SYNTHESIS OF POTENTIAL ANTI-VIRAL AGENTS POSSESSING THE TETRAHYDROPENTAPRISMANE RING SYSTEM

by

HOI-LUN ALLAN TSE

B.Sc.(Hon.), The University of Bradford, 1979

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

May 1982

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of CHEMISTRY

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

Date 10th May, 1982

ABSTRACT

This thesis describes the syntheses of the molecules 11-aza-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,9}$.$0^{5,10}$]decane (28) and 4,5-dimethyl-11-aza-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,9}$.$0^{5,10}$]decane (29). Owing to their structural similarities to 1-aminoadamantane (an anti-viral and anti-Parkinson's disease agent), they might possess activities against influenza viruses and/or Parkinson' disease. The key intermediates involved were the two cage ketols namely, 10-exo-hydroxytetracyclo-[5.3.0.$0^{2,6}$.$0^{4,9}$]decan-3-one (33a) and 6,7-dimethyl-10-exo-hydroxytetracyclo[5.3.0.$0^{2,6}$.$0^{4,9}$]decan-3-one (33b) which were prepared via a three-step sequence starting from p-benzoquinone , 1,3-butadiene and 2,3-dimethyl-1,3-butadiene respectively. The incorporation of the required nitrogen atoms was done by transforming the ketone groups of compound 33a and 33b into the corresponding oxime and oxime ether. Generation of the amine functional groups and building of the nitrogen bridges were achieved in a single step by reduction of the oxime derivatives employing aluminium hydride as the reducing agent. The syntheses of compound (28) and (29) were therefore accomplished via a five-step reaction sequence (scheme III) starting from p-benzonquinone and the corresponding butadienes.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

ACKNOWLEDGEMENT

I wish to express my deep gratitude to Dr. J. R. Scheffer and Dr. E. Piers for their advice, support and encouragement throughout the course of this work.

I would like to thank Dr. A. Cheung, Dr. L. Lau and Mr. H. Wong for their assistance during the preparation of the manuscript of this thesis.

Thanks are also due to the technical staff of the Department of Chemistry for their service.

Finally, I wish to thank Dr. S. Sacks of the U.B.C. Faculty of Medicine for performing the biological testing.

The financial support from the University of British Columbia in the form of a Teaching Assistantship is gratefully acknowledged.

Introduction

A. Background

Viruses constitute an exceedingly interesting example of nucleoprotein complexes with a defined function. They are capable of dormant existence and replication only inside the cells of their hosts (which, depending on virus species, may be bacteria, plants or animals), fashioning and controlling the host's metabolism to their own purposes. In their ability to reproduce their own kind, to be capable of mutation and to exchange genetic material provided by more than one parent, they exhibit the most salient characteristics of living organisms. Yet they can be isolated in a pure form and treated as distinct chemical entities. Ever since W.M. Stanley's isolation of tobacco mosaic virus in 1935[1] by crystallisation and the analysis of its chemical composition which showed that it was composed mostly of protein as well as some nucleic acid, viruses have been the favourite subject of investigation in molecular biology.

In general, viruses can be divided into three categories - bacterial viruses (bacteriophages), animal and plant viruses. There are many similarities between these kinds of viruses. Their basic structure is the same in that all contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) (never both) which is surrounded by a layer, or capsid, of protein. All viruses are chemically simple when compared to cells since they contain few, if any, enzymes and their actual structure is relatively simple.

Although the exact mechanisms of infection by various kinds of viruses are different, the general pattern remains the same. The virus is adsorbed onto the cell membrane of the host cell (in some cases, the whole virus particle is incorporated into the cell), the viral nucleic acid is then released into the cytoplasm. By controlling the host's metabolism, proteins and nucleic acids which are essential for replication are synthesized. Reorganisation of these materials occurs during the late stage of infection and a large number of virus particles are formed; the release of newly formed particles into the environment may or may not be concomitant with host cell disruption.

As demonstrated by Hershey and Chase in 1952[2] by double labelling experiments (^{35}S for protein, ^{32}P for deoxyribonucleic acid), the infective and reproductive part of bacteriophages was the nucleic acid, the external protein coat apparently functioning mainly as a protective coat. It is widely believed that the same is true for animal and plant viruses.

It has been known that quite a number of human diseases are caused by viruses, for example smallpox, measles and some tumors. Fifty to seventy-five per cent of the adult population throughout the world suffers from some form of mucocutaneous lesions produced by herpes viruses[3]. In addition, the same group of viruses is responsible for more serious illness such as herpetic encephalitis and keratoconjunctivitis. The incidence of herpes progenitalis has increased dramatically in recent years and may be considered as one of the most common types of

venereal disease. Although many viral diseases such as the common cold are self-limiting, with a low mortality and high morbidity, they cause much discomfort to the individual and represent millions of lost hours with serious economic repercussions. A drug which would prevent, cure or shorten the duration of these illness would have enormous impact.

A virus is so much simpler in its constitution than a bacterium that many of the points of attack on the latter are just not possible with the former such as the muramic acid type cell wall and the enzymes associated with it. However, the mechanism of viral replication suggests several points of attack for inhibition. An antiviral agent may work directly on the virus particle itself, prevent adsorption onto or incorporation into the host cell, inhibit viral replication or interfere with the synthesis of the protein coat. Since the infective cycle of the virus is so intimately tied up with the host cell's metabolism, it is obvious that any chemotherapeutic agent that would inhibit virus propagation would also inhibit the metabolism of the host cell. Viral chemotherapy, therefore, is a quest for selective toxicity.

In order to cover all the possibilities of influencing a virus infection or its sequelae, the term "antiviral agent" has been defined in very broad terms[4] as "a substance other than a virus, a virus-containing vaccine or specific antibody, which can produce either a protective or therapeutic effect to the clear, detectable advantage of the virus infected host. Any material that can significantly enhance antibody formation,

improve antibody activity, improve non-specific resistance, speed convalescence or depress symptoms would also be considered an antiviral agent despite the fact that such an agent has no direct action on the invasion, synthesis or migration of the virus".

Over the past two decades, antiviral chemotherapy has presented a major challenge to medical science. Although numerous antiviral compounds have been reported from experimental screening programs, only a few have been studied clinically and even fewer have become commercially available drugs. The need for a broad spectrum antiviral agent is pressing. Unlike the development of antibiotics, the possibility of finding a broad spectrum agent such as a "pencillin equivalent" is rather remote. One major reason being the capability of the virus to undergo mutation and produce a new type of virus. It is not uncommon for a virus which is highly susceptible to a drug to become inert to it after being treated for some time. Most currently available drugs or those in clinical trials are effective against only specific viruses and, in some cases, against only one particular strain in a group of viruses. Nevertheless, the search for effective antiviral agents is continuing.

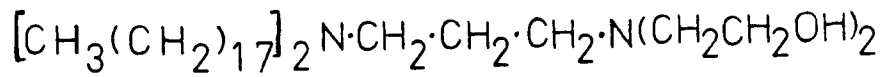
Numerous chemicals have been found to be active towards various kinds of viruses. Some of the more important antiviral agents are described below.

Interferon and Interferon Inducers

Interferon is a low molecular weight protein produced in

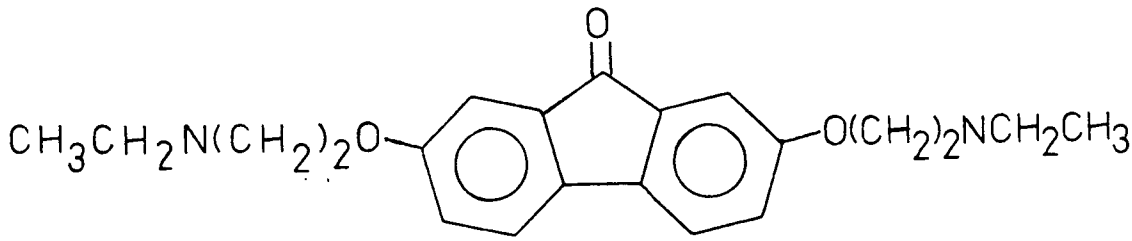
the body as a defense against viral infection. Cellular synthesis of interferon is stimulated by either viral antigen or by a chemical inducer. In terms of combating viral infection, natural body defense mechanisms would be the ideal system. It was shown that interferon was effective in treating rubella infection[5] and herpes zoster[6]. Other preliminary results confirmed the efficacy of interferon as an antiviral agent.

Interferon inducers are chemicals that can induce the production of interferon when incorporated into the cells. The most widely investigated inducer is the poly-inosinic acid poly-cytidylic acid complex (poly I:C) which is a double-stranded polyribonucleotide. The interferon-inducing ability of poly I:C was first demonstrated in cell systems in 1968[7] and was shortly followed by details of its curative effects on a herpes infection of a rabbit's eye[8], and on various virus infections of animals[9]. Poly I:C had been incorporated into a complex with poly-1-lysine and carboxymethyl cellulose[10] and promising results were obtained in monkeys against, among other viruses, yellow fever and rabies[11]. Nevertheless, the high toxicity of poly I:C precluded its use in man other than for topical applications[12-14].



1

Other inducers include N,N-dioctadecyl-N'N'-bis(2-hydroxyethyl)-1,3-propane diamine 1 which provides protection against lethal infections of encephalomyocarditis and Semliki Forest virus and supressed pock formation by vaccinia virus[15]. Chemical studies have further indicated that the drug also provides protection against rhinovirus-induced diseases[16-17].



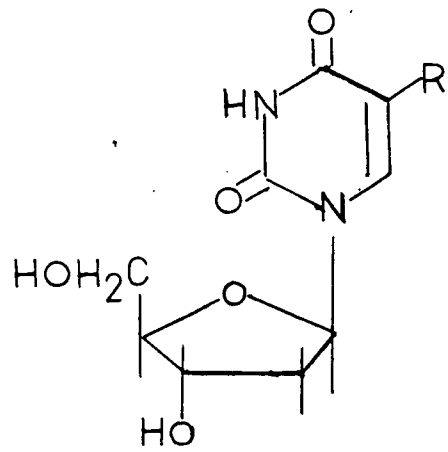
2

2,7-Bis(2-diethylaminoethoxy)-9-fluorenone (tilorone, 2) dihydrochloride was also found to be able to induce high levels of interferon[18-23]. However further studies demonstrated that tilorone failed to elicit detectable interferon in humans and toxicity was observed when the compound was administered either orally or topically. Therefore the drug was deemed unsuitable for clinical trial.

Although experimental data confirm the eligibility of interferon as an antiviral drug, several barriers stand in the way of its application. Interferon is species-specific which therefore limits the source for clinical use. Technologically, at the present state of the art, it is not feasible to produce human interferon on a commercial scale. Finally, the instability of interferon in body fluids requires doses which

are probably well in excess of the effective level.

Purine and Pyrimidine Derivatives



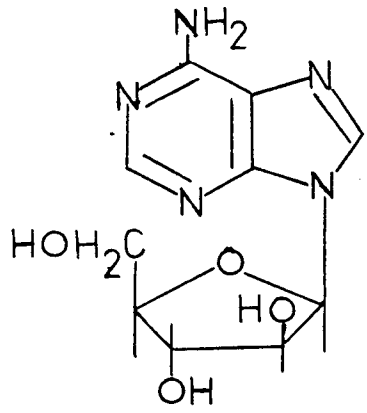
3

A large number of purine and pyrimidine analogues have been synthesized and tested as antiviral agents. The most well known of these is 5-iodo-2'-deoxyuridine 3 (R=I, IDUR). The compound was proved by Herrmann to be a potent viral inhibitor of herpes simplex and vaccinia viruses[24]. Subsequent tests carried out by Kaufman[25] showed that IDUR was highly effective against herpetic corneal infections. Further clinical studies substantiated the efficacy of IDUR against herpes keratitis and currently, it is commercially available for the treatment of this disease. Other studies indicated that when IDUR was applied as a dimethyl sulphoxide solution (topically), the duration of the disease caused by cutaneous herpes was shortened by 63% when compared to untreated placebo controls[26]. It was also reported effective against varicella-zoster (shingles) when applied topically as a 40% dimethyl sulphoxide solution[27].

Numerous IDUR analogues have been synthesized and tested

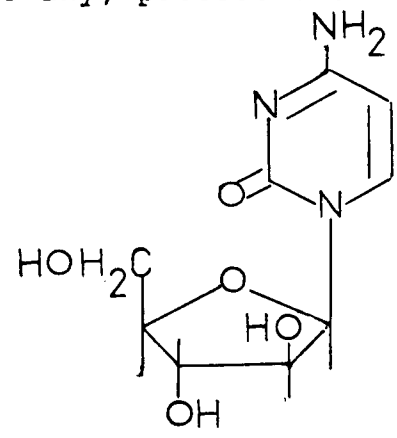
against various DNA viruses, for example the 5-methylamino- (3, R=$NHCH_3$) and 5-trifluoromethyl- (3, R=CF_3) derivatives. 5-Trifluoromethyl-2'-deoxyuridine has been known for quite some time and was found to be more potent than IDUR against herpes keratitis in rabbits. Futhermore, the compound is active against IDUR resistant herpes and is less toxic than IDUR.

Recently two IDUR analogues were synthesized[28] namely the E-5-(2-bromovinyl)- (R=CH:CHBr) and E-5-(2-iodovinyl)- (R=CH:CHI) derivatives. Both showed marked inhibitory effects on the replication of herpes simplex virus type 1. In comparison to IDUR, both compounds were more selective in their antiviral activity and did not affect the growth or metabolism of the host (primary rabbit kidney) cells unless drug concentrations used were 5000- to 10,000-fold greater than required. When tested in nude mice, E-5-(2-bromovinyl)-2'-deoxyuridine was found to suppress the development of herpetic lesions and resulting mortality whether the drug was administered topically or systemically. Under the same conditions, IDUR offered little, if any, protection.



Ara A

4a



Ara C

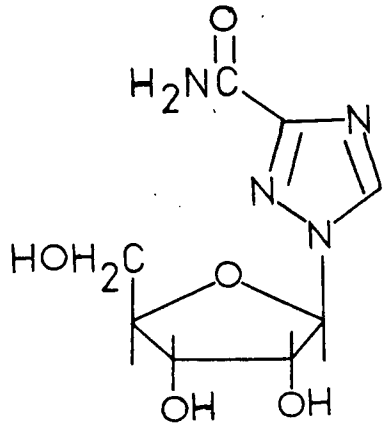
4b

Two other nucleosides have also shown promise as antiviral agents particularly against herpes keratitis - 9-β-D-arabinofuranosyl adenine (Ara-A) 4a and 1-β-D-arabinosyl cystosine (Ara-C) 4b.

Ara-A was found to be active in vitro against herpes simplex and vaccinia viruses[29] as well as cytomegalovirus both in vitro[30] and in vivo[31]. In addition to the broad spectrum of activity in vitro against DNA viruses, activity against herpes keratitis in hamsters and intracerebrally innoculated herpes simplex and vaccinia viruses in mice were also observed[32]. Ara-A has also exhibited activity against herpes keratitis in man[33] and is preferred over IDUR in treating epithelial keratitis due to its lower toxicity. Recently, Ara-A was approved by the Food and Drug Administration (FDA) of the United States for marketing by Warner-Lambert Co.[34] under the name "Vidarabine" and is highly effective in treating herpes simplex encephalitis. Vidarabine was claimed as a true antiviral agent by Warner-Lambert Co., probably due to the fact that the drug interferes directly with viral replication.

Ara-C has a spectrum of antiviral activity similiar to Ara-A. It is active in vitro against DNA viruses such as herpes viruses, varicella-zoster, cytomegaloviruses and vaccinia viruses[35].

Ribavirin 5 (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is not a purine or pyrimidine derivative but due to its similiar chemical structure, is included here for the sake of convenience.

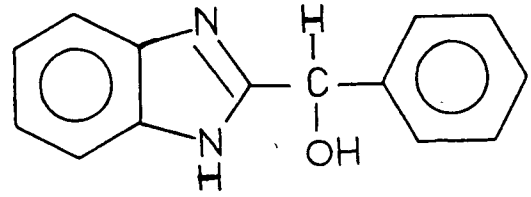


5

Ribavirin is a broad spectrum antiviral agent which was first synthesized by Simon et al. [36] and was found to be effective against both DNA and RNA viruses[37-38]. It has been shown to be a potent agent against herpes infections. The mode of action of ribavirin, according to Jon P. Miller and David G. Streeter of ICN Pharmaceuticals Inc.[39], is inhibition of an enzyme which has an important function in cells infected by herpes viruses, thus interfering with the biosynthesis of viral DNA. Promising results from treatment of herpes zoster (shingles), herpatitis A with ribavirin were obtained in clinical trials. Clinical studies have also substantiated the efficacy of ribavirin against influenza which is a family of RNA viruses. It has been reported that ribavirin specifically inhibits the synthesis of influenza viral protein while having no discernible effects on the host[39]. Ribavirin has been registered under the trade name "Varizole" by ICN Pharmaceuticals Inc. of Irvine, California, and is already being marketed in Mexico for viral respiratory infections and in

Brazil for viral herpatitis.

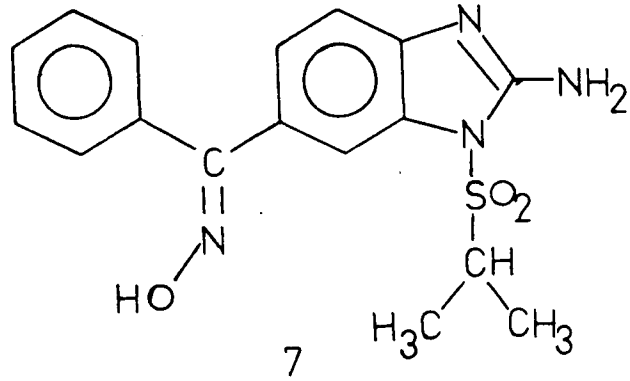
Other Heterocyclic Compound



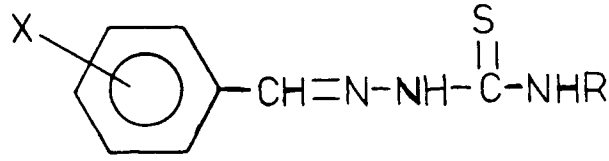
6

Benzimidazoles and thiosemicarbazones are the two most important classes in this group. α-Hydroxybenzylbenzimidazole (HBB) 6 and its derivatives have been extensively studied since they were found to inhibit selectively the replication of several picornaviruses (for example polio and Echo) by interfering with viral RNA synthesis[40]. A large number of HBB analogues were tested for potency against Echo 6 virus with the result that only two passed the stringent tests. These two were HBB itself and 2-(α-methyl-α-hydroxybenzyl)-benzimidazole[41]. Studies of the effect of N-substitution in HBB have shown that these derivatives were highly active against polio viruses in tissue cultures[42] as were N-substituted α-methoxybenzyl-benzimidazoles[43]. The N-propyl derivatives are most reactive in both cases. Enviroxime, 7, is a derivative of benzimidazole recently developed by Lily Research Laboratories[44] and is claimed to be highly potent against the rhinovirus family (which is responsible for the common cold) in vitro. Although enviroxime has not been tested clinically , it

has been shown to be effective against more than 60 types of rhinoviruses when tested <u>in vitro</u> using mostly human cell cultures including cells derived from the human trachea.



