramolecular cyclization of *o*-quinodimethanes[10] (*o*-QDM) **12**, generated by thermolysis of benzocyclobutene precursors and thermal chelotropic elimination of sulfur dioxide from 1,3-dihydrobenzo[c]thiophene-2,2-dioxides **13** as depicted in scheme 4.



scheme 4

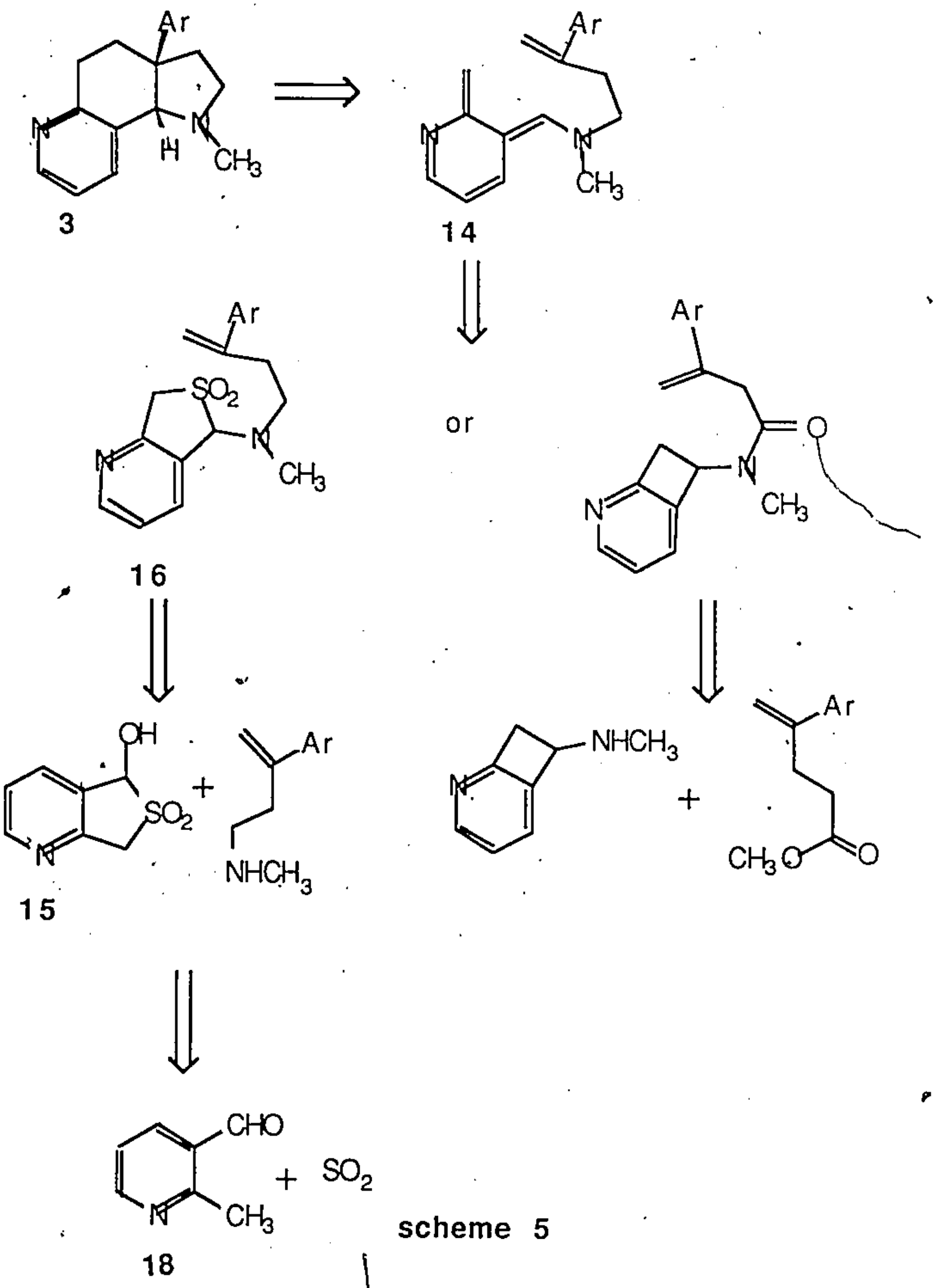
---

[10] also known as *o*-xylylenes and quinodimethides.

The use of *o*-QDMs in organic synthesis is well established and has been reviewed by several authors[11]. Therefore, the evidence present in the wide variety of literature published dealing with *o*-QDMs as convenient, very reactive, intermediates for the synthesis of polycyclic ring systems inherent to natural products, would suggest that an *o*-QDM pyridine derivative could be employed as a diene in an intramolecular Diels-Alder (DA) reaction for the synthesis of *Sceletium* alkaloid A-4. That is, retrosynthetically, as illustrated in scheme 5, the *o*-QDM-DA reaction would represent the final step in the synthesis.

---

[11] J. L. Charlton and M. M. Alauddin, *Tetrahedron*, 43, 2873 (1987) and references cited therein.

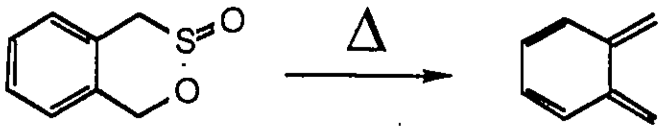


scheme 5

Although this scheme suggests two methods of generating the *o*-QDM intermediate, there are actually six ways that have been developped up to date[11]. These include:

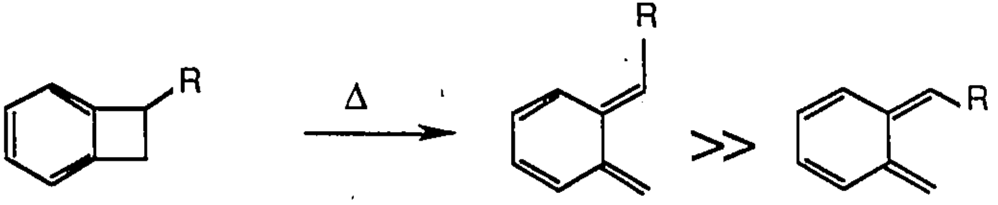
1- Chelotropic elimination of sulfur dioxide from sulfones and sultines.

Cava in 1959 was the first to generate and trap an *o*-quinodimethane with dienophiles by thermal elimination of sulfur dioxide from benz-dihydrothiophene-2,2-dioxide. Since then a multitude of papers have been published on this topic including several on the generation of *o*-QDM by thermal elimination of sulfur dioxide from a sultine, first achieved by Durst *et al* in 1974.



2- Thermolysis of benzocyclobutenes

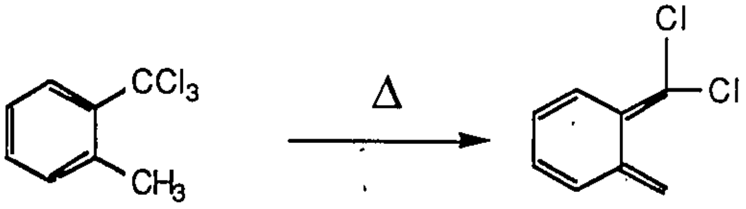
The thermal ring opening of a benzocyclobutene proceeds via a thermally allowed conrotatory electrocyclic ring opening favoring, if a substituent is present on the 4-membered ring, the sterically less hindered (E)-*o*-QDM **12a** over the (Z) form **12b**. These substituted benzocyclobutenes also open at a lower temperature than the parent benzocyclobutene (110°–140°C vs 200°C).

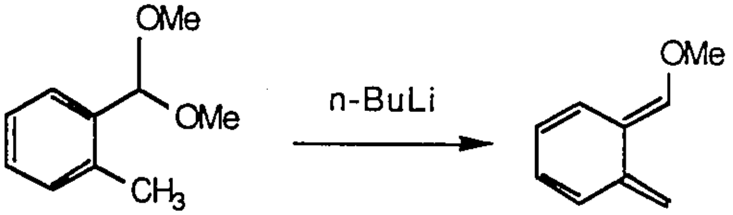


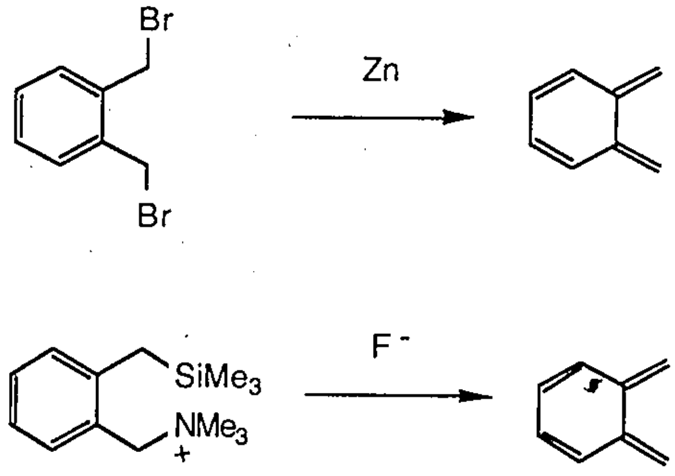
12a **12b**

3- 1,4-Elimination

Thermal eliminations, base-catalyzed eliminations, reductive eliminations and fluoride ion catalyzed eliminations generate *o*-QDMs by what is generally referred to as the 1,4-elimination process. Examples of each are shown below.

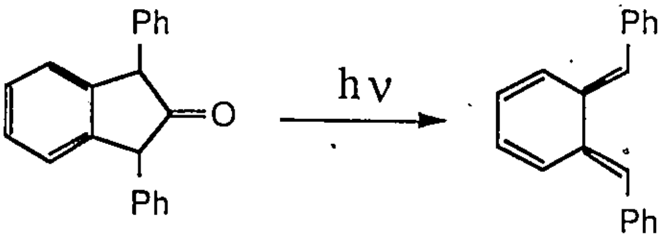






4- Photochemical expulsion of carbon monoxide

Photochemical expulsion of carbon monoxide from substituted 2-indanones may also lead to α,α'-disubstituted *o*-QDMs[12].

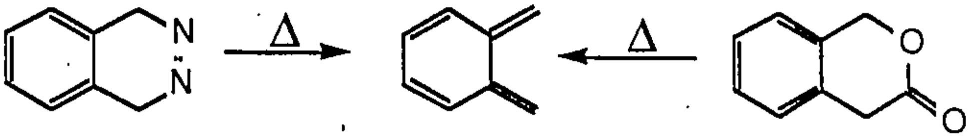


---

[12] G. Quinkert and H. Stark, *Angew. Chem. Int. Ed. Engl.* 22, 637 (1983).

5- Diels-Alder cycloreversion

The loss of nitrogen from 3,4-dihydrodiazanaphthalene and carbon dioxide from isochromanone exemplify the Diels-Alder cycloreversion process for the generation of *o*-QDMs[13,14].

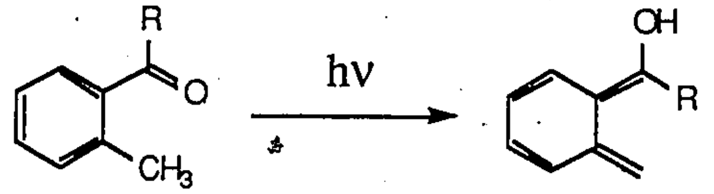


6- Photoenolization and Photorearrangement

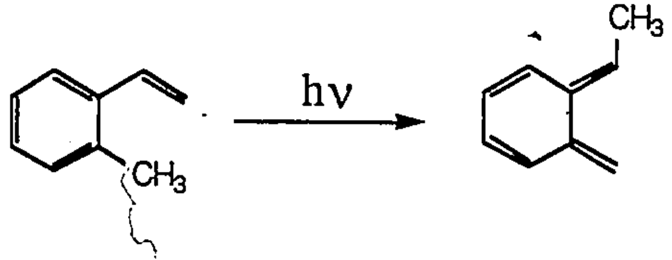
Irradiation of *o*-alkylbenzaldehydes or alkylbenzophenones produces α-hydroxy-*o*-QDMs by a process involving excitation to an n* triplet state followed by intramolecular hydrogen abstraction giving a triplet diradical which then decays to the longer-lived E isomer[15].

---

[13] T. Durst and L Tetrault-Ryan, *Tetrahedron Lett.*, 2353 (1978).
[14] W. Oppolzer, Heterocycles 14, 1615 (1980).
[15] T. Durst, E. C. Kozma and J. Charlton, *J. Org. Chem.*, 50, 4829 (1985).



The photolysis of *o*-alkylstyrenes also produces *o*-QDMs via a [1,5] sigmatropic shift[16].



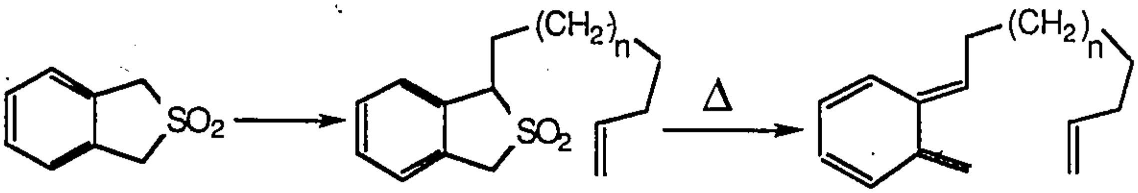
The method chosen for the preparation of the pyridine *o*-QDM **14** shown in scheme 5 depended on certain variables, mainly; the availability of starting materials, the overall yield and the ease with which the method could be carried out.

The two methods shown in this scheme, *i.e.* thermolysis of a cyclobutapyridine and chelotropic elimination of sulfur dioxide from a 1,3-dihydrothieno[3,4-b]pyridine-2,2-dioxide, were first considered for the generation of the pyridine *o*-QDM required for our approach.

---

[16]. J. M. Hornback and R. D. Barrows, *J. Org. Chem.*, 47, 4285 (1982).

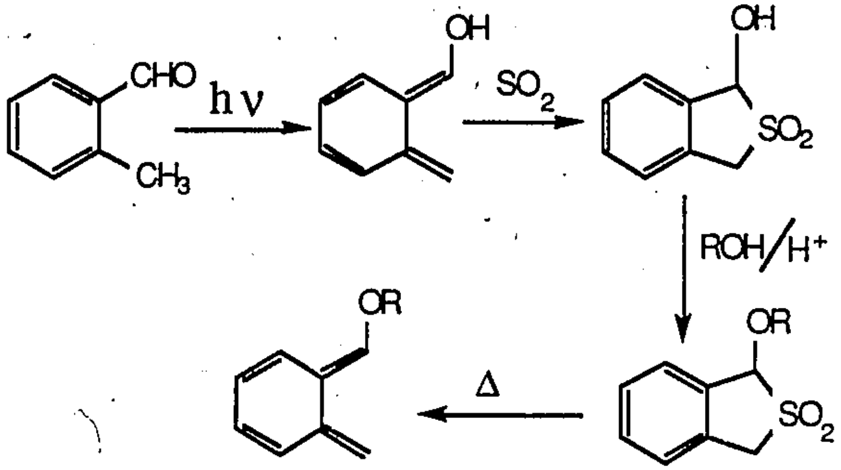
The thermolysis method, although being the most frequently used for the generation of *o*-QDMs, had two serious drawbacks; the difficulty in the synthesis and corresponding low yields of the cyclobutapyridines obtained (17%-35%)[17,18]. Therefore, the synthesis of a 2,3-pyridine sulfone as an *o*-QDM precursor to **14** was finally considered as the most convenient method. Oppolzer *et al* [13] found that the readily available unsubstituted sulfone could be substituted with appropriate substituents and thermolized to the *o*-QDM, rendering sulfones as the preferred precursors for the generation of *o*-QDMs.



Based on the reports that photochemically generated *o*-QDMs could be trapped reversibly by SO_2, Charlton and Durst[19] demonstrated the subsequent facile conversion of the resulting sulfones to a variety of α-alkoxy, acyloxy and alkylbenzothiophene-2,2-dioxides.

---

[17] J.M. Riemann and W.S. Trahanovsky, *Tetrahedron Lett.*, 22, 1867 (1977).
[18] R.P. Thummel and D.K. Kohli, *J. Org. Chem.*, 25, 4882 (1978).
[19] J. Charlton and T. Durst, *Tetrahedron Lett.*, 25, 2663 (1984).



This appeared to be a very straightforward route to *o*-QDM precursors from reasonably simple starting materials. Therefore, the reversible trapping of a 1-hydroxypyridine-*o*-QDM by sulfur dioxide would be attempted to synthesize 1-hydroxydihydrothieno[3,4-b]pyridine-2,2-dioxide **15**, precursor to sulfone **16.** The synthesis and attempted photolysis of 2-methylpyridine-3-carboxaldehyde as well as the multitude of other reactions performed in an attempt to prepare the *o*-QDM precursor **15** will now be discussed.

RESULTS AND DISCUSSION

INTRODUCTION

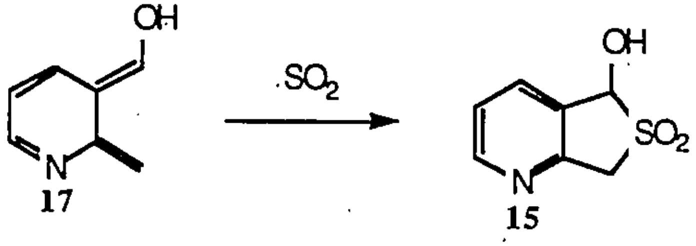
Our original plan required the preparation of a suitably substituted sulfone which could be further elaborated into an *o*-QDM precursor which contained the appropriate internal dienophile. This intermediate following an intramolecular Diels-Alder reaction would afford *Sceletium* alkaloid A-4 **3** directly. According to the *o*-QDM methodology, well established for the benzene series, pyridine *o*-QDMs could be generated by chelotropic elimination of sulfur dioxide from 1,3-dihydrothieno[3,4-b]pyridine-2,2-dioxide derivatives. As mentioned earlier, photochemically generated pyridine *o*-QDMs could be trapped reversibly by SO_2 and as in the benzene series possibly converted to 1-alkoxy, acyloxy and alkyl-dihydrothieno[3,4-b]pyridine-2,2-dioxides. Therefore, the reversible trapping of 1-hydroxypyridine-*o*-QDM by SO_2 would yield the suitable sulfone precursor **15**. Although the synthesis and photolysis of 2-methylpyridine-3-carboxaldehyde in the presence of SO_2 appeared to be a very straightforward route to sulfone **15** some problems were encountered which lengthend its initially "straightforward" synthesis.

The following sections therefore do not describe the synthesis of *Sceletium* alkaloid A-4 **3** but discuss the various approaches to sulfone **15** and some of the chemistry involved. The work in this thesis could form the background for a new approach to *Sceletium* alkaloid A-4 **3**.

PART A

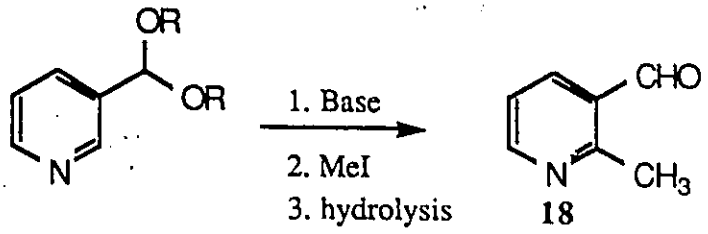
SYNTHESIS OF 2-METHYLPYRIDINE-3-CARBOXALDEHYDE

As previously mentioned in the introduction, the reversible trapping of 1-hydroxy-*o*-QDM **17** by sulfur dioxide would yield 1-hydroxy-3-dihydrothieno[3,4-b]pyridine-2,2-dioxide **15** which is needed to generate the *o*-QDM precursor **16**. Simple photolysis of 2-methylpyridine-3-carboxaldehyde **18** in the presence of sulfur dioxide would give sulfone **15**.



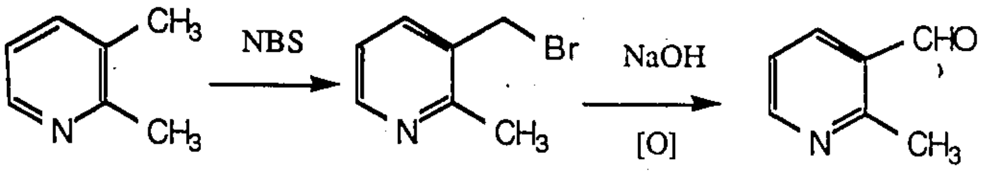
After conducting a survey of the literature, no previous synthesis of 2-methylpyridine-3-carboxaldehyde was found. Therefore, a number of approaches to aldehyde **18** were investigated. These include:

a) Orthometalation of pyridine-3-carboxaldehyde derivatives;

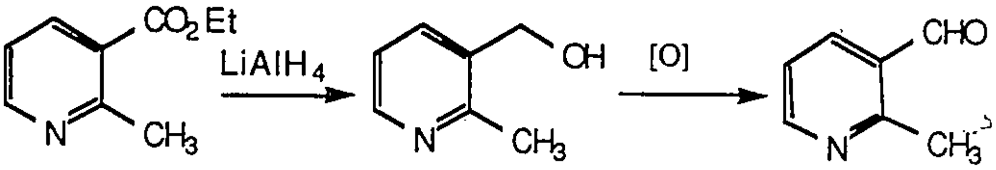


18

b) Regioselective monobromination of 2,3-dimethylpyridine followed by conversion of the 3-bromomethyl derivative to the aldehyde function;

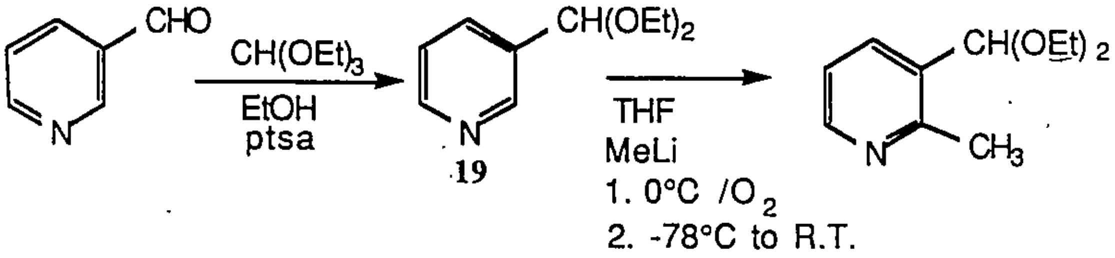


c) Reduction of ethyl 2-methylnicotinate followed by appropriate oxidation of the resulting 3-hydroxymethyl to the aldehyde function;



Of the three approaches just mentioned the most convenient one and hence the one which should have been attempted first is obviously (c). However at that time, ethyl 2-methylnicotinate was not commercially available , and its preparation was judged to be a very tedious and ineffective synthesis. Therefore, methods (a) and (b) were attempted first. The three approaches will now be described sequentially.

The first approach to **18** involved methylation at position two of pyridine-3-carboxaldehyde diethyl acetal **19** with methyllithium. The initial step consisted of protecting the aldehyde function by *trans*-acetalation which would prevent addition to the carbonyl function and hopefully the resulting diethyl acetal would direct the methyllithium to give mainly addition at C-2, as opposed to C-4 as observed by Beak and Snieckus in orthometalation reactions[16]. The second step involved simply adding methyllithium to a solution of acetal followed by air oxidation to produce **18**. The overall reaction is shown in scheme 6.



scheme 6

Pyridine-3-carboxaldehyde was converted to pyridine-3-carboxaldehyde diethyl acetal **19** in 87% yield via *trans*-acetalation using triethylorthoformate in ethanol. Next, methylation at position

---

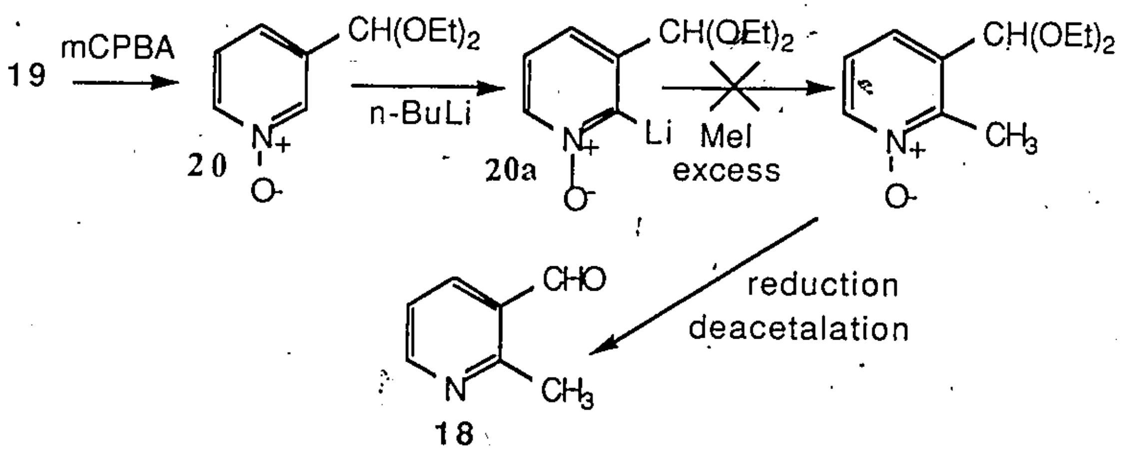
[16] P. Beak, V. Snieckus, *Acc. Chem. Res.*, **15**, 306 (1982) and references cited therein.

two was attempted by addition of methyllithium to a solution of the diethyl acetal in tetrahydrofuran (THF) both at 0°C and -78°C. Following work-up, only starting material was recovered in both cases. No addition was observed as revealed by the ^{1}H NMR which did not show any evidence of an aromatic methyl group at δ 2.5 -3 ppm. The diethyl acetal **19** did however present a further possibility as an intermediate to **18**.

R.A. Abramovitch[17] and coworkers have shown that the reaction of pyridine-1-oxides with *n*-butyllithium (*n*-BuLi) at low temperature and in non-protic solvents gives 2-lithiopyridine-1-oxides which react with carbon dioxide and esters to yield acids and ketones respectively in roughly 50% overall yield. Hence, 2-lithiopyridine-1-oxide carboxaldehyde diethyl acetal **20a** could potentially be trapped by an electrophile, methyl iodide, to yield after reduction and deacetalation, 2-methylpyridine-3-carboxaldehyde **18** (shown below).

---

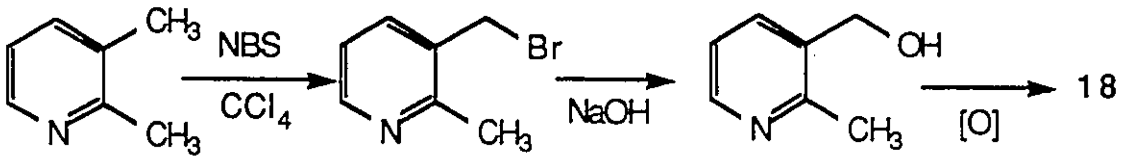
[17] R.A. Abramovitch, R.T. Coutts, and E.M. Smith, *J. Org. Chem.*, 37, 3584 (1972).