7



<u>8a</u> X=H , R=H

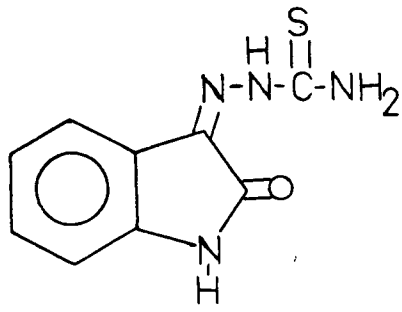
<u>8b</u> X=p-CH_3CONH , R=H

<u>8c</u> X=H , R=$CH(CH_3)C_2H_5$

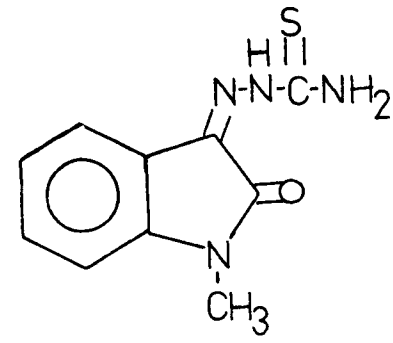
<u>8d</u> X=p-CH_3CONH , R=$CH(CH_3)C_2H_5$

The initial discovery that thiosemicarbazones possessed antiviral activity was made by Hamre[45-47] who observed a dramatic effect on mortality when benzaldehyde thiosemicarbazone <u>8a</u>, the p-acetamide homologue <u>8b</u> and their N-isobutyl homologues <u>8c</u> and <u>8d</u> were administered to mice innoculated intranasally with vaccinia viruses. This development ultimately led to a study of other thiosemicarbazones by Thompson et al.[48] who

observed a positive effect against vaccinia viruses with isatin β-thiosemicarbazones 9.



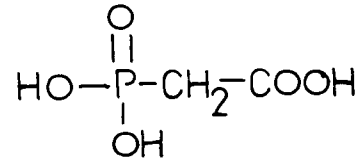
9



10

Further studies carried out by Bauer led to the discovery of N-methylisatin β-thiosemicarbazone (Methisazone) 10 which was found effective against both DNA and some RNA viruses[49] *in vivo* and *in vitro*. These included polio virus, certain rhinoviruses, some arboviruses and influenza A and B. Clinically the use of the drug has been confined to DNA viruses where it has shown a prophylactic effect against smallpox[50].

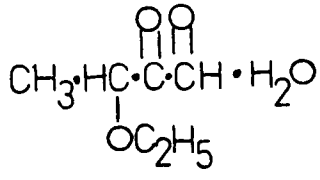
Aliphatic Compounds



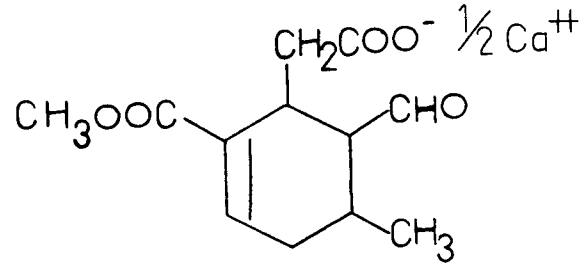
11

Phosphonoacetic acid 11 has been known for over 50 years and was studied by Lacy R. Overby and his associates at Abbott Laboratories in Chicago. It was found to be highly

active against herpes simplex 1 and 2 when screened *in vitro*[51]. *In vivo* studies on corneal herpes simplex virus infections in rabbits showed that 5% phosphonoacetic acid prepared as the sodium salt suppressed herpes keratitis in laboratory animals[52]. It has also been found effective in mice against virus infections of the central nervous system when administered by intraperitoneal injection[53]. Like "Vidarabine", phosphonoacetic acid inhibits the herpes-specific DNA polymerase, but it appears to bind at a different site and works through a different mechanism[54-55].



12

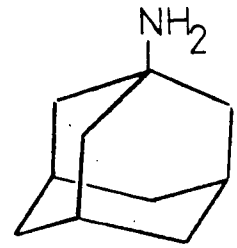


13

Two other compounds have also attracted attention, namely 3-ethoxy-2-oxobutanal hydrate (Kethoxal) 12 and calcium elenoate 13. Kethoxal has been known since 1957 as a virucidal agent for a wide variety of DNA and RNA viruses. It has been found active in tissue cultures against Cocksackie A 21 virus and also has shown activity in hamsters infected with parainfluenza 3 virus intranasally and treated intranasally[56]. Calcium elenolate is also a wide spectrum extracellular virus inactivator. The free acid can be obtained from extracts of olive plants. The salt 13 has a low minimal effective concentration when treated intranasally in hamsters infected with parainfluenza 3 and

showed no toxic effects[57-59].

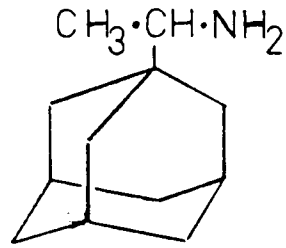
Alicyclic Compounds



14

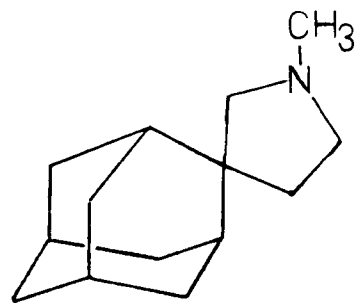
Adamantane derivatives are the most extensively studied class of antiviral compounds in this group and perhaps the most thoroughly studied antiviral agents. The discovery of the antiviral activity of 1-aminoadamantane (Amantadine) 14 against certain strains of influenza virus and its lack of toxicity[60-61] led to quite early clinical studies[62]. Amantadine is particularly active against the A 2 strain of influenza virus, less effective against the C strain and ineffective against the B strain. In man, the efficacy of amantadine was demonstrated in controlled clinical trials and shown to be most effective when administered prophylactically at the time of infection or in the early phase of the disease. Therapeutically, it was reported to shorten the course of the disease, reduce severity of clinical symptoms and shorten the duration of fever. This drug is currently sold in its hydrochloride form under the name "Symmetrel" by Endo Laboratories. While not yet approved for use in the United States, the drug is widely used in Europe and the Soviet Union. Detailed studies on the mode of action of the drug indicated that adsorption of virus onto the cell surfaces

was apparently unaffected but that penetration of the virus nucleic acid was blocked[63-64].



15

Rimantadine 15, a homologue of amantadine, in addition to being more effective in vitro against influenza A 2, was also reported to inhibit other RNA viruses such as rubella, rubeola, respiratory syncytial and parainfluenza viruses in vitro[65].



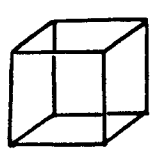
16

A number of 2-substituted adamantanes have recently been claimed as antiviral agents. The most outstanding one is the spiro compound 16 which was claimed to be three times more active in vivo against influenza A 2 Japan and A 2 Hong Kong than amantadine[66]. A broader spectrum of activity was also observed which included activity against Cocksackie A 21 and rhino 2 viruses.

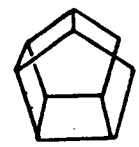
Besides the aforementioned compounds, almost every conceivable variation on nitrogen-containing adamantane derivatives has been claimed in the patent literatures to have antiviral activity against influenza strains and related RNA viruses. Occasionally DNA viruses were also included in the spectrum of activity.

B. Synthetic Strategy

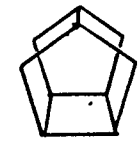
The discovery of the antiviral and, perhaps more importantly, the anti-Parkinson's disease properties of Amantadine[39] has stimulated intensive research in the synthesis and biological testing of other potential antiviral and anti-Parkinson's disease agents related to it. In obvious analogy to the main structural features found in Symmetrel, most research has centered on polycyclic so-called "cage" organic compounds with pendant nitrogen-containing side chains[4,67]. The amino and alkylamino derivatives of almost every tri-, tetra- and pentacyclic octane, nonane, decane and undecane have been synthesized and claimed in the patent literature to possess activity against influenza virus[4]. One example is the synthesis of tricyclo[4.4.0.0^{3,8}]decan-1-ylamine 17 and α-methyltricyclo-[4.4.0.0^{3,8}]decan-1-methylamine 18 by Deslongchamps and co-workers[68-69] as illustrated in scheme I. Other symmetrical polycyclic ring skeletons which have been investigated with a view towards antiviral activity include 19 (cubane), pentacyclo-[6.2.0.0^{2,7}.0^{4,10}.0^{5,9}]decane 20, tetracyclo[5.3.0.0^{2,6}.0^{4,9}]-decane 21 and tricyclo[3.3.0.0^{3,7}]octane 22 to name a few.



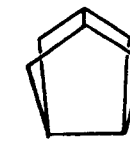
19



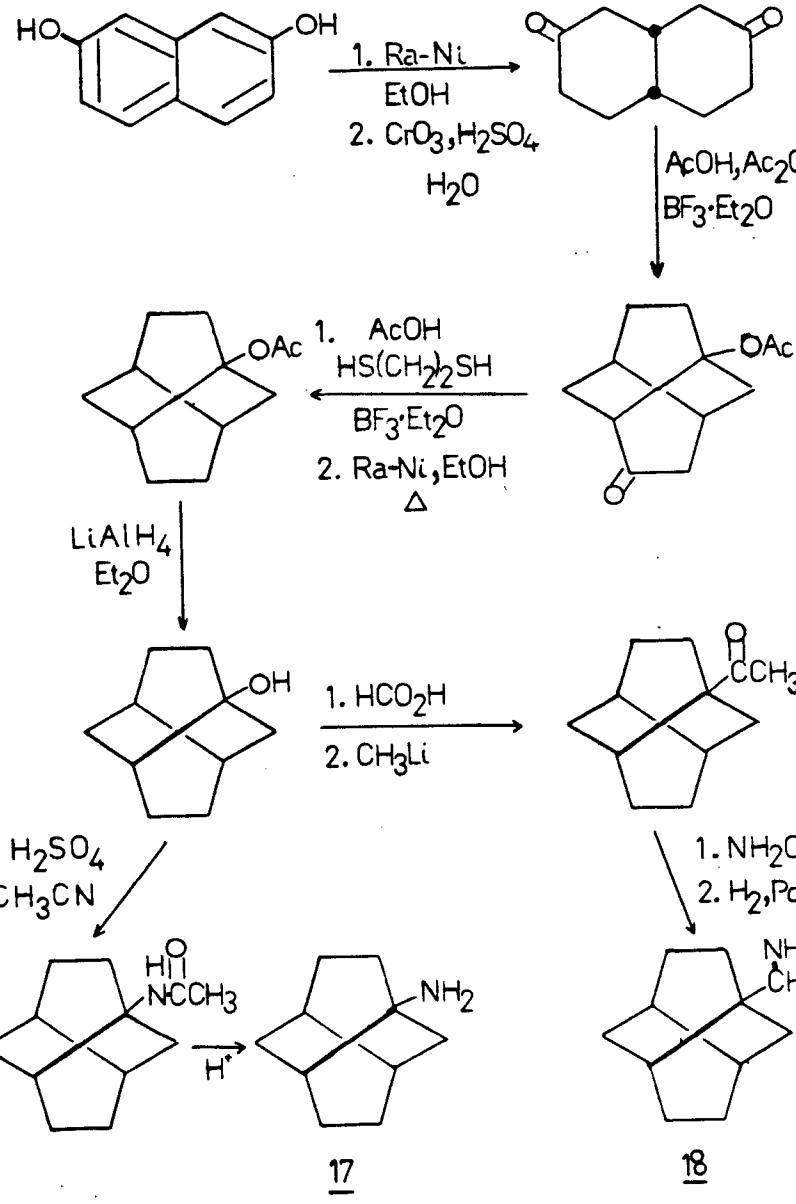
20



21



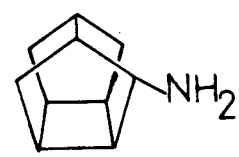
22



SCHEME I

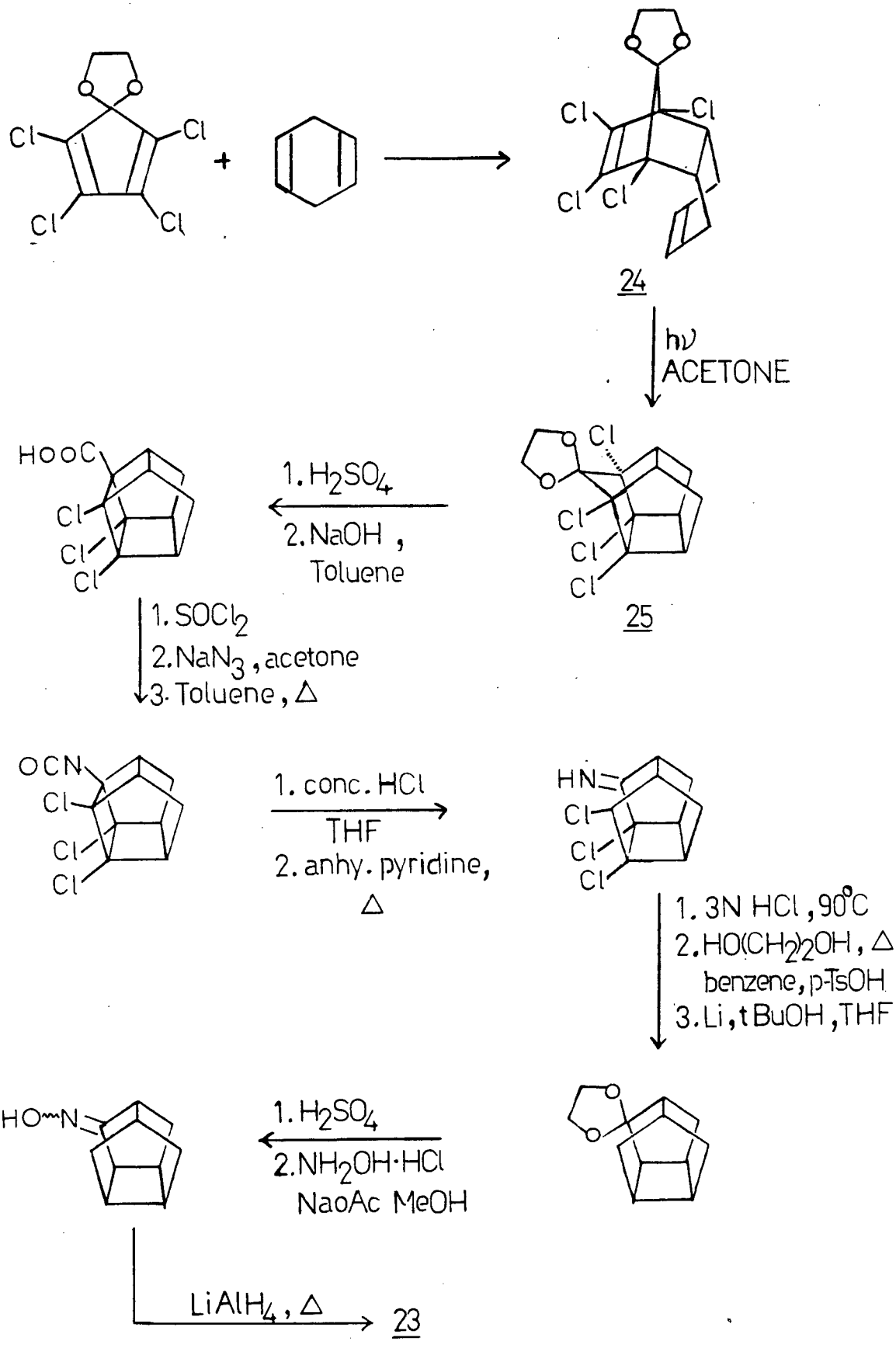
As can be imagined, the syntheses of nitrogen-substituted derivatives of these and other complex polycyclic systems is not a simple task; arduous multistep procedures are often required which severely limit both the amount and variety of compounds which can be produced. In contrast, one major reason for the extensive interest in adamantane-based antiviral agents has been their ready synthetic availability. Facile general synthetic routes to other cage compounds would enable further studies of their properties as antiviral and anti-Parkinson's agents.

During the course of studying the photochemistry of reduced napthoquinones and their derivatives, Scheffer and co-workers[70] discovered a new and remarkably facile general entry into the tetrahydropentaprismane (tetracyclo[5.3.0.$0^{2,6}$.$0^{4,9}$]decane) ring system. This synthetic route allows numerous substituent variations in the compounds produced and in addition will permit the synthesis of relative large amount of materials. However, before turning into the details of the procedure, it is appropriate to discuss previous patented work on the tetrahydropentaprismane system.



23

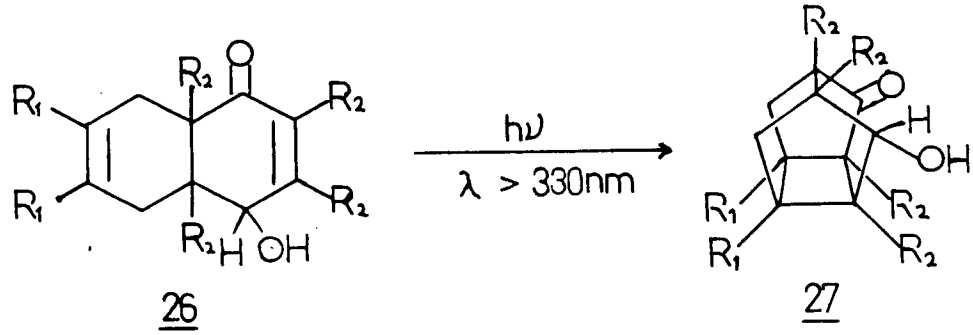
R. J. Stedman at Smith Kline and French Laboratories has described the synthesis of compound 23 as well as a number of related derivatives[71]. The synthetic sequence to 23 involves 15


Cl
Cl
Cl
Cl
+
Cl
Cl
Cl
Cl
24
hν
ACETONE
HOOC
Cl
Cl
Cl
1. H2SO4
2. NaOH ,
Toluene
Cl
Cl
Cl
Cl
25
1. SOCl2
2. NaN3 , acetone
3. Toluene , Δ
OCN
Cl
Cl
Cl
1. conc. HCl
THF
2. anhy. pyridine,
Δ
HN
Cl
Cl
Cl
1. 3N HCl , 90°C
2. HO(CH2)2OH , Δ
benzene, p-TsOH
3. Li, tBuOH , THF
HO
N
1. H2SO4
2. NH2OH·HCl
NaoAc MeOH
LiAlH4 , Δ
23

SCHEME II

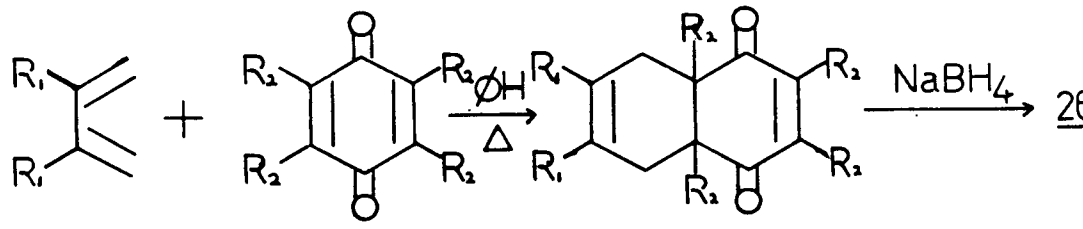
steps of which the key cage compound forming reaction is the photoconversion of 24 to 25 (scheme II). In addition to being synthetically long, the pathway offers little opportunity for substituent variation; furthermore, the starting materials are expensive and not readily available (1,4-cyclohexadiene and tetrachlorocyclopentadiene ethylene ketal).