Oxidation of **19** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at 25°C afforded the N-oxide in 53% yield following purification. The oxide was readily identified by its 300 MHz ^1H NMR spectrum:δ8.42(s,1H,H_a);δ8.26(d,1H,J=6.71Hz,H_b);δ7.47(d,1H,J=7.42Hz, H_c);δ7.33(dd,1H,J=7.42Hz,6.71Hz,H_d);δ5.50(s,1H,$C\underline{H}(OEt_2)$);δ3.56(q,4H,$CH(OC\underline{H}_2CH_3)_2$);$\delta$1.23 (t,6H,$CH(OCH_2C\underline{H}_3)_2$). A large upfield shift of both protons α (H_a and H_b) to the nitrogen was observed in going from of **19** to **20** , *i.e.* δ8.78 vs δ8.42 ppm for H_a and δ8.26 vs δ8.60 for H_b. Although one would expect a downfield shift for the *o*- and *p* -protons, R.A. Abramovitch[17] also observes a similar upfield shift for N-oxides.

The 2-pyridyl-1-oxide anion was generated by the addition of *n*-BuLi to a solution of the N-oxide in THF or in ether.,at -78°C. In each case the anion solution was quenched with methyl iodide and the reaction mixture was allowed to warm to room temperature. Workup afforded a black oily product whose TLC showed that many highly polar products had been formed. The ^{1}H NMR spectrum of the crude product showed broad, ill defined absorption patterns, possibly suggesting the formation of polymeric products or products possibly resulting from O-methylation of the N-oxide. There was no evidence of an aromatic methyl group in the δ 2.5 to 3 ppm range. This reaction was repeated under various conditions with similar results; no indication of any methylated material. A possible reason for the inability to generate cleanly the desired 2-lithio species may be due to the diethyl acetal substituent directing deprotonation preferentially para to itself, as do 3-alkyl substituents[18] thus producing 6-lithiation and possibly 2,6-dilithiation products, in addition to the 2-lithiation product expected.

The second approach to **18** involved radical bromination of 2,3-lutidine **21** to give the 3-bromomethyl derivative **22**; subsequent treatment with sodium hydroxide (NaOH) would afford the corresponding alcohol **23** which upon oxidation with a suitable oxidizing agent would give aldehyde **18** (scheme 7).



scheme 7

---

[18] R.A. Abramovitch, E.M. Smith, E.E. Knaus and M. Saha, *J. Org. Chem.*, 37, 1690 (1972).

The synthesis of the 3-bromomethyl derivative **22** was attempted by preferential radical monobromination of the C-3 methyl of 2,3-lutidine **21** using N-bromosuccinimide (NBS) according to a procedure reported by Rapoport[19] *et al* . The mixture after concentration at reduced pressure contained mainly polybrominated products, as determined by NMR. The procedure was repeated using benzoylperoxide instead of AIBN as the free radical initiator and monitored closely by NMR. The reaction was stopped after two hours (disappearence of the starting material's C-3 methyl group ^{1}H NMR signal: δ 2.43 ppm) to prevent polybromination. After filtering off the succinimide and concentrating the solution, the mixture contained mainly (35% yield) 3-(bromomethyl)-2-methylpyridine **22** [^{1}H NMR (CCl_4): δ 6.80-8.24(m,3H); δ 4.24(s,2H); δ 2.52(s,3H)]. As a result of the low yields of 3-bromomethyl derivative **22** obtained by this method, a slight modification was performed. To the solution of 2,3-lutidine **21** in carbon tetrachloride (CCl_4), was added one equivalent of benzoic acid followed by addition of NBS. It was rationalized that bromination of the salt of **21** might increase the yield of the 3-bromomethyl derivative **22** by preventing N-bromination of the pyridine ring and possible self-alkylation of **22**. However, no improvement in yield was observed.

---

[19] H. Rapoport, E. Ghera and B. David, *J. Org. Chem.*, 46, 2059 (1981).

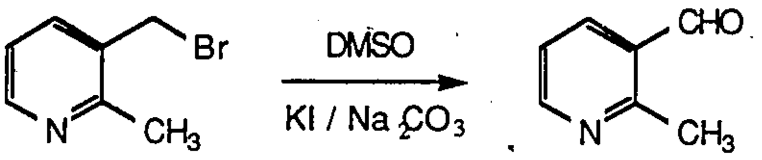
A solution of the crude 3-bromomethyl derivative **22** obtained above was reacted with 15% NaOH in dioxane at reflux for 1.5 hours. Workup afforded a reddish-black oil whose TLC showed the presence of very polar material. There was no evidence of any alcohol formation.

Primary and secondary halides and sulfonate esters can be oxidized to aldehydes and ketones with dimethyl sulfoxide (DMSO)[20]. S. Macomber and P. Bauer[21] modified the existing procedure by catalyzing the oxidation with iodide which gave reasonable yields (65%-92%) in relatively short reaction times (5-60 min.). In view of this, DMSO oxidation of the 3-bromomethyl derivative 22 was attempted using a DMSO, potassium iodide (KI), and sodium carbonate (Na_2CO_3) mixture according to Macomber's procedure (scheme 8). Workup and purification afforded 2-methyl-3-pyridine carboxaldehyde **18** in 8-13% yield [^{1}H NMR($CDCl_3$): δ10.31 (s,1H,C$\underline{H}$O);δ8.55(dd,1H,J=4.87Hz,2.41Hz);δ8.05(dd,1H,J=7.85Hz,2.41Hz; δ7.23(dd,1H,J=7.85Hz,4.87Hz); δ 2.82(s,3H,CH_3)].

---

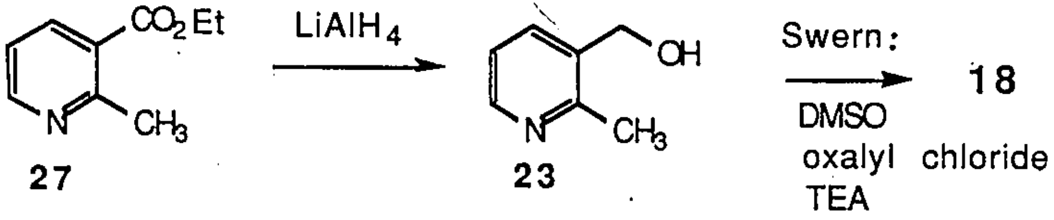
[20] A.P. Johnson and A. Pelter, *J. Chem. Soc.*, **520** (1964) and references cited therein.

[21] R. S. Macomber and D. P. Bauer, *J. Org. Chem.*, 40, 1990 (1975).



scheme 8

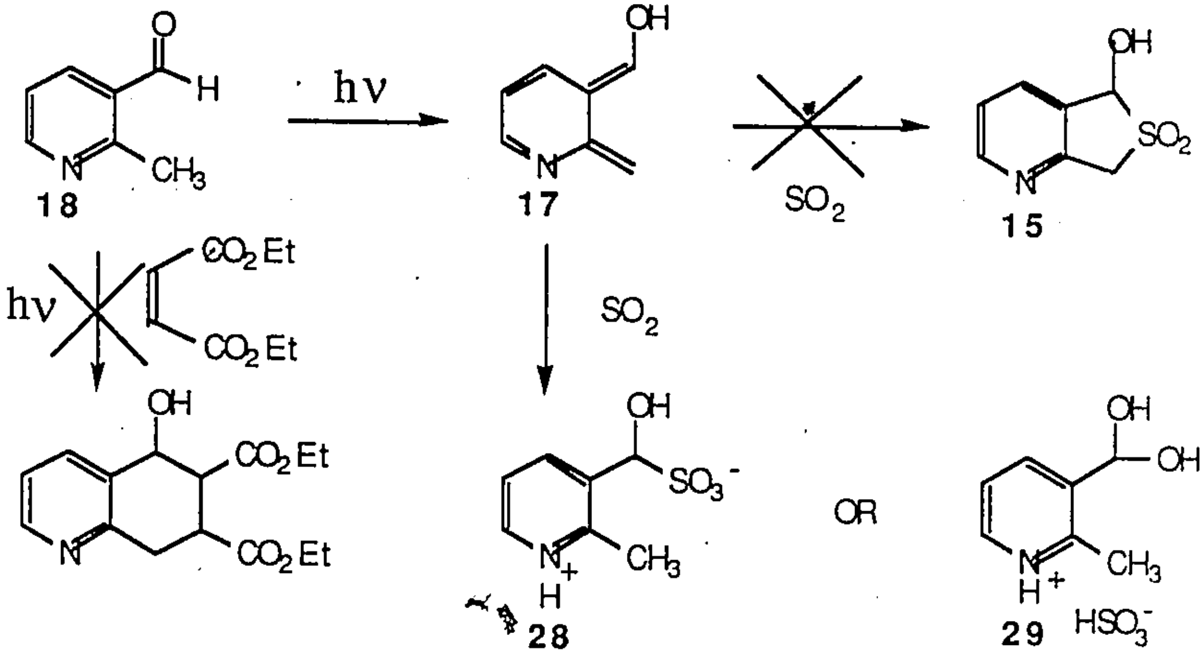
The extremely low yields of aldehyde obtained by the 3-bromomethyl derivative **22** oxidation method and fortuitous, sudden availability of ethyl 2-methylnicotinate **27** via Lancaster Synthesis, led to a fourth approach involving lithium aluminium hydride ($LiAlH_4$) reduction of this ester to afford alcohol **23**, followed by oxidation with a suitable reagent to yield aldehyde **18** as shown in scheme 9.



scheme 9

The $LiAlH_4$ reduction of ester **27** afforded alcohol **23** in 93-98% overall yield. The spectroscopic data confirmed the assignment *i.e.* ^1H NMR: δ 8.41(dd, 1H, J=4.83Hz, 0.74Hz); δ 7.51(dd, 1H, J=7.68Hz, 0.74Hz); δ 7.18(dd, 1H, J=7.68Hz, 4.83Hz); δ 4.70(s, 2H $C\underline{H}_2OH$); δ 3.52(b, 1H, OH); δ 2.32(s, 3H ,CH_3). I.R.(film): 3360 (OH,broad); 1585 (pyridine C=C,C=N); 1050 (CH_2OH)cm^{-1}. M.S.: M^+=123(b.p.); M^+-1=122(54.1%); M^+-H_2O=105(36.1%). The 300 MHz ^{1}H NMR spectrum of **23** is reproduced in figure 1.

Oxidation of **23** with pyridinium chlorochromate, (PCC)[22], gave aldehyde **18** in 21% yield. The low yield obtained is most likely due to complexation of chromium with the product (2-methylpyridine carboxaldehyde) with subsequent "loss" during workup. Fortunately Swern oxidation[23] afforded the desired aldehyde in yields ranging between 52% and 80%.



scheme 10

---

[22] E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 23, 2647 (1975).
[23] R. E. Ireland and D.W. Norbeck, *J. Org. Chem.*, 50, 2198 (1985).

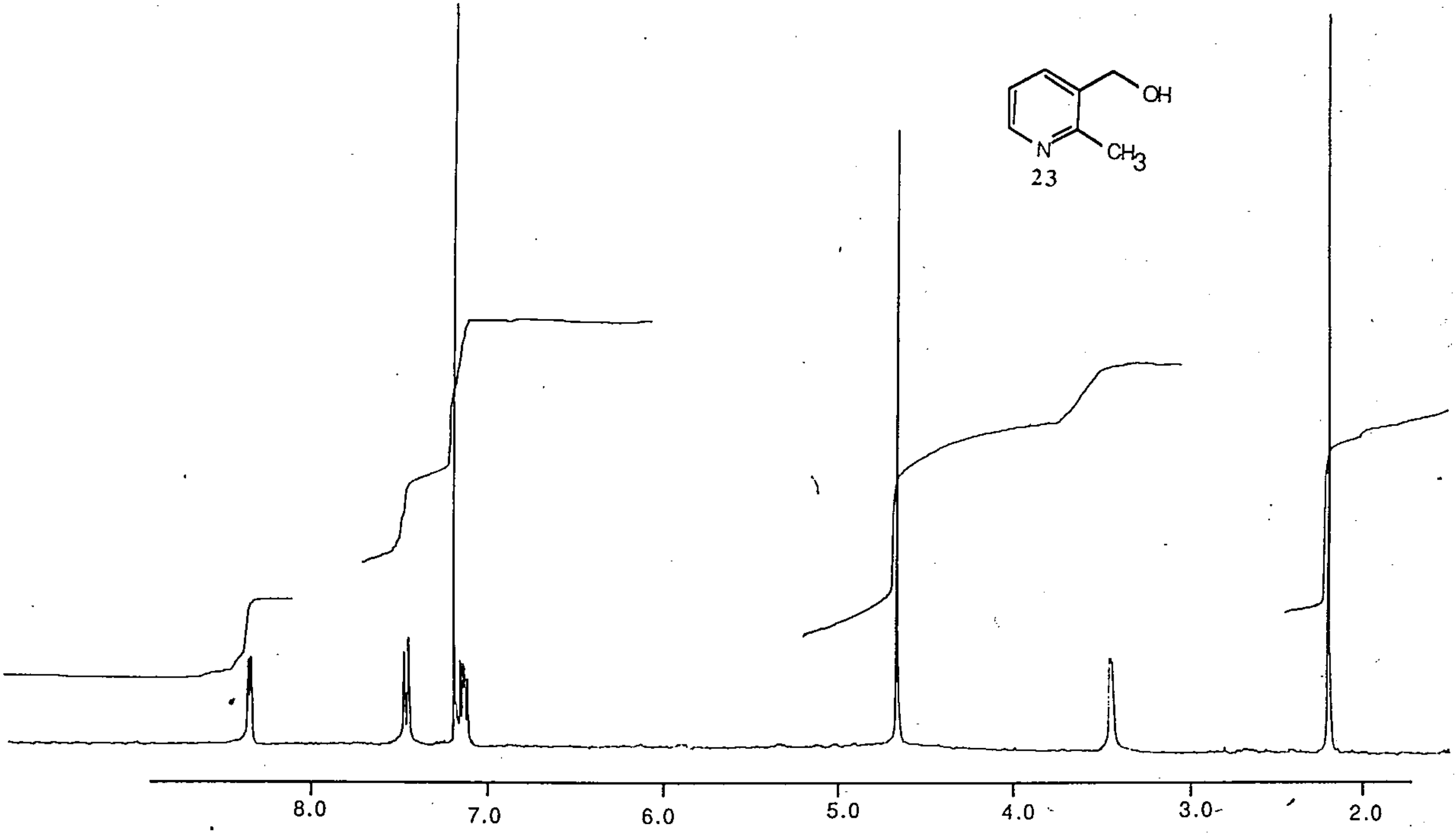


FIGURE 1: ^{1}H NMR Spectrum of **23**

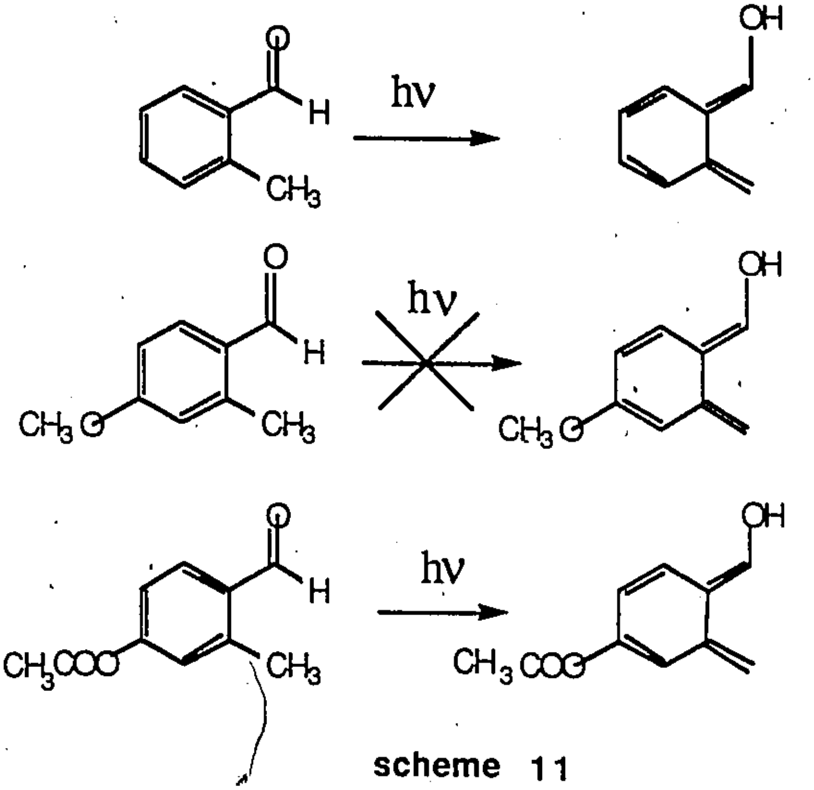
Aldehyde **18** was dissolved in benzene, the solution was purged with nitrogen, saturated with sulfur dioxide and photolyzed overnight in a 1 mm pyrex tube using a Hanovia 450 watt medium pressure mercury lamp. No sulfone or starting material were recovered following aqueous workup. The reaction was repeated and monitored by thin layer chromatography (TLC). The TLCs indicated the presence of a very polar product and some starting aldehyde. The reaction was stopped (after 18 hrs) and the benzene removed under reduced pressure. The product isolated gave the following pmr data in DMSO-d_6 (300MHz): δ8.66 (dd,1H, J=4.90Hz,1.46Hz); δ8.61 (dd,1H, J=7.81Hz,1.46Hz); δ7.92 (dd,1H, J=7.81Hz, 4.90Hz); δ5.40 (s,1H, $C\underline{H}OHSO_3^-$) ; δ2.43 (s,3H,CH_3); the OH groups may be masked by the large DMSO peak at δ3.52ppm. The two structures **28** and **29** shown in scheme 10 are both in reasonable agreement with the pmr data and could have been formed via bisulfite addition or hydration of the aldehyde function or its protonated form. The bisulfite itself could result from:

$$H_2O + SO_2 \longrightarrow H_2SO_3 .$$

Was the 1-hydroxy *o*-QDM **17** actually being formed and not trapped by SO_2? To answer this question, **18** was photolyzed overnight in the presence of one equivalent of diethyl fumarate. Isolation of starting materials (aldehyde and fumarate) suggested the fact that **17** was not being formed at all. The energy of the n-π* transition in the aldehyde was probably not sufficient to achieve intramolecular proton abstraction. For example; Charlton[24] has shown that whereas *o*-tolualdehyde traps SO_2 photochemically 4-methoxy 2-methyl-benzaldehyde does not (scheme 11). It was rationalized that the latter compound does not have sufficiently high n-π* transition energy to achieve the proton abstraction needed for *o*-QDM formation. However when the methoxy group is replaced by an acetoxy or mesyloxy group, the n-π* transition energy is sufficient to achieve proton abstraction, the *o*-QDM is formed (scheme 11) and SO_2 is trapped. The n-π* transition energy for 2-methyl-3-pyridinecarboxaldehyde **18** is apparently insufficient to give the desired photoenolization. This suggestion could be investigated by obtaining appropriate U.V. spectra and determining the n-π* energy. Since the emphasis of this thesis was to find a synthetic route to **15** this aspect was not investigated.

---

[24] Private communication.



scheme 11

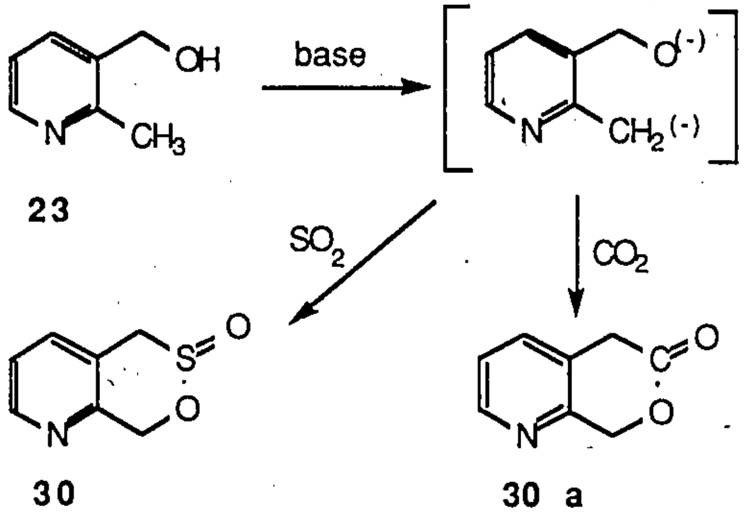
Since aldehyde **18** could not be photolyzed in the presence of sulfur dioxide to give the 1-hydroxy sulfone **15**, another alternative was considered involving the synthesis of a corresponding sultine **30**, possible precursor to *o*-QDM **17** (scheme 12), based on earlier work by Durst *et al*[25] in which they have shown that sultines yield *o*-QDMs by sulfur dioxide extrusion at relatively low temperatures.

In this attempted synthesis of sultine **30** (scheme 12) , alcohol **23** was treated with NaH and *n*-BuLi, the dianion obtained quenched

---

[25] T. Durst, J. Charlton and D.B. Mount, *Can. J. Chem.* **64**, 246 (1986).

by bubbling in SO_2 and finally the reaction mixture acidified with HCl. Unfortunately, alcohol **23** was the only compound isolated.



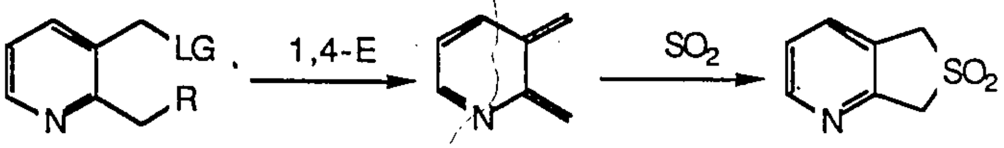
scheme 12

The reaction was repeated several times under various conditions without success. In view of these results, other methods had to be investigated for the synthesis of a sulfone precursor to 1-hydroxy *o*-QDM **17**.

PART B

FLUORIDE-INDUCED 1,4-ELIMINATION

As described briefly in the introduction, the 1,4-elimination (1,4-E) process which includes thermal eliminations, base catalyzed eliminations, reductive eliminations and fluoride-catalyzed eliminations has also been used to generate *o*-QDMs. Based on this concept, the next approach consisted of generating an *o*-QDM by a selected 1,4-elimination process and trapping it with SO_2 to give the unsubstituted sulfone **31** (scheme 13).



31

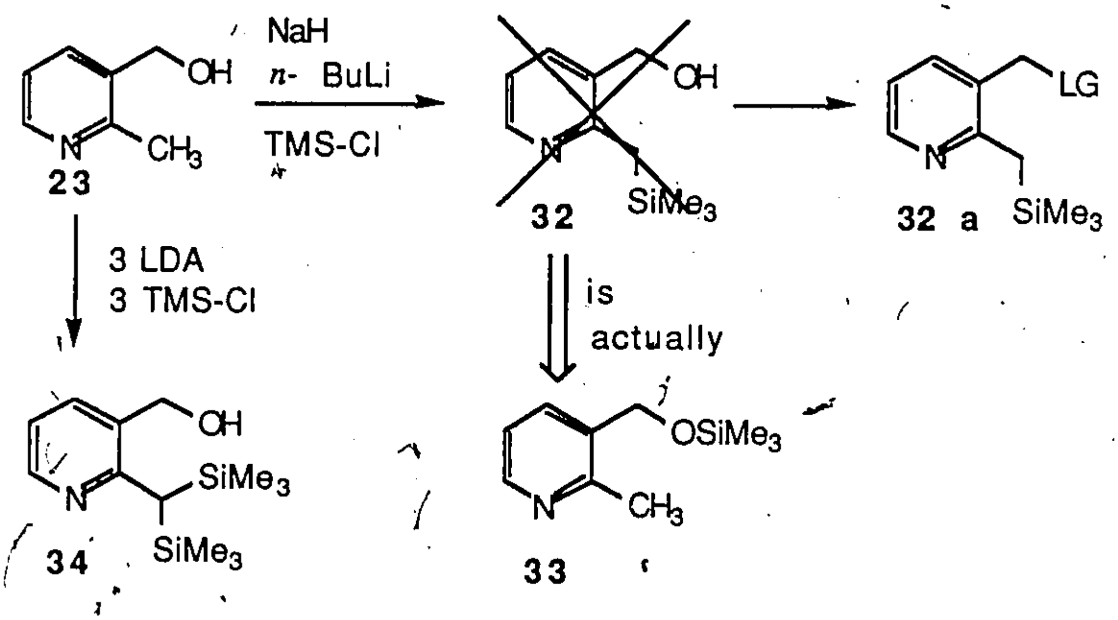
scheme 13

Analogous to the synthetic method developped by T. Saegusa[26], whereby *o*-QDMs are generated by fluoride induced 1,4-elimination of *o*-(α-trimethylsilylalkyl)benzyltrimethylammonium halides, it was thought that the corresponding pyridine analog should also behave in a similar manner. The required precursor would be

---

[26] T. Saegusa, M. Nakatsuka, Y. Ito, *J. Am. Chem. Soc.*, **102**, 863 (1980).

synthesized from alcohol **23** by silylation of the C-2 methyl and conversion of the hydroxyl group to a suitable leaving group according to scheme 14.

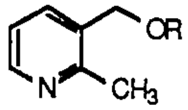


scheme 14

Silylation was attempted by adding a solution of alcohol **23** in THF to a stirred suspension of NaH (1eq.) in THF at 0°C. After the addition was complete, the reaction mixture was stirred for 5 minutes at 0°C and then cooled to -78°C. One equivalent of *n*-BuLi was added dropwise. After the addition was complete, the reaction mixture was stirred for 10 minutes at -78°C, quenched with excess trimethylsilylchloride (TMS-Cl) and allowed to reach R.T. The product obtained was shown be the O-silylated derivative 33. The ^{1}H NMR showed signals at δ8.34(m,1H); δ7.63(m,1H); δ7.55(m,1H); δ4.61(s,2H,C$\underline{H}_2$OSiMe$_3$); δ2.43(s,3H,CH$_3$); δ0.12(s,9H,OSi(CH$_3$)$_3$). This product was surprisingly stable towards dilute acid hydrolysis.

The silylation experiment was repeated several times (table 1). However, the dianion did not form under these conditions, *i.e.* deprotonation of the C-2 methyl group did not occur resulting in O-silylation exclusively.

Table 1: Attempted silylation of **23**

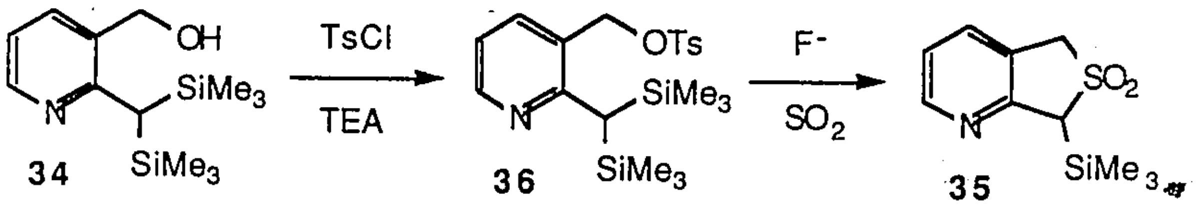


base	T(°C)	time	silylating agent	product
2 LDA	-78°	10 min.	TMS-Cl	R= TMS
NaH/*n*-BuLi	0°/-78°	5min./10min.	TBDMS-otf	R= TBDMS
2 *n*-BuLi	-78°	10min.	TBDMS-otf	R= TBDMS
2 *sec*-BuLi/TMEDA	-78°	10min.	TBDMS-otf	R=TBDMS

To ensure that C-silylation would occur, **23** was subjected to treatment with 3 eq. of LDA at -78°C, the reaction mixture stirred for 10 minutes and 3 eq. of TMS-Cl added. Surprisingly, this time silylation did occur, unfortunately twice, and compound **34** was isolated in 59% yield [^{1}H NMR: δ8.17(m,1H); δ 7.29(m,1H); δ

6.72(m,1H); δ 4.35(s, 2H, C<u>H</u>$_2$OH); δ 2.32(s,1H, CH$_2$O<u>H</u>); δ 1.71(s,1H, C<u>H</u>(SiMe$_3$)$_2$) integration of silyl methyl hydrogens=18H(δ 0.00 reference)]. No C-monosilylated product **32** resulted from these reactions. It is difficult to rationalize the fact that treating **23** with 3 eq. of LDA and TMS-Cl results in the incorporation of 2 silyl groups at C-2 whereas no incorporation occurs with 2 eq. of LDA and TMS-Cl. One would expect at least the formation of a small amount of **32**;unfortunately no evidence of its formation was detected.

Even though **32a** could not be obtained, the accessibility of the disilylated compound **36**, prepared from **34** by tosylation using TsCl/TEA/CH$_2$Cl$_2$, allowed us to test the concept outlined in scheme 15.

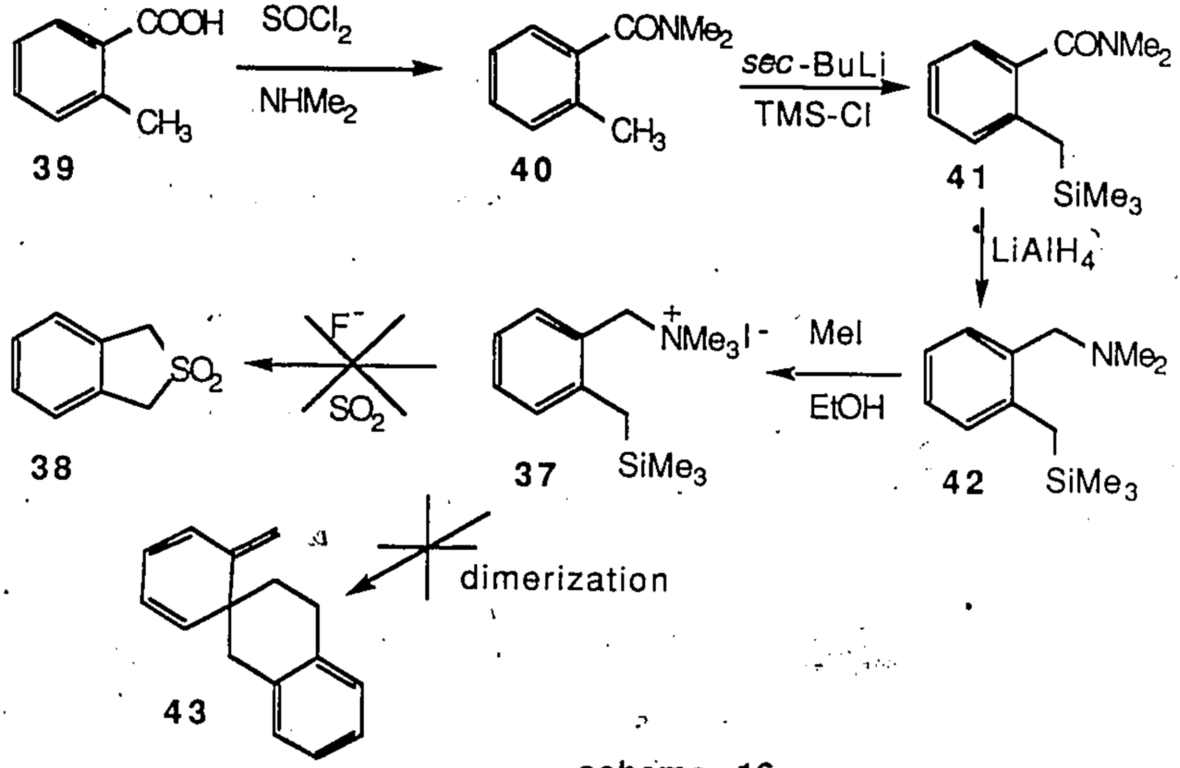


scheme 15

Reaction of **36** with fluoride in acetonitrile saturated with SO$_2$ followed by aqueous workup gave no sulfone **35**; no starting material was recovered. Consequently, a model experiment was performed to verify that an *o*-QDM generated via fluoride-induced

1,4-elimination reaction would indeed trap SO_2 to form the expected sulfone.

Based on Saegusa's aformentioned report , *o*-(α-trimethylsilylmethyl) benzyltrimethylammonium iodide **37** was synthesized and reacted with F^- in the presence of SO_2. The sequence of reactions involved are depicted in scheme 16.



scheme 16

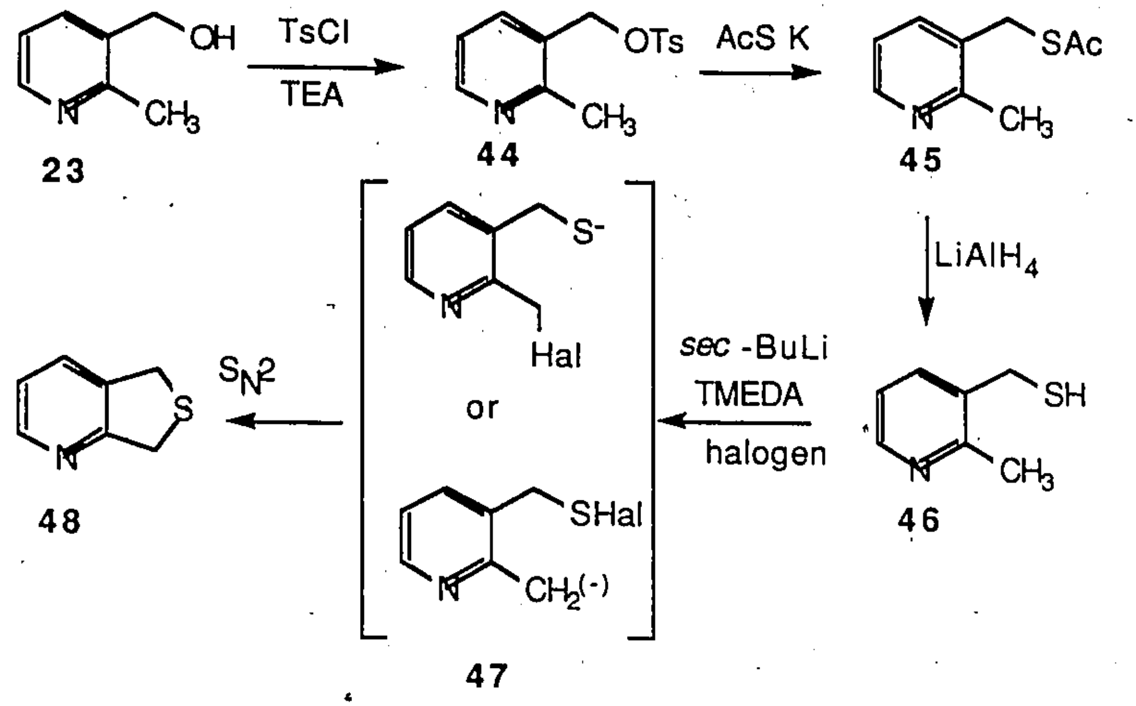
o-Toluic acid **39** was converted to the corresponding dimethylamide **40** by treatment with thionyl chloride ($SOCl_2$) and dimethyl amine. Silylation was achieved by the use of 1 eq. of *sec* -BuLi and excess TMS-Cl[27] . These reaction conditions generated in addition to the monosilylated amide **41**, a small amount of disilylated amide which could be separated by distillation [^{1}H NMR of **41**: δ7.18(s, 4H); δ2.98(s, 3H, CH_3); δ2.58(s, 3H, CH_3); δ1.44(s,2H,$C\underline{H}_2SiMe_3$); δ0.00(s,9H,$CH_2Si(C\underline{H}_3)_3$). The monosilylated amide was converted to amine **42** by $LiAlH_4$ reduction. Addition of methyl iodide in ethanol[28] gave **37** as fine white crystals in 30% overall yield [M.S.(FAB): M^+(cation)=236 (17.4%)]. The fluoride-induced 1,4-elimination and simultaneous trapping of the *o*-QDM with SO_2 was attempted by adding tetrabutylammonium fluoride (TBAF) in an acetonitrile solution which had previously been purged with nitrogen and saturated with SO_2. Upon workup no desired sulfone **38** or dimer[26] **43** were detected. It appears that the SO_2 prevents the fluoride induced 1,4-elimination reaction possibly by complexing with the F^-.

A final attempt using intermediates described earlier in this chapter is outlined in scheme 17:

---

[27] F. N. Jones, M. F. Zinn, C. R. Hauser, *J. Org. Chem.*, 28, 663, (1963).

[28] W. R. Brasen and C. R. Hauser, "Organic Syntheses"; Wiley: New York, 1963; collect. vol. IV, p585.



scheme 17

The 4-thio derivative **46** shown in figure 2 [^1H NMR($CDCl_3$; 60MHz): δ8.37(m, 1H); δ7.52(m, 1H); δ7.09(m, 1H); δ3.67(d, 2H, J=7.0Hz, C<u>H</u>$_2$SH); δ2.58(s,3H,CH_3); δ1.80(t,1H,J=7.0Hz,CH_2S<u>H</u>).] was synthesized in 70% yield by displacement of the tosyl group of **44** with potassium thioacetate followed by reduction with $LiAlH_4$. The thiol **46** was treated with 2 eq. of sec-Buli/TMEDA in THF at -78°C for 15 minutes and then reacted with 1 eq. of NBS or hexachloroethane. It was expected that one of the two possible anions **47** if formed would spontaneously cyclize to sulfide **48**. Aqueous workup afforded a dark brown oil which was purified by flash chromatography using hexanes/ethyl acetate (7:3). Only very polar material (TLC) was isolated whose pmr spectrum contained very broad, ill defined absorption paterns; possibly polymeric material. No evidence of the formation of **48** or the recovery of **46** was obtained.

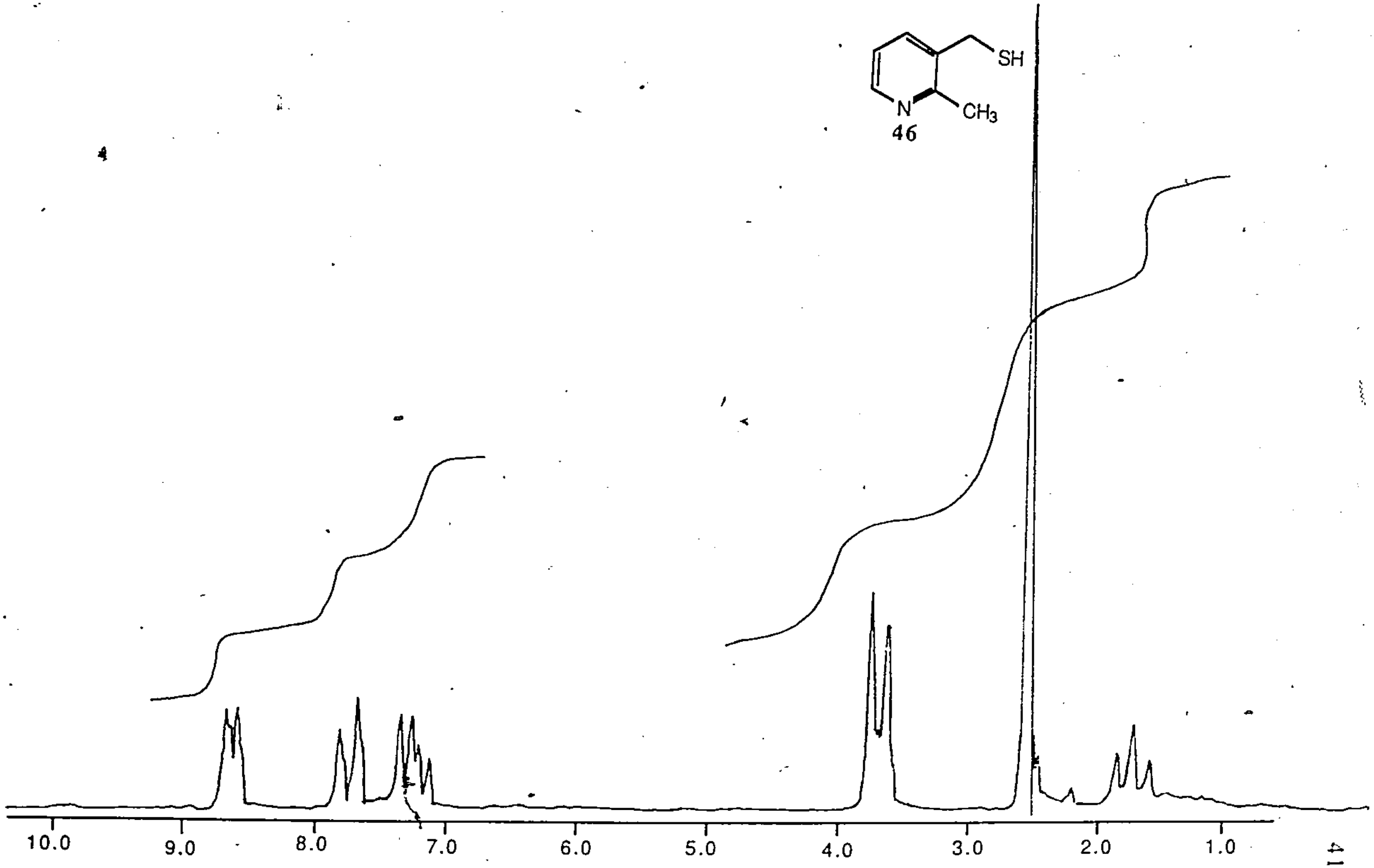
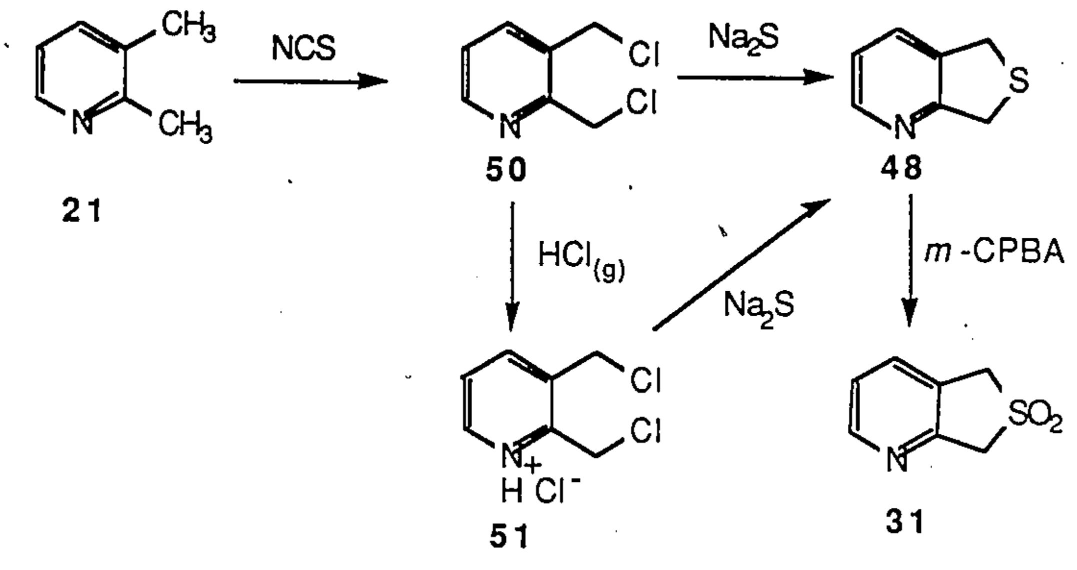


FIGURE 2: ^{1}H NMR Spectrum of 46

PART C

SYNTHESIS OF 1,3-DIHYDROTHIENO[3,4-b]PYRIDINE-2,2-DIOXIDE

In view of the results obtained in previous attempts to synthesize cyclic sulfide **48** , it was decided to synthesize **48** via the classic method reported by Klemm *et al* [29] (scheme 18). Klemm had prepared the dichloride **50**, isolated as the hydrochloride salt **51**, via NCS chlorination of 2,3-lutidine **21**. This compound was treated with sodium sulfide to afford cyclic sulfide **48**. Oxidation of **48** with *m*-CPBA at 0°C over a period of 12 hours afforded a mixture of sulfoxide and the sulfone **31** of which the sulfone **31** was isolated in 25% yield.

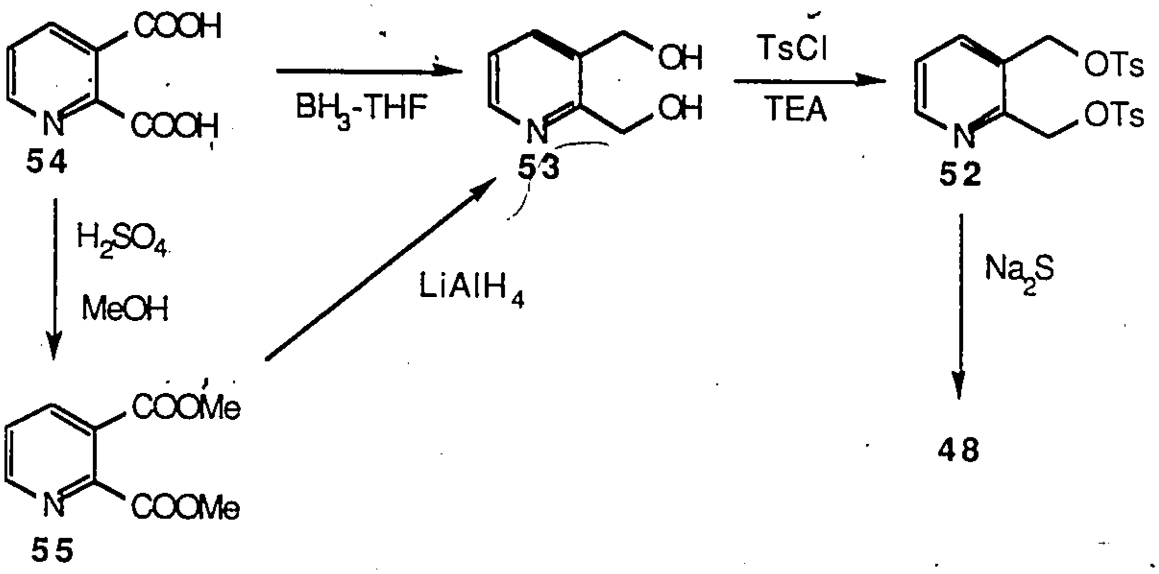


scheme 18

---

[29] L. H. Klemm, W. O. Johnson and P. W. White, *J. Heterocycl. Chem.*, **9**, 873 (1972).

Initial attempts to produce the dichloride **50** were not very satisfactory. Since **50** also had extremely irritating properties (skin irritant, lachrymator), a modified version of scheme 18 using a ditosylate rather than the dichloride was investigated (scheme 19).



scheme 19

According to W.R. Ashcroft *et al*[30], reduction of dimethyl pyridine 2,3-dicarboxylate **55** with $LiALH_4$ affords **53** in roughly 60% yield (scheme 19). Hence, pyridine-2,3-dicarboxylic acid **54** was converted to dimethyl pyridine-2,3-dicarboxylate **55** in 61% yield by refluxing in acidic methanol. $LiALH_4$ reduction of the diester as

---

[30] W.R. Ashcroft, M. G. Beal and J. A. Joule, *J. Chem. Soc.* , Perkin Trans. I, 3013 (1981).

described in Ashcroft's procedure gave **53** in only 35% yield. This low yield may be due to chelation of the 1,4-diol (bidentate ligand) to the aluminium salts, thus rendering extraction extremely difficult.

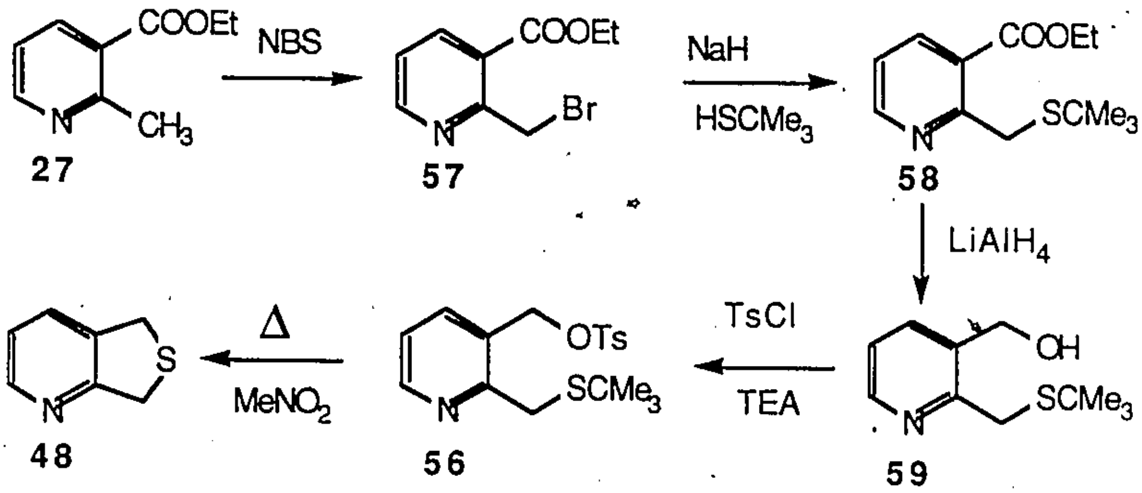
H.C. Brown[31] and coworkers reported that aromatic dicarboxylic acids are reduced relatively rapidly (6 hours) and quantitatively to the corresponding diols by borane in THF at 0°C. For example, related phthalic acid was converted to the corresponding diol in 95% yield. Hence, a borane-THF solution was added to a suspension of the diacid **54** in THF at 0°C. The reaction mixture was stored overnight and worked up according to the prescribed procedure. Evaporation of the ethereal extracts afforded the diol in 32% yield (the spectroscopic data were consistent with the reported values). The reduction was repeated and following destruction of excess hydride with a THF-H_2O solution, the THF was removed under reduced pressure and the aqueous suspension extracted with ethyl acetate using a continuous extractor. This did not improve the yield.

Unfortunately attempted tosylation under the usual conditions ($TsCl/CH_2Cl_2/TEA/0°C$) did not give the expected ditosylate. This compound may have limited stability and undergoes intra or intermolecular alkylation of the pyridine nitrogen.

---

[31] H. C. Brown, S. Krishnamurty, T. P. Stocky, N. M. Yoon and C. S. Pak, *J. Org. Chem.*, 38, 2786 (1973).

Before returning to the Klemm route involving the unpleasant dichloride **50** a final "new" approach to **31** was investigated. This approach was analogous to the one involving the "spontaneous" cyclization of the 4-thioderivative **47**. It was anticipated that the sulfur atom in **56** could displace a C-3 tosyloxy group to give the cyclic sulfide **48** (scheme 20).



scheme 20

Ester **27** was monobrominated according to a procedure by Hurst[32] and Wibberly to afford ethyl 2-(bromomethyl)nicotinate **57** in 51% yield. The bromoester **57** was converted to ethyl 2-(t-butylthiomethyl)nicotinate **58** [^{1}H NMR($CDCl_3$; 300MHz): δ8.60(dd,

---

[32] J. Hurst and D. G. Wibberley, *J. Chem. Soc.*, 22, 119 (1962).

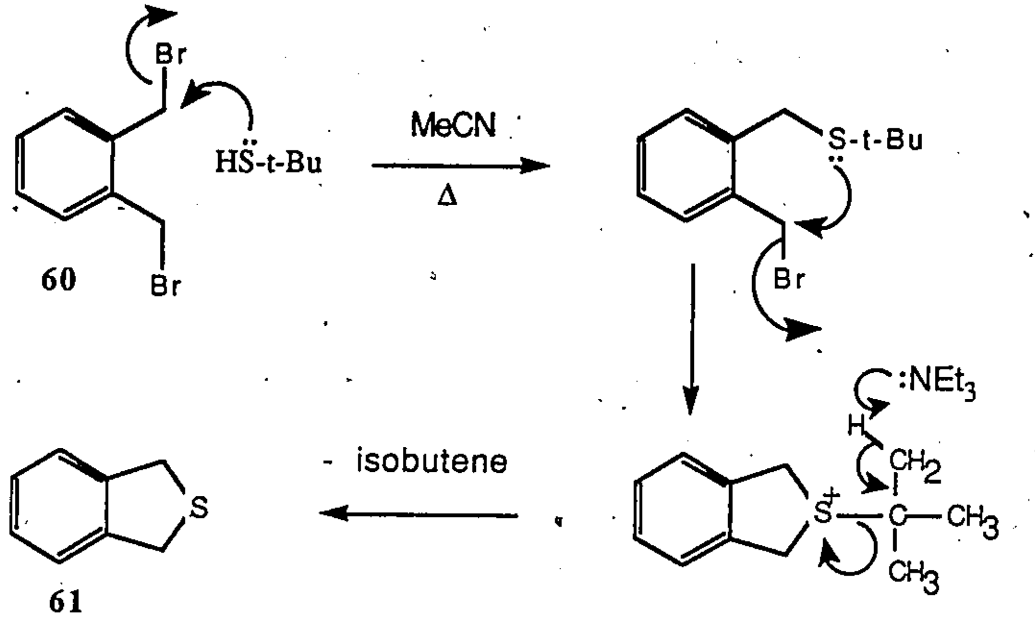
1H, J=4.82Hz,1.81Hz); δ8.16(dd, 1H, J=7.85Hz, 1.81Hz); δ7.22(dd, 1H, J=7.85Hz,4.82Hz); δ4.38(q,2H,OC$\underline{H}_2$CH$_3$); δ1.31(t,3H,OCH$_2$C$\underline{H}_3$)] in 62% yield by treatment with sodium *t*-butylthiolate in THF. LiALH$_4$ reduction of **58** afforded alcohol **59** (99%) which was tosylated with TsCl and TEA in methylene chloride to afford the tosyl derivative **56** in over 90% yield. A solution **56** in nitromethane was refluxed overnight to give sulfide **48** [^{1}H NMR(CDCl$_3$; 300MHz): δ8.42(d, 1H, J=4.82Hz); δ7.55(d, 1H, J=7.80Hz), δ7.11(dd,1H, J=7.80Hz, 4.82Hz); δ4.30(s, 2H, methylene,C-2); δ4.23(s,2H, methylene,C-1)] in 73% yield presumably via thermal loss of isobutene and tosic acid (see also scheme 21).