Scheffer's approach to the tetrahydropentaprismane system also involves a photochemical step, namely the intramolecular [2+2] photocyclisation of 26 leading to 27 (equation 1). A



26 27 (1)

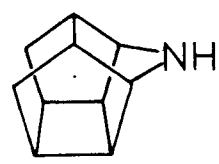
number of differently substituted compounds of the general structure 27 have been successfully synthesized and in all cases the yield is good to excellent. These include 27a (R_1=R_2=CH_3); 27b (R_1=H, R_2=CH_3); 27c (R_1=R_2=H); 27d (R_1=CH_3, R_2=H). The



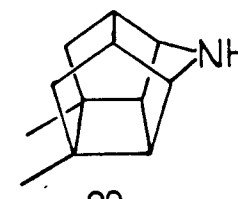
26 (2)

corresponding adducts 26a-d are readily prepared via the two step sequence shown above (equation 2). Both reactions leading to 26 are well known and are easily performed. In addition, a large number of 1,3-dienes and quinones are either commercially available or readily synthesized, thus highly functionalised tetrahydropentaprismanes can be prepared readily.

The objective of this project is to synthesize the molecules 11-aza-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane 28 and its dimethyl analogue 4,5-dimethyl-11-aza-pentacyclo-[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane 29. Owing to their structural

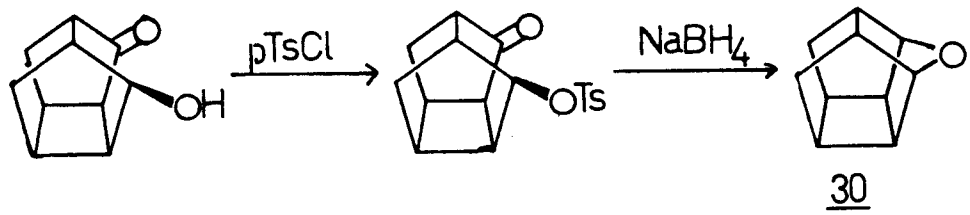


28



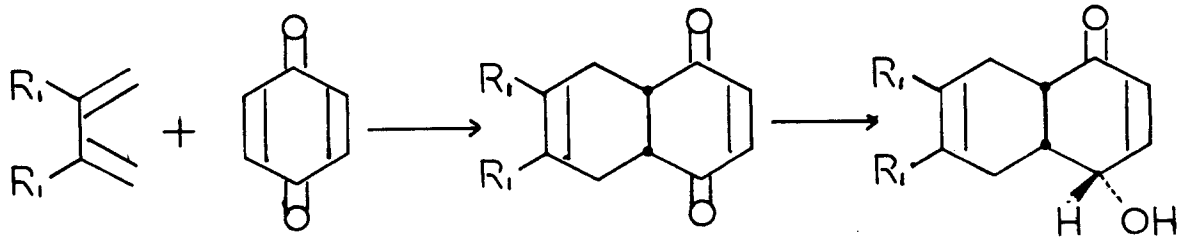
29

similarities to 1-aminoadamantane, these compounds might possess activity against influenza viruses and/or Parkinson's disease. The synthetic strategy involved in the synthesis of these two compounds is based on two key processes: (1) Exploitation of the three-step entry to the tetrahydropentaprismane skeleton, and (2) building the heteroatom bridge by transannular cyclisation. The transannular cyclisation methodology has been ultilised successfully for the synthesis of the bridged ether (11-oxa-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane) 30 by Scheffer and co-workers[70] as depicted by equation 3. The synthetic plans designed for amines 28 and 29 are shown in scheme III.



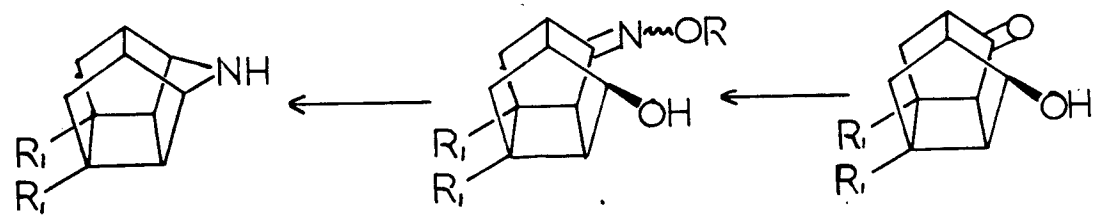
(3)

30



31a R_1=H
31b R_1=CH_3

32a R_1=H
32b R_1=CH_3



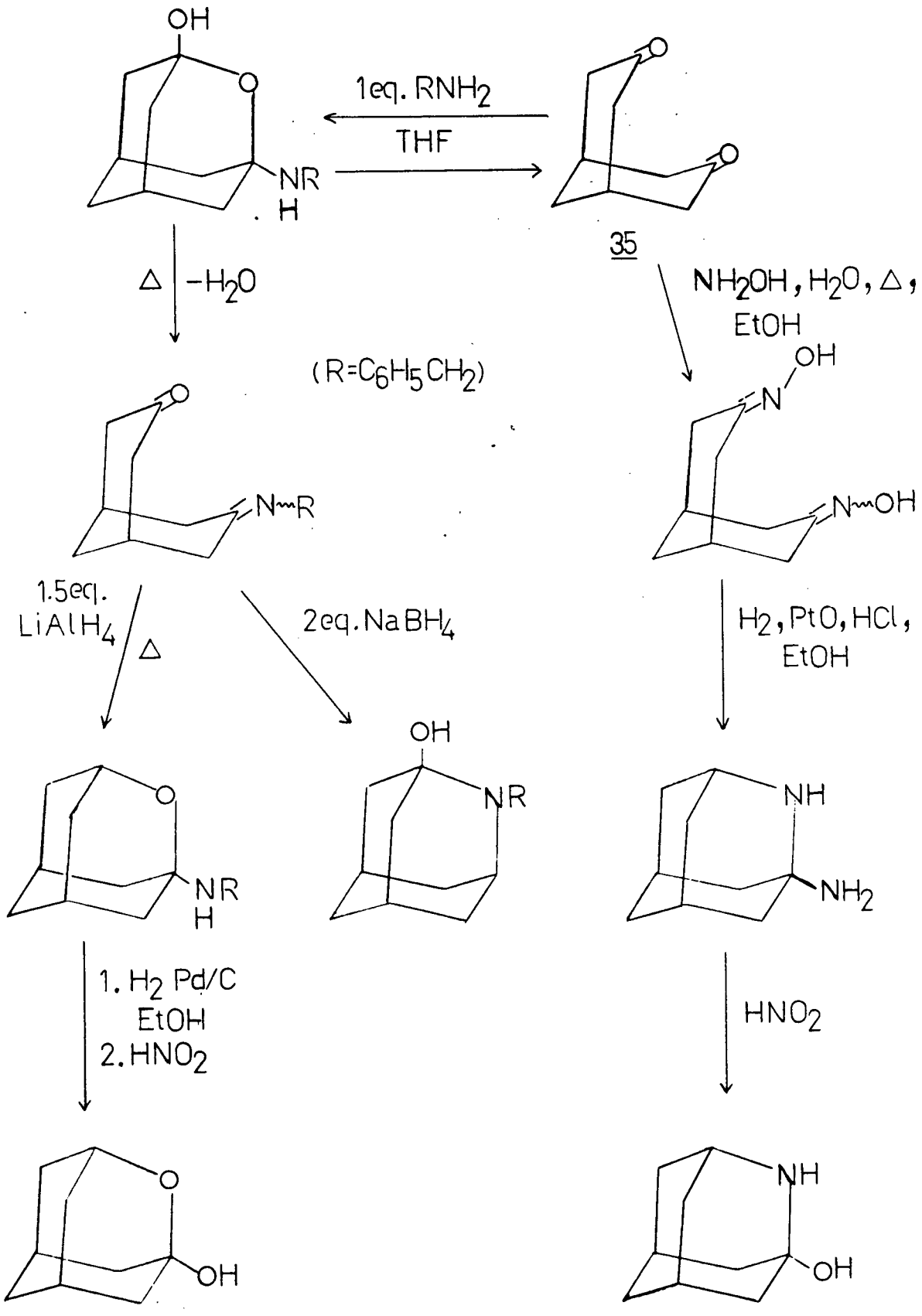
28 R_1=H
29 R_1=CH_3

34a R_1=H, R=H
34b R_1=CH_3, R=CH_3

33a R_1=H
33b R_1=CH_3

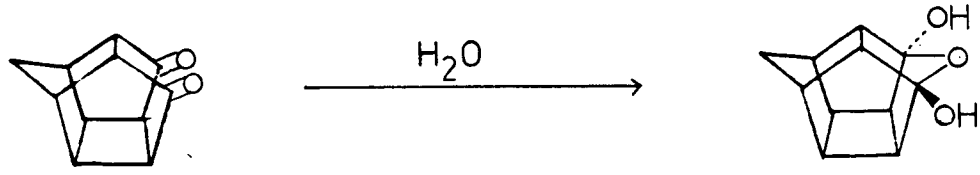
SCHEME III

Transannular cyclisations of appropriately functionalised molecules often provide a convenient method for preparation of


OH
1eq. RNH2
THF
NR
H
35
Δ
-H2O
NH2OH, H2O, Δ,
EtOH
(R=C6H5CH2)
OH
N
N~R
N~OH
1.5eq.
LiAlH4
Δ
2eq. NaBH4
H2, PtO, HCl,
EtOH
OH
NR
NH
NH2
1. H2 Pd/C
EtOH
2. HNO2
HNO2
O
OH
NH
OH

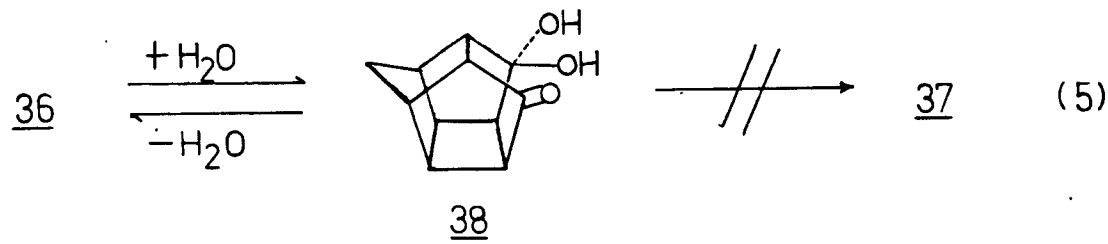
SCHEME IV

heterocage compounds which are otherwise difficult to obtain. A well known example is the synthesis of 1-substituted 2-heteroadamantanes using bicyclo[3.3.1]nona-3,7-dione 35 as starting material[72]. Both the oxygen and nitrogen bridged compounds are obtained in good yield and only a few steps are involved (scheme IV). This example fully demonstrated the versatility of the methodology in constructing heterocage compounds. Another example from the literature, which is more related to the syntheses of compounds 28 and 29, is the preparation of hetero-birdcage compounds such as 37 from pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]undecan-3,6-dione 36[73,74]. The transannular cyclisation of diketone 36 was first reported by Cookson and co-workers[75]. They reported that cyclic hydrate 37 was formed slowly when 36 was exposed to atmospheric moisture (equation 4). In contrast, Sasaki and co-workers found that



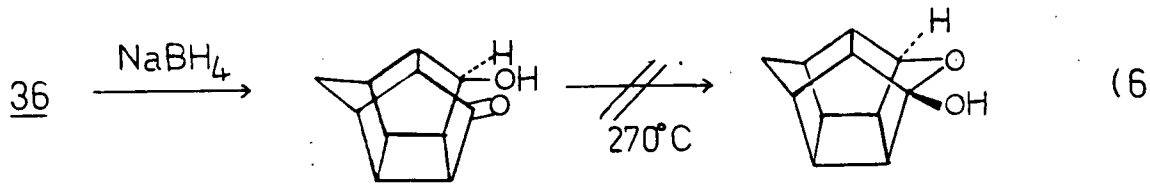
36 37 (4)

even after heating compound 36 in aqueous ethyl acetate at 60°C for three days, the cyclic hydrate could not be isolated. Instead the monohydrate 38 was obtained. Heating compound 38 at 180°C reconverted it to the dione 36 with loss of water, and no trace of the transannular cyclized hydrate could be detected (equation 5)[73]. In addition, the known keto-alcohol 39[75] did



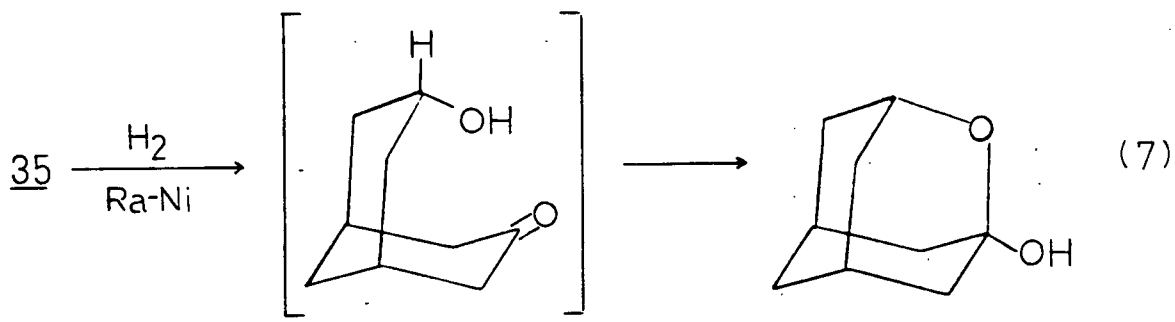
38

not cyclize to the hemi-ketal even on heating at 270°C (equation 6). All these data indicated that the diketone 36 has a lower



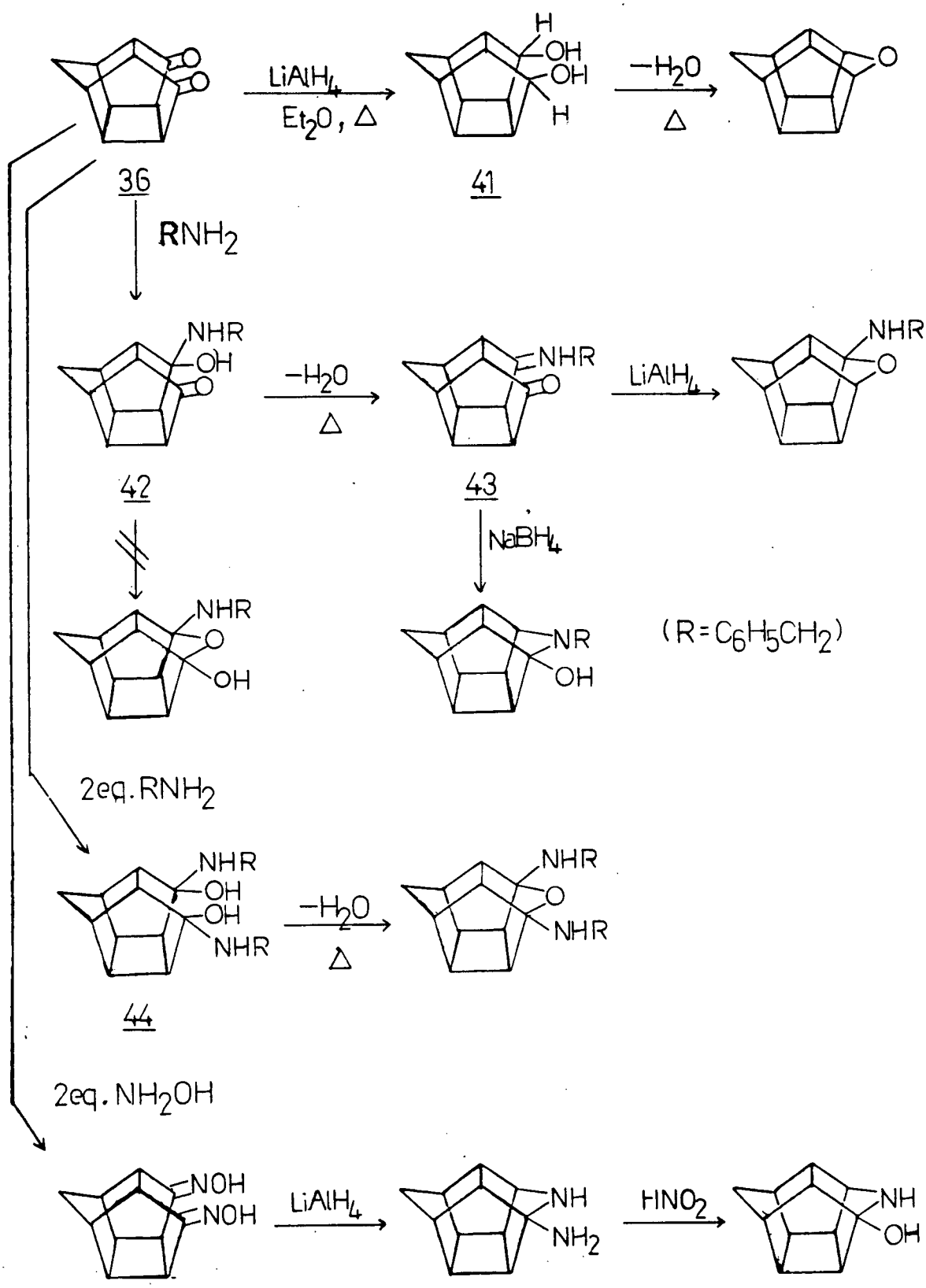
39

transannular cyclisation reactivity as compared with system 35 which is known to afford 1-hydroxy-2-oxa-adamantane on hydrogenation with Raney-Nickel[76], presumably via the intermediacy of the keto-alcohol 40 (equation 7). Other trans-



40

annular cyclisations involving diketone 36 are illustrated in scheme V[73]. An interesting point to note is the selectivities of

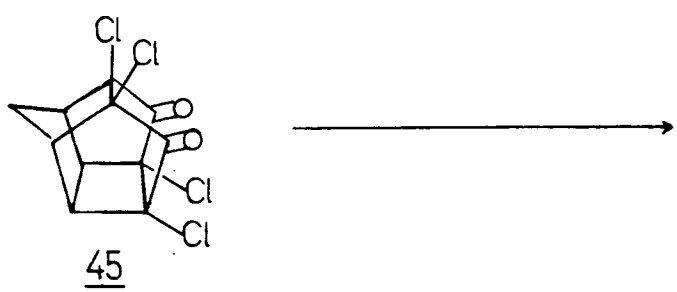

LiAlH4
Et2O, Δ
−H2O
Δ
36
41
RNH2
NHR
OH
−H2O
Δ
LiAlH4
42
43
NaBH4
NR
OH
(R=C6H5CH2)
2eq. RNH2
NHR
OH
OH
NHR
−H2O
Δ
NHR
O
NHR
44
2eq. NH2OH
NOH
NOH
LiAlH4
NH
NH2
HNO2
NH
OH

SCHEME V

43 towards metal hydride reagents. Similar selectivities have also been reported for the bicyclo[3.3.1]nona-3,7-dione 35. The facile dehydration of the glycol type derivatives such as 41 and 44 to the corresponding oxa-bridged products could be rationalised by considering a relief of steric crowding of the two hydroxyl groups which are pointing toward each other.

Summarising the results on transannular cyclisations of dione 36, we can conclude that the transannular cyclisation reactivity of the three position OH group or its metal complex against the six position CO group is very low . The isolation of the ketol 39, the hydrate 38 and monoamine adduct 42 justify this conclusion. On the other hand, very facile cyclisation is well known for the bicyclo[3.3.1]nona-3,7-dione (scheme IV).

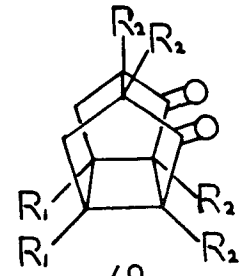
One approach to increase the transannular cyclisation reactivity of 36, as envisaged by Singh[74], in order to prepare the oxa-birdcage compounds via a shorter route, is to activate the carbonyl groups with electron withdrawing groups. As expected, incorporation of electron withdrawing groups onto the diketone 36 rendered it highly susceptible to transannular



45 → 46 R=R'=OH; 47 R=OH R=OC_2H_5; 48 R=R=NHOH (8)

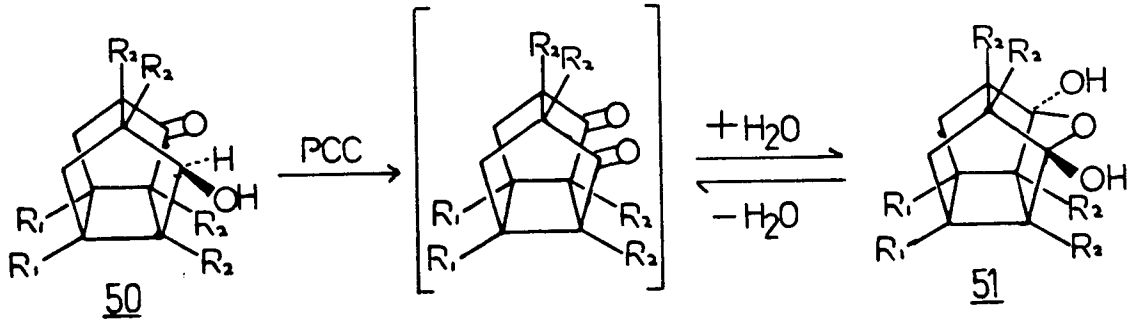
nucleophilic reactions. Thus, tetrachloro cage diketone 45[75] afforded oxa-birdcages 46-48 in excellent yield when refluxed with aqueous 1,4-dioxane, ethanol, and hydroxylamine respectively[74] (equation 8). Moreover , the cyclic hydrate 46 was also obtained when 45 was exposed to atmospheric moisture for a prolonged period.

In contrast to the pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]-undecan-3,6-dione 36, the tetracyclo[5.3.0.$0^{2,6}$.$0^{4,9}$]decan-5,8-dione 49 undergoes extremely facile transannular cyclisations



49

leading to oxa-bridged compounds. As reported by Scheffer and co-workers[70] the diketones 49 (R_1=R_2=H and R_1=CH_3, R_2=H), which are produced by oxidation of the corresponding keto-alcohols 50 (R_1=R_2=H and R_1=CH_3, R_2=H), are extremely sensitive to atmospheric moisture, in fact, the cyclized hydrates 51 (R_1=R_2=H and R_1=CH_3, R_2=H) are the products isolated (equation 9).

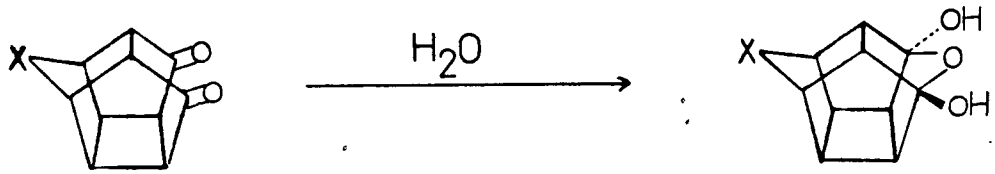


50 PCC → [ ] $\underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}}$ 51 (9)

(PCC=Pyridinium chlorochromate)

Furthermore, tosylation of 50 (R_1=R_2=H) followed by sodium borohydride reduction afforded the cyclic ether (equation 3) in very high yield.

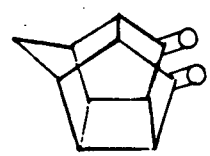
As pointed out earlier by Cookson[75], the formation of the transannular cyclized hydrate of 52 (equation 10) depends to a



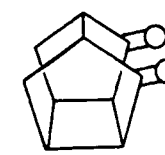
52 (10)

large extent on the distance and angle between the two carbonyl groups. Due to the rigidity of the cage structure, the distance and angle will in turn depend to a certain extent on the size of the bridge X. Cookson has reported that the formation of the cyclic hydrate 52 (X=CH_2CH_2) was a highly facile process as compared with its one carbon-bridged analogue 52 (X=CH_2).

Examination of the models of compounds 36 and 53 reveals



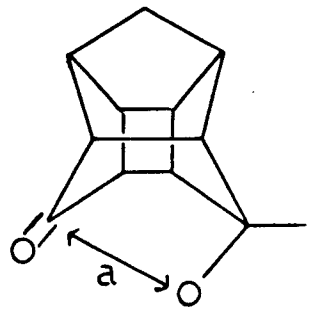
36



53

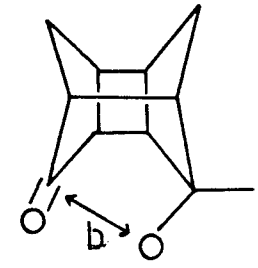
that the one-carbon bridge in 36 causes the other side of the cage to expand, thus the distance and angle between the two carbonyl groups are greater than those of 53. Moreover, the distance between the sp^2 carbonyl carbon atom and the alkoxy oxygen attached to the sp^3 carbon of the intermediate

during cyclisation in 36 is greater than that of 53 which again would lower the cyclisation reactivity of 36.



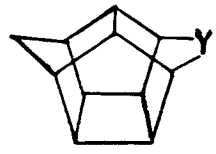
36

a > b

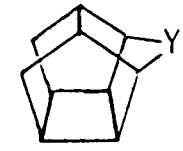


53

Finally, transannular cyclisation of compound 36 would lead to a birdcage molecule of the structure 54 which is highly strained while cyclisation of compound 53 produces a "half-birdcage" molecule 55 which is obviously less strained and therefore more



54



55

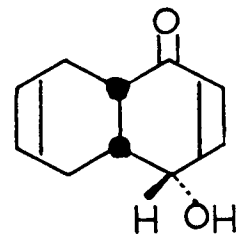
favourable from a thermodynamic point of view.

The above qualitative description provides a satisfactory explanation of the difference in transannular cyclisation reactivity between molecules 36 and 53 and prompts us to ultilise it for the syntheses of compounds 28 and 29.

Results and Discussion

A. Synthesis of 11-Aza-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane

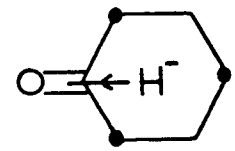
The first intermediate of the synthesis, the tetrahydronapthoquinone 31a, was prepared via the Diels-Alder addition of 1,3-butadiene to p-benzoquinone following the procedure of van Tamelen and co-workers[77] (71%). Compound 31a was found to be relatively unstable. Upon standing at room temperature, it decomposed slowly and changed from yellow needles to greyish white powder. Reduction of 31a using sodium borohydride as the reducing agent afforded the hydroxycyclohexeneone[70] 32a (70%). The stereospecificity of the reduction can be explained by Baldwin's "approach vector analysis" concept[78].



32a

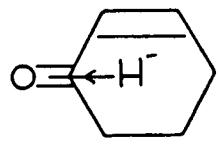
As postulated by Baldwin, during the course of hydride reduction of alicyclic ketones such as cyclohexanone, the hydride reagent would attack the carbonyl group along a plane containing the C-O bond and orthogonal to the plane containing the ketone and its two substituents; the angle between the line of attack of the hydride and the C-O bond is approximated to be 110° based on inversions in the bent or banana bond model of

unsaturation[79]. The projection of the trajectory of the hydride attack is shown as 56. Since the hydride can attack from either



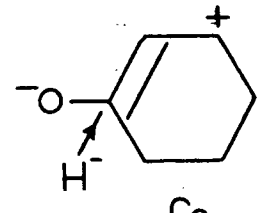
56

the top or bottom face of the molecule, it is evident that axial substituents at both the α and β positions, with respect to the ketonic function, could impede the motion of the hydride reagent on these trajectories. For an α,β-unsaturated ketone such as cyclohexenone, there are two resonance forms. As a result there are two modes of hydride attack as depicted with 57 and 58. The corresponding resultant approach vector is derived by summation of vectors for the two structures 57 and 58 (weights c_1 and c_2) as in 59. Projection 59 shows that approach of the hydride to



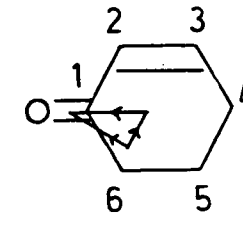
C_1

57



C_2

58



59

the enone carbonyl should be very sensitive to quasi-axial substituents at C(6) and C(5). In Baldwin's analysis of sixteen cases of cyclohexenone reduction[78] this approach vector analysis method leads to excellent agreement with experiments, in that quasi-axial substituents at C(6) and C(5) of 59 appear to

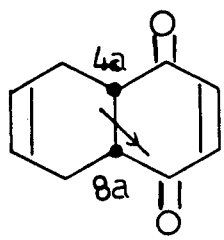
control the stereochemistry of reduction totally, whereas those at C(4) show very little effect. The weightings of substituents, formulated by Baldwin based on their size and proximity to the hydride trajectory, are shown below according to their relative effect.

6 quasi-axial CH_3 > 6 quasi-axial H > 5-quasi-axial H

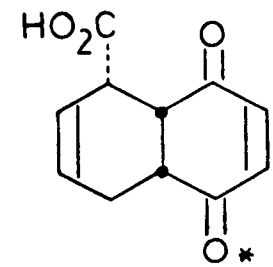
and

5 quasi-axial CH_3 > 6 quasi-axial H.

Examination of models of 31a reveals that both the CH_2 group at C(4a) and the hydrogen at C(8a) occupy the quasi-axial positions. According to Baldwin's rule, the quasi-axial CH_2 at the C(4a) position causes greater impedence to the hydride reagent. As a result, the sodium borohydride attacks the ketonic function from the top face and produces the hydroxycyclohexeneone 32a whose OH group is anti to the bridgehead hydrogens. A similar result for compound 60 was also reported by Baldwin[78] (the ketone marked by an asterik was reduced to the hydroxyl group).



31a

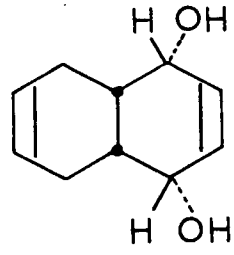


60

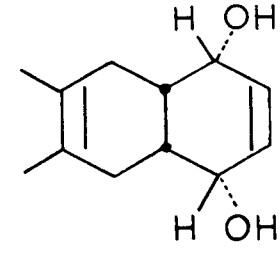
The sodium borohydride reduction of 31a turned out to be a difficult reaction. It was highly sensitive to the purity of the substrate and to a lesser extent, the purity of the solvent

used. Small amounts of impurities (as detected by thin layer chromatography) present in the substrate caused the yield to drop drastically. Attempting to use ethanol instead of methanol as solvent resulted in complete failure of the reaction for unknown reasons. Futhermore, when the scale of the reaction exceeded a certain limit (ca. 2g of napthoquinone), a substantial drop in reaction yield was observed.

Hoping to improve the production of 32a, other reduction methods were explored. Diisobutyl aluminium hydride reduction of 31a carried out at 0°c using benzene as solvent[80] afforded only a small amount of desired product. A substantial amount of a new product was formed instead which was not identified. Reduction of 31a employing sodium borohydride and cerium trichloride[81] gave only minute amounts of 32a. However a new product was produced in good yield (>90%) which was suspected to be compound 61. In fact, this method was later employed to synthesize the cyclohexene diol 62[82]. Reduction of 31a using sodium borohydride as the reducing agent with the presence of ammoniun chloride[83] also did not provide any improvement.



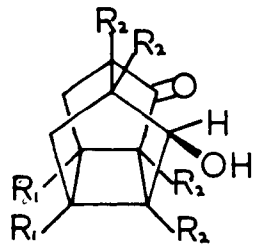
61



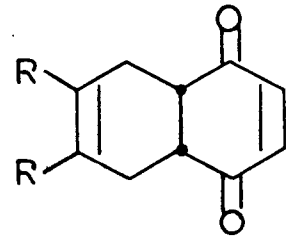
62

After these unsuccessful attempts, we decided to follow the original method.

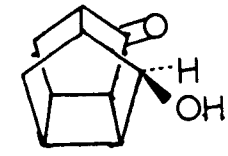
Photolysis of 32a in benzene (λ > 330nm) provided the cage keto-alcohol 33a in good yield (90%). As mentioned earlier, a number of differently substituted cage keto-alcohols such as 27a and 27b were also prepared successfully[70].



27a $R_1=R_2=CH_3$
b $R_1=H, R_2=CH_3$

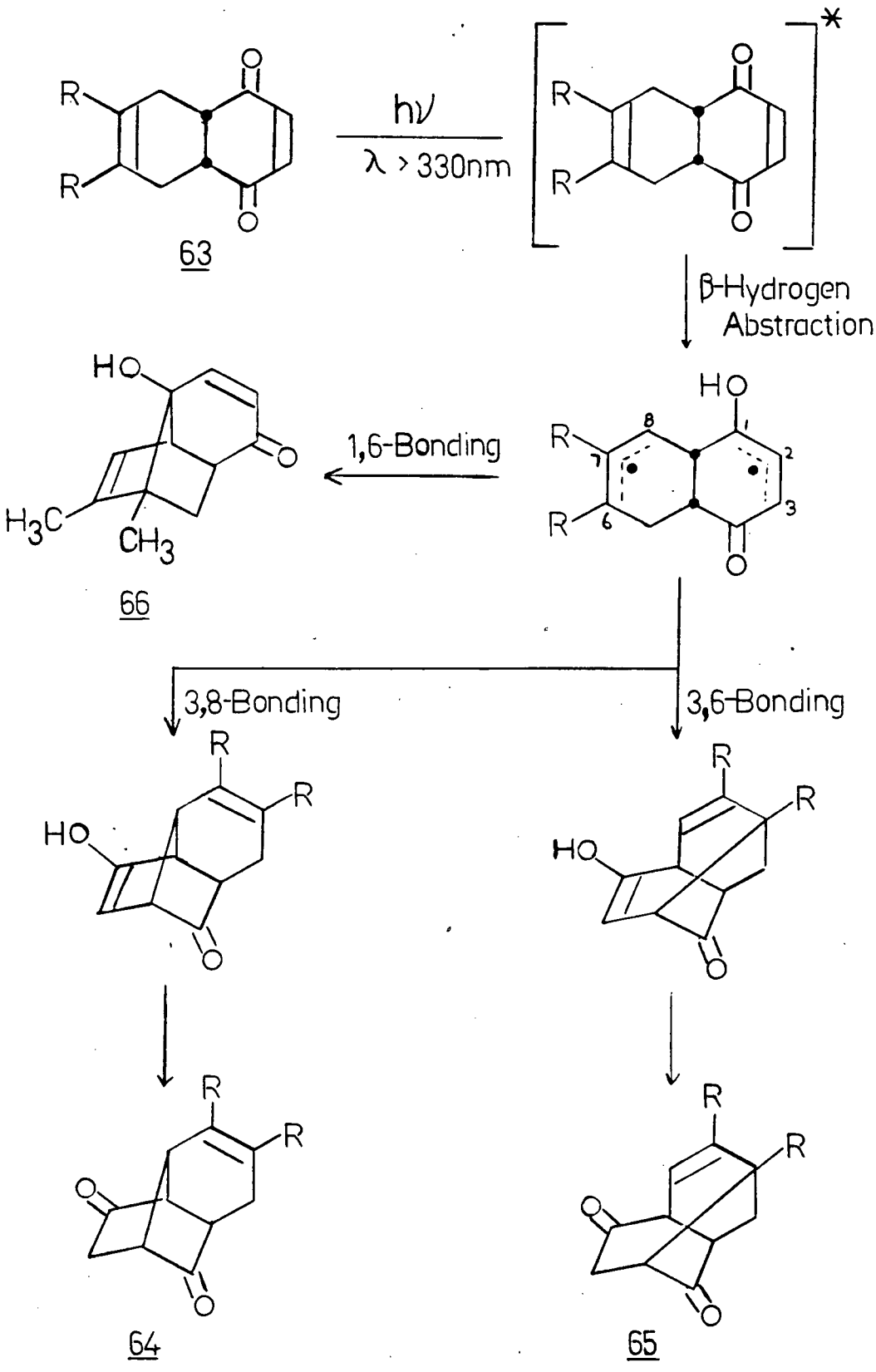


63



33a

The photochemistry of napthoquinols and napthoquinones was first reported by Scheffer and co-workers during the course of their investigation of the tetrahydronapthoquinones 63a (R=H) and 63b ($R=CH_3$)[84]. They found that when compounds 63a and 63b were photolysed under the same conditions as for 32a, no cage products can be obtained. Instead photoproducts 64 ((a) R=H, (b) $R=CH_3$), 65 ((a) R=H, (b) $R=CH_3$) and 66 (only for 63b) were isolated (scheme VI). In contrast, the endo Diels-Alder adducts of p-benzoquinone with cyclic 1,3-dienes are well known to give cage products upon photolysis via internal 2+2 cyclisation[85]. The proposed mechanism for the formation of these tricyclic products is summarised in scheme VI. The excited napthoquinone molecule undergoes β-hydrogen abstraction via a five-membered transition state, forming a biradical species which then recombines in different fashions leading to