Although sulfide **48** was obtained in an acceptable 73% yield in the cyclization step, the overall sequence to **48** from the ester **27** is five steps , the first step occurring in only 50% yield. Thus the overall yield of **48** from **27** was only 18% and thus not suitable for a large scale synthesis.

This led to the reinvestigation of the formation of the dichloride **50**. The NCS chlorination was repeated by carefully monitoring the reaction by ^{1}H NMR. When completion was approached (89% estimated by ^{1}H NMR), the unreacted NCS and succinimide were removed by filtration, the solvent removed under reduced pressure and the resulting oil purified by HPLC. It turned out that even with careful monitoring of the reaction, polychlorination was occurring in a ratio of 4:6 in favor of the dichloride. The dichloride was not converted into its hydrochloride salt but used immediately after preparation.

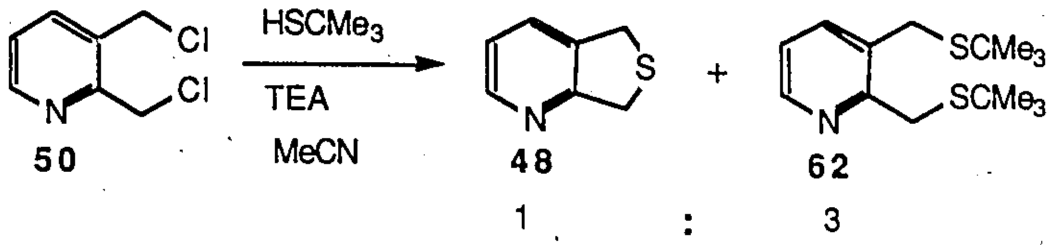
Since the hygroscopic properties of Na_2S result in a complicated workup due to the use of ethanol needed to solubilize the Na_2S and since the cyclization of **56** to **48** (scheme 20) was relatively clean, affording the cyclic sulfide **48** in good yield (73%), it was decided to investigate the conversion of the dichloride **50** to cyclic sulfide **48** via this methodology. It involved treatment of **50** with 1 eq. of *t*-butylthiol and TEA to produce the corresponding sulfide followed by cyclization via chloride displacement and thermal loss of isobutene to afford **48**.

Before attempting this reaction sequence on dichloride **50**, a model experiment was performed to verify that the related α,α'-dibromo-*o*-xylene **60** when treated with *t*-butylthiol would yield the corresponding cyclic sulfide **61** (scheme 21).



scheme 21

The dibromide was heated in refluxing acetonitrile for 30 minutes in the presence of 1 eq. of *t*-butylthiol and TEA. The formation of sulfide **61** in ~40% yield was verified by 1H NMR [δ 7.00 (s,4H,aromatic); δ 4.06(s,4H,methylene)]. The dichloride **50** was subjected to the same reaction conditions. However, in this case only 15% of sulfide **48** was isolated along with 45% of 2,3-di(*t*-butylthiomethyl)pyridine **62**. In this example the intermolecular chloride displacement by *t*-butylthiol was obviously much faster than the intramolecular one between the chloride and the *t*-butylthio group resulting in predominant formation of **62** over **48**. When the reaction was repeated at R.T. (3 days) in dilute solution, only dichloride was isolated, no products resulting from displacement were formed (scheme 22).



scheme 22

In the end, the Na_2S reaction was repeated according to Klemm's procedure. Cyclic sulfide **48** was obtained, in 53% yield. The overall yield from 2,3-lutidine **21** to sulfide **48** was 17%. Even though this is comparable to the 18% obtained using scheme 20, this became the method of choice since it involved a 2-step rather than 5-step sequence.

The final step in the synthesis of sulfone **31** involved oxidation of **48** with a suitable oxidizing agent. According to Klemm's procedure (p42) this was achieved with *m*-CPBA at 0°C over a period of 12 hours , the solution cooled to -20°C and stirred for another 48 hours to afford sulfone **31** in only 25% yield. The cooling from 0°C to -20°C and long reaction time did not seem efficient. The following modification was used: the sulfide was dissolved in chloroform, the solution cooled in a dry ice-acetone bath and *m*-CPBA added. The cooling bath was removed and the reaction mixture allowed to reach R.T. (reaction time: 2.5 hours). Following basic workup and purification by Chromatotron, sulfone **31** was obtained in 50% yield. The spectroscopic data were generally consistent with the reported values with the only difference being that the 4 methylene hydrogens show up as 2 singlets at δ 4.44 and δ 4.48 ppm at 300MHz as opposed to one broad singlet at δ 4.43 ppm reported by Klemm (presumably taken on a 60MHz instrument). The 300 MHz ^{1}H NMR spectrum of **31** is reproduced in figure 3.

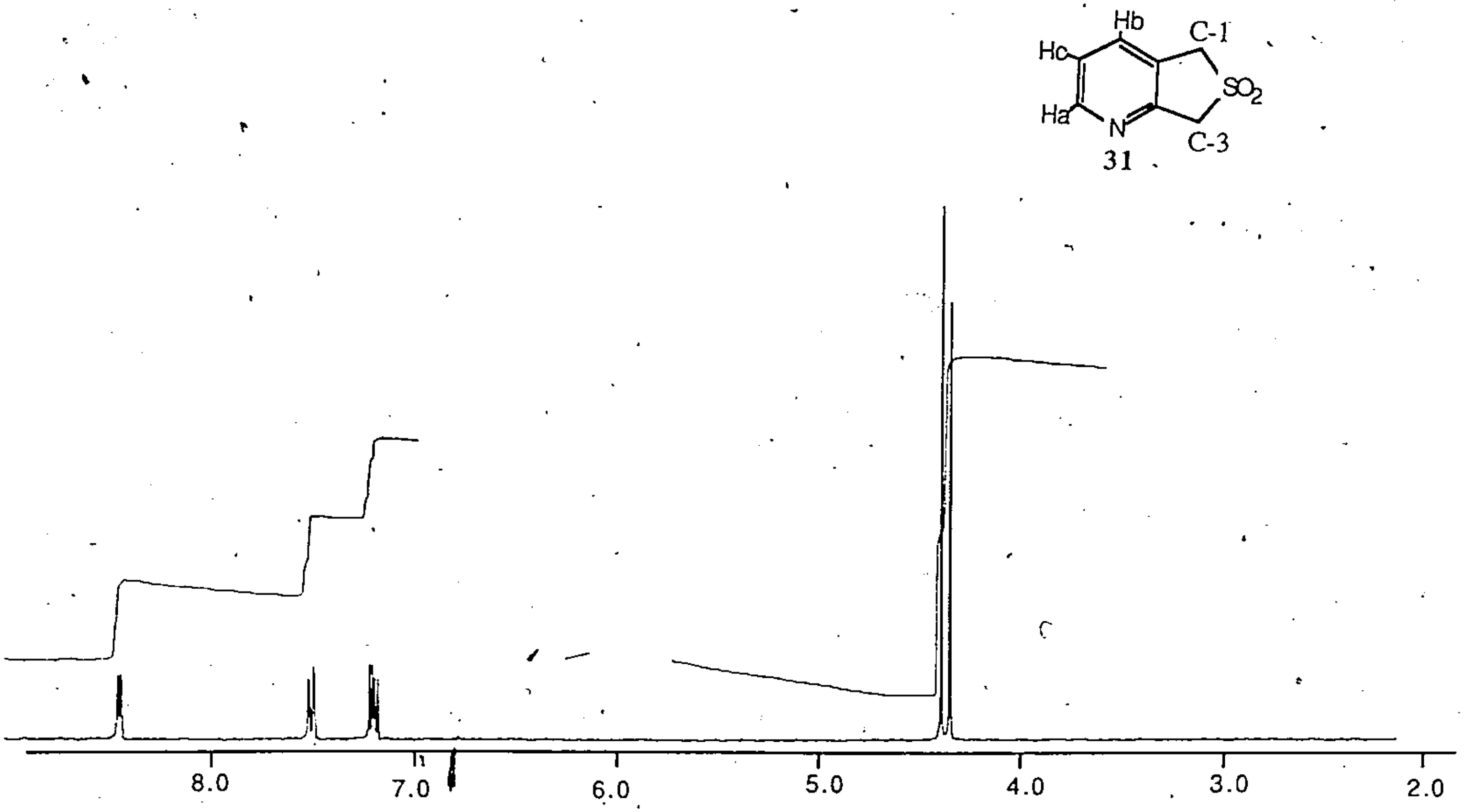
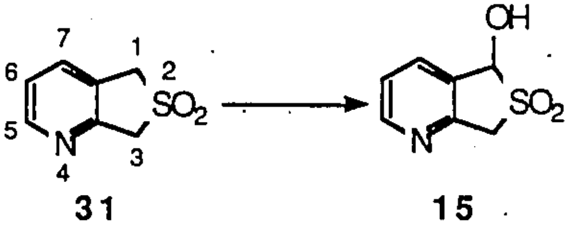


FIGURE 3: ^{1}H NMR Spectrum of 31

PART D

FUNCTIONALIZATION OF 1,3-DIHYDROTHIENO[3,4-b]-PYRIDINE-2,2-DIOXIDE

The next step in the proposed synthesis of 1-hydroxydihydrothieno[3,4-b]pyridine-2,2-dioxide **15** involved 1-hydroxylation of **31**. Before attempting this hydroxylation reaction, the carbanion chemistry of **31** had to be studied in order to verify that functionalization was possible on this system.

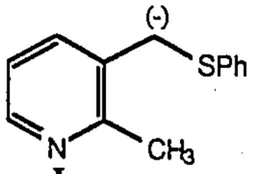


pyridine sulfone numbering system

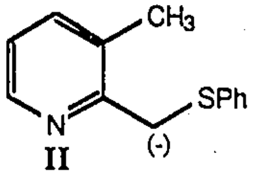
Rapoport *et al* [19] have shown that carbanion formation and reaction is influenced by the presence of sulfur groups in the pyridine side chains. In the absence of sulfur substituents, metalation of 2,3-lutidine occurs at the more acidic C-2 methyl[33]. They have shown that the presence of anion-stabilizing sulfur groups (thiophenyl) led to smooth metalation with LDA at low temperature of the C-3 and the C-2 methylene groups of I and II respectively:

---

[33] H. L. Lochte, T. H. Cheavens, *J. Am. Chem. Soc.*, 79, 1667 (1957).

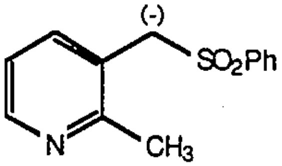


I

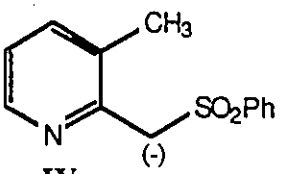


II

Conversion of the sulfides **I** and **II** to the corresponding sulfones **III** and **IV** revealed the significant difference in the reactivity of the α-thiophenyl anions (at C-3 and C-2) of **III** and **IV**.

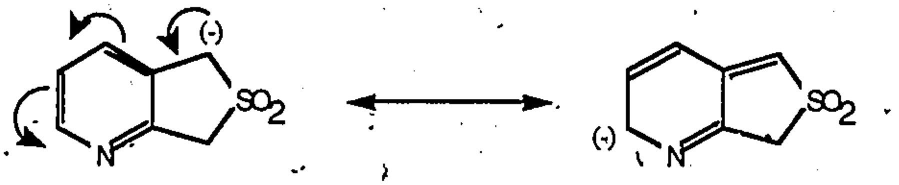


III



IV

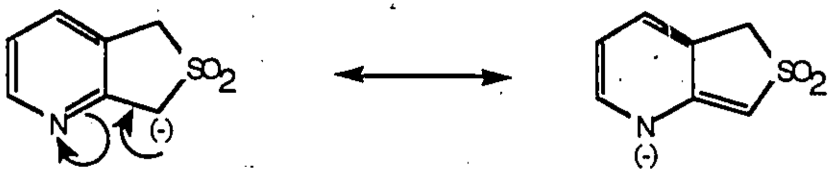
The anion of sulfone **III**, obtained by metalation with LDA, reacted readily with various alkylating agents such as butyl iodide and ethylbromoacetate. In contrast, the anion of sulfone **IV**, though readily formed under analogous conditions as demonstrated by D_2O quenching, was unreactive under similar conditions with the above reagents. The difference in reactivity may arise from the greater stabilization of the C-2 sulfonyl carbanion due to additional resonance interaction with the pyridine nitrogen making it unreactive towards typical alkylating reagents. In view of these reports the reactivity of the C-1 and C-3 anions of sulfone **31** needed to be explored.



31 b

Not a significant contributor to stabilizing the C-1 anion

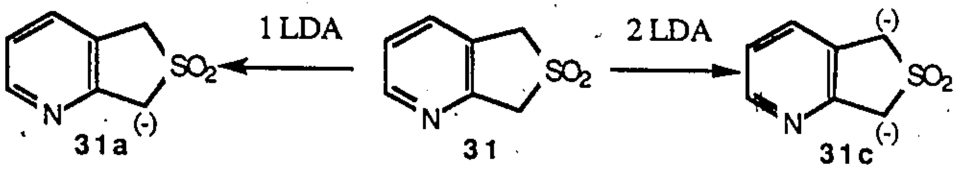
The C-1 anion **31b** is mainly stabilized by the electron withdrawing effect of the SO_2 group (above). There is no direct stabilization due to resonance interaction with the pyridine nitrogen. In contrast, the C-3 anion **31a** is significantly stabilized by both the SO_2 group and direct resonance interaction with the pyridine nitrogen as shown below.



31 a

This form is a significant contributor to stabilizing the C-3 anion

As expected, monoanion formation (**31a**) occurred preferentially at C-3 upon addition of 1 equivalent of LDA to a solution of the sulfone **31** in THF at -78°C for 10 minutes. The THF solution was an olive green colour. The 1,3-dianion **31c** was obtained by reaction of **31** with 2 LDA at -78°C for 15 minutes. Its THF solution was also an olive green colour.



Both the monoanion **31a** and the 1,3-dianion **31c** were reacted with several different electrophiles. The results are shown in Table 2.

Table 2: Carbanion reactions performed on sulfone **31**

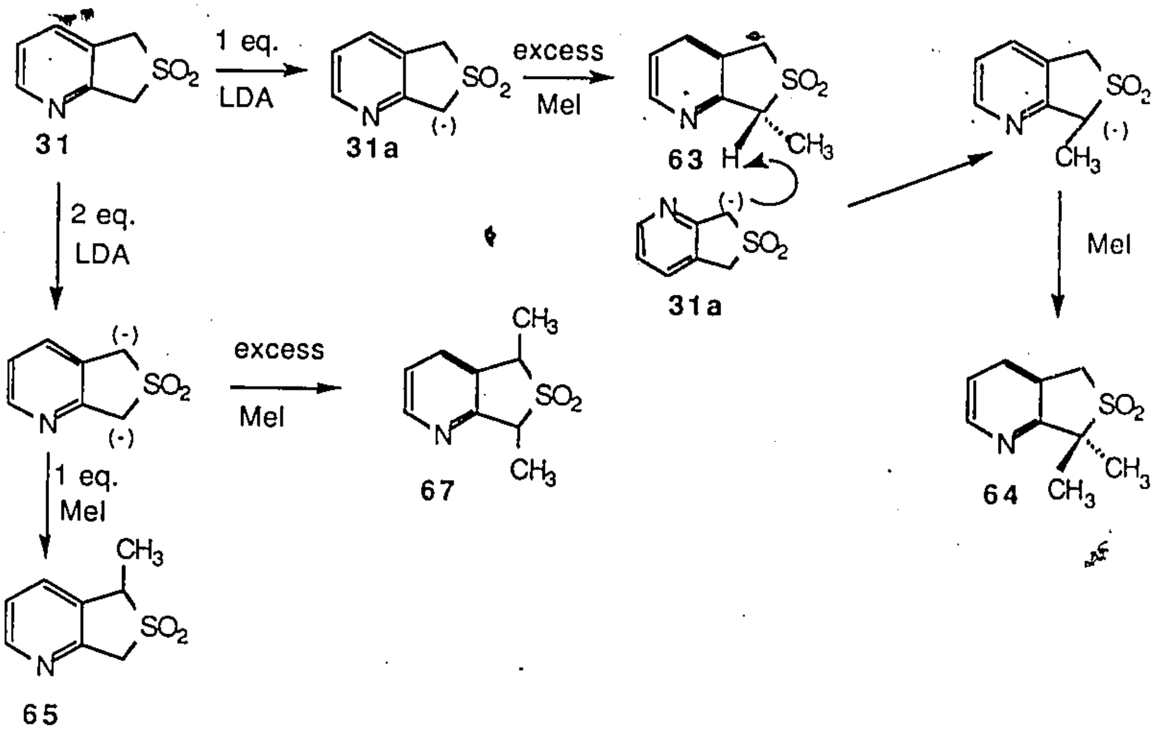
reaction	electrophile	product	%yield
monoanion	CH_3I excess	**63,64**	85(4:1)
dianion	CH_3I(1 eq)	**65**	76
dianion	CH_3I excess	**67**	85
monoanion	CH_3SSCH_3(1 eq)	**68,69**	66(1:1)
dianion	CH_3SSCH_3(1 eq)	**68**	67
monoanion	PhCHO(1 eq)	**70**	83
dianion	PhCHO(1 eq)	**71,72**	80(3:1)
dianion	$PhCH_2Br$(1 eq)	**73,74**	33;19
dianion	$Br(CH_2)_3Br$(1 eq)	**76**	26
dianion	MoOPH(1 eq)	–	–

When methyl iodide (CH_3I) was reacted with the monoanion, an inseparable mixture of the 3-monomethylated product and 3,3-dimethylated product was isolated in 85% yield. This mixture was subjected to G.C.-M.S. which indicated the presence of 2 compounds namely **63** (M^+=183) and **64** (M^+-SO_2=197). The pmr spectrum also indicated a mixture. For example the methyl region showed a singlet at δ= 1.67 ppm and a doublet at 1.73 ppm (J=7.1 Hz). These peaks were assigned to the dimethylated product **64** and the C-3 monomethylated compound **63** respectively. The integration indicated a 4:1 ratio of **63** to **64**. Small amounts of other C-methyl groups were also visible suggesting the possible presence of the C-1 methylated isomer and even 1,3-dimethylated compounds. In addition to these peaks the spectrum showed a multiplet at δ4.37-4.31(3H) and the expected pyridine hydrogen signals at δ8.58(m,1H); δ7.61(m,1H), and δ7.30(m,1H).

Compound **64** most probably resulted from hydrogen abstraction on carbon 3 of **63** by sulfone anion **31a** as depicted in scheme 23. Dialkylation of sulfones is a common occurrence[34].

---

[34] T. Durst. In "Comprehensive Organic Chemistry", D.H.R. Barton and W.D. Ollis, ed. Pergamon Press, Vol 3, p186, 1979.



scheme 23

Reaction of 1 equivalent of CH_3I with the dianion **31c** afforded the monomethylated product **65** as a clear yellow oil in 76% overall yield. Minor impurities having an additional methyl group were also visible by G.C.-M.S. and nmr. The ^1H NMR reproduced in figure 4 showed signals at δ1.68(d,3H,J=7.1Hz) due to the CH_3 group, a partly hidden quartet at δ4.40(1H,J=7.1Hz) and two singlets at δ4.44 and δ4.43 ppm which presumably represent the inner two lines of the AB quartet due to the remaining C-3 methylene group.

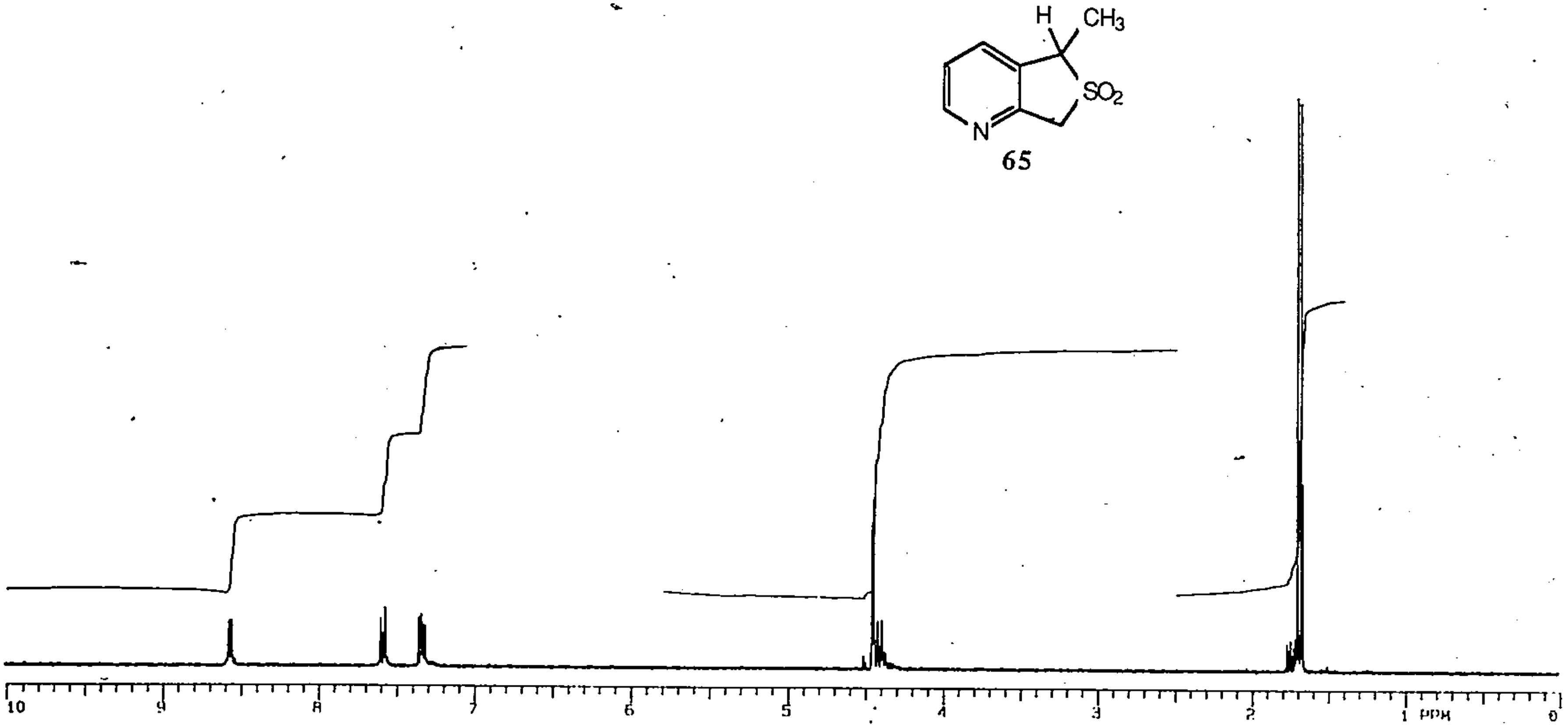


FIGURE 4: ^{1}H NMR Spectrum of 65

The pyridine hydrogens gave the expected pattern [δ8.55(dd,1H,J =4.95Hz,1.51Hz); δ7.58(dd, 1H, J=7.84Hz,1.51Hz); δ7.33(dd, 1H,J =7.84Hz,4.95Hz). The major impurity appears to be a dimethylated compound, presumably the 1,1-dimethylated isomer based on a singlet methyl peak at δ1.66 ppm (compared to δ1.67 for compound **64**).

The assignment for the compounds **63**, **64**, and **65** are somewhat tentative. Nevertheless the small chemical shift difference observed for the methyl, methylene and methine peaks are as expected assuming that those bonded to C-3 would be slightly deshielded relative to the comparable groups at C-1 due to the adjacent nitrogen function. Thus the C-3 methyl group in **63** occurs at δ1.73 ppm compared to δ1.68 ppm for **65**. Similarly the remaining methylene hydrogens occur in the region δ4.37- δ4.31 ppm for **63** compared to δ4.44- δ4.43 ppm for **65**.

When 2 equivalents of CH_3I were reacted with the dianion **31c** a mixture of diastereoisomers corresponding to 1,3-dimethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **67** was isolated in 85% yield (scheme 23). The ^1H NMR showed signals at δ8.57-8.55(m,1H), δ7.57-7.54(m,1H); δ7.34-7.27(m,1H); δ4.36-4.27(m, 2H, methylene, C-1 and C-3); δ1.77-1.64(m, 6H, CH_3 at C-1 and CH_3 at C-3). Minor impurities, possibly trimethylated material (M^+-SO_2=147) were also observed by G.C.-M.S.

Generation of the dianion **31c** followed by addition of 1 equivalent of dimethyldisulfide afforded a monosubstituted product assigned structure **68** in 67% yield. Its assignment as the 1-thiomethyl derivative **68** follows from the expected greater reactivity at the 1-position in the dianion **31c**. The pmr spectrum showed, in addition to the aromatic signals, two singlets at δ5.18 ppm(1H) and δ2.32 ppm(3H) due to the methine and S-methyl groups respectively, and an AB quartet (δ_A=4.53 ppm; δ_B=4.42 ppm, J_{AB}=16.6Hz) due to the remaining CH_2 group at C-3.

However reaction of the monoanion with 1 eq. of dimethyldisulfide afforded an inseparable 1:1 mixture of the 1- and the 3-thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **68** and **69** in 66% overall yield. The mixture was analyzed by ^{1}H NMR and G.C.-M.S. Comparison of the pmr spectra of the 1:1 mixture with that of **68** made identification and differentiation of **69** from **68** possible.

The ^{1}H NMR of the mixture clearly showed signals due to **68** above. In addition, the following peaks were observed: δ8.65(dd,1H, J=4.83Hz, 0.68Hz); δ7.64(dd, 1H, J=7.35Hz, 0.68Hz); δ7.34(dd, 1H, J=7.35Hz,4.83Hz); δ5.17(s,1H, methine,C-3); δ4.50,4.35(AB quartet, 2H, J=15.7Hz, methylene, C-1) δ2.37(s, 3H, SCH_3). The ^{1}H NMR chemical shifts of both thioderivatives **68** and **69** are shown in Table 3. The spectra of **68** and the 1:1 mixture are reproduced in figures 5 and 6 respectively.