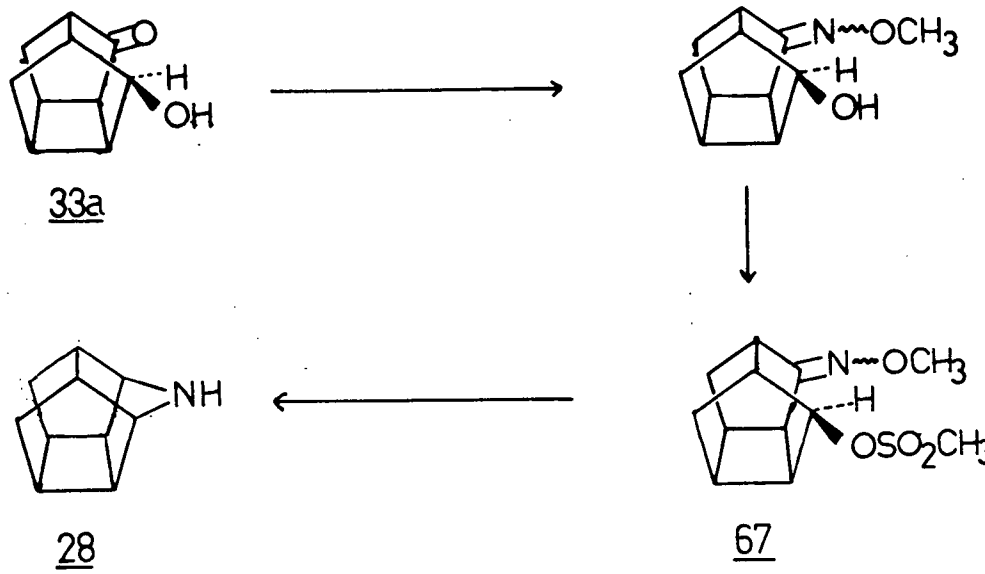

R
R
O
O
63
hν
λ > 330nm
R
R
O
O
*
β-Hydrogen
Abstraction
HO
R
R
8
1
7
2
6
3
O
1,6-Bonding
HO
O
H3C
CH3
66
3,8-Bonding
3,6-Bonding
R
R
HO
O
R
R
HO
O
R
R
O
O
64
R
R
O
O
65

SCHEME VI

the observed products[84]. Thus by transforming one of the carbonyl groups in compounds 63a and 63b into a hydroxyl group, the photolysis pathway was altered completely.

There appear to be at least two possible reasons for this. Firstly, the carbonyl group of the biradical resulting from hydrogen abstraction undoubtedly exerts a stabilising influence on this species through resonance and hence facilitates hydrogen abstraction. Secondly, the enone chromophore of the cyclohexenones such as 32a is a poorer electron acceptor as compared to the 2-ene-1,4-dione moiety of the precursor, 63a which, it would be argued, indicates that a charge-transfer interaction between the cyclohexene double bond and the excited ene-dione system is required for subsequent γ-hydrogen transfer[70]. Intramolecular excited-state carbonyl(acceptor) - amine(donor) charge-transfer interactions leading to internal hydrogen abstractions are well established. The fact that amines and di-, tri-, and tetrasubstituted alkenes have similar ionisation potentials lends support to the idea that intramolecular charge-transfer exciplex formation may be important in the photochemistry of 63a and other related compounds[86].

The original plan of the synthesis after obtaining 33a was to prepare the corresponding oxime methyl ether by condensing it with methoxyamine hydrochloride. Mesylation of the oxime ether followed by reduction would therefore provide the desired product 28 (scheme VII). Thus by refluxing 33a with methoxyamine hydrochloride in methanol and water in the presence



33a

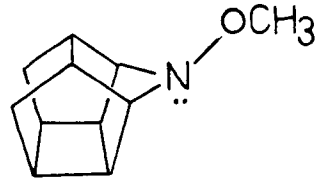
28

67

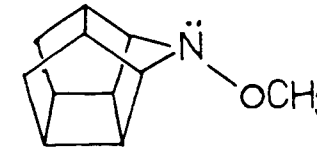
SCHEME VII

of potassium acetate for 65 hours, the oxime ether was produced. The mesylate 67 was prepared by reacting the oxime ether with methanesulphonyl chloride in methylene chloride at 0°C in the presence of triethylamine and a trace amount of 4-dimethylamino pyridine (70%). Compound 67 was then subjected to reduction using sodium trifluoroacetoxyborohydride as the reducing agent[87]. The reduction afforded a complex mixture. Attempts to purify this mixture met with failure, and this reduction method was then abandoned. The next attempt was to reduce 67 employing borane-methyl sulphide as the reducing agent[88]. Again, a mixture was obtained from which a highly volatile pale yellow oil with a distinctve smell was isolated (35%). The mass spectrum of this compound displayed an intense peak at m/e 177, presumably the molecular ion peak, and suggested a molecular formula of $C_{11}H_{15}NO$. The 20MHz ^{13}C NMR spectrum consisted of eleven peaks located between δ 23 and δ 73 and appeared in the

form of five doublets and one singlet. Its 400 MHz ^{1}H NMR spectrum was fairly simple, displaying sharp doublets and broad singlets. Futhermore, there were two sharp singlets at δ 3.53 and δ 3.59, both integrating for three hydrogens, which indicated the presence of two methoxy groups. Combining all the spectral data, it was deduced that this material was a mixture of compounds 68 and 69. The two sharp singlets appearing in the ^{1}H NMR spectrum could then be assigned to the presence of the two isomers differing in configuration at the apical nitrogen atom.



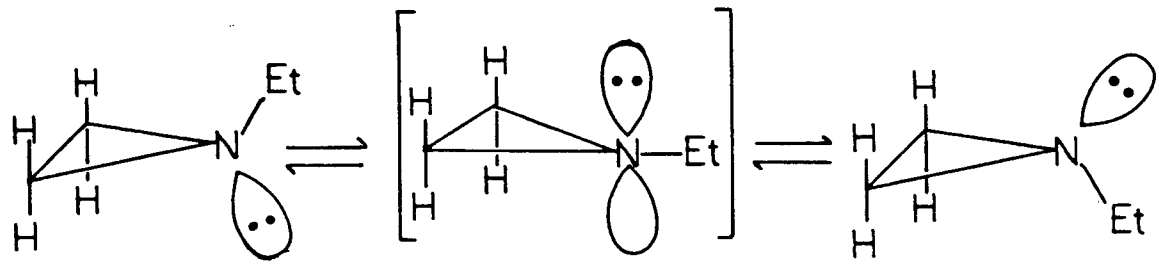
68



69

It is known[89] that if an atom possesses a nonbonding pair of electrons and is bonded to three other groups in a pyramidal fashion, it may undergo unimolecular inversion of configuration. At the transition state to this pyramidal inversion , the central atom is trigonally hybridised and the lone pair is in a p orbital. The nitrogen inversion process has been studied extensively. In an early study, Bottini and Roberts[90] observed that nitrogen inversion in aziridines is detectable by variable temperature NMR methods. One compound that was studied was 1-ethylaziridine 70. The NMR spectrum of 70 obtained at room temperature showed the characteristic bands of the ethyl group and two triplet band systems which were interpreted as being due

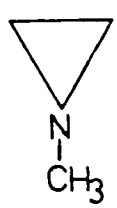
to the two non-equivalent groups of ring hydrogens which are either cis or trans to the N-ethyl group (equation 11). On



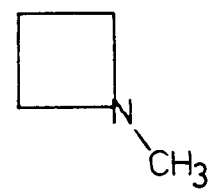
(11)

70

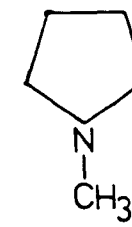
heating to 108°±5°C, the ring hydrogens appeared to lose their identity with respect to the ethyl group and a broad singlet was observed. As can be imagined, when compound 70 undergoes inversion, the energy of the transition state would be relatively high as compared to the open chain analogue due to severe bond angle strain (the nitrogen atom is sp^2 hybridised). One would therefore expect that when the ring size is increased, the inversion barrier would be lowered and the process accelerated. This was indeed observed in the series 71 - 73[91].



71



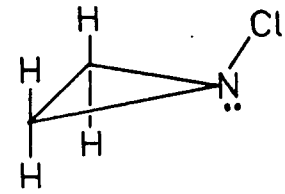
72



73

Besides bond angle strain, the inversion barrier could also be raised by replacing the N-alkyl substituent with one that is more electronegative. By this means the S character of the ground state lone pair is increased[89]; since the transition state lone pair must still be p-hybridised, the barrier is

increased. An example to illustrate this phenomenon is compound 74 in which the coalescence temperature of the ring hydrogen signals lies above the temperature at which the sample decomposes (>180°C) (cf. Compound 70).



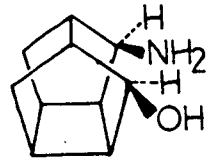
74

The isolation of the syn and anti isomers (compounds 68 and 69) was therefore not unexpected. The transition state for the inversion process involves an increase in the C-N-C bond angle in order to obtain a sp^2 configuration, and since the cage structure is highly rigid, the process is energetically unfavourable. Moreover, the nitrogen atom is attached to the electronegative oxygen which would further increase the inversion barrier for the reason mentioned above. In accord with these observations, the NMR spectrum obtained at 55°C was identical to that obtained at room temperature.

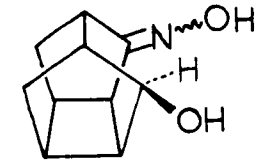
At this stage, we felt much relieved and there remained only one step to finish the synthesis. Several methods were attempted in order to replace the methoxy group by a hydrogen atom. Sodium amalgam reduction[92], hydrogenation over palladium on charcoal[93] and lithium aluminium hydride reduction[94] provided no fruitful results. In each of the above cases, the starting material was recovered unchanged even after prolonged reaction times and using large excesses of reagents. Zinc-acetic acid

reduction[94] afforded a complex mixture, and no attempt at purification was carried out. Finally, we decided to abandon the route.

After reviewing the original synthetic plan, we considered a change in strategy. Instead of effecting the preparation of the amino functional group and cyclisation in a single step, it was felt that carrying out these reactions in two separate steps might provide fruitful results. The new plan was therefore to first transform the cage keto-alcohol 33a into an amino-alcohol 75, and then to modify the hydroxyl group into a good leaving



75

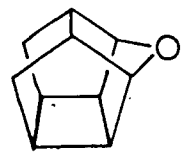


34a

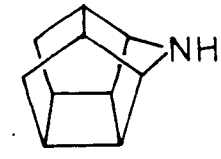
group such as mesylate which we expected once formed, would cyclized spontaneously to give 28. With this idea in mind, reductive amination of 33a with ammonium acetate in the presence of sodium cyanoborohydride was attempted[95]. Even by prolonging the reaction time, no reaction was observed, and the starting material was recovered totally unchanged. Since the oxime methyl ether of 33a had been prepared successfully, we expected to obtain the oxime 34a by adopting the same method. By refluxing keto-alcohol 33a with hydroxylamine hydrochloride in methanol and water overnight in the presence of potassium acetate, oxime 34a[96] was in fact produced (75%).

Expecting to obtain the amino-alcohol 75, 34a was subjected

to aluminium hydride reduction following the procedure of Brown and Yoon[97]. The reaction led to a mixture which was difficult to purify. The first successful separation was achieved by preparative gas liquid chromatography (8% OV17, 150°C) and a compound was isolated which was not 75 but appeared to be the desired final product 28. This compound displayed an intense peak at m/e 147, presumably the molecular ion peak, in its mass spectrum; in addition, its 270MHz ^{1}H NMR spectrum was almost identical with that of the cyclic ether 30. From the ^{1}H NMR data (page 63), the structure of this compound was confirmed to be 28 beyond doubt.



30



28

After much effort, it was found that by chromatographing the reaction residue on an alumina column (neutral, Woelm, activity grade III) and eluting with chloroform-methanol (93:7), the desired amine 28 could be isolated in 30% yield. Compound 28 was a volatile solid; an attempt to recrystallize it from chloroform turned out to be disastrous. The amine decomposed and at least three compounds were formed (as detected by gas liquid chromatography) which were not identified. To overcome this problem, the picric acid salt was prepared by mixing a saturated picric acid solution in benzene with a concentrated solution of the amine in chloroform. The salt which was formed

precipitated out from the solution and was isolated by filtration (80%). The picrate of 28 was extremely stable, non-volatile and was fully characterised. The amine-picrate was reconverted to the free amine by treatment with lithium hydroxide, and dry hydrogen chloride was then bubbled through a chloroform solution of the reliberated amine until the pH was less than 2. Removal of solvent afforded the hydrochloride of compound 28 (87%). The biological testing of the amine-hydrochloride is being carried out by Dr. Steven Sacks of the U.B.C. Faculty of Medicine. The compound was found to be inactive towards herpes viruses while the results of the tests of potency against influenza viruses are still pending.

The 270 MHz ^{1}H NMR spectrum of the hydrochloride of 28 is extremely simple and interesting (figure 1). The simplicity of the spectrum is explained by the presence of a mirror plane in the molecule. As indicated in the spectrum, the inner C(3) and C(6) hydrogens in this ring system experience deshielding via steric compression resulting in a relatively large chemical shift difference between the inner and outer hydrogens at these positions. It is well known[98] that when a substituent atom is held rigidly at a distance from the resonating nucleus that is less than the sum of the van der Waals radii, the substituent atom will repel electrons from the resonating atom which is therefore deshielded. The magnitude of the effect falls off very rapidly with increasing internuclear distance and it depends critically on the size and polarisibility of the nuclei. A similar deshielding effect has been observed in the

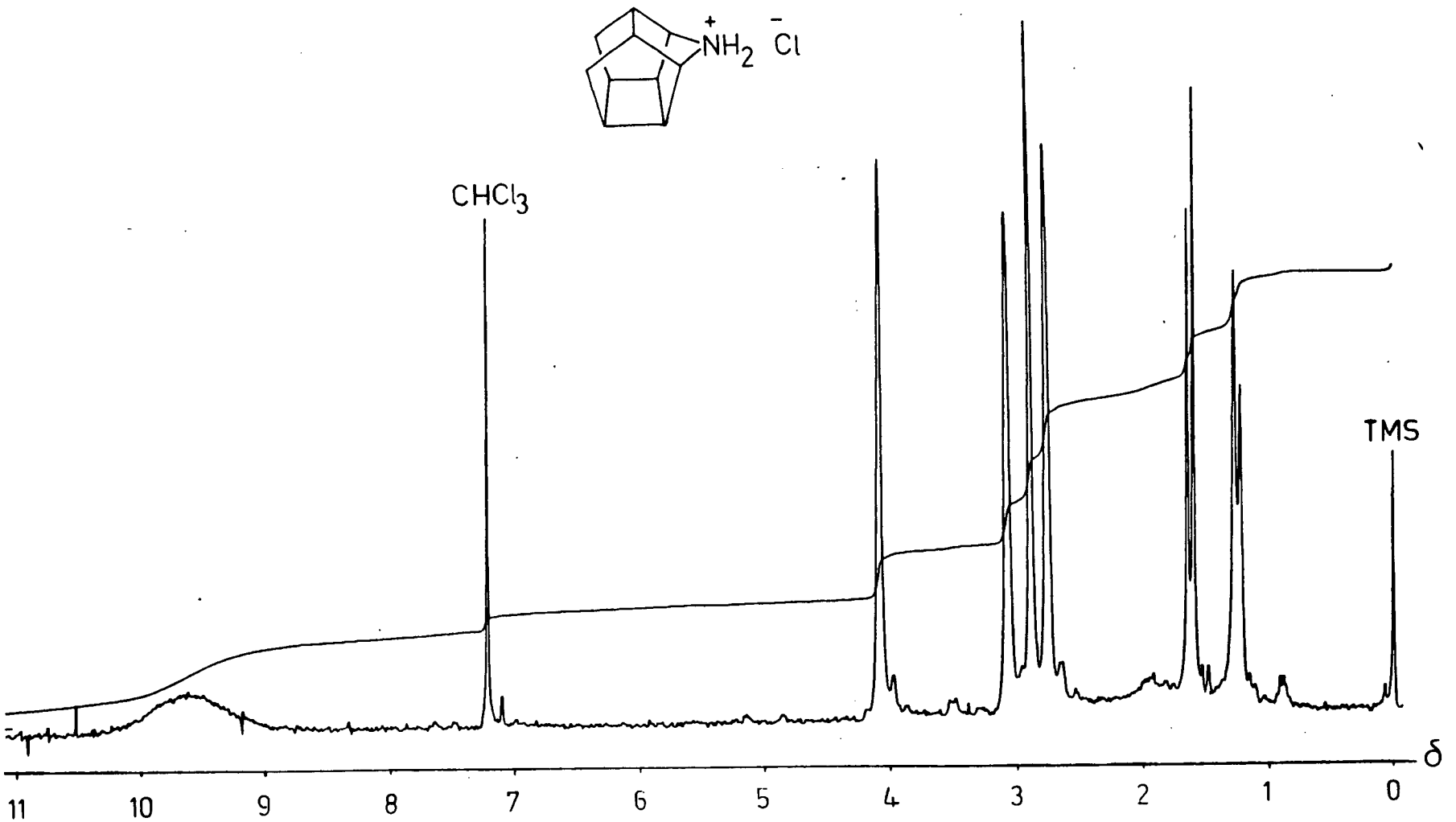
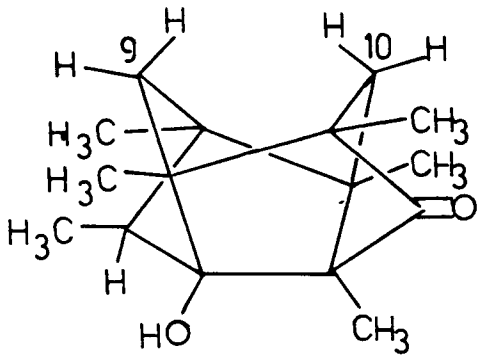
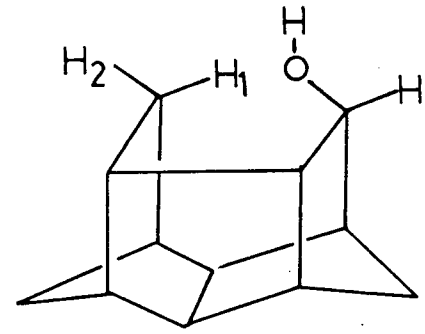


Figure 1 A 270 MHz ^{1}H NMR spectrum of the hydrochloride of compound 28

tetracyclo[4.2.1.$1^{2,5}$.$0^{3,7}$]decane cage structure, for example compound 76, in which the chemical shift differences of the inner and outer H's at C(9) and C(10) are 1.01 δ and 0.8 δ respectively[99]. Possibly the most dramatic example which has been observed is in the cage compound 77 where the chemical shifts of H_1 and H_2 are δ 3.55 and δ 0.88 respectively[100].



76



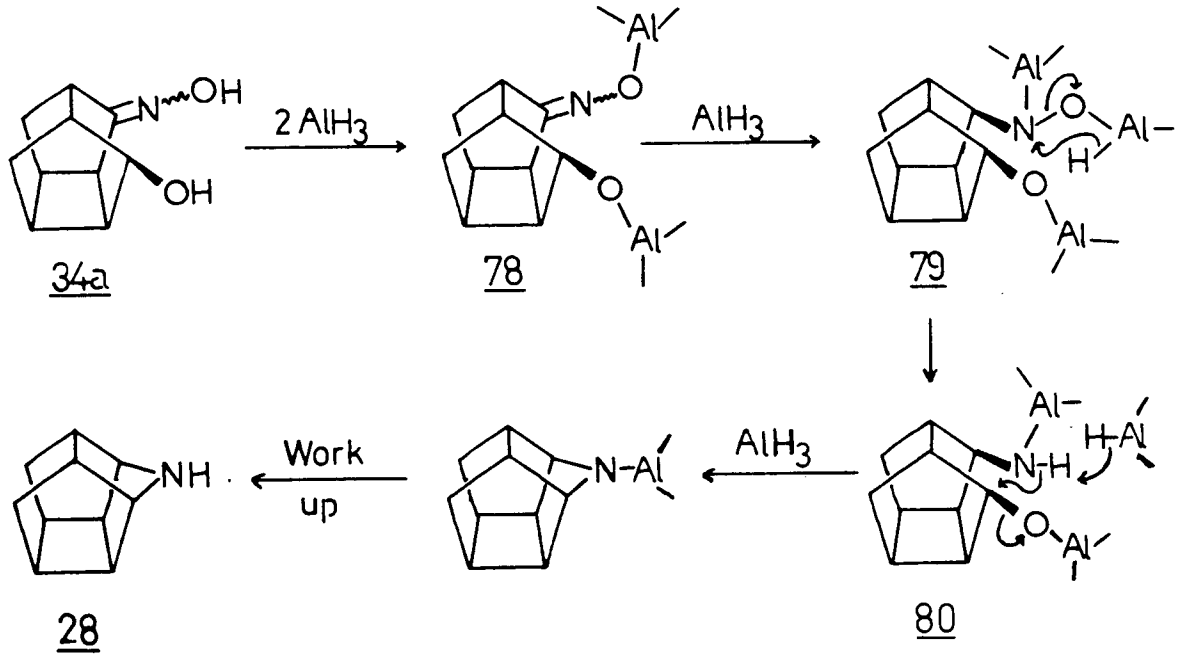
77

The doublet centred at δ 1.25 (J=13Hz) represents the outer hydrogen atoms at C(3) and C(6). The other doublet centred at δ 1.62 (J=13Hz) represents the inner hydrogens at C(3) and C(6). The singlet at δ 4.12 is assigned to the hydrogen atoms at C(1) and C(8) due to its low chemical shift (adjacent to nitrogen). The singlet at δ 2.77 is assumed to be the C(4) and C(5) hydrogen signals since they are furthest away from the nitrogen as compared with the C(2), C(7) and C(9), C(10) hydrogens. Definite assignments of the two remaining singlets at δ 2.91 and δ 3.10 were not attempted.

Even though a D_2O-exchanged spectrum was not obtained, the broad peak centred at δ 9.69 is assigned with confidence to the

hydrogens attached to nitrogen. The structure of the compound was further confirmed by its 20 MHz ^{13}C NMR spectrum which displayed five signals at δ 24.68, δ 34.39, δ 40.23, δ 41.24 and δ 64.62. The signal at δ 24.68 was assigned to C(3) and C(6) while the one at δ 64.62 was assigned to C(1) and C(8) due to their relatively low chemical shifts (adjacent to nitrogen). The signal at δ 34.39 was assigned to C(4) and C(5) since they are furthest away from the nitrogen. Definite assignment of the remaining resonances was not attempted.

It was unexpected to obtain the amine 28 from the aluminium hydride reduction of oxime 34a. The proposed mechanism of the reaction is illustrated in scheme VIII. We suggest that the first step is the reaction of the oxime with the hydride to form a derivative 78 with evolution of hydrogen. Addition of another molecule of alumimium hydride to the carbon-nitrogen double bond could then occur, forming 79. Cleavage of the nitrogen-oxygen

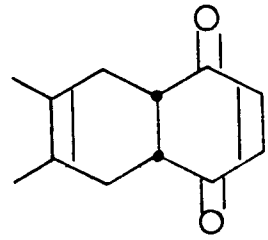


SCHEME VIII

bond with concomitant hydride transfer to the nitrogen would produce 80. The sequence of 34a to 80 was originally proposed by Brown and Yoon[97]. Compound 80 could then be attacked by another molecule of aluminium hydride and give the corresponding cyclized intermediate which on work up, would give the amine 28.

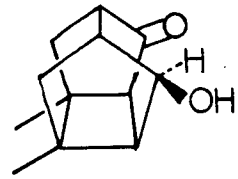
Synthesis of 4,5-Dimethyl-11-aza-pentacyclo-[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane

The 6,7-dimethyl-4aβ,5,8,8aβ-tetrahydro-1,4-napthoquinone (31b) was prepared via the Diels-Alder addition of 2,3-dimethyl-1,3-butadiene to p-benzoquinone following the method of Mandelbaum and Cais[101] (80%). The problems associated



31b

with the sodium borohydride reduction of 31a were also encountered here. Again by controlling the purity of the napthoquinone and the solvent, these problems were minimised and the corresponding hydroxycyclohexenone 32b[70] was obtained (70%). Irradiation (λ > 330nm) of compound 32b as a benzene solution provided the cage keto-alcohol 33b (70%). The oxime of 33b was

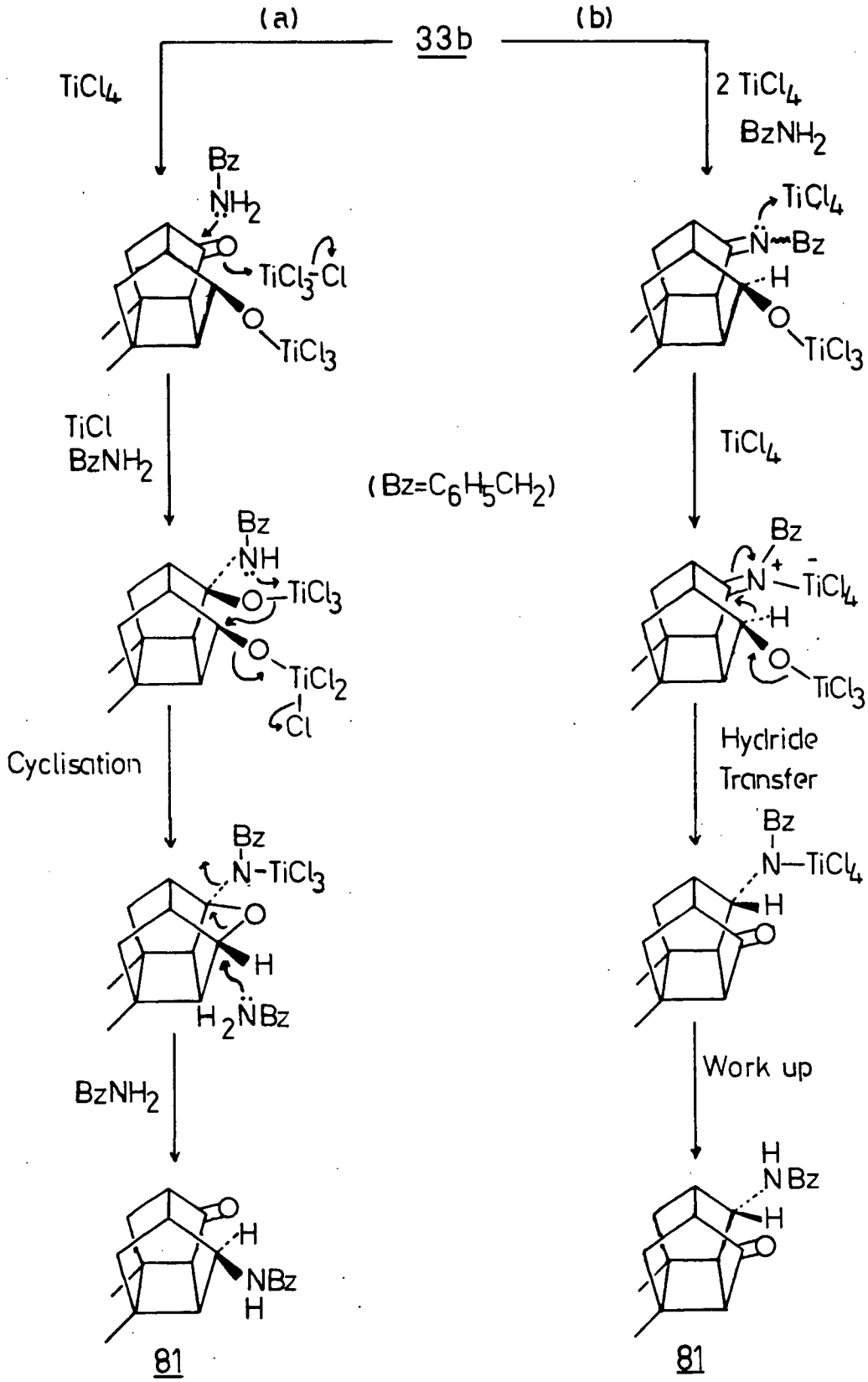


33b

prepared by employing the same method used for preparing 34a and then subjected to aluminium hydride reduction. An unexpected problem arose, namely the relative insolubility of the dimethyl oxime in tetrahydrofuran (THF), the solvent recommended for the reaction[97]. An attempt to use the dimethyl oxime as a suspension in THF was unsuccessful; substantial amounts of the starting material were recovered and only trace amounts of the desired product 29 could be isolated. To overcome this problem, it was decided to use other suitable nitrogen derivatives of 33b as precursors for 29.

The first derivative that was investigated was the corresponding benzylimine, which presumably could be obtained by condensing 33b with benzylamine. Unfortunately, even by prolonging the reaction period and using a large excess of amine, the desired imine could not be obtained and the starting material was recovered. Hoping to improve the reaction, the experiment was repeated using titanium tetrachloride as catalyst[102]. A new product was obtained (40%) together with the starting material and small amounts of unidentified side product. This new product displayed an intense absorption band at 1730 cm^{-1} (C=O) and a weak but sharp band at 3300 cm^{-1} (N-H) in its infrared spectrum. Combining these data with those obtained from a high resolution mass spectrum (m/e 281.1779), ^{13}C and ^{1}H NMR spectra, this new compound was tentatively assigned the structure 81.

Two mechanisms are proposed for the formation of 81 which are depicted in scheme IX. For path a, coordination of titanium


(a)
33b
(b)
TiCl4
2 TiCl4
BzNH2
Bz
NH2
TiCl3-Cl
O
TiCl3
TiCl4
N-Bz
H
TiCl
BzNH2
(Bz=C6H5CH2)
TiCl4
Bz
NH
TiCl3
TiCl2
Cl
Bz
N+
TiCl4
Cyclisation
Hydride
Transfer
Bz
N-TiCl3
N—TiCl4
H
H2NBz
Work up
BzNH2
NBz
81
81

SCHEME IX

with the carbonyl oxygen could occur which would facilitate attack of the carbonyl carbon by the amine. Coordination of the hydroxyl oxygen with titanium together with formation of hydrogen chloride might also occur concomitantly. Transannular cyclisation could then follow, forming the cyclic ether which might be attacked by the benzylamine and 81 would be formed.

For path b, we propose that the first step would be the formation of the imine. Reaction of the hydroxyl group with the Lewis acid might also occur concurrently. Coordination of titanium with the imino nitrogen could then occur followed by intramolecular hydride transfer (analogous hydride transfer process in other structurally similar cage systems had been observed[103]) and regenerate the ketone functional group. Cleavage of the titanium and nitrogen bond during work up would give 81.

The next nitrogen derivative which was considered to be suitable as a precursor for 29 was the oxime methyl ether 34b. Thus, by refluxing 33b with methoxyamine hydrochloride overnight in methanol and water in the presence of potassium acetate, the desired oxime ether was prepared in excellent yield (92%). An interesting point to note is the apparent higher reactivity of the carbonyl group in 33b as compared with that of 33a; the condensation of 33a with methoxyamine hydrochloride leading to the corresponding oxime ether took a much longer time (more than 60 hours) to complete for unknown reasons. Subjecting 34b to aluminium hydride reduction gave the amine 29 after chromatographic purification (21%) using an alumina column

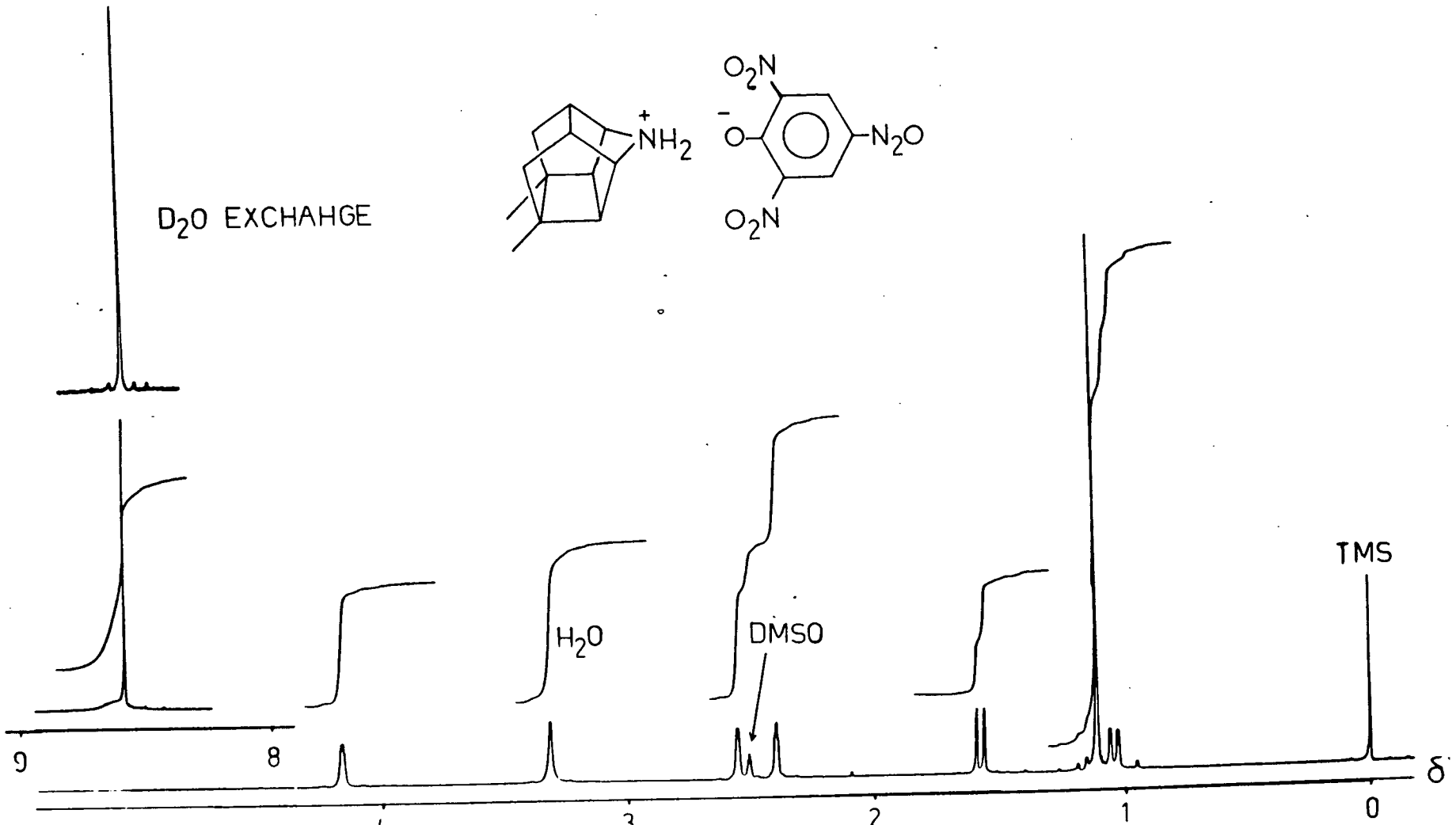
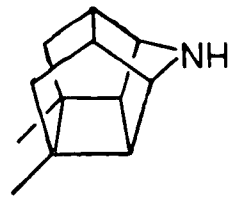


Figure 2 A 400 MHz ^{1}H NMR spectrum of the picrate of compound 29

(neutral, Woelm, activity grade III) and eluting with chloroform-methanol (92:8).



29

The 400 MHz ^{1}H NMR spectrum of the picrate of 29 (figure 2) resembles that of the hydrochloride of 28 (figure 1). Again, due to the existence of a mirror symmetry plane, the spectrum is simplified. The doublet centred at δ 1.05 (J=12 Hz) is assigned to the outer hydrogen atoms at C(3) and C(6) while the doublet centred at δ 1.57 (J=12Hz) is assigned as the inner hydrogen atoms at these positions. The relatively large difference in chemical shift between the inner and outer hydrogens can also be explained by the deshielding effect via steric crowding of the inner hydrogens[99 100]. The sharp singlet at δ 1.16 represents the two methyl group hydogens at C(4) and C(5). The singlet at δ 4.16 is assigned to the hydrogen atoms at C(1) and C(8) due to their low chemical shift (adjacent to nitrogen). Ambiguity arises in the assignment of the two broad singlets at δ 2.40 and δ 2.56; undoubtedly these two signals represent the C(2), C(7) and C(9), C(10) hydrogens but a definite assignment cannot be made without extra information. A final point concerning the spectrum is the apparent "loss" of the amino hydrogen signals. The sharp singlet at δ 8.57 is definitely the two aromatic ring hydrogens of the picrate; closer examination reveals that the

base of the peak is somewhat broadened and the total integration of this signal is between three and four hydrogens. Upon D_2O exchange, this broad shoulder disappeared. Therefore, we suggest that the shoulder is the signal of the amino hydrogens and since it is so broad, the integration is inaccurate.