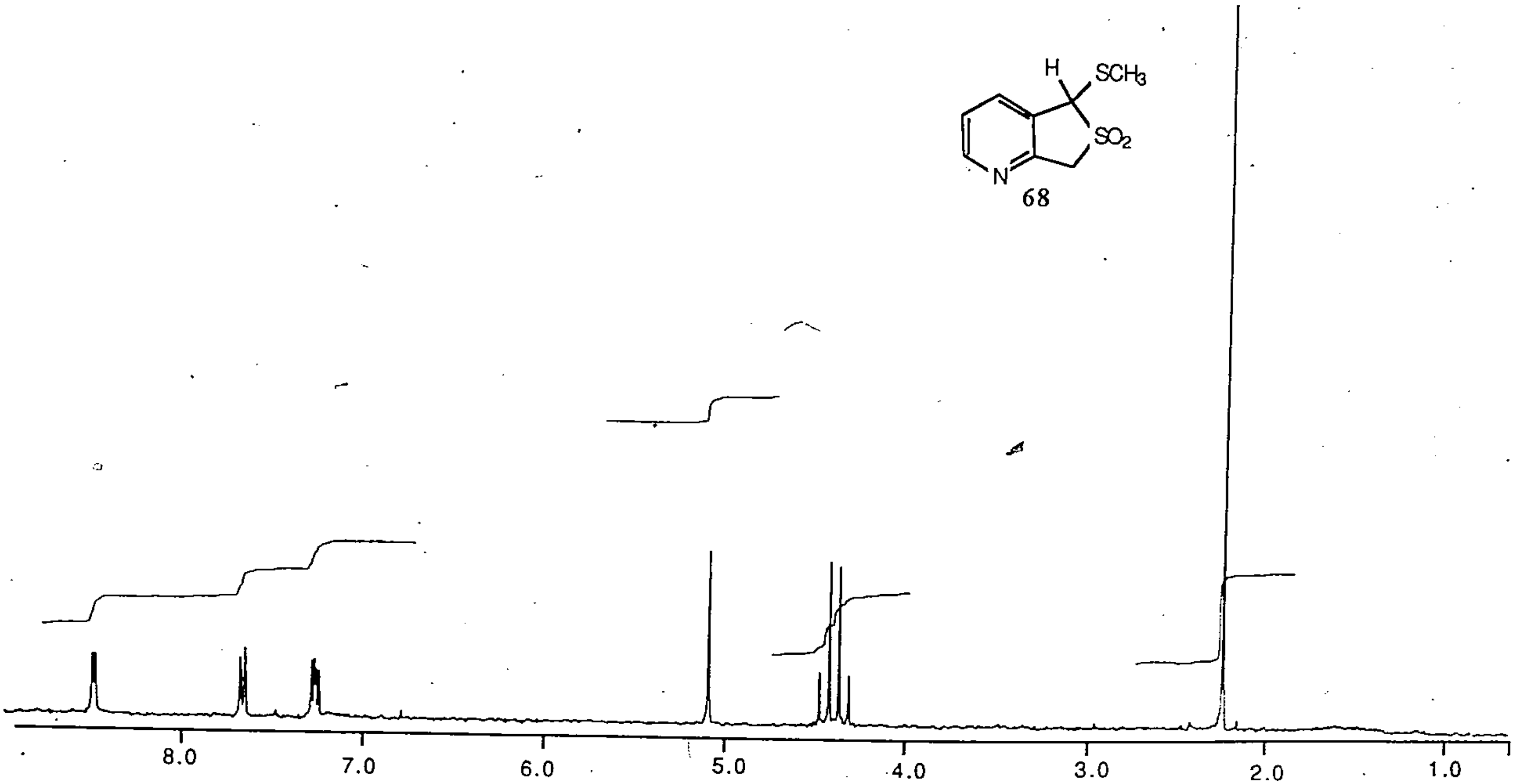


FIGURE 5: ^{1}H NMR Spectrum of 68

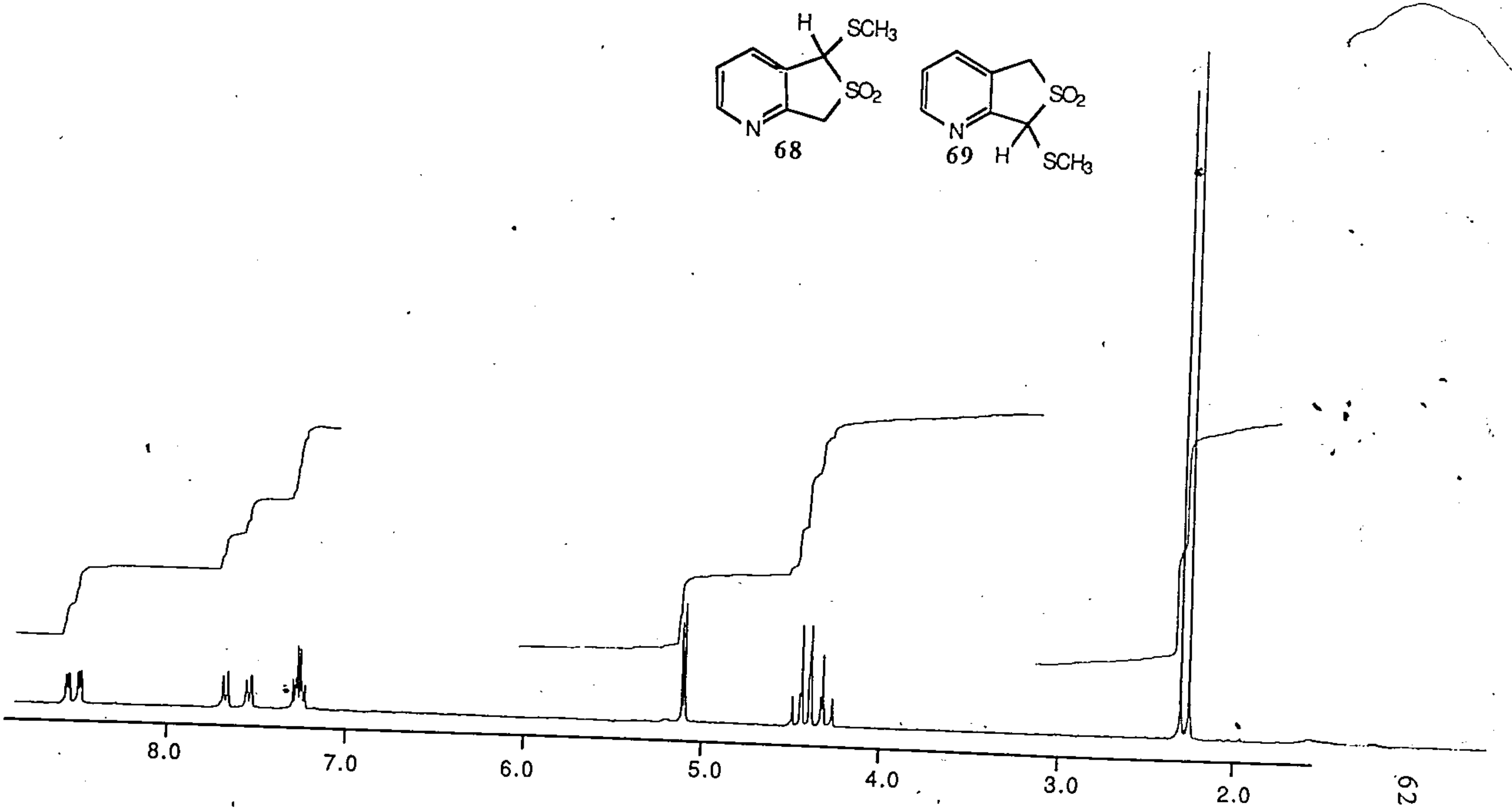
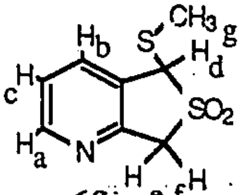
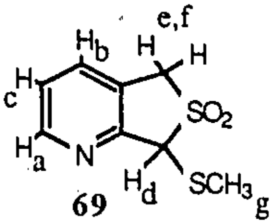


FIGURE 6: ^{1}H NMR Spectrum of the 1:1 mixture of **68** and **69**

Table 3: Chemical shifts* and coupling constants of **68** and **69**.


68

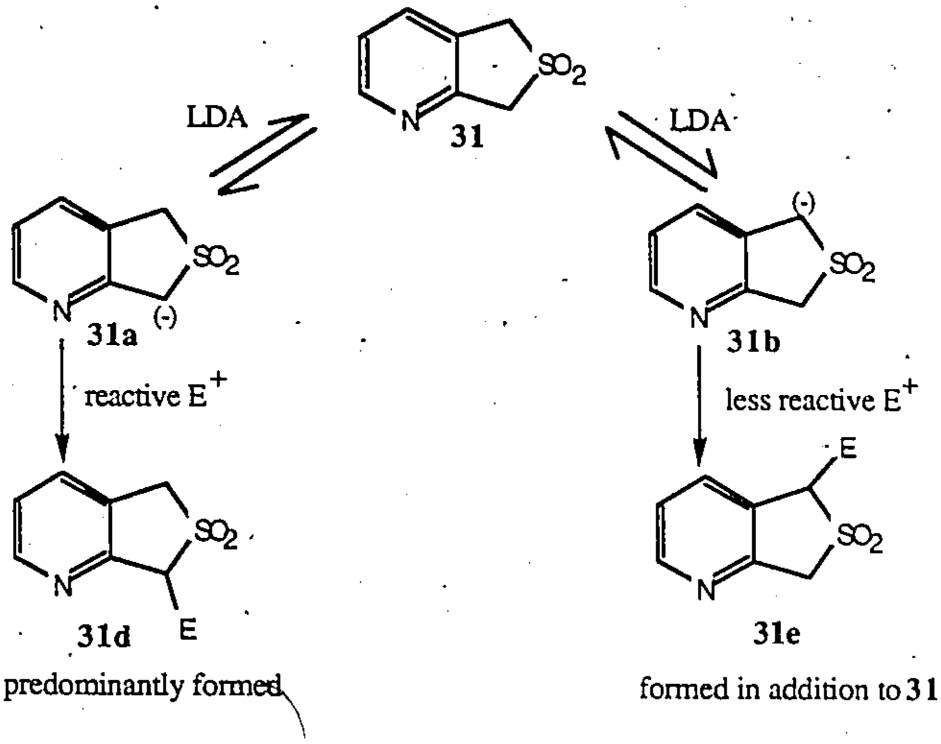

69

Proton	δ (ppm)	J (Hz)	δ(ppm)	J(Hz)
H_a	8.59	4.96;0.89	8.65	4.83;0.68
H_b	7.77	7.82;0.89	7.64	7.35;0.68
H_c	7.37	7.82;4.96	7.34	7.35;4.83
H_d	5.18	--	5.17	--
H_e,H_f	4.53;4.42	16.6	4.50;4.35	15.7
H_g	2.32	--	2.37	--

*The δ values and the coupling constants J were obtained from 300 MHz ^{1}H NMR spectra.

The chemical shift difference for the methylene proton peaks are as expected assuming again that those bonded to C-3 would be slightly deshielded relative to the comparable group at C-1 due to the adjacent nitrogen function. Thus, the C-3 methylene group (H_e,H_f) in **68** occur at δ4.53 and δ4.42 ppm compared to δ4.50 and 4.35 ppm for **69**. Similarly, the C-3 S-methyl group occurs at δ2.37 ppm for **69** compared to δ2.32 ppm for **68**. The chemical shift difference observed for the pyridine H_b peak is not surprising considering that this proton is deshielded by the adjacent sulfur atom in **68** relative to the C-3 methylene group in **69**. Thus H_b in **68** occurs at δ7.77 ppm compared to δ7.64 ppm for **69**.

Although the monoanion reaction afforded a 1:1 mixture of **68** to **69**, this does not imply a 1:1 ratio of anions **31a** to **31b**. Rapoport[19] has shown in open chain compounds that the anion analogous to **31a** reacts much more slowly with electrophiles than that analogous to **31b** (see structures **III** and **IV** at the beginning of this section). If the reaction of sulfone **31** with LDA gives a mixture of **[illegible]a** and **31b** consisting of mainly **31a** and a small amount of **31b** and if **31a** and **31b** can be interconverted utilizing the starting sulfone **31** as a relay then relatively large amounts of the 1-substituted product would be expected from the reaction of the anion mixture with poor electrophiles because **31b** is a more reactive species. However, the product resulting from the reaction at the 3-position would be expected as the major product from the reaction of the above anion mixture with a reactive electrophile since such a species would not discriminate between the two anions. This situation is illustrated in scheme 24.

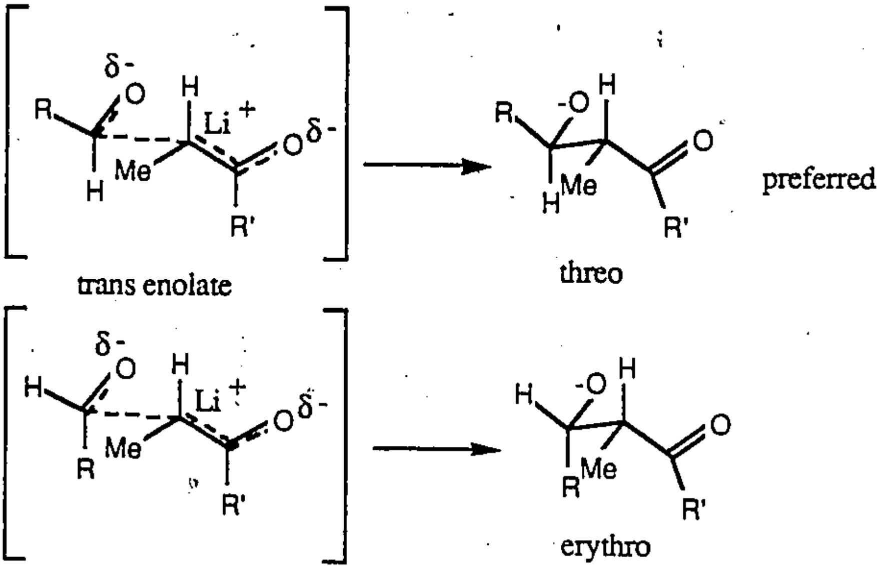


scheme 24

From the results observed and the above rationalization, it appears that dimethyldisulfide is a less reactive electrophile giving a mixture of the 1- and 3-thiomethyl derivatives **68** and **69** respectively compared to predominantly the 3-methyl derivative **63** obtained with the more reactive methyl iodide.

The reaction of the monoanion with benzaldehyde afforded crystalline 3-(α-hydroxybenzyl)dihydrothieno[3,4-b]pyridine-2,2-dioxide **70** (m.p.=142-144°C) exclusively in 83% yield. The formation of only one diastereoisomer could be rationalized utilizing the concepts and transition states which have been invoked to explain the stereoselectivity in the aldol condensation reaction[35].

According to this concept, reaction of a trans enolate with an aldehyde leads preferentially to the threo diastereoisomer via the transition state (*i*) shown below.



i

The anion **31a** can be considered as an aza analog of a trans enolate. Reaction of benzaldehyde with **31a** could occur via the two transition states (*i i*) and (*iii*) leading to the threo and erythro products respectively as shown in scheme 25. As in the aldol the threo product should be favored since its transition state has fewer unfavorable interactions. In the aldol series the threo adducts

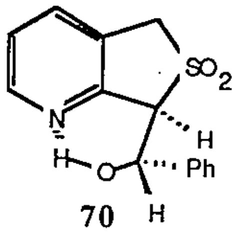
---

[35] C.H. Heathcock in "Comprehensive Carbanion Chemistry", E. Buncel and T. Durst, ed. Elsevier, part B, chapter 4, p177 (1984).

typically have larger coupling constants (7-9 Hz) than the corresponding erythro isomers (3-6 Hz)[36]. The nmr spectrum of product **70** reproduced in figure 7 showed a vicinal coupling constant of 7.63 Hz. The infrared showed strong intramolecular hydrogen bonding at 3350 cm^{-1}. This H-bonding undoubtedly involves the pyridine nitrogen and not the SO_2 group since the latter group is known to be very non-basic[34]. Inspection of a molecular model of the threo isomer, **70**, in which there is H-bonding between the OH and the N indicates a dihedral angle of 160°-170° in agreement with the 7.63 Hz coupling constant. If the erythro structure were assigned to **70** the dihedral angle would be approximately 30° and thus a small coupling constant would have been expected.

---

[36] D.A. Evans, J.V. Nelson, and T.R. Taber, "Topics in Stereochemistry", vol 13, p5 (1982).



70

threo

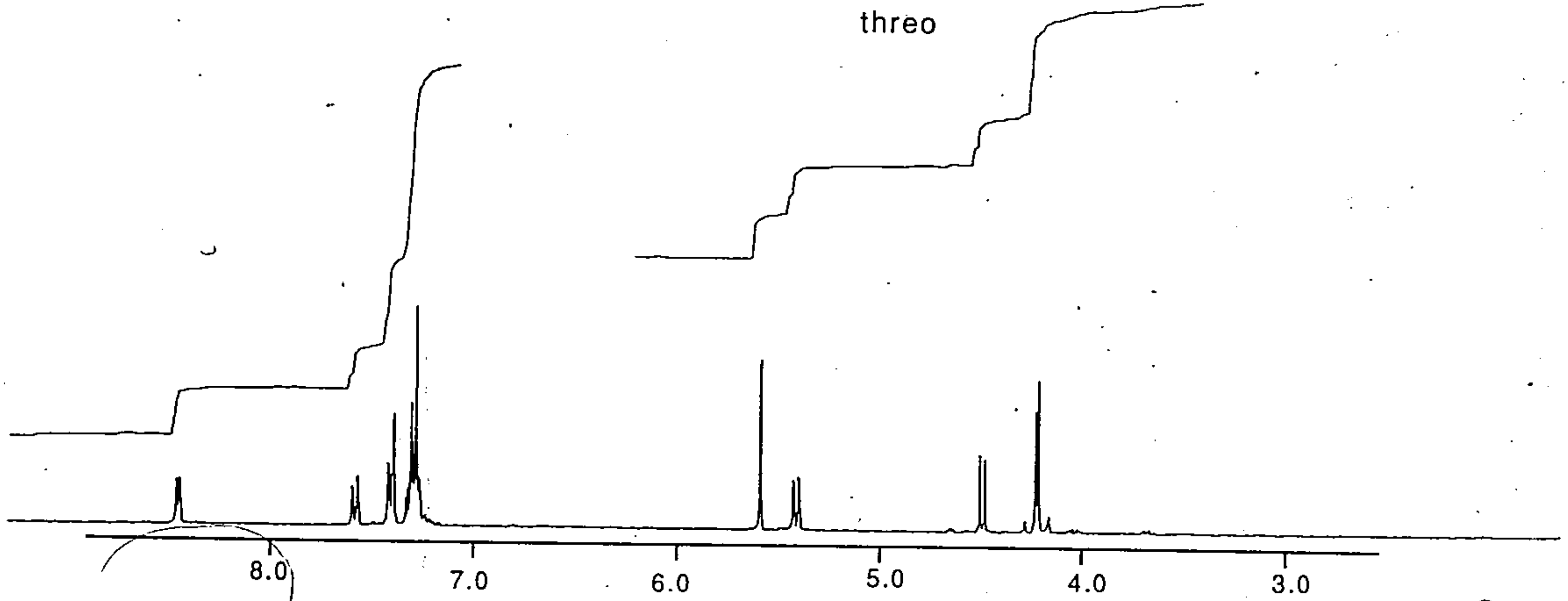
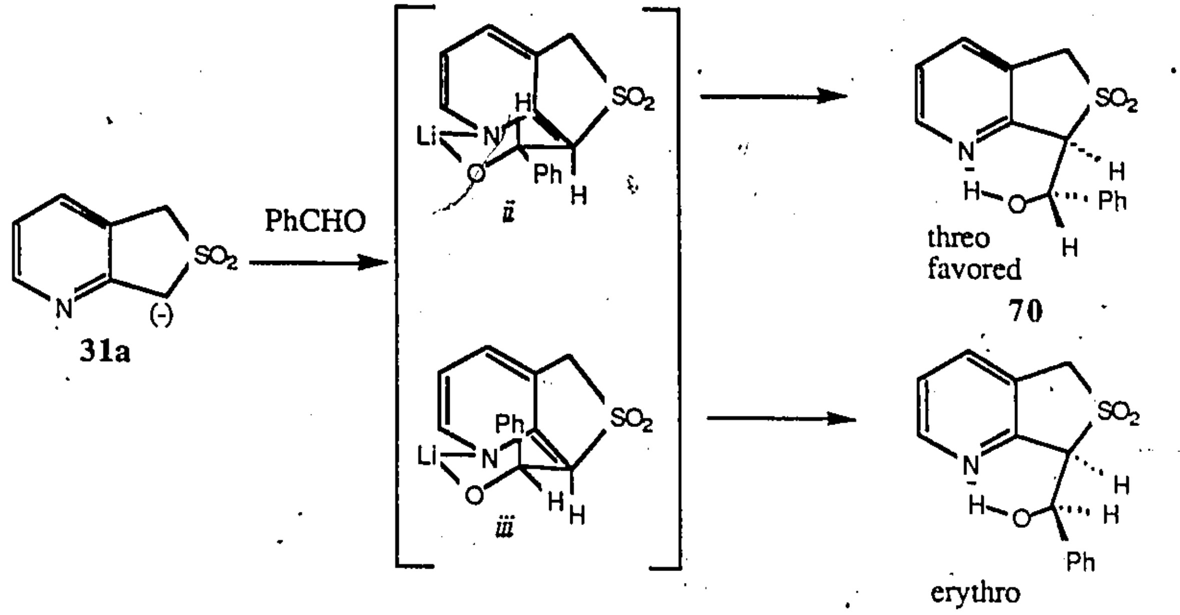
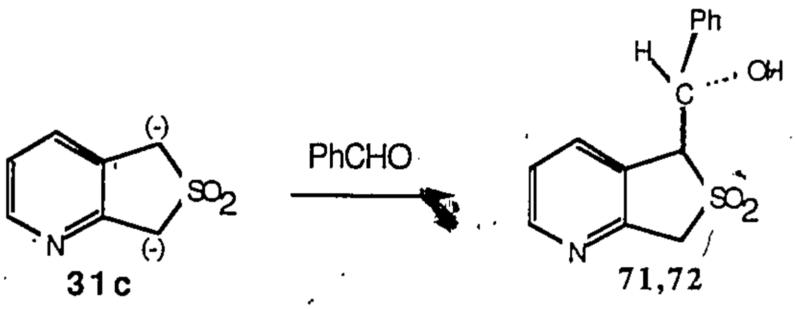


FIGURE 7: ^{1}H NMR Spectrum of **70**

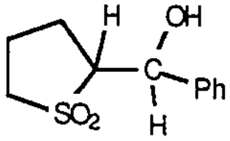


scheme 25

However, when 1 equivalent of PhCHO was used to quench the dianion, a mixture of compounds corresponding to a 1:1 adduct between benzaldehyde and the sulfone **31** was isolated as shown by C.I.-M.S.[$M^{+}+1=276$ (b.p.); $M^{+}+1-H_2O=256$ (26%); $M^{+}+1-SO_2=212$ (18%); $M^{+}+1-(SO_2+H_2O)=194$ (46.5%); $M^{+}+1-[CH(OH)Ph]=170$ (25%)] in 80% yield.



The nmr spectrum of this mixture clearly indicated the absence of any of the adduct **70**. It is tempting to suggest that the product consists of a 3:1 mixture of 1-(α-hydroxybenzyl) derivatives **71,72** shown above since most of the peaks occur as pairs in a 3:1 ratio. In addition two apparent AB quartets, expected for the remaining CH_2 group in **71,72** are found in the range δ4.3-4.7 ppm. However closer inspection of the nmr spectrum reproduced in figure 8 indicates a number of inconsistencies. For example, the integration of the area δ4.3-4.7 ppm due to the supposed CH_2 group is almost 4H when compared to the 2 sets of peaks due to H_a (δ8.5 ppm) ortho to the pyridine nitrogen. The double set of peaks near δ7.0 ppm (1H when compared to Ha) show a pattern typical of the H_b proton of the pyridine ring in the other adducts, but the position is considerably upfield compared to the other compounds (δ7.0 vs 7.4 ppm). Attempts to assign the three sets of doublets of doublets (δ6.41 and 6.56 ppm; δ5.02 and 5.80ppm; δ2.67 and 4.08ppm) to the three spin system (*i*) shown below, also creates difficulties since none of the CH peaks would be expected either as far downfield as δ6.41; 6.56 ppm or as far upfield as δ2.67; 4.08 ppm. Thus presently available data do not allow us to assign a structure to any of the components of the mixture.



i

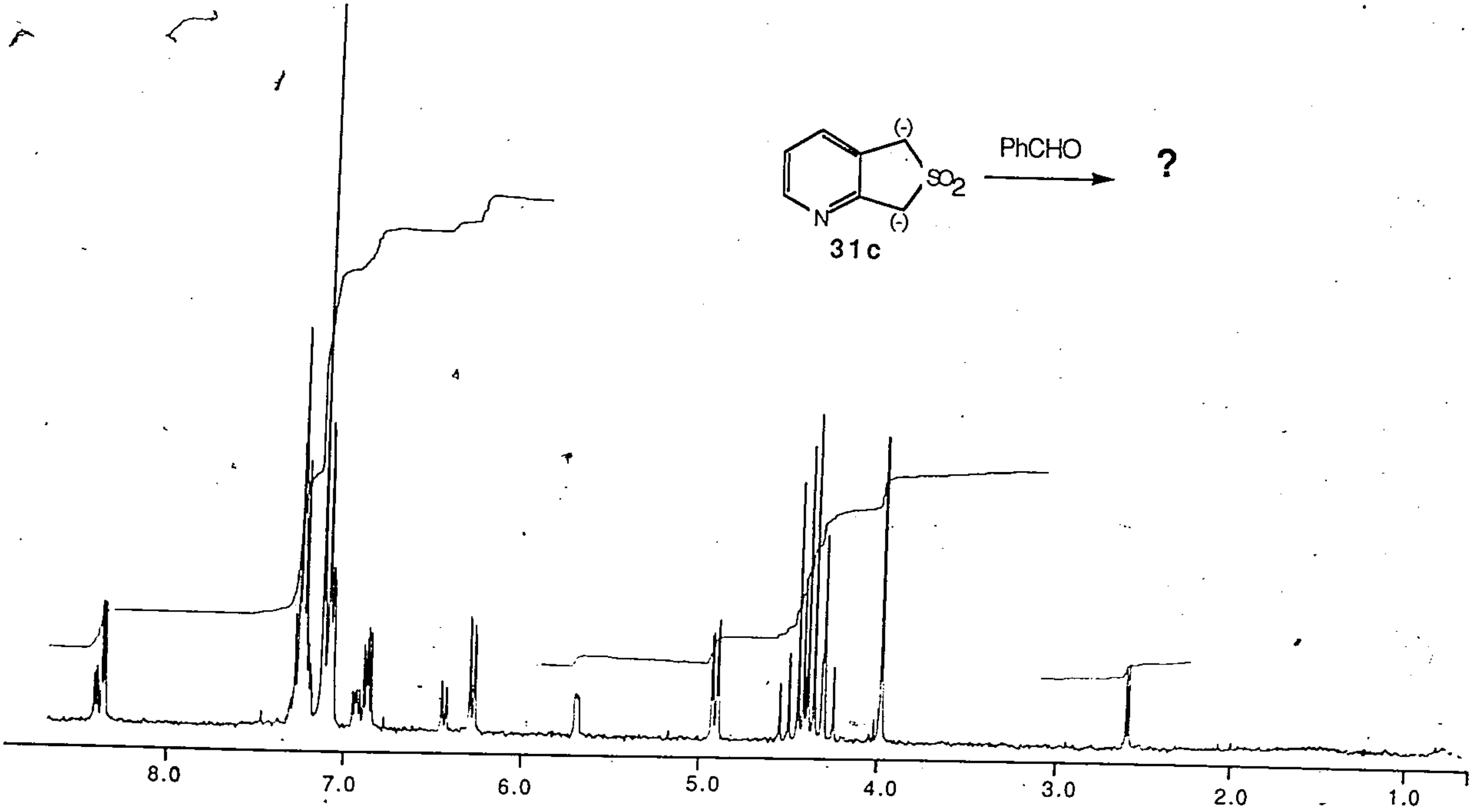
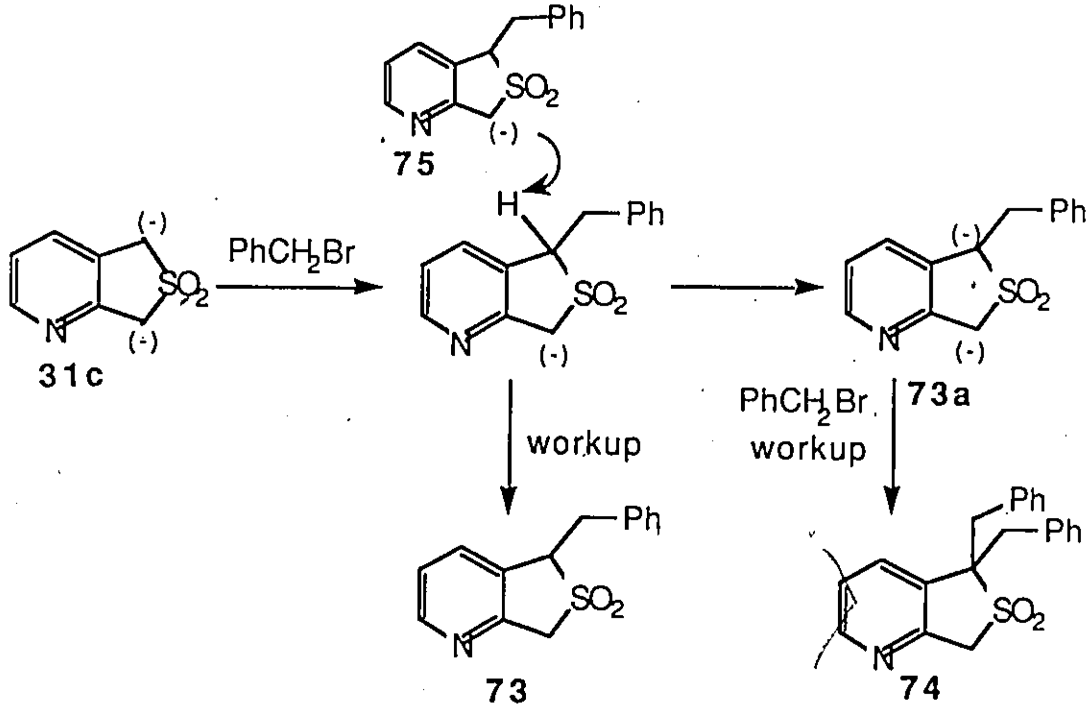


FIGURE 8: ^{1}H NMR Spectrum of the mixture resulting from reaction of dianion **31c** with benzaldehyde

The dianion **31c**/benzyl bromide reaction gave the expected 1-benzyldihydrothieno[3,4-b]pyridine-2,2-dioxide **73** in 33% yield as a white solid (m.p.:172-173° C) as well as 1,1-dibenzyldihydrothieno[3,4-b]pyridine-2,2-dioxide **74** in 19% yield, also a white solid (m.p.:131-132°C). In addition to the aromatic peaks, the nmr spectrum of **73** showed an AB quartet at δ4.39, δ4.38 ppm for the C-3 methylene group (2H) with a coupling constant of 16.4 Hz and three doublets of doublets observed at δ4.52 ppm (1H, J=9.45Hz, 5.55Hz) for the C-1 methine group and δ3.65 ppm (1H,J=14.1Hz, 5.55Hz) and δ3.00 ppm (1H, J=14.1Hz, 9.45Hz) for the two benzyl protons.