Experimental

General

Melting points were determined on a Fisher-Johns hot-stage or Gallenkamp (sealed tube samples) melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer Model 701B, 257 and 137 spectrophotometers using potassium bromide discs for solid samples and a thin film pressed between two sodium chloride plates for pure liquids. The IR spectra were calibrated with the 1601cm^{-1} band of polystyrene. The assignment of each absorption is indicated in parentheses after each band. Proton nuclear magnetic resonance (NMR) spectra were recorded with Varian HA-100, Nicolet-Oxford H-270 or Bruker WH-400 spectrometers. ^{13}C NMR spectra were recored with Varian CFT-20 and Bruker WP-80 spectrometers. The signal positions are reported using tetramethylsilane as internal standard. For ^{1}H NMR spectra, the multiplicity, integrated peak area, coupling constant and proton assignments (if possible) are indicated in parentheses after the signal. Mass spectra (ms) were obtained on a Varian/MAT Atlas CH-4B mass spectrometer which was operated at an ionising potential of 70 electron volts. Elemental analyses were performed by the departmental microanalyst, Mr. P. Borda. For gas liquid chromatography (GLC), a Hewlett Packard 5380A flame ionisation model was used; K grade nitrogen was the carrier gas. The column used was 5% OV 17 on Chromosorb W 80/100 mesh operated at a flow of 30 ml per minute. For silica gel column

chromatography, the "flash chromatography" technique[104] was employed. The columns were slurry packed in the eluting solvent with Silica Gel 60 (from E. Merck), 230-400 mesh ASTM. For alumina column chromatography, Woelm alumina (from ICN) of activity grade III (deactivated according to instructions) was used; the column were slurry packed in the eluent and run without application of pressure. Tetrahydrofuran (THF) was purified by refluxing over sodium metal in the presence of benzophenone until a persistent deep blue colour was observed, then distilled prior to use.

Lithium aluminium hydride (LAH) solution in THF was prepared following the procedure of Brown and Yoon[97]. In one typical preparation, about 9g of LAH (95+% pure, Alfa) was added to 125ml of purified THF. The mixture was stirred overnight under nitrogen and filtered through one and a half inches of Celite (previously dried in the oven) and one inch of sand packed on a sintered glass funnel, a slightly turbid colourless solution was obtained. The hydride concentration was determined to be 1.45M by allowing 0.5ml aliquots of the solution to react with a 1:1 mixture of THF and 1M sulphuric acid and measuring the volume of hydrogen evloved. 100% Sulphuric acid was prepared by mixing calculated amounts of fuming sulphuric acid (containing 30% sulphur trioxide) and concentrated sulphuric acid (96.7%). The resulting mixture was standardised with 0.1M sodium hydroxide solution. In a typical preparation, 10.201g of concentrated sulphuric acid was mixed with 5.007g of fuming sulphuric acid. The resulting acid solution was found to

contain 99.87% sulphuric acid by weight.

4aβ,5,8,8aβ-Tetrahydro-1,4-napthoquinone (31a)

p-Benzoquinone (32.05g, 0.297mol) (purified by sublimation) was placed in the cylindrical flask of a Parr hydrogenation apparatus followed by the addition of 225ml of benzene. The quinone was partially dissolved and the resulting mixture was cooled in an ice bath. 1,3-Butadiene (35.6ml) was condensed (in dry-ice-acetone) and rapidly introduced into the cooled mixture. The flask was stoppered and secured onto the hydrogenation apparatus. The reaction mixture was allowed to stand for twenty days with occassional shaking. At the end of the reaction period, a yellow solution was obtained. The solution was filtered and the benzene removed under reduced pressure to provide a yellow solid which was recrystallised from cyclohexane. The desired napthoquinone (34.08g, 71%) was obtained in form of yellow needles, melting point 51-52°C (lit.[77] 52-54°C).

4aβ,5,8,8aβ-Tetrahydronapthoquin-1-one-4-α-ol (32a)

Napthoquinone (31a) (500mg, 3.05mmol) was dissolved in 10ml of methanol and cooled in an ice bath. Sodium borohydride (46.2mg, 1.22mmol) suspended in 2ml of ice cold methanol was added slowly over a period of 10 minutes with stirring. After stirring the reaction mixture at the temperature of the ice bath for 35 minutes, about 15ml of water was added and the resulting pale yellow solution was extracted with six 20ml portions of chloroform. The combined extracts were washed with brine and dried over anhydrous sodium sulphate. Removal of the solvent

and recrystallisation of the residue from cyclohexane-benzene afforded 350mg (70%) of napthoquinol (32a, melting point 130-131°C (lit.[70] 128-128.5°C).

Compound 32a displayed the following spectral characteristics: IR (KBr) 3300cm^{-1} (OH), 1680cm^{-1} (C=O conjugated); ms (parent) m/e 164; ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1H, J=10Hz), δ 5.95 (dd, 1H, J_1=10Hz, J_2=2.5Hz), δ 5.70 (m, 2H), δ 4.85-4.95 (m, 1H), δ 2.60-2.95 (m, 3H), δ 2.30 (s, 1H, exc with D_2O), δ 1.90-2.30 (m, 3H).

10-Exo-hydroxytetracyclo[5.3.0.0^{2,6}.0^{4,9}]decan-3-one (33a)

Napthoquinol (32a) (400mg, 2.44mmol) was dissolved in 350ml of benzene and the resulting solution was purged with nitrogen for 90 minutes. Internal irradiation (450W Hanovia lamp, uranium glass filter, Pyrex immersion well) of 32a was monitored by GLC (at 180°C, retention time of 32a is 3.21 minutes, retention time of 33a is 3.80 minutes) and stopped after 16 hours (less than 1% of 32a remained). Benzene was removed under reduced pressure to afford a yellow oily residue which was purified by silica gel column chromatography using ethyl acetate-petroleum ether (30-60°C) (7:3) as eluent. In this way 356mg (89%) of 33a was isolated which was then recrystallised from petroleum ether (65-110°C)-benzene; melting point 231-233°C (sealed tube).

The cage ketol (33a) displayed the following spectral characteristics: IR (KBr) 3400cm^{-1} (OH), 1730cm^{-1} (C=O); ms (parent) m/e 164; ^{1}H NMR ($CDCl_3$) δ 4.14 (br s, 1H), δ 3.16-3.05

(m, 1H), δ 2.86-2.70 (m, 2H), δ 2.60-2.50 (m, 2H), δ 2.40-2.30 (m, 1H), δ 2.14 (quasi triplet, 2H), δ 1.83-1.95 (m, 1H), δ 1.58 (s, 1H, exc with D_2O), δ 1.30-1.40 (m, 1H).

10-Exo-hydroxytetracyclo[5.3.0.$0^{2\ 6}$.$0^{4\ 9}$]decane-3-ketoxime (34a)

The cage keto-alcohol (33a) (1.31g, 8.0mmol) was dissolved in 25ml of methanol with stirring in a 100ml round bottom flask. Hydroxylamine hydrochloride (2.63g, 37.9 mmol) and potassium acetate (1.87g, 19.1mmol) were added to the above solution with stirring whereupon a white suspension was formed. The flask was then equipped with a reflux condenser and the suspension was heated in an oil bath with stirring while water was introduced slowly until a clear colourless solution was obtained. After refluxing overnight, methanol was removed under reduced pressure and the oxime precipitated as a white solid which was collected by filtration and washed thoroughly with water. The solid was dried in vacuo to give 972mg of desired oxime. The aqueous residue was extracted with four 20ml portions of ethyl acetate and the combined extracts washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and brine and dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure provided another 95mg of oxime. The total yield of the reaction was 1.067g (75%). The crude oxime was recrystallised from a mixture of ethyl acetate and small amount of ethyl alcohol, melting point of 34a is 209.5-211°C.

Oxime 34a displayed the following spectral characteristics:

IR (KBr) 3300cm^{-1} (OH), 1675cm^{-1} (C=N); ms (parent) m/e 179; ^{1}H NMR (DMSO d_6) δ 4.53 (s slightly split, 2H, exc with D_2O), δ 3.67 (br s, 2H), δ 3.46-3.33 (m, 2H), δ 3.32 (s, superimposed on the multiplet, 2H, exc with D_2O), δ 2.84-2.48 (m, 8H), δ 2.30 (br d 1H, J=10Hz), δ 2.23 (br d, 1H, J=10Hz), δ 1.92 (two superimposed doublets, 2H), δ 1.74 (two superimposed doublets, 2H), δ 1.55 (d futher split, 2H, J=12Hz), δ 0.80-0.90 (m, 2H).

Anal. Calcd for $C_{10}H_{13}O_2N$: C 67.02, H 7.31, N 7.82. Found C 67.20, H 7.34, N 7.76.

11-Aza-pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane (28)

An oven-dried two-necked 50ml round bottom flask equipped with a magnetic stirring bar, rubber septum, and a reflux condenser attached to a dry nitrogen source was charged with 7.5ml (2.52M, 19mmol) LAH solution in THF via a syringe. Sulphuric acid (100%) (503ul, 9.5mmol) was added dropwise over a period of 20 minutes while the solution was vigorously stirred in a cold water bath (5-10°C) by means of a magnetic stirrer. Hydrogen was evolved with the precipitation of lithium sulphate and the resulting grey suspension was allowed to stir for another hour at room temperature. To this suspension at room temperature was added slowly 450mg (2.5mmol) of oxime dissolved in 20ml of THF. Hydrogen was again evolved vigorously, and when it ceased the reaction mixture was refluxed for 7 hours. The excess hydride was quenched with 4ml 1:1 aqueous THF while the reaction mixture was cooled in a cold water bath (5-10°C). This was followed by the addition of 10ml of aqueous sodium hydroxide

solution (3.75M) at room temperature. The original voluminous precipitate coagulated to a smaller gelatinous mass. The THF layer was decanted and the aqueous phase was extracted with three 15ml portions of ether. The combined organic extracts were dried over anhydrous potassium carbonate and then filtered. Slow removal of solvent under reduced pressure gave a white solid which was chromatographed on an alumina column using methanol-chloroform (7:93) as eluent. The desired cage amine (28) (110mg, 30%) was isolated which proved to be homogeneous on GLC (at 165°C, the retention time of 28 is 1.40 minutes).

Compound 28 displayed the following spectral characteristics : ms (parent) m/e 147; ^{1}H NMR (CD_3OD) δ 3.74 (br s, 2H, C(1) and C(8) methines), δ 2.65 (br s, 4H, C(2), C(7), C(9) and C(10) methines), δ 2.35 (br s, 2H, C(4) and C(5) methines), δ 1.53 (d, 2H, J=12Hz, C(3) and C(6) inner H'S), δ 1.18 (br d, 2H, J=12Hz, C(3) and C(6) outer H's).

Picrate of Compound 28

To 77mg (0.52mmol) of the cage amine in 2ml of chloroform, 4ml of picric acid solution (prepared by dissolving 1g of crude picric acid in 15ml of benzene followed by drying over anhydrous calcium chloride) was added. After standing at room temperature for 1-2 minutes, bright yellow needles precipitated. The mixture was kept in the refrigerator overnight; 158mg (80%) of picrate was obtained by filtration which had a melting point of 228.5-230°C.

The picrate of compound 28 displayed the following spectral

characteristics : IR (KBr) 2900cm^{-1} (secondary amine salt), 1320cm^{-1} (NO_2); ^{1}H NMR (DMSO d_6) δ 8.80-8.60 (br shoulder, 2H, NH_2), δ 8.56 (s, superimposed on the shoulder, 2H, aromatic ring H's), δ 4.09 (s, 2H, C(1) and C(8) methines), δ 2.82 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 2.68 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 2.58 (s, 2H, C(4) and C(5) methines), δ 1.56 (d, 2H, J=13.5Hz, C(3) and C(6) inner H's), δ 1.19 (br d, 2H, J=13.5Hz, C(3) and C(6) outer H's); ^{13}C NMR (DMSO d_6) (from δ 0-100) δ 24.05 (C(3) and C(6)), δ 33.81 (C(4) and C(5)), δ 39.74 (C(2), C(7) or C(9), C(10)), δ 40.65 (C(2), C(7) or C(9), C(10)), δ 63.98 (C(1) and C(8)).

Anal. Calcd for $C_{16}H_{16}N_4O_7$: C 51.07, H 4.29, N 14.89. Found C 50.99, H 4.35, N 15.00.

Amine Hydrochloride of Compound 28

The amine picrate of 28 (890mg, 2.37mmol) was suspended in 7ml of chloroform in a 60ml separatory funnel, 2g (83.3mmol) of lithium hydroxide and 15ml of water were added and the contents were mixed thoroughly. The organic phase was removed and the aqueous phase was extracted with three 15ml portions of chloroform. The organic extracts were combined and dried over anhydrous sodium sulphate and then filtered. Dry hydrogen chloride gas was bubbled through the solution until the pH was less than 2 (as indicated by pH paper). Chloroform was removed under reduced pressure whereupon a pale yellow solid was obtained which was redissolved in 10ml methanol and treated with a small amount of Norit. Removal of Norit and solvent gave

376mg (87%) of the hydrochloride as a white solid. Recrystallisation from cyclohexane-ethanol provided the hydrochloride in the form of white needles. The hydrochloride does not have a distinct melting point. It starts to decompose when heated to about 250°C and becomes completely black in colour at 310°C.

The hydrochloride displayed the following spectral characteristics: IR (KBr) 2900cm^{-1} (secondary amine salt); ms (parent) m/e 147; ^{1}H NMR ($CDCl_3$) δ 9.69 (broad shoulder, 2H, NH_2), δ 4.12 (s, 2H, C(1) and C(8) methines), δ 3.10 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 2.91 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 2.77 (s, 2H, C(4) and C(5) methines), δ 1.62 (d, 2H, J=13Hz, C(3) and C(6) inner H's), δ 1.25 (d, 2H, J=13Hz, C(3) and C(6) outer H's); ^{13}C NMR ($CDCl_3$) δ 64.62 (C(1) and C(8)), δ 41.24 (C(2), C(7) or C(9), C(10)), δ 40.23 (C(2), C(7) or C(9), C(10)), δ 34.39 (C(4) and C(5)), δ 24.68 (C(3) and C(6)). For detailed description of assignments, see results and discussion.

Anal. Calcd for $C_{10}H_{14}NCl$: C 65.39, H 7.68, N 7.63. Found C 65.51, H 7.59, N 7.57.

6,7-Dimethyl-4aβ,5,8,8aβ-tetrahydro-1,4-napthoquinone (31b)

A 25ml round bottom flask was charged with 2.00g (18.52mmol) of p-benzoquinone (purified by sublimation) and 2ml of benzene. After stirring for 5 minutes at room temperature, 2,3-dimethyl-1,3-butadiene (1.67g, 20.36mmol) was rapidly introduced. The flask was then equipped with a reflux condenser

with a drying tube attached and the mixture was heated to 60-65°C in an oil bath with stirring. After heating for 10 minutes, an orange solution was formed; on futher heating, a yellow solid was precipitated. After a total heating time of three and a half hours, the reaction mixture was cooled to room temperature. Benzene was removed under reduced pressure, and a yellow solid residue was obtained which was dried further in vacuo. Recrystallisation of the residue from a mixture of cyclohexane and small amount of acetone provided 2.81g (80%) of napthoquinone (31b) as yellow needles, melting point 110-111.5°C (lit.[101] 115-117°C).

Compound 31b displayed the following spectral characteristics: IR (KBr) 1680cm^{-1} (C=O), 1600cm^{-1} (C=C conjugated); ^{1}H NMR ($CDCl_3$) δ 6.58 (s, 2H, C(2) and C(3) H's), δ 3.10 (m, 2H, C(4a) and C(8a) methines), δ 2.20 (m, 4H, C(5) and C(8) methylenes), δ 1.63 (s, 6H, C(6) and C(7) methyls).

6,7-Dimethyl-4aβ,5,8,8aβ-tetrahydronapthoquin-1-one-4-α-ol (32b)

A 50ml round bottom flask was charged with 2.17g (11.42mmol) of 31b and 30ml of methanol. The mixture was stirred magnetically and a pale yellow suspension was formed. To the stirred suspension cooled in an ice bath, sodium borohydride (173mg, 4.55mmol) suspended in 4ml of ice cold methanol was added slowly over a period of 5 minutes with vigorous stirring. After stirring for 1 hour at ice bath temperature, about 2ml of saturated ammonium chloride solution was added and the reaction mixture was allowed to warm to room

temperature; a light brown solution was obtained. The methanol was removed under reduced pressure and the residue was transferred to separatory funnel with the aid of about 30ml of water and small amount of chloroform. Extraction was carried out with seven 30ml portions of chloroform and the combined extracts washed successively with water and dried over anhydrous sodium sulphate. After removal of the drying agent, a yellow solution was obtained. The solvent was stripped off under reduced pressure, and the resulting pale yellow solid recrystallised from cyclohexane-ethyl acetate. This provided the napthoquinol (32b) as white needles (1.56g, 71%) with a melting point of 119-122°C (lit.[70] 122-122.5°C).

The napthoquinol displayed the following spectral characteristics : IR (KBr) 1685cm^{-1} (C=O conjugated); ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H, C(6) or C(7) methyl), δ 1.66 (s, 3H, C(6) or C(7) methyl), δ 1.91 (s, 1H, exc with D_2O), δ 1.88-2.28 (m, 3H, C(4a) methine, C(5) methylene), δ 2.50-2.90 (m, 3H, C(8a) methine, C(8) methylene), δ 4.82-5.02 (m, 1H, C(4) methine), δ 5.99 (dd, 1H, J_1=10Hz, J_2=2Hz, C(2) H), δ 6.71 (d of t, 1H, J_1=10Hz, J_2=2Hz, C(3) H).

6,7-Dimethyl-10-exo-hydroxytetracyclo-[5.3.0.0^{2,6}.0^{4,9}]decan-3-one (33b)

A solution of napthoquinol 32b (1.16g, 6.04mmol) in 500ml of benzene was purged with nitrogen for 90 minutes and irradiated internally (Pyrex immersion well, 450W Hanovia lamp, uranium glass filter), the photolysis was followed by GLC (at

180°C, the retention time of 32b is 5.12 minutes and the retention time of the photoproduct (33b) is 3.32 minutes) and stopped after three and a half hours (less than 1% of 32b remained). Benzene was removed under reduced pressure and a yellow oily residue was obtained. The residue was purified by silica gel column chromatography using a 1:1 mixture of ethyl acetate and petroleum ether (65-110°C) as eluent. A white solid was isolated which on recrystallisation from petroleum ether (65-110°C) and a small amount of ethyl acetate, provided 0.83g (71%) of the cage keto-alcohol (33b) as white cubic shaped crystals of melting point 194-196°C (sealed tube).