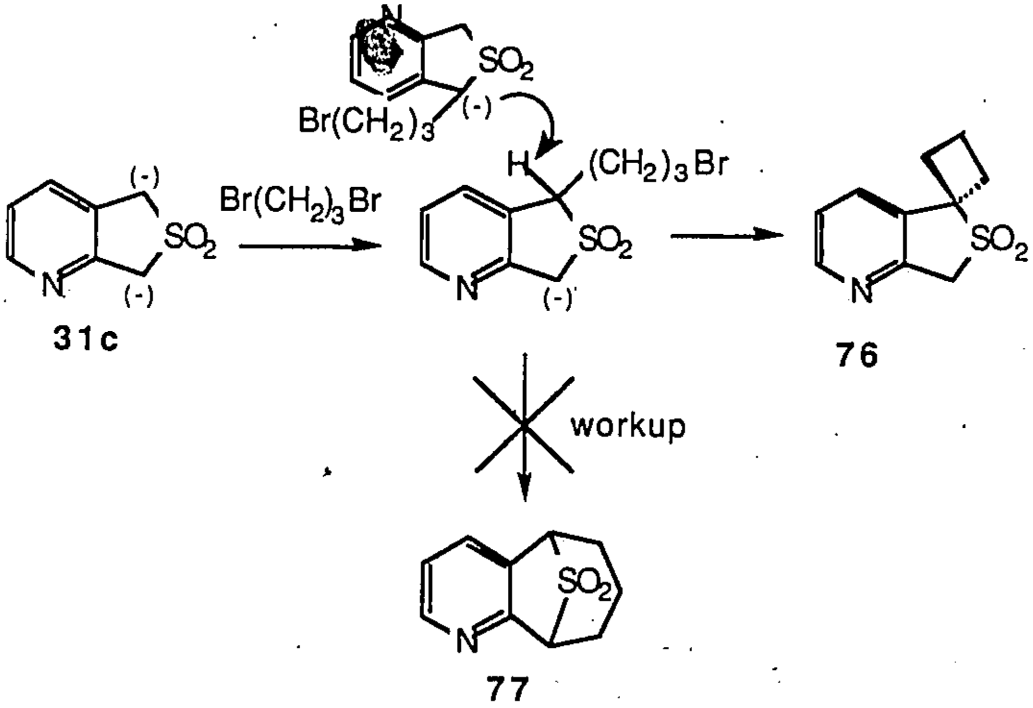
The nmr spectrum of **74** showed a singlet at δ3.59 ppm for the C-3 methylene group (2H) and an AB quartet at δ3.48, δ3.33 ppm integrating to 4 protons (two benzyl groups) with a coupling constant of 14.3 Hz. This AB quartet results from the pseudo-chiral center at C-1 which renders the 2 protons of each benzyl group diastereotopic. These benzyl groups are obviously identical.

The formation of the 1,1-dibenzyl derivative **74** as opposed to a 1,3-dibenzyl derivative can be rationalized using the same concepts outlined for the formation of the 3-methyl derivative **63** and the mixture of 1- and 3-thiomethyl derivatives **68** and **69** respectively mentioned earlier. That is: even though the C-3 anion **75** (scheme 26) is present as the major species after reaction of benzyl bromide with the dianion **31c** it is expected to be rather unreactive towards benzyl bromide. A small amount of the dianion **73a** could be formed from **75**, the C-1 anion of **73a** being more reactive than the C-3 anion would react with benzyl bromide to give the 1,1-disubstituted product **74** rather than a 1,3-disubstituted one as shown in scheme 26.



scheme 26

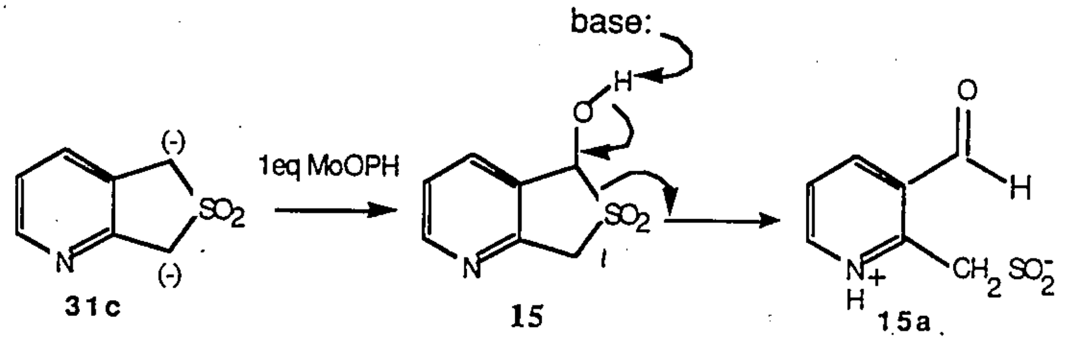
The same argument can be invoked to explain the product obtained using 1,3-dibromopropane ($BrCH_2CH_2CH_2Br$). In this particular case, dihydrothieno[3,4-b]pyridine-2,2-dioxide-1-spiro-cyclobutane **76** (m.p.=121-123°C) was isolated in 26% yield (scheme 27). None of the predicted bridged pyridine sulfone **77** was observed as confirmed by ^{1}H NMR and M.S. *i.e* the ^{1}H NMR showed a signal at δ 4.37(s,2H) for the methylene protons α to the sulfone as opposed to the presence of 2 sets of doublets of doublets (dd) for the 2 methine protons α and α' to the sulfone which would have been present in the ^{1}H NMR of the expected product 77.



scheme 27

From the results observed, it was obvious various electrophiles could be incorporated at the 1- or the 3-position. Therefore, incorporation of a hydroxyl group at the 1-position using a suitable reagent would in principle give the desired hydroxy sulfone **15** initially conceived for the synthesis of the *Sceletium* alkaloid A-4 precursor **16** (scheme 5).

This hydroxylation reaction was attempted using MoOPH [oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide] as the hydroxylating agent[37] (scheme 28). Addition of one eq. of MoOPH to the dianion solution at -78°C caused the reaction mixture to turn from the original olive green to dark red. The reaction mixture was allowed to warm to R.T. and then quenched with 10% aq. Na_2SO_3. The ^1H NMR of the crude product showed no evidence of either the starting sulfone **31** or the desired 1-hydroxy sulfone **15**; it consisted solely of absorption patterns consistent with HMPA. If sulfone **15** was formed, it may have reacted with the pyridine present in the reagent or with another molecule of **15** which acting as a base may have produced the water soluble sulfinic acid **15a** as shown in scheme 28.



scheme 28

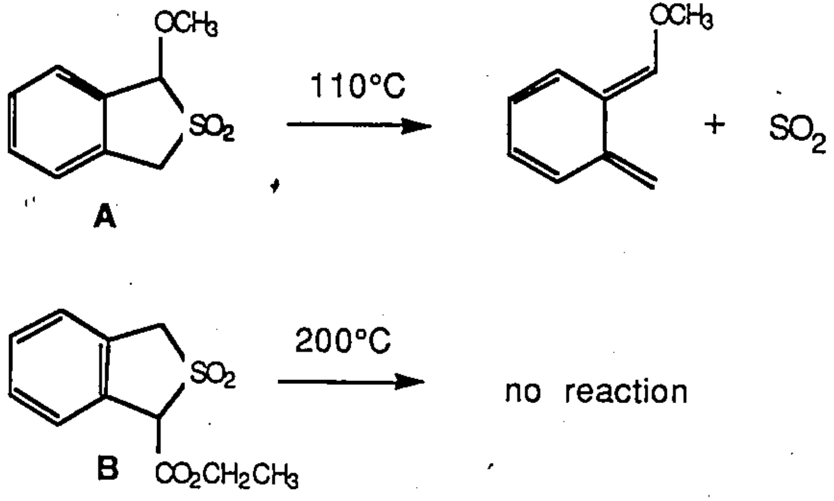
---

[37] Org. Syn. 64, 127.

PART E

THERMOLYSIS OF 1,3-DIHYDROTHIENO[3,4-b]-PYRIDINE-2,2-DIOXIDE

Mass spectroscopy has been used to predict the possibility of carrying out thermolysis reactions. For example the E.I.-M.S. of the alkoxy sulfone **A** shows a facile loss of SO_2 and no molecular ion while the carboalkoxy sulfone **B** gives a molecular ion peak which is ~75% of the base peak. In qualitative agreement with these data the thermal extrusion of SO_2 from **A** occurs readily at about 110° while **B** is recovered unchanged after heating for several hours at 200°C[15].



In general, the E.I.-M.S. of the pyridine sulfones **31** and **63** to **65** showed facile loss of SO_2 since a molecular ion peak less than 6% of the base peak or no molecular ion peak was observed, the base peak in these cases corresponding to M^+-SO_2. The C.I.-M.S. of the remaining pyridine sulfones followed a similar trend, with the $M^{+}+1-SO_2$ peak being the base peak or greater than 50% of the base peak with one exeption. The $M^{+}+1$ peaks were also greater than 50% of the base peak as expected for C.I.-M.S. Further M.S. fragmentations were not discussed in this part of the thesis. The major M.S. peaks together with peak assignments are reported in the experimental section.

Based on these results, one would have expected the thermolysis of these compounds to produce facile chelotropic elimination of SO_2. The parent sulfone **31** was therefore heated neat at 280°C. Unfortunately, no elimination of SO_2 occurred, sulfone **31** sublimed on the sides of the flask. It was then decided to investigate the flash vacuum pyrolysis (FVP) of **31** and some of its derivatives.

The FVP involves the volatilization of a compound followed by passage through a furnace for a short period of time . The product is collected by a dry ice-acetone cooled trap. A series of experiments at different furnace temperatures were attempted using this flash pyrolysis apparatus reproduced in figure 9. The pressure was 0.1 mm for all runs, but increased to 0.25 mm as the material volatilized through the hot furnace onto the dry ice-acetone trap. At a furnace temperature of about 300°C, starting sulfone **31** was partly recovered. At 400°C, both starting material and an inseparable mixture of products were obtained. The substance collected on the trap was yellow. At 500°C, and higher, a mixture of inseparable materials was again obtained. An increase in the rate of volatilization of **31** resulted only in decomposition giving a dark yellow material on the trap. The ^{1}H NMR spectrum of the products did not show any evidence of **31** or of spiro[di-pyridine-*o*-QDM] expected from dimerization. The same type of results were observed when 1-thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **68** was pyrolyzed. Finally, trapping of the expected *o*-quinodimethane with diethylfumarate was attempted. The diethylfumarate was smeared on the dry ice-acetone trap such that when sulfone **31** was volatilized, the o-QDM if formed, would be trapped by the diethylfumarate and later collected from the trap. However, when the experiment was performed at 500°C, a mixture of diethylfumarate and sulfone **31** was recovered. No desired product was isolated. As a result, the pyrolysis of other derivatives was not attempted.

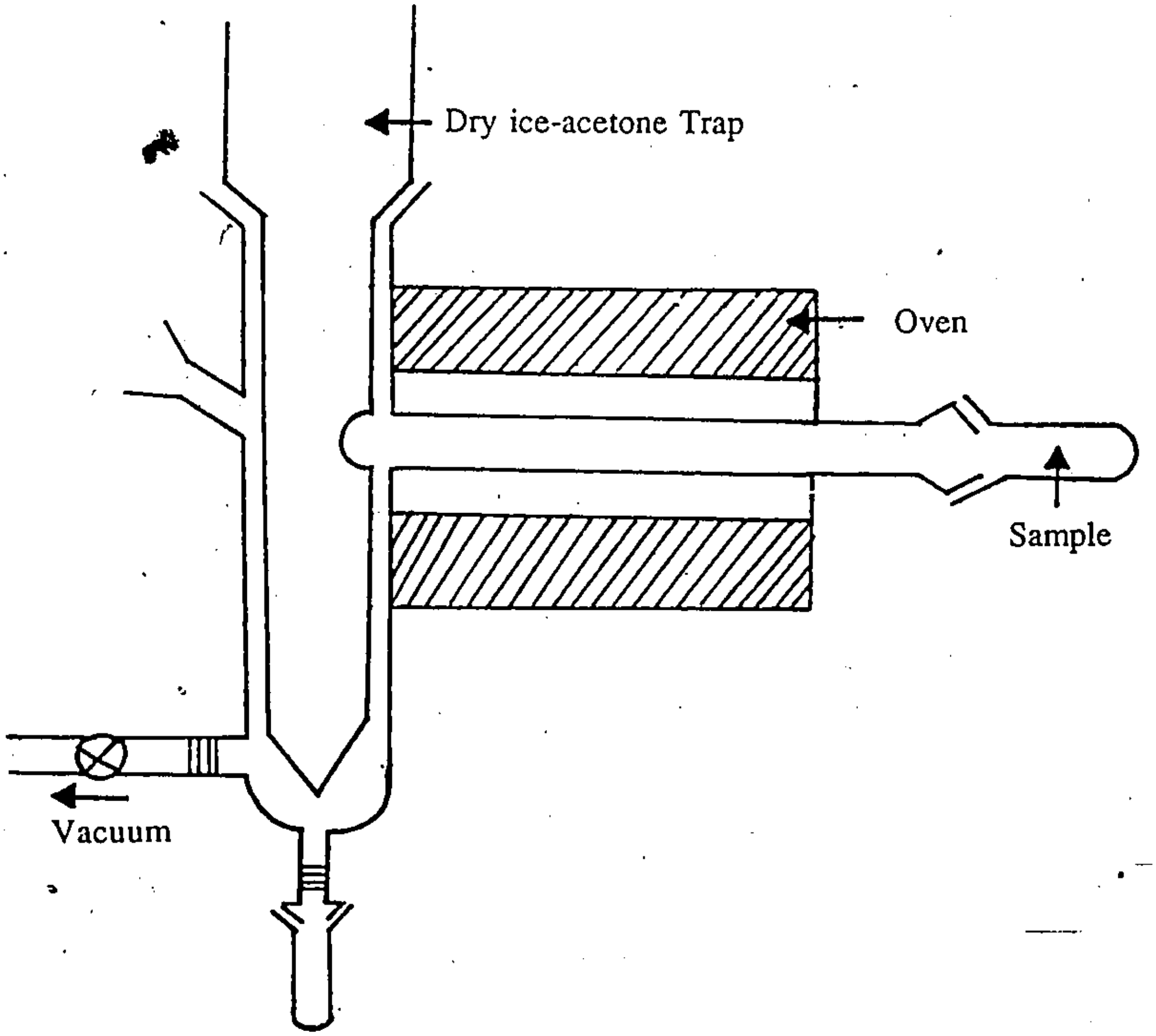


FIGURE 9: Flash Vacuum Pyrolysis Apparatus

EXPERIMENTAL

GENERAL

Melting points were determined by use of a Gallenkamp digital melting point apparatus and are uncorrected. Infrared (I.R.) spectra were run as films on sodium chloride plates for oils, and in chloroform ($CHCl_3$) for solids using a Perkin Elmer 783 spectrophotometer. Frequencies are reported in cm^{-1} . Mass spectra were recorded on an AEIMS 9025 instrument. The peak intensities are given as a % of the base peak (100%) intensity.

Proton NMR spectra were taken in deuterochloroform ($CDCl_3$), unless otherwise noted, using a Varian XL-300 300MHz spectrometer. The chemical shifts are reported in ppm downfield relative to the internal standard tetramethylsilane (delta scale). The coupling patterns are noted as singlets (s), doublets (d), triplets (t), quartets (q), doublets of doublets (dd), broad (b) or multiplet (m).

Column chromatography was accomplished using Baker or Terochem 60-200 mesh silica as the adsorbant. Thin layer chromatography (TLC) was performed on Merk 60 F-254 and Kieselgel 60 F-254 precoated silica plates of 0.25mm thickness. Purifications by Chromatotron were performed on a Harrison Research Chromatotron model 7924 using silica gel coated rotors (1mm, 2mm, and 4mm thickness).

Tetrahydrofuran (THF) was distilled over sodium-benzophenone under a nitrogen atmosphere prior to use. Diisopropylamine, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride under a nitrogen atmosphere. All other solvents or reagents were distilled or were of reagent grade quality.

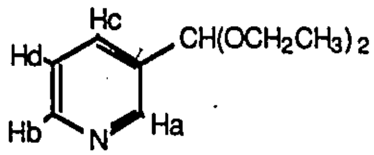
Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Buchi evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of nitrogen.

PART A

Pyridine-3-carboxaldehyde diethylacetal 19

Triethylorthoformate (27mL;16.4mmol) was added to a stirred solution of 3-pyridinecarboxaldehyde (15.8g; 5.4mmol) in absolute ethanol (50mL). *p*-Toluenesulfonic acid (200mg) was added and the solution refluxed overnight. The reaction mixture was neutralized with a saturated $NaHCO_3$ solution (20mL), extracted with CH_2CL_2 (2x75mL) and the organic layer washed with H_2O (2x50mL). The combined organic extracts were dried and concentrated. The crude diethylacetal was purified by flash chromatography using hexanes/ethyl acetate (1:1) as the eluent, to give 3-

pyridinecarboxaldehyde diethylacetal **19** (8.50g) as a clear yellow oil in 87% yield.



19

^{1}H NMR ($CDCl_3$;60MHz): δ 8.78(s,1H,H_a); δ 8.60 (m,1H,H_b); δ7.83(m, 1H, H_c); δ7.39(dd, 1H, J=7.84Hz, J=4.50Hz, H_d); δ5.60(s, 1H, $C\underline{H}(OEt)_2$); δ3.63(q, 4H, $CH(OC\underline{H}_2CH_3)_2$); δ1.29(t, 6H, $CH(OCH_2C\underline{H}_3)_2$).

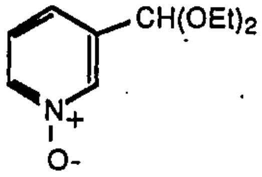
Attempted synthesis of 2-methylpyridine-3-carboxaldehyde diethyl acetal

Methyllithium (8.7mL;9.57mmol,1.1M in ether,Aldrich) was added to a cooled solution (0°C) of **20** (1.58g;8.7mmol) in THF (20mL). The reaction mixture was stirred for 1 h, then quenched with a saturated $NH_4{}^+Cl^-$ solution and extracted with ether (2x50mL). The combined ethereal extracts were washed with H_2O (2x10mL), brine (2x10mL), dried and concentrated. NMR analysis of the crude product indicated starting material **19**. The reaction was repeated at -78°C with similar results.

Pyridine-3-carboxaldehyde diethylacetal N-oxide 20

A solution of *m*-CPBA (14.1g;8.1mmol) in $CHCl_3$ (100mL) was slowly added to a cooled solution (0°C) of **20** (12.8g;7.1mmol) in

$CHCl_3$ (100mL). After the addition was complete, the reaction mixture was allowed to warm to R.T. (2 h). The excess *m*-CPBA was destroyed with a 10% solution of $NaHSO_3$ (3x50mL). The organic layer was washed with a saturated solution of $NaHCO_3$ (3x50mL), H_2O (2x50mL), brine (2x50mL) dried and concentrated. The crude product was purified by HPLC using ethyl acetate/methanol (9:1) as the eluent to afford pyridine-3-carboxaldehyde diethylacetal N-oxide **20** (7.33g) as a clear yellow oil in 53% yield.



20

^1H NMR($CDCl_3$): δ8.42(s,1H,H_a); δ8.26(d, 1H, J=6.71Hz, H_b); δ7.47(d, 1H, J=7.42Hz, H_c); δ7.33(dd, 1H, J=7.42Hz, 6.71Hz, H_d); δ5.50(s, 1H ,C<u>H</u>(OEt)$_2$); δ3.56(q, 4H, CH(OC<u>H</u>$_2$CH$_3$)$_2$); δ1.23(t, 6H, CH(OCH$_2$C<u>H</u>$_3$)$_2$).

<u>Attempted synthesis of 2-methylpyridine-3-carboxaldehyde diethylacetal N-oxide</u>

To a solution of LDA prepared by addition of *n*-BuLi (1.42mL;4.02mmol;2.83M) to diisopropylamine (0.41g;4.02mmol) at -78°C in THF (25mL), was added a solution of **20** (0.53g;2.68mmol) in THF (15mL). The reaction mixture was stirred for 2 h at -78°C and then allowed to warm to R.T.(1 h). MeI (2 equivalents) was added and the solution stirred for 1 h. The reaction mixture was quenched with a saturated $NH_4^+Cl^-$ solution (10mL) and extracted with ether (2x50mL). The combined ethereal extracts were washed with dilute HCl (10%;2x10mL), H_2O (2x10mL), brine (10mL), dried and concentrated to afford a black oily residue whose TLC showed that many highly polar products had been formed. The ^1H NMR spectrum of the crude product showed broad, ill defined absorption patterns, possibly suggesting the formation of polymeric products. The reaction was repeated under various conditions with similar results.

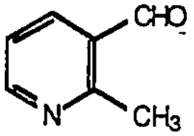
Attempted synthesis of 3-(hydroxymethyl)-2-methylpyridine **23**

A mixture of 2,3-lutidine **21** (1.60g;15.0mmol), benzoylperoxide (0.5g) and NBS (3.60g;15.0mmol) in CCl_4 (100mL) was refluxed for 1.5 h until almost all of **21** had reacted (TLC). The mixture, after concentration at reduced pressure, contained mainly 3-(bromomethyl)-2-methylpyridine **22** (0.97g;35% yield). [^1H NMR(CCl_4;60 MHz): δ6.80-8.24(m,3H); δ4.24(s,2H); δ2.52(s,3H)] and small amounts of less polar brominated products (TLC). The concentrated mixture was diluted with dioxane (20mL), a 15% NaOH solution added (10mL) and the reaction mixture refluxed for 1.5 h. The resulting dark red solution was extracted with ether (3x75mL). The combined ethereal extracts were washed with H_2O (2x20mL), brine (20mL), dried and concentrated. None of the desired alcohol **23** was isolated.

2-methylpyridine-3-carboxaldehyde **18**

Method A; oxidation of **22**:

To a stirred solution of Na_2CO_3 (1.69g;15.0mmol) and KI (2.50g;15.0mmol) in DMSO (50mL) was added a solution of **22** [prepared as previously described by monobromination of **21** (1.60g;15.0mmol) with NBS (3.60g;15.0mmol)] in CCl_4 (25mL). The reaction mixture was refluxed for 1 h, then rapidly cooled in ice and poured over ice cooled brine. The reaction mixture was extracted with ether (3x50mL), the black suspension which formed was removed by filtration and the combined ethereal extracts were washed with H_2O (2x20mL), brine (20mL), dried and concentrated. The crude aldehyde was purified by flash chromatography using hexanes/ethyl acetate (3:7) as the eluent to give 2-methyl-3-pyridine carboxaldehyde **18** as a clear yellow oil in 13% yield (0.23g).



18

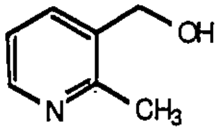
^1H NMR($CDCl_3$;60MHz): δ10.31(s, 1H, C<u>H</u>O); δ8.55(dd, 1H, J=4.87Hz, 2.41Hz, H_a); δ8.05(dd, 1H, J=7.85Hz, 2.41Hz, H_b); δ7.23(dd, 1H, J=7.85Hz, 4.87HZ, H_c); δ2.82(s, 3H, CH_3).

M.S.(m/z): M^+=121 (25%); M^+-H_2O=105 (100%).

Method B; oxidation of 3-(hydroxymethyl)-2-methylpyridine **23**;

i) synthesis of **23**:

A solution of ethyl 2-methylnicotinate **27** (1.06g;6.42mmol) in THF (25mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.24g;0.42mmol) in THF (25mL) at 0°C. The reaction mixture was stirred for 0.5 h at R.T. and then refluxed for 1 h. The excess hydride was destroyed by the addition of H_2O (1mL), 10% NaOH (1mL), and again H_2O (3mL). The reaction mixture was diluted with ether (75mL) and dried. The aluminium salts were removed by suction filtration and rinsed with small portions of ether (5x10mL). The combined ethereal extracts were concentrated to yield 0.76g (96% yield) of 3-(hydroxymethyl)-2-methylpyridine **23**. When the reaction was performed on a large scale (~10g of ester) **23** was purified by HPLC using hexanes/ethyl acetate (7:3) as the eluent.



23

^1H NMR($CDCl_3$;300MHz): δ8.41(dd, 1H, J=4.83Hz, 0.74Hz); δ7.51(dd, 1H, J=7.68Hz, 0.74Hz); δ7.18(dd, 1H, J=7.68Hz, 4.83Hz); δ4.70(s, 2H, $C\underline{H}_2OH$); δ3.52(b, 1H, OH); δ2.32(s, 3H, CH_3).

M.S.(m/z): $M^+=123$ (100%); $M^+-1=122$ (54.1%); $M^+-H_2O=105$(36%).

I.R.(film):3360 (OH broad); 1585 (C=C,C=N); 1050 (CH_2OH) cm^{-1}.

ii) oxidation of **23**:

a) PCC oxidation: 3-(hydroxymethyl)-2-methylpyridine **23** (0.39g;3.15mmol) in CH_2Cl_2 (15mL) was added in one portion to a slurry of pyridinium chlorochromate[22] (1.02g;4.73mmol) in CH_2Cl_2 (20mL) at 0°C. A black slurry formed immediately. After the reaction mixture was stirred for 2 h at R.T., anhydrous ether (25mL) was added and the supernatant decanted from the black gum. The black gum was rinsed with ether, the combined organic phases were filtered through coarse silica gel (BDH silica gel Kieselgel 60) and concentrated to yield 81mg of crude 2-methylpyridine-3-carboxaldehyde **18** (21% crude yield). The ^1H NMR was consistent with the spectrum of **18** obtained by method A.

b) Swern oxidation[23]: Oxalyl chloride (0.61g;4.81mmol) was added to a cooled (-78°C) solution of DMSO (0.75g;9.6mmol) in CH_2Cl_2 (10mL) and the solution stirred for 5 minutes. A solution of **23** (0.49g;4.0mmol) in CH_2Cl_2 (5mL) was added dropwise, and the reation mixture stirred for another 10 minutes. Following the addition of TEA (0.97g;9.6mmol), the reaction mixture was allowed to warm to R.T. and stirred for 1.5 h and then quenched with H_2O, (10mL) and extracted with CH_2Cl_2 (3x50mL). The combined organic extracts were washed with H_2O (2x10mL), dried and concentrated to afford 306mg (79% crude yield) of **18**. Following purification by flash chromatography using hexanes/ethyl acetate (7:3) as the eluent, 252mg (52% yield) of 2-methyl 3-pyridine carboxaldehyde **18** was obtained. The spectroscopic data were identical to those of **18** obtained previously.

Attempted photolysis of 2-methylpyridine-3-carboxaldehyde **18** in the presence of SO_2.

2-Methylpyridine-3-carboxaldehyde **18** (0.50g;4.1mmol) was dissolved in benzene (20mL), the solution then purged with nitrogen, saturated with sulfur dioxide (SO_2 gas bubbled in for 15 minutes) and photolyzed overnight in a 1-mm Pyrex tube using a Hanovia 450 watt medium pressure mercury lamp. A yellow fluffy precipitate formed. The solvent was removed under reduced pressure to afford a dark yellow solid . ^1H NMR(DMSO-d_6, 300MHz): δ8.66(dd, 1H, J=4.90Hz, 1.46Hz); δ8.61(dd, 1H, J=7.81Hz, 1.46Hz); δ7.92(dd, 1H, J=7.81Hz, 4.90Hz); δ5.40(s, 1H, C<u>H</u>$(OH)_2$ or C<u>H</u>$(OH)SO_3^-$); δ2.43(s, 3H, CH_3); both OHs masked by the broad DMSO peak at δ3.52ppm. The photolysis of **18** was repeated using diethyl fumarate as the *o*-QDM trap. 2-Methylpyridine-3-carboxaldehyde **18** and diethyl fumarate were recovered.

Attempted synthesis of sultine **30**

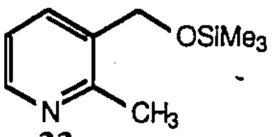
A solution of alcohol **23** (0.52g;4.2mmol) in THF (20mL) was slowly added to a stirred suspension of NaH (0.11g;4.6mmol;60% suspension in oil, Aldrich) (washed with hexanes) in THF (20mL) at 0°C. After the addition was complete, the reaction mixture was stirred for 5 minutes, cooled to -78°C. *n*-BuLi (1.68mL;4.2mmol;2.5M) was added dropwise and the reaction mixture stirred for 10 minutes followed by saturation with SO_2 (bubbled in for 20 minutes). The THF was removed under reduced pressure and the aqueous phase acidified with conc. HCl forming a yellow precipitate. The aqueous suspension was taken up in CH_2Cl_2 (50mL) and washed with a saturated $NaHCO_3$ solution. The aqueous phase was back-extracted with CH_2Cl_2 (2x25mL) and the combined organic extracts washed with H_2O (2x10mL), dried and concentrated. Alcohol **23** was the only compound isolated. This reaction was repeated under various conditions (2 LDA, SO_2; 2 LDA, CO_2) with identical results, *i.e.* recovery of starting material.

PART B

Attempted synthesis of 2-(trimethylsilylmethyl)-3-(hydroxymethyl)pyridine **32**

Method A; silylation of **23**:

A solution of **23** (0.49g;4.0mmol) in THF (20mL) was slowly added to a stirred suspension of NaH (0.11g;4.6mmol, 60% suspension in oil, Aldrich) (washed with hexanes) in THF (20mL) at 0°C. After the addition was complete, the reaction mixture was stirred for 5 minutes, then cooled to -78°C. *n*-BuLi (1.6mL;4.0mmol;2.5M) was added dropwise and the reaction mixture stirred for 10 minutes followed by the addition of excess TMS-Cl. After the reaction mixture was allowed to warm to R.T., a saturated $NH_4^+Cl^-$ solution (5mL) was added followed by 10% HCl (10mL). The reaction mixture was stirred for 10 minutes, neutralized with a saturated $NaHCO_3$ solution and extracted with ether (3x75mL). The combined ethereal extracts were washed with H_2O (2x20mL), brine (20mL) and concentrated to give 0.48g of a clear yellow oil. Further purification by flash chromatography using hexanes/ethyl acetate (1:1) as the eluent afforded 0.35g of a mixture of 3-(trimethylsilyloxymethyl)-2-methylpyridine **33** and 3-(hydroxymethyl)-2-methylpyridine **23**.



33

^1H NMR($CDCl_3$;300MHz): δ8.34(m, 1H); δ7.63(m, 1H); δ7.55(m, 1H); δ4.61(s, 2H, $C\underline{H}_2OSiMe_3$); δ2.43(s, 3H, CH_3); δ0.12(s, 9H, $OSi(CH_3)_3$).

^{13}C INEPT NMR($CDCl_3$;300MHz): δ 147.31(CH); δ134.14(CH); δ121.16(CH); δ61.62(CH_2); δ21.52(CH_3); δ-0.57(CH_3).

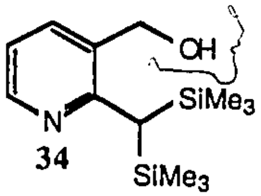
M.S.(m/z): M^+=195 (47.7%); M^+-15 (89%); M^+- Si(OH)Me3=106 (100%).

I.R.(film): 2950 (C-H); 1565 (C=C,C=N); 1255(CH_3 bend); 1070 (Si-O); 840 (Si-CH_3) cm^{-1}.

Table 1 (p35) summarizes the various bases and silylating agents used in subsequent attempts to synthesize 2-(trimethylsilylmethyl)-3-methylpyridine **32** via this method.

Method B; silylation of **23** using excess base to generate the dianion:

To a cooled solution of TMS-Cl (1.42g;13.1mmol) and LDA prepared by the addition of *n*-BuLi (5.25mL;13.1mmol;2.5M) to diisopropylamine (0.44g;13.1mmol) at -78°C in THF (50mL) was added a solution of **23** (0.53g;4.3mmol) in THF (10mL). The reaction mixture was stirred for 0.75 h and allowed to warm to R.T. Dilute HCl (10%) was added and the reaction mixture stirred overnight. The reaction mixture was neutralized with a saturated solution of $NaHCO_3$, and extracted with ether (3x50mL). The combined ethereal extracts were washed with H_2O (2x25mL), brine (25mL), dried and concentrated to give a clear yellow oil. Purification by flash chromatography using hexanes/ethyl acetate (1:1) as the eluent afforded 0.68g (59% yield) of 2-[bis(trimethylsilylmethyl)]-3-(hydroxymethyl)pyridine **34**.



34

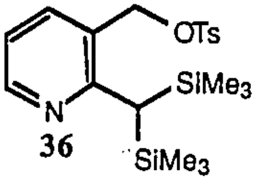
^1H NMR (CCl_4, 60MHz): δ8.17(m, 1H); δ7.29(m, 1H); δ6.72(m, 1H); δ4.35(s, 2H, C$\underline{H_2}$OH); δ2.32(b, 1H, OH); δ1.17(s, 1H,C$\underline{H}$($SiMe_3$)$_2$); δ0.00(s, 18H ,CH(Si(CH_3)$_3$)$_2$).

I.R.(film): 2950 (CH); 1565 (C=C,C=N); 1070 (Si-O); 840 (Si-C) cm^{-1}.

M.S.(m/z): M^+=267 (27%); M^+-15=252 (39.5%).

2,2-[Bis(trimethylsilylmethyl)]-3-(methyl-*p*-toluene sulfonate)pyridine **36**

TEA (0.026g;25.8mmol) and *p*-toluenesulfonylchloride (0.05g;25.8mmol) were added to a solution of alcohol **34** (0.07g;25.8mmol) in CH_2Cl_2 (10mL) at 0°C. The reaction mixture was kept at 0°C overnight, the $HNEt_3{}^+Cl^-$ salts were then removed by filtration and the CH_2Cl_2 removed under reduced pressure to afford 0.79g (72.5% yield) of tosylate **36**. Tosylate **36** was used immediately without further purification.



36

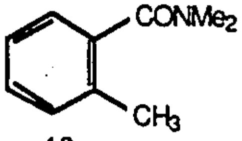
^{1}H NMR($CDCl_3$, 60MHz): 8.27-δ6.52(m, 7H); δ4.29(s, 2H, C$\underline{H}_2$OTs); δ2.37(s, 3H, CH_3); δ1.71(s, 1H, C$\underline{H}$($SiMe_3$)$_2$); δ0.00(s, 18H, CH(Si(C$\underline{H}_3$)$_3$)$_2$).

Attempted synthesis of sulfone **35**

Tosylate **34** (0.08g;0.19mmol) was dissolved in CH_3CN (10mL) and the solution saturated with SO_2 by bubbling in SO_2 gas for 20 minutes. Cesium fluoride (0.03g;0.20mmol) was added and the reaction mixture stirred overnight. A yellow precipitate formed. The reaction mixture was extracted with ether (3x25mL) and the combined ethereal extracts washed with H_2O (2x10mL), brine (10mL), dried and concentrated. No desired sulfone **35** was isolated.

o-Methyl N,N-dimethylbenzamide **40**

A solution of *o*-toluic acid (3.50g;26mmol) in benzene (100mL) was added to a solution of $SOCl_2$ (13.8g;116mmol) in benzene (100mL) and the reaction mixture was refluxed for 2 h, then cooled to R.T. and concentrated. The resulting acid chloride was transferred dropwise to a solution of aqueous dimethylamine (1.74g;39mmol) in 10% NaOH (20mL) and stirred for 1 h. The reaction mixture was extracted with ether (3x75mL), the combined ethereal extracts washed with H_2O (2x20mL), brine (20mL), dried and concentrated to afford 3.34g of crude **40**. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as the eluent gave 3.14g (74% yield) of *o*-methyl N,N-dimethylbenzamide **40**.

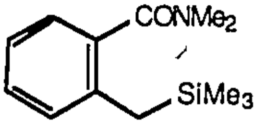


40

^{1}H NMR($CDCl_3$;60MHz): δ7.18(s, 4H); δ2.98(s, 3H, CH_3); δ2.58(s, 3H, CH_3); δ2.20(s, 3H, CH_3).

0-(α-Trimethylsilylmethyl)N,N-dimethylbenzylamide **41**

TMEDA (1.37g;11.6mmol), *sec*-BuLi (7.50mL;11.8mmol;1.3M) and TMS-Cl (3.2g;24.5mmol) were added sequentially at -78°C to a solution of amide **40** (1.6g;9.8mmol) in THF (25mL). The reaction mixture was allowed to warm to R.T. in which time a color change occurred; going from a dark red to a light yellow. The reaction mixture was quenched with H_2O, extracted with ether (3x50mL) and the combined ethereal extracts washed with H_2O (2x20mL), brine (20mL), dried and concentrated to give 2.42g of a yellow oil. The mixture of *0*-(α-trimethylsilylmethyl)N,N-dimethylbenzylamide **41** and disilylated material isolated was separated by distillation at 0.25 torr.



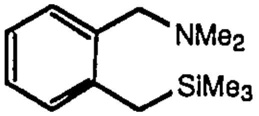
41

^{1}H NMR($CDCl_3$;60MHz): δ7.18(s, 4H); δ2.98(s, 3H, CH_3); δ2.58(s, 3H, CH_3); δ1.44(s, 2H, C$\underline{H}_2$SiMe$_3$); δ0.00(s, 9H, CH_2Si(C$\underline{H}_3$)$_3$).

M.S.(m/z): $M^+=235$ (15.7%); $M^+-15=220$ (100%).

O-(α-Trimethylsilylmethyl)benzyl N,N-dimethylamine **42**

A solution of amide **41** (2.42g;8.0mmol) in THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.36g;9.5mmol) in THF at 0°C. After the addition was complete, the reaction mixture was stirred at R.T. for 0.5 h and then refluxed for 1 h. The reaction mixture was ice cooled and excess hydride destroyed by the addition of H_2O (2mL), 10% NaOH (2mL) and again H_2O (6mL). The reaction mixture was diluted with ether (50mL) and dried. The aluminium salts were removed by suction filtration and rinsed with ether (3x20mL). The combined ethereal extracts were concentrated to give 1.96g of crude amine **42** further purified by distillation at 0.25 torr to afford 1.23g (70% yield) of *O*-(α-trimethylsilylmethyl)benzyl N,N-dimethylamine **42**.



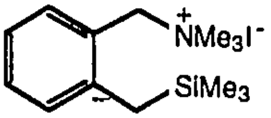
42

^1H NMR($CDCl_3$;60MHz): δ7.12(s,4H); δ3.35(s, 2H, $C\underline{H}_2NMe_2$); δ2.98(s, 3H, CH_3); δ2.58(s, 3H, CH_3); δ1.44(s, 2H, $C\underline{H}_2SiMe_3$); δ0.00(s, 9H, $Si(CH_3)_3$).

M.S.(m/z): $M^+=220$ (21.3%); $SiMe_3^+=73$ (100%).

O-(α-Trimethylsilylmethyl)benzyltrimethylammonium iodide 37

Methyl iodide (0.74g;12.3mmol) was slowly added to a stirred solution of amine **42** (1.20g;4.1mmol) in absolute ethanol. The reaction mixture was refluxed for 0.5 h, cooled to R.T. and concentrated. Ether was added to the reaction mixture until the solution became cloudy and then stored at 0°C overnight. The supernatant was decanted and the crystals were suction filtered. *O*-(α-Trimethylsilylmethyl)benzyltrimethylammonium iodide **37** was obtained in 30% yield (0.57g).



37

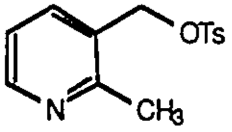
M.S.(FAB): M^+(cation)=236 (17.4%).

Attempted synthesis of sulfone 38 by fluoride-induced 1,4-elimination with SO_2 trap.

Acetonitrile (5mL) was purged with nitrogen and saturated with SO_2 by bubbling in SO_2 for 5 minutes. Salt **37** (0.16g;0.44mmol) followed by TBAF (0.44mL;;0.44mmol;1.0M) were added and the stirred suspension heated to 50°C for 1.5 h. The reaction mixture was cooled (0°C) and extracted with ether (3x10mL). The combined ethereal extracts were washed with H_2O (5mL), brine (5ml), dried and concentrated. Unfortunately no desired sulfone **38** was isolated.

3-(Methyl-*p*-toluenesulfonate)-2-methylpyridine **44**

TEA (0.98g;9.8mmol) and *p*-toluenesulfonyl chloride (1.85g;9.8mmol) were added to a solution of 3-(hydroxymethyl)-2-methylpyridine **23** (1.0g;8.1mmol) in CH_2Cl_2 (20mL) at 0°C. The reaction mixture was kept at 0°C overnight, the $HNEt_3^+Cl^-$ salts were removed by filtration and the CH_2Cl_2 concentrated to afford 1.59g of tosylate **44** (62% yield) which was used without purification.

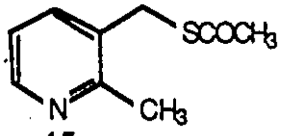


44

^{1}H NMR(CCl_4;60MHz): 8.19-δ6.55(m, 7H); δ4.25(s, 2H, $C\underline{H}_2OTs$); δ2.32(s, 3H, CH_3); δ2.10(s, 3H, CH_3).

3-(Methylthioacetate)-2-methylpyridine **45**

A solution of tosylate **44** (1.59g;6.0mmol) in ethanol (20mL) was added to a stirred solution of potassium thioacetate prepared by adding thioacetic acid (0.46g;6.0mmol) to a solution of KOH (0.34g;6.0mmol) in ethanol (20mL). The reaction mixture was stirred at R.T. overnight. The ethanol was removed under reduced pressure and the oily red residue taken up in ether (50mL), the organic layer was washed with 10% NaOH (10mL), H_2O (2x10mL), brine (10mL), and then concentrated to yield crude **45**. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as the eluent afforded 0.56g (51.6%) of 3-(methylthioacetate)-2-methylpyridine **45**.



45

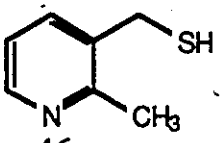
^{1}H NMR(CDCl$_3$;60MHz): δ8.35(m, 1H); δ7.53(m, 1H); δ7.02(m, 1H); δ4.51(s, 2H, C$\underline{H}_2$SCOCH$_3$); δ2.55(s, 3H, CH$_3$); δ2.25(s, 3H, COCH$_3$).

M.S.(m/z): M$^+$=181 (12.4%); M$^+$-SAc=106 (100%).

I.R.(film): 1690(CO); 1570 (C=C,C=N); no OH absorption.

<u>3-(Thiomethyl)-2-methylpyridine</u> **46**

A solution of the thioacetate **45** (0.90g;4.97mmol) in THF (25mL) was added to a stirred suspension of LiAlH$_4$ (0.23g;5.97mmol) in THF (20mL) at 0°C. After the addition was complete, the reaction mixture was allowed to warm to R.T. and stirred for 15 minutes. The excess hydride was destroyed by the addition of H$_2$O (1mL), 10% NaOH (1mL), and again H$_2$O (3mL) at 0°C. The reaction mixture was diluted with ether and dried. The aluminium salts were removed by suction filtration and rinsed with ether (3x10mL). The combined ethereal extracts were concentrated to give 0.49g (70% yield) of 3-(thiomethyl)-2-methylpyridine **46**.



46

^{1}H NMR($CDCl_3$;60MHz): δ8.37(m, 1H); δ7.52(m, 1H); δ7.09(m, 1H); δ3.67(d, 2H, J=7.0Hz, C$\underline{H_2}$SH); δ2.58(s, 3H, CH_3); δ1.80(t, 1H, J=7.0Hz, $CH_2S\underline{H}$).

M.S.(m/z): M^+=139 (50.8%); M^+-SH=106 (100%); M^+-H_2S=105 (35.4%).

<u>Attempted synthesis of sulfide **48** via cyclization of the monohalogenated anion **47**.</u>

TMEDA (0.90g;7.8mmol) and *sec*-BuLi (6.0mL;7.8mmol;1.3M) were added sequentially at -78°C to a stirred solution of thiol **46** (0.48g;3.4mmol) in THF (15mL). The reaction mixture was stirred for 15 minutes and NBS (0.61g;3.2mmol) or hexachloroethane (0.76g;3.2mmol) added in one portion. The reaction mixture was allowed to warm to R.T., quenched with H_2O (5mL) and extracted with ether (3x15mL). The combined ethereal extracts were washed with H_2O (2x10mL), brine (10mL), then dried and concentrated to give a dark brown oil which following purification by flash chromatography using hexanes/ethyl acetate (7:3) did not contain any trace of either sulfide **48** or thiol **46**. Only very polar material (TLC) was isolated whose pmr spectrum contained very broad, ill defined absorption paterns; possibly polymeric material.

PART C

2,3-Bis(hydroxymethyl)pyridine 53

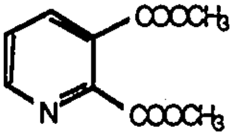
Method A; $LiAlH_4$ reduction of 2,3-pyridinedicarboxylic acid 54:

To a stirred suspension of $LiAlH_4$ (3.5g;31mmol) in THF (75mL), 2,3-pyridinedicarboxylic acid **54** (5.2g;31mmol) was added in small aliquots (0.5g/aliquot) at 0°C. After the addition was complete, the reaction mixture was stirred at R.T. for 1 h, and refluxed for 1.5 h. The excess hydride was destroyed by addition of H_2O (6mL), 10% NaOH (6mL), and again H_2O (12mL). The reaction mixture was diluted with ether (50mL), dried. The aluminium salts were removed by filtration and rinsed with ether (3x20mL) and the combined ethereal extracts concentrated. No desired diol **53** was recovered.

Method B; $LiAlH_4$ reduction of dimethyl pyridine-2,3-dicarboxylate 55:

i) synthesis of **55**:

Concentrated H_2SO_4 (2mL) was added to a stirred suspension of 2,3-pyridinedicarboxylic acid **54** (2.0g;10mmol) in methanol (50mL) and the reaction mixture refluxed for 2 h. The reaction mixture was neutralized with a saturated $NaHCO_3$ solution, then extracted with CH_2Cl_2 (3x50mL). The combined organic extracts were washed with H_2O (2x20mL), dried and concentrated to yield 1.40g (61% yield) of crystalline dimethyl pyridine-2,3-dicarboxylate 55 (m.p.: 55.5°C -56.7°C) recrystallized from diethyl ether.

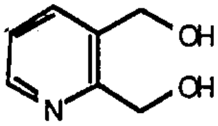


55

^1H NMR($CDCl_3$;300MHz): δ8.52(dd, 1H, J=4.82Hz, 1.66Hz); δ8.16(dd, 1H, J=7.95Hz, 1.66Hz); δ7.48(dd, 1H, J=7.95Hz, 4.82Hz); δ3.99(s, 1H, CH_3); δ3.92(s, 3H, CH_3).

ii) $LiAlH_4$ reduction of **55**:

A solution of dimethyl 2,3-dicarboxylate **55** (1.35g;6.0mmol) in THF (50mL) was slowly added to a stirred suspension of $LiAlH_4$ (0.51g;13.2mmol) in THF (20mL) at 0°C. The reaction mixture was allowed to warm to R.T., then refluxed for 1.5 h. The excess hydride was destroyed as described earlier. After concentrating the ethereal extracts, 2,3-bis(hydroxymethyl)pyridine **53** was isolated in 35% yield (0.27g).



53

The spectroscopic data were indentical with the values reported by Ashcroft *et al* [30].

Method C; borane-THF[31] reduction of <u>2,3-pyridinedicarboxylic acid</u> 54:

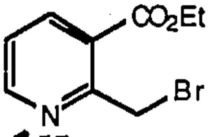
To a stirred suspension of 2,3-pyridinedicarboxylic acid **54** (1.0g;5.1mmol) in THF (50mL) was added dropwise a borane-THF solution (15.2mL;15.2mmol;1M) at 0°C. The reaction mixture was stirred overnight at R.T., and the excess hydride destroyed by the addition of a 50% H_2O-THF mixture (15mL). K_2CO_3 was added until the aqueous phase was saturated and the reaction mixture then extracted with ether (3x50mL). The combined ethereal extracts were dried and concentrated to yield 0.23g (32% yield) of diol **53**. The extraction with ethyl acetate using a continuous extractor did not improve the yield. The spectroscopic data were identical to the reported values.

<u>Attempted synthesis of 2,3-bis(methyl-*p*-toluenesulfonate)pyridine</u> **52**

TEA (0.37g;3.6mmol) and *p*-toluenesulfonylchloride (0.70g;3.6mmol) were added sequentially to a cooled (0°C) solution of diol **53** (0.23g;1.6mmol) in CH_2Cl_2 (25mL). The reaction mixture was kept at 0°C overnight. The $HNEt_3{}^+Cl^-$ salts were removed by filtration and the CH_2Cl_2 concentrated. No ditosylate **52** was isolated.

Ethyl 2-(bromomethyl)nicotinate **57**

Ethyl 2-(bromomethyl)nicotinate **57** was obtained in 51% yield according to a procedure described by Hurst and Wibberly[32].

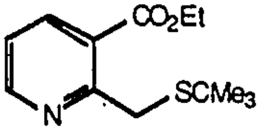


57

^{1}H NMR(CDCl$_3$;300MHz): δ8.70(dd, 1H, J=4.81Hz, 1.75Hz); δ8.26(dd, 1H, J=7.93Hz, 1.75Hz); δ7.34(dd, 1H, J=7.93Hz, 4.81Hz); δ5.10(s, 2H, C$\underline{H}_2$Br); δ4.41(q, 2H, OC$\underline{H}_2$CH$_3$); δ1.41(t, 3H, OCH$_2$C$\underline{H}_3$).

Ethyl 2-(*t*-butylthiomethyl)nicotinate **58**

A solution of bromide **57** (0.73g;3.0mmol) in THF (5mL) was added to a stirred suspension of sodium *t*-butylthiolate prepared by the addition of *t*-butylthiol (0.18g;3.0mmol) to a stirred suspension of NaH (0.16g;3.0mmol; 60% suspension in oil, Aldrich) (washed with hexanes) in THF at 0°C. The reaction mixture was stirred at R.T. overnight, quenched with H_2O (1mL), and extracted with ether (3x20mL). The combined ethereal extracts were washed with H_2O (2x10mL), brine (10mL), dried and concentrated to yield a dark yellow oil. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as the eluent afforded 0.47g (62% yield) of ethyl 2-(*t*-butylthiomethyl)nicotinate **58**.



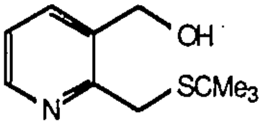
58

^1H NMR($CDCl_3$;300MHz): δ8.60(dd, 1H, J=4.82Hz, 1.81Hz); δ8.16(dd, 1H, J=7.85Hz, 1.81Hz); δ7.22(dd, 1H, J=7.85Hz, 4.82Hz); δ4.38(q, 2H, $OC\underline{H_2}CH_3$); δ1.31(t, 3H, $OCH_2C\underline{H_3}$).

M.S.(m/z): M^+=253 (23.7%); M^+-(*t*-butyl)=197 (100%)

<u>3-(Hydroxymethyl)-2-(*t*-butylthiomethyl)pyridine</u> 59

A solution of ethyl 2-(*t*-butylthiomethyl)nicotinate 58 (0.72g;2.8mmol) in THF (20mL) was added to a stirred suspension of $LiAlH_4$ (0.80g;2.13mmol) in THF (50mL) at 0°C. After the addition was complete, the reaction mixture was stirred at R.T. for 1 h. The excess hydride was destroyed in the usual manner and following concentration of the combined ethereal extracts, 0.60g of a yellow oil was recovered. Purification by flash chromatography using hexanes/ethyl acetate (8:2 then 6:4) as the eluent afforded 0.57g of crystalline 3-(hydroxymethyl)-2-(*t*-bultylthiomethyl)pyridine 59 (99% yield), m.p.:84°C-86°C.



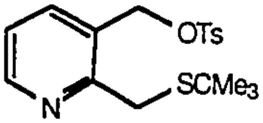
59

^{1}H NMR($CDCl_3$;300MHz): δ8.43(dd, 1H, J=4.84Hz, 1.76Hz); δ7.70(dd, 1H, J=7.58Hz, 1.76Hz); δ7.18(dd, 1H, J=7.58Hz, 4.84Hz); δ4.75(d, 2H, J=5.86Hz, C$\underline{H}_2$OH); δ4.03(s, 2H, C$\underline{H}_2$SCMe$_3$); δ2.82(b, 1H, CH$_2$O$\underline{H}$); δ1.36(s, 9H, C(C$\underline{H}_3$)$_3$).

M.S.(m/z): M^+=211 (2.8%); M^+-(H_2O+1)= 136 (25.4%); M^+-(S-*t*-butyl)=122 (66.4%).

3-(Methyl,*p*-toluenesulfonate)-2-(*t*-butylthiomethyl)pyridine **56**

TEA (0.32g;3.1mmol) and *p*-toluenesulfonylchloride (0.60g;3.1mmol) were added sequentially to a solution of **59** (0.55g;2.6mmol) in CH_2Cl_2 (10mL) at 0°C. The reaction mixture was kept at 0°C overnight, the $HNEt_3^+Cl^-$ salts removed by filtration and the CH_2Cl_2 concentrated to afford 1.04g (>90% yield) of tosylate **56** which was used without further purification in the next step.



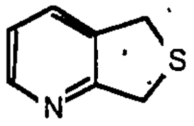
56

^{1}H NMR(CCl_4;60MHz): δ6.72-8.38(m, 7H); δ5.14(s, 2H,C$\underline{H}_2$OTs); δ3.80(s, 2H, C$\underline{H}_2$SCMe$_3$); δ2.42(s, 3H, CH$_3$); δ1.31(s, 9H, C(C$\underline{H}_3$)$_3$).

1,3-Dihydrothieno[3,4-b]pyridine **48**

Method A; cyclization of sulfide **56** via thermal loss of isobutene.

A solution of 3-(methyl-*p*-toluenesulfonate)-2-(*t*-butylthiomethyl)-pyridine **56** (1.04g;2.8mmol) in $MeNO_2$ (50mL) was refluxed overnight. The reaction mixture was concentrated and the resulting gummy residue taken up in ether. The organic phase was washed with 4% NaOH (2x10mL), H_2O (2x10mL), brine (10mL), dried and concentrated to give 0.72g of a red oil. Purification by Chromatotron using hexanes/ethyl acetate (7:3) as the eluent afforded 0.28g (73% yield) of cyclic sulfide **48**.

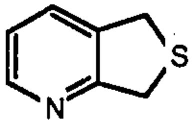


48

^1H NMR($CDCl_3$;300MHz): δ8.42(d, 1H, J=4.82Hz); δ7.55(d, 1H, J=7.80Hz), δ7.11(dd, 1H, J=7.80Hz,4.82Hz); δ4.30(s, 2H, methylene, C-2); δ4.23(s, 2H, methylene, C-1).

Benzothiophene **61**

A solution of *o*-(bromomethyl)benzylbromide **60** (0.60g;2.4mmol), *t*-butylthiol (0.20g;2.4mmol) and TEA (0.24g;2.4mmol) in MeCN (25mL) was refluxed for 2 h. The reaction mixture was extracted with ether (2x20mL) and the combined ethereal extracts washed with H_2O (2x5mL), brine (5mL), dried and concentrated. Following purification by flash chromatography using hexanes/ethyl acetate (1:1) as the eluent, 0.13g (40% yield) of benzothiophene **61** was isolated.



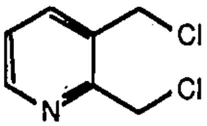
61

^{1}H NMR(CDCl$_3$;60MHz): δ7.00(s, 4H, aromatic); δ4.06(s, 4H, methylene).

M.S(m/z): M$^+$= 136 (68.7%); M$^+$-1=135 (100%).

2,3-Bis(chloromethyl)pyridine **50**

A solution of 2,3-lutidine (10.0g;93mmol), NCS (24.9g;187mmol) and benzoylperoxide (0.30g) was refluxed for 24 h. The reaction mixture was cooled (0°C), succinimide and unreacted NCS removed by filtration. Fresh NCS (9.4g;71mmol) was added and the reaction mixture refluxed for an additional 24 h. The cooled (0°C) reaction mixture was filtered and concentrated. The crude dichloride was purified by HPLC using hexanes/ethyl acetate (5.6:1) as the eluent to afford 2.96g (31% yield) of 2,3-bis(dichloromethyl)pyridine **50**.



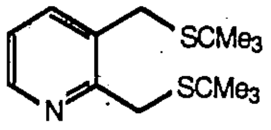
50

The spectroscopic data were identical to the values reported by Klemm *et al* [29].

1,3-Dihydrothieno[3,4-b]pyridine **48**

Method B; *t*-butylthiol 1,4-elimination of chloride and thermal elimination of isobutene:

A solution of 2,3-bis(chloromethyl)pyridine **50** (0.90g;4.7mmol), *t*-butylthiol (0.43g;4.7mmol) and TEA (0.48g;4.7mmol) in MeCN (50mL) was refluxed for 6 h. The reaction mixture was extracted with ether and the combined ethereal extracts washed with H_2O (2x10mL), brine (10mL), dried and concentrated. Following purification by Chromatotron using hexanes/ethyl acetate (6:4) as the eluent, sulfide **48** was obtained in 15% yield with mainly 2,3-bis(*t*-butylthiomethyl)pyridine **62** being formed in a 1:3 ratio respectively.



62

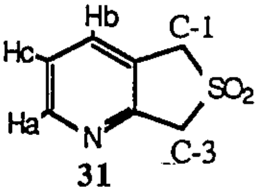
^{1}H NMR($CDCl_3$;60MHz): δ8.30(m, 1H); δ7.58(m, 1H); δ7.01(m, 1H); δ4.00(s, 2H, C$\underline{H}_2$SMe$_3$, methylene, C-2); δ3.85(s, 2H, C$\underline{H}_2$SMe$_3$, methylene, C-3); δ1.35(s, 9H, CH$_2$S(C$\underline{H}_3$)$_3$, C-2); δ1.33(s, 9H, CH$_2$S(C$\underline{H}_3$)$_3$, C-3).

Method C; Na_2S 1,4-elimination of chloride:

1,3-Dihydrothieno[3,4-b]pyridine was obtained in 73% (0.53g) yield by treatment of 2,3-bis(chloromethyl)pyridine **50** (0.97g;5.5mmol) with Na_2S (6.3g;26.3 mmol) in 80% aqueous ethanol as described by Klemm and Johnson[29]. The spectroscopic data were identical with the values reported in method A.

1,3-dihydrothieno[3,4-b]pyridine-2,2-dioxide **31**

A solution of *m*-CPBA (0.79g;3.9mmol;85%) in $CHCl_3$ (30mL) was added dropwise over a period of 15 minutes to a stirred solution of sulfide **48** (0.25g;1.8mmol) in $CHCl_3$ (10mL) at -78°C. The reaction mixture was allowed to warm to R.T. and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% NaOH (2x5mL), the aqueous layer back-extracted with CH_2Cl_2 (3x10mL) and the combined organic extracts concentrated. Purification of the resulting oil by Chromatotron using ethyl acetate as the eluent afforded 0.15g (50% yield) of crystalline sulfone **31** (m.p.:128.5°C; lit[29].:128-129°C).



31

^{1}H NMR($CDCl_3$;300MHz): δ8.57(dd, 1H, J=4.92Hz, 1.10Hz, H_a); δ7.62(dd, 1H, J=7.82Hz, 1.10Hz, H_b); δ7.31(dd, 1H, J=7.84Hz, 4.92Hz, H_c); δ4.49(s, 1H, methylene; C-3); δ4.44(s, 1H, methylene, C-1).

M.S.(m/z): M^+=169 (5.9%); M^+-SO_2=105 (100%)

PART D

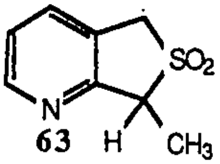
General procedure for the generation of monoanion **31a** and dianion **31c**:

A solution of sulfone **31** in THF was added dropwise to a stirred solution of LDA prepared by the addition of *n*-BuLi to diisopropylamine in THF at -78°C. After addition was complete, the reaction mixture was stirred at -78°C for 15 minutes during which time it turned a olive green color. The reaction mixture was allowed to react with a specific electrophile and stirred at -78°C for 10 minutes, a color change from green to pale yellow was observed in each case. The reaction mixture was allowed to warm to R.T. quenched with H_2O, extracted with ether, the combined ethereal extracts washed with H_2O, brine, dried and concentrated.

3-Methyldihydrothieno[3,4-b]pyridine-2,2-dioxide 63

The sulfone monoanion generated using 1 eq. of LDA was quenched with excess CH_3I. Following workup, the resulting clear yellow oil was purified by Chromatotron using hexanes/ethyl acetate

(1:9) as the eluent to afford in 85% yield, an inseparable 4:1 mixture of 3-methyldihydrothieno[3,4-b]pyridine-2,2-dioxide **63** and 3,3-dimethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **64.**

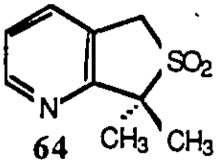


63

^{1}H NMR($CDCl_3$;300MHz): δ8.58(m, 1H); δ7.61(m, 1H), δ7.30(m, 1H); δ4.37-4.31(m, 3H, methine at C-3, and methylene at C-1); δ1.73(d, 3H, J=7.1Hz, CH_3).

M.S.(m/z): M^+=183 (1.1%); M^+-SO_2=119 (75%).

I.R.(film): 2950 (CH); 1575 (C=C,C=N); 1315,1120 (SO_2) cm^{-1}.

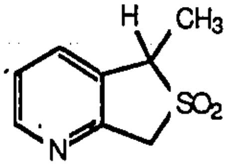


64

The 3,3-dimethyl compound **64** was identified by M.S.(m/z): M^+-SO_2=133 (23.3%); M^+-(SO_2+CH_3)=118 (100%) and by the singlet at δ 1.67ppm(6H, 2CH_3 at C-3) in the ^{1}H NMR of **63**.

1-Mehyldihydrothieno[3,4-b]pyridine-2,2-dioxide 65

The sulfone dianion generated using 2 eq. of LDA was quenched with 1 eq. of CH_3I. Following workup and purification by Chromatotron using hexanes/ethyl acetate (1:9) as the eluent, crystalline 1-methyldihydrothieno[3,4-b]pyridine-2,2-dioxide 65 was obtained in 76% yield (m.p.: 95°C-97°C).



65

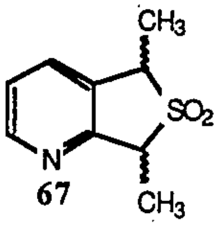
^1H NMR($CDCl_3$;300MHz): δ8.55(dd, 1H, J=4.95Hz, 1.51Hz); δ7.58(dd, 1H, J=7.84Hz, 1.51Hz); δ7.33(dd, 1H, J=7.84Hz, 4.95Hz); δ4.44(s, 1H, methylene, C-3); δ4.43(s, 1H, methylene, C-3) δ4.40(q, 1H, J=7.1Hz, methine, C-1); δ1.68(d, 3H, J=7.1Hz, CH_3).

M.S.(m/z): M^+-SO_2=119 (100%); M.S.(C.I.): M^++1=184 (67.3%).

I.R.($CHCl_3$): 2950 (CH); 1575 (C=C,C=N);1325,1130 (SO_2).

1,3-Dimethyldihydrothieno[3,4-b]pyridine-2,2-dioxide 67

The sulfone dianion generated using 2 eq. of LDA was quenched with excess CH_3I. Following workup, purification by Chromatotron using hexanes/ethyl acetate (2:8) as the eluent afforded 1,3-dimethylhydrothieno[3,4-b]pyridine-2,2-dioxide **67** in 85% yield as a mixture of diastereoisomers.



67

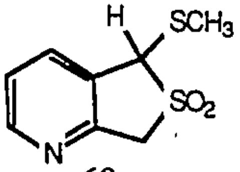
^{1}H NMR(CDCl$_3$;300MHz): δ8.57-8.55(m,1H), δ7.57-7.54(m,1H); δ7.34-7.27(m,1H); δ4.36-4.27(m,2H,methine,C-1 and C-3); δ1.77-1.64(m,6H,CH$_3$ at C-1 and CH$_3$ at C-3).

M.S.(m/z): M$^+$-SO$_2$=133 (58.7%); M$^+$-(SO$_2$+1)=132 (100%); + some trimethylated material i.e. M$^+$-SO$_2$=147 (88.4%); M$^+$-(SO$_2$+1)=146 (100%).

I.R.(film): 2950 (CH); 1570 (C=C,C=N); 1310,1130 (SO$_2$) cm^{-1}.

1-Thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **68**

The sulfone dianion generated using 2 eq. of LDA was quenched with 1 eq. of methyldisulfide. Following workup, purification using hexanes/ethyl acetate(8:2) afforded 1-thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide **69** in 68% yield.



68

^{1}H NMR(CDCl$_3$;300MHz): δ8.59(dd, 1H, J=4.96Hz, 0.89Hz); δ7.77(dd, 1H, J=7.82Hz, 0.89Hz); δ7.37(dd, 1H, J=7.82Hz, 4.96Hz); δ5.18(s, 1H, methine, C-1); δ4.53,4.42(AB quartet, 2H, J=16.6Hz, methylene, C-3); δ2.32(s, 3H, SCH$_3$).

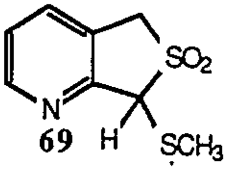
M.S.(C.I.): M$^+$+1=216 (81.7%); M$^+$+1-SO$_2$=152 (100%);

Exact mass (M$^+$-SO$_2$); calculated: 151.0454; found: 151.0417

I.R.(film): 2950 (CH); 1575 (C=C,C=N); 1325,1130 (SO$_2$); 725 (C-S) cm^{-1}.

3-Thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide 69

The sulfone monoanion generated using 1 eq. of LDA was quenched with 1 eq. of dimethyldisulfide. Following workup, purification by Chromatotron using hexanes/ethyl acetate (8:2) afforded an inseparable 1:1 mixture of 1-thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide 68 and 3-thiomethyldihydrothieno[3,4-b]pyridine-2,2-dioxide 69 in 66% yield.



69

^{1}H NMR(CDCl$_3$;300MHz): δ8.65(dd, 1H, J=4.83Hz, 0.68Hz); δ7.64(dd, 1H, J=7.35Hz, 0.68Hz); δ7.34(dd, 1H, J=7.35Hz, 4.83Hz);

δ5.17(s, 1H, methine, C-3); δ4.50,4.35(AB quartet, 2H, J=15.7Hz, methylene, C-1) δ2.37(s, 3H, SCH_3).

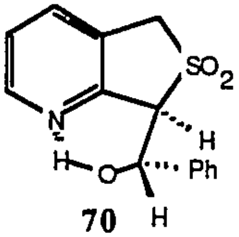
M.S.(C.I.): $M^{+}+1=216$ (100%); $M^{+}+1-SO_2=152$ (96.5%)

Exact mass ($M^{+}-SO_2$); calculated: 151.0454; found: 151.0469

I.R.(film): 2950 (CH); 1570 (C=C,C=N); 1310,1130 (SO_2); 730 (C-S) cm^{-1}.

3-(α-Hydroxybenzyl)dihydrothienopyridine-2,2-dioxide **70**

The sulfone monoanion generated using 1 eq. of LDA was quenched with 1 eq. of benzaldehyde. Following workup, purification by Chromatotron using hexanes/ethyl acetate (4:6) as the eluent afforded crystilline 3-(α-hydroxybenzyl)dihydrothienopyridine-2,2-dioxide **70** in 83% yield (m.p.:142.5°C-144.5°C).



70

threo

1H NMR(CDCl3;300MHz): δ8.56(dd, 1H, J=3.40Hz, 0.87Hz); δ7.68(dd, 1H, J=7.84Hz, 0.87Hz); δ7.50(dd, 1H, J=7.84Hz, 3.40Hz); δ7.43-7.30(m, 5H, phenyl); δ5.65(d, 1H, J=2.22Hz, OH); δ5.48(dd, H, J=7.63Hz, 2.22Hz,C<u>H</u>(OH)Ph); δ4.54(d, 1H, J=7.63Hz, methine, C-3); δ4.29(dd, 2H,J=15.8Hz, methylene, C-1).

M.S.(C.I.): M^++1=276 (53%); M^++1-H_2O=258 (45%);M^++1-SO_2=212 (13%); M^++1-(H_2O+SO_2)=194 (42%); M^++1-[CH(OH)Ph]=170 (100%).

I.R.($CHCl_3$): 3350 (OH,b); 1575 (C=C,C=N); 1325,1135 (SO_2); 700 (mono subs. benzene) cm^{-1}.

Reaction of the dianion **31c** with benzaldehyde

The sulfone dianion generated using 1 eq. of LDA was quenched with 1 eq. of benzaldehyde. Following workup, purification by Chromatotron afforded a mixture of compounds corresponding to a 1:1 adduct between benzaldehyde and the sulfone **31** (in 80% yield) as shown by the C.I.-M.S.:

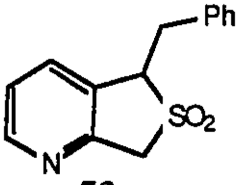
M.S.(C.I.): M^++1=276 (100%); M^++1-H_2O=256 (26%); M^++1-SO_2=212 (18%);M^++1-(SO_2+H_2O)=194 (46.5%); M^++1-[CH(OH)Ph]=170 (25%).

The ^1H NMR($CDCl_3$;300MHz) showed 2 doublets of doublets at: δ 8.52(J=4.98Hz,1.59Hz) and δ8.48(J=4.94Hz,1.38Hz) integrating to a total of 1H; 2 multiplets at δ7.35 and δ7.20 integrating to a total of 6H; 3 sets of doublets of doublets at δ7.05(J=4.98Hz,7.76Hz) and δ6.98(J=7.98Hz,4.94Hz); δ6.55(J=7.27Hz) and δ6.39(J=8.86Hz); δ5.81(J=7.27Hz,2.31Hz) and δ5.02(1H,J=8.86Hz,2.98Hz) each set integrating to a total of 1H; 2 apparent AB quartets between δ4.65 and δ4.40 integrating to a total of 4H and finally 2 doublets at δ4.07(J=2.98) and δ2.68(J=4.83Hz) integrating to a total of 1H.

I.R.(film): 3350 (OH,b); 1575 (C=C,C=N); 1315,1115 (SO_2); 700 (mono subs. benzene) cm^{-1}.

1-Benzyldihydrothieno[3,4-b]pyridine-2,2-dioxide 73

The sulfone dianion generated using 2 eq. of LDA was quenched with 1 eq. of benzyl bromide. Following workup, purification by Chromatotron using hexanes/ethyl acetate (8:2) as the eluent afforded 1-benzyldihydrothieno[3,4-b]pyridine-2,2-dioxide 73 in 83% yield as a white solid (m.p.:172.4-173.0) as well as 1,1-dibenzyldihydrothieno[3,4-b]pyridine-2,2-dioxide 74 in 19% yield, also a white solid (m.p.:131.0-132.1).



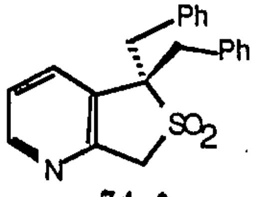
73

^{1}H NMR($CDCl_3$;300MHz): δ8.52(dd, 1H, J=4.80Hz, 1.19Hz); δ7.34-7.00(m, 7H, phenyl+Hb and Hc); δ4.52(dd, 1H, J=9.45Hz, 5.55Hz, methine, C-1); δ4.39,4.38(AB quartet, 2H, J=16.4Hz, methylene, C-3) δ3.65(dd, 1H, J=14.1Hz, 5.55Hz, CH_2Ph); δ3.00(dd, 1H, J=14.1Hz, 9.45Hz, CH_2Ph).

M.S.(C.I.): M^++1=260 (100%); M^++1-SO_2=196 (46.5%),

Exact mass (M^+-SO_2); calculated: 195.1047 found: 195.1017

I.R.(film): 3010(CH,arom.); 1610 (benzene ring,m); 1575 (C=C,C=N); 1315,1145 (SO_2) cm^{-1}.



74

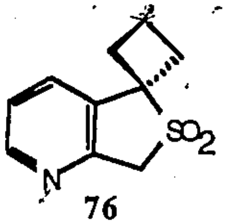
^1H NMR($CDCl_3$;300MHz): δ8.48(dd, 1H, J=4.89Hz, 1.54Hz); δ7.64(dd, 1H, J=7.94Hz, 1.54Hz), δ7.36(dd, 1H, J=7.94Hz, 4.89Hz); δ7.22-7.16(m, 5H, phenyl); δ7.15-7.10(m, 5H, phenyl); δ3.59(s, 2H, methylene, C-3); δ3.48,3.33(AB quartet, 4H, J=14.3Hz, CH_2Ph).

M.S.(C.I.): $M^++1=350$ (100%); $M^++1-SO_2=286$ (24.5%).

I.R.(film): 3010 (CH, arom.); 1610 (benzene ring, m); 1575 (C=C,C=N);1315,1145 (SO_2) cm^{-1}.

Dihydrothieno[3,4-b]pyridine-2,2-dioxide-1-spiro-cyclobutane **76**

The sulfone dianion generated using 2 eq. of LDA was quenched with 1 eq. of 1,3-dibromopropane. Following workup, purification by Chromatotron using hexanes/ethyl acetate (2:8) as the eluent afforded dihydrothieno[3,4-b]pyridine-2,2-dioxide-1-spiro-cyclobutane **76** in 26% yield (m.p.: 121-123°C).



76

^{1}H NMR(CDCl$_3$;300MHz): δ8.53(dd, 1H, J=4.89Hz, 1.44Hz); δ7.84(dd, 1H, J=7.86Hz, 1.44Hz); δ7.37(dd, 1H, J=7.86Hz, 4.89Hz); δ4.37(s, 2H, methylene,C-3); δ3.19-3.10(m, 2H, CH$_2$); δ2.41-2.26(m, 2H, CH$_2$); δ2.25-2.20(m, 2H, CH$_2$).

M.S.(C.I.): M$^+$+1=210 (100%); M$^+$+1-SO$_2$=146 (70.3%)

Exact mass (M$^+$-SO$_2$); calculated: 145.0891; found: 145.0833

I.R.(CHCl$_3$): 3000 (CH); 2875 (CH$_2$,cyclobutane,w); 1575 (C=C,C=N); 1320,1140 (SO$_2$) cm^{-1}.

Attempted synthesis of 1-hydroxydihydrothieno[3,4-b]pyridine-2,2-dioxide 15

The sulfone dianion generated using 2 eq. of LDA was quenched with 1 eq. of MoOPH. Following workup, 0.05g of a yellow oil was isolated. The ^{1}H NMR showed absorption signals consistent with HMPA. There was no evidence for the formation of sulfone 15.

PART E

Pyrolysis experiments

All flash vacuum pyrolysis experiments were carried out in an apparatus designed by Dr. David Smith of the University of Leicester. The apparatus consisted of a bulb to bulb heater, a furnace and a dry ice-acetone trap as reproduced in figure 9 (p79). The pressure was about 1.0mm for all run, but decreased to 0.25mm as the material passed through the furnace into the trap. The time taken to pass through the furnace varied between 5 and 15 minutes. When the temperature of the furnace was 300°C or lower, only starting material was recovered, whereas at 400°C small amounts of sulfone 31 remained, accompanied by an inseparable mixture of products. At 500°C, an inseparable mixture of products was again formed. The ^1H NMR indicated the absence of the desired product at any of the temperatures utilized. At higher volatilization temperatures, only a dark yellow-black material was collected on the trap. This consisted of an inseparable series of compounds.

CLAIMS TO ORIGINAL RESEARCH

1- The preparation of 2-methyl 3-pyridine carboxaldehyde **18** is reported and its photolysis in the presence of SO_2 and diethylfumarate was attempted.

2- The preparation of 3-(Methyl,*p*-toluenesulfonate)-2-(*t*-butylthiomethyl)pyridine **56** is described. When **56** was heated in the presence of triethylamine, cyclization to 1,3-dihydrothieno[3,4-b]pyridine **48** via loss of isobutene was observed. This represents a new method of generating thiane rings.

3- 1,3-Dihydrothieno[3,4-b]pyridine-2,2-dioxide **31** was converted to both its monoanion and dianion by treatment with 1 and 2 equivalents of LDA respectively. Reaction of the monoanion with electrophiles introduced substitution at the C-3 position whereas reaction of the dianion with 1 equivalent of electrophile introduced substitution at the C-1 position. Reaction of the dianion with 2 equivalents of electrophile and with bis-electrophiles gave 1,3- and 1,1-disubstitution respectively.

4- The parent sulfone **31** and its derivatives were shown to lose SO_2 readily by M.S. However, thermal extrusion seems to be more difficult to achieve than for the corresponding benzene analogs.