Compound 33b displayed the following spectral characteristics : IR (KBr) 1730cm^{-1} (C=O), 3400cm^{-1} (O-H); ms (parent) m/e 192; ^{1}H NMR ($CDCl_3$) δ 1.05 (dd, 1H, J_1=12.5Hz, J_2=3Hz), δ 1.14 (s, 3H, C(6) or C(7) methyl), δ 1.29 (s, 3H, C(6) or C(7) methyl), δ 1.59 (s, 1H, exc with D_2O), δ 1.73 (dd, 1H, J_1=12.5Hz, J_2=3Hz), δ 2.05 (d, 1H, J=13Hz, C(1) or C(2) methine), δ 2.17 (d, 1H, J=13Hz, C(1) or C(2) methine), δ 2.18 (dd, 1H, J_1=9Hz, J_2=2.5Hz), δ 2.30 (dd, 1H, J_1=9Hz, J_2=2.5Hz), δ 2.38 (d futher split, 1H, J=9Hz, C(4) or C(9) methine), δ 2.50 (d futher split, 1H, J=9Hz, C(4) or C(9) methine), δ 4.06 (br s, 1H, C(10) methine).

6,7-Dimethyl-10-exo-hydroxytetracyclo[5.3.0.$0^{2,6}$.$0^{4,9}$]-decane-3-ketoxime methyl ether (34b)

The cage keto-alcohol (33b) (318mg, 1.66mmol) was dissolved in 5ml of methanol in a 50ml round bottom flask. Methoxyamine

hydrochloride (1.11g, 13.25mmol) and potassium acetate (650mg, 6.63mmol) were added to the above solution with stirring whereupon a heavy suspension was formed. The flask was then equipped with a reflux condenser and the suspension was heated with stirring with slow addition of water until a clear colourless solution was formed. This solution was refluxed for 20 hours. After cooling the reaction mixture to room temperature, the methanol was removed under reduced pressure and the residue was diluted with water and extracted with four 20ml portions of ethyl acetate. The combined extracts were washed with water, brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and a yellow oil was obtained. Purification by distillation using a Kugelrohr oven (oven temperature 140°C, pressure 0.1mmHg) afforded 337mg (92%) of the oxime ether 34b as a colourless oil.

Compound 34b displayed the following spectral characteristics : IR (film) 1650cm^{-1} (C=N), 3375cm^{-1} (O-H); ms (parent) m/e 221; ^{1}H NMR ($CDCl_3$) δ 0.84 (dd, 1H, J_1=6Hz, J_2=3Hz), δ 0.87 (dd, 1H, J_1=6Hz, J_2=3Hz), δ 1.02 (quasi doublet, 3H, "J"=4Hz, C(6) or C(7) methyl), δ 1.23 (s, 3H, C(6) or C(7) methyl), δ 1.40-1.60 (br shoulder, 1H, exc with D_2O), δ 1.54 (dd, superimposed on the shoulder, 1H, J_1=13Hz, J_2=3Hz), δ 1.82 (dd, 1H, J_1=13Hz, J_2=3Hz), δ 1.95-2.04 (two superimposed doublets, 1H), δ 2.23 (quasi triplet futher split, 1H), δ 2.41 (d futher split, 1/2 H, J=9Hz), δ 2.47 (d futher split, 1/2 H, J=9Hz), δ 2.53 (dd, 1/2 H, J_1=9Hz, J_2=2.5Hz), δ 2.73 (d futher split, 1/2 H, J=10Hz), δ 3.12 (dd, 1/2 H, J_1=9Hz, J_2=2.5Hz),

δ 3.45 (d futher split, 1/2 H, J=10Hz), δ 3.77-3.82 (two sharp singlets, ratio=7:5, total 3H, two non-equivalent O-methyls), δ 3.97 (quasi doublet, 1H, "J"=5Hz, C(5) methine).

Picrate of 4,5-Dimethyl-11-aza-pentacyclo-[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]decane

An oven-dried 25ml two necked flask equipped with a rubber septum, a magnetic stirring bar, and a reflux condenser connected to a source of dry nitrogen was charged with 3.37ml of LAH solution (1.45M, 4.88mmol) in THF. Sulphuric acid (100%) (130ul, 2.46mmol) was added dropwise over a period of 10 minutes while the LAH solution was vigorously stirred in a cold water bath (5-10°C). A white precipitate of lithium sulphate was produced together with vigorous evolution of hydrogen, and a grey suspension was formed which was allowed to stir for one hour at room temperature. To this suspension at room temperature was added slowly with stirring 180mg (0.81mmol) of oxime ether (34b) dissolved in 5ml of THF. The reaction mixture was then refluxed for 8 hours. After the reaction had cooled to room temperature, the flask was immersed in a cold water bath (5-10°C) and 1ml of 1:1 aqueous THF was introduced slowly to decompose the excess hydride. This was followed by the addition of 4ml (3.13M) aqueous sodium hydroxide solution. The original voluminous precipitate coagulated to a much smaller gelatinous mass. The THF solution was decanted and the aqueous phase was extracted with three 10ml portions of ether. The combined organic extracts were dried over anhydrous sodium sulphate and

the solvent evaporated under reduced pressure to afford a white solid residue. The residue was purified by alumina column chromatography using methanol-chloroform (8:92) as eluent. In this way, 30mg (21%) of the desired cage amine (29) was isolated which was homogeneous by GLC (at 165°C, the retention time of 29 is 1.66 minutes).

To 30mg (0.17mmol) of the cage amine dissolved in 2ml of chloroform , 60mg (0.26mmol) of dry picric acid dissolved in 1ml of benzene was added. The picrate was precipitated in the form of yellow needles which were found to have a melting point of 262-265°C.

The picrate displayed the following spectral characteristics : IR (KBr) 2950cm^{-1} (secondary amine salt), 1320-1360cm^{-1} (NO_2); ^1H NMR (DMSO d_6) δ 1.05 (d, 2H, J=12Hz, C(3) and C(6) outer H's), δ 1.16 (s, 6H, C(4) and C(5) methyls), δ 1.57 (d, 2H, J=12Hz, C(3) and C(6) inner H's), δ 2.40 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 2.56 (s, 2H, C(2), C(7) or C(9), C(10) methines), δ 4.16 (br s, 2H, C(1) and C(8) methines), δ 8.57 (s, 2H, aromatic ring H's), δ 8.55-8.75 (broad shoulder, 2H, exc with D_2O, NH_2). For detailed description of assignments, see results and discussion.

Anal. Calcd for $C_{18}H_{20}N_4O_7$: C 53.46, H 4.99, N 13.85. Found C 53.26, H 4.79, H 13.63.

References

1. W.M.Stanley, Science, 81, 644(1935).
2. A.D.Hershey and M.Chase, J. Gen. Physiology, 36, 39(1952).
3. A.B.Sabin, N. Engl. J. Med., 293, 986(1975).
4. D.W.Swallow, "Progress in Medicinal Chemistry", vol.8, G.P.Ellis and G.B.West editors, chapter 4, London, Butterworths, 1971.
5. J.M.Best and J.E.Banatvala, J. Biol. Stand., 3, 107(1975).
6. G.Emodi, T.Rufli, M.Just and R.Hernadez, Scand. J. Infec. Dis. , 7, 1(1975)
7. A.K.Field, A.A.Tytell, G.P.Lampson and M.R.Hilleman, Proc. Nat. Acad. Sci. (U.S.), 61, 340(1968).
8. J.H.Park and S.Baron, Science, 162, 811(1968).
9. M.Nemes, A.A.Tytell, G.P.Lampson, A.K.Field and M.R.Hilleman Proc. Soc. Exp. Biol. Med., 132, 776(1969).
10. H.B.Levy, G.Baer, S.Baron, C.F.Gibbs, M.Idarola, W.London and J.M.Rice, I. R. C. S., 2, 1643(1974).
11. E.L.Stephen, W.L.Pannier, M.L.Sammons, S.Baron, H.B.Levy and R.O.Spertzel, Fed. Proc., 34, 960(1975).
12. R.H.Adamson and S.Fabro, Nature, 223, 718(1969).
13. A.D.Steinberg, S.Baron and N.Talal, Proc. Nat. Acad. Sci. (U.S.) 63, 1102(1969).
14. P.J.Price, W.A.Suk, E.M.Zimmerman, G.J.Spahn, A.F.Gazdar and S.Baron, J. Nat. Cancer Inst., 50, 1299(1973).
15. W.W.Hoffman, J.J.Korst, J.F.Niblack and J.H.Cronin,

Antimicrob. Agents Chemotherapy, 3, 498(1973).

16. C.Panusarn, E.D.Stanley, V.Dirda, M.Rubenis and G.G.Jackson, N. Eng. J. Med., 291, 57(1974).

17. R.G.Douglas, Jr. And R.F.Betts, Infect. Immun., 9, 506(1974).

18. R.F.Krueger and G.D.Mayer, Science, 169, 1213(1970).

19. R.F.Krueger and G.D.Mayer, Science, 169, 1214(1970).

20. W.L.Albrecht, E.R.Andrews, R.W.Fleming, J.M.Grisar, S.W.Horgan, A.D.Sill, F.W.Sweet and L.Wenstrup, Abstract No. 160, Nat. Meeting Am. Chem. Soc. Chicago, III., Sept. 1970.

21. W.L.Albrecht, E.R.Andrews, R.W.Fleming, J.M.Grisar, S.W.Horgan, A.D.Sill, F.W.Sweet and L.Wenstrup, paper presented at the Int. Colloq. On Interferon and Interferon Inducers, Louvain, Sept. 1971.

22. R.Krueger, G.D.Mayer, K.P.Camyre and Yoshimura, paper presented at the 11th Intersci. Conf. Antimicrob. Agents Chemotherapy, Alantic City, N.J., Oct. 1971.

23. J.F.Niblack, paper presented at the 23rd Int. Congress of Pure and Applied Chem., Boston, Mass. 1971.

24. E.C.Herrman, Jr., Proc. Soc. Exp. Biol. Med., 107, 142(1961).

25. H.E.Kaufman, Proc. Soc. Exp. Biol. Med., 109, 251(1962).

26. F.O.MacCllum and B.E.Juel-Jensen, Brit. Med. J., 2, 805(1966).

27. F.O.MacCllum, B.E.Juel-Jensen, A.M.R.Mackenzie and M.C.Mike, Brit. Med. J., 4, 776(1970).

28. E.De Clerg, J.Descamps, P.De Somer, P.J.Barr, A.S.Jones and R.T.Walker, Proc. Nat. Acad. Sci. (U.S.), 76, 2947-2951(1979).

29. M.P. de Garilhe and J.de Rudden, C. R. Acad. Sci. 259, 2725(1964).

30. R.W.Sidwell, G.Arnett and D.J.Dixon, 7th Intersci. Conf. Antimicrob. Agents Chemotherapy Abstract No. 64 (1967).

31. R.W.Sidwell, G.J.Dixon, S.M.Sellers and E.M.Schabel, Jr., Appl. Microbiol., 16, 370(1968).

32. F.M.Schabel, Jr., Chemotherapy, 13, 321(1968).

33. D.Pavan-Langston and C.H.Dohlman, Am. J. Opthalmol., 74, 81(1972).

34. Chem. Eng. News, Oct. 30th, 8(1978).

35. J.M.Campell, R.F.Maes, T.J.Wiktor and H.Koprowski, Virology, 34, 701(1968).

36. L.N.Simon, R.W.Sidwell, G.P.Khare, D.G.Streeter, J.P.Miller, J.T.Witkowski, J.H.Huffman and R.K.Robins, Virus Res. Symp. Mol. Biol. Proc., 415-428(1973).

37. L.N.Simon, R.W.Sidwell, G.P.Khare, J.P.Miller, J.T.Witkowski, and R.K.Robins, Antimicrob. Agents Chemotherapy, 3, 517(1973).

38. L.N.Simon, R.W.Sidwell, G.P.Khare, L.B.Allen, J.T.Witkowski, J.H.Huffman and R.K.Robins, Antimicrob. Agents Chemotherapy, 3, 242(1973).

39. Thomas H. Maugh II, Science, 192, 128-132(1976).

40. H.J.Eggers and I.Tamm, J. Exp. Med., 113, 657(1961).

41. H.J.Eggers and I.Tamm, R.Bablanian, A.F.Wagner and

K.Folkers, Nature, 223, 785(1969).

42. D.G.O'Sullivan, D.Pantic and A.K.Wallis, Experientia, 23, 704(1967).

43. D.G.O'Sullivan, D.Pantic and A.K.Wallis, Experientia, 24, 1185(1968).

44. Chem. Eng. News, Sept. 1st, 5(1980).

45. D.Hamre, J.Bernstein and R.Donvick, Proc. Soc. Exp. Biol., 73, 275(1950).

46. K.A.Brownlee and D.Hamre, J. Bacteriol., 61, 127(1951).

47. K.A.Brownlee , D.Hamre and R.Donvick, J. Immunol., 67, 305(1951).

48. R.L.Thompson, S.A.Minton, J.E.Officer and G.H.Hitchings, J. Immunol., 70, 229(1953).

49. D.J.Bauer, K.Apostolov and J.W.T.Selway, Ann. N.Y. Acad. Sci., 173, 314(1970).

50. G.H.Werner, Norw. Press. Med., 1, 805(1972).

51. N.L.Shipowitz, R.R.Bower, R.N.Appell, C.W.Nirdeen, L.R.Overby, W.R.Roderick, J.B.Schleicher and A.M.Von Esch, Appl. Microbiol., 26, 264(1973).

52. D.D.Gerstein, C.R.Dawson and J.O.Oh, Antimicrob. Agents Chemotherapy, 7, 285(1975).

53. R.G.Duff, N.L.Shipowitz and L.R.Overby, 15th Intersci. Conf. Antimicrob. Agents Chemotherapy, paper No. 241, Sept. 1975.

54. J.C.H.Mao, E.E.Robinshaw and L.R.Overby, J. Virol., 15, 1281(1975).

55. J.C.H.Mao, E.E.Robinshaw and L.R.Overby, J.B.Schleicher,

A.Reuter and N.L.Shipkowitz,
Antimicrob. Agents Chemotherapy, 6, 360(1974).

56. H.E.Renis, Ann. N.Y. Acad. Sci., 173, 527(1970).

57. M.G.Soret, Antimicrob. Agents Chemotherapy, 160(1969).

58. H.E.Renis, Antimicrob. Agents Chemotherapy, 167(1969).

59. G.A.Elliot, D.A.Buthala and E.N.DeYoung,
Antimicrob. Agents Chemotherapy, 173(1969).

60. C.E.Hoffman, R.F.Haff and E.M.Neumayer, Fed. Proc., 23,
Abstract No. 1716-1720 (1964).

61. W.L.Davis, R.R.Grunert, R.F.Haff, J.W.McGahen,
E.M.Neumayer, M.Paulshock, J.C.Watts, T.R.Wood,
E.C.Herrmann, Jr. And C.E.Hoffmann,
Science, 144, 862(1964).

62. G.G.Jackson, R.C.Muldoon and L.K.Akers,
Antimicrob. Agents Chemotherapy, 703(1963).

63. T.R.Wood, Ann. N.Y. Acad. Sci., 130, 419(1965).

64. N.Kato and H.J.Eggers, Virology, 37, 632(1969).

65. A.A.Tsunoda, H.F.Maassab, K.W.Cochran and W.C.Eveland,
Antimicrob. Agents Chemotherapy, 553(1965).

66. K.Lundahl, J.Schut, J.L.M.A.Schlatmann, G.B.Paerels and
A.Peters, J. Med. Chem., 15, 129(1972).

67. D.L.Swallow, "Progress in Drug Research", vol. 22,
E.Jucker editor, Birkhauser, Basel and Stuttgart,
p. 268-326(1978).

68. P.Delongchamps, Chemical Abstracts, 75, 76469D(1971).

69. P.Delongchamps, Chemical Abstracts, 83, 9327H(1975).

70. W.K.Appel, T.Greenhough, J.R.Scheffer, J.Trotter and

L.Walsh, J. Am. Chem. Soc., 102, 1159(1980).

71. (a). R.J.Stedman, Chemical Abstracts, 71, 101418P(1969).
(b). R.J.Stedman, Chemical Abstracts, 76, 72123J(1972).

72. Andre R.Gagneux and Rene Meier, Tetrahedron Lett., 1365-1368(1969).

73. T.Sasaki, S.Eguchi, T.Kiriyama and O.Hiroaki, Tetrahedron, 30, 2707(1974).

74. P. Singh, J. Org. Chem., 44, 843(1979).

75. R.C.Cookson, E,Grundwell, R.R.Hill and J.Hudec, J. Chem. Soc., 3062(1964).

76. H.Setter, P.Tacke and J.Gartner, Chem. Ber., 93, 3480(1964).

77. E.E.van Tamelen, M.Shamma, A.W.Burgsthaler, J.Wolinski, R.Tamm and P.E.Aldrich, J. Am. Chem. Soc., 91, 7315(1969).

78. J.E.Baldwin, J. Chem. Soc. Chem. Comm., 738(1976).

79. L.Pauling, "The Nature of Chemical Bond", 3rd edition, Cornell University Press, New York, 1960, p. 136.

80. K.E.Wilson, R.T.Seidner and S.Masamune, J. Chem. Soc. Chem. Comm., 213(1970).

81. Jean-Louis Luche, J. Am. Chem. Soc., 100, 2226(1978).

82. J.R.Scheffer and S.Shephard, unpublished results.

83. G.W.K.Cavill and R.J.Quinn, Australian Journal of Chemistry, 26, 595(1973).

84. J.R.Scheffer, K.S.Bhandari, R.E.Gayler and R.A.Wostradowiski, J. Am. Chem. Soc., 97, 2178(1975).

85. (a). reference 75.

(b). P.E.Eaton and S.A.Cerefice,
J. Chem. Soc. Chem. Comm., 1494(1970).
(c). J.C.Barborak, L.Watts and R.Petit, J. Am. Chem. Soc., 88 , 1328(1966).

86. Reference 70 and references cited therein.

87. N.Umino, T.Iwakuma, M.Ikezaki and N.Itoh, Chem. Pharm. Bull., 26, 2897(1977).

88. H.Feuer and D.M.Braustein, J. Org. Chem., 34, 1817(1969).

89. J.Lambert, H.F.Shurvell, L.Verbit, R.G.Cooks and G.H.Stout "Organic Structural Analysis", Macmillan, N.Y., 1976, p. 126-129.

90. A.T.Bottini and J.D.Roberts, J. Am. Chem. Soc., 80, 5203(1958).

91. H.Gunther, "NMR Spectroscopy (An Introduction)" translated by R.W.Gleason, John Wiley and Sons, 1980, p. 225.

92. G.E.Keck, S.Fleming, D.Nickell and P.Weider, Syn. Comm., 9, 281(1979).

93. A.P.Kozikowski and H.Ishida, J. Am. Chem. Soc., 102, 4265(1980).

94. J.J.Turfariello, G.B.Mullen, J.T.Tegeler, E.J.Trybulski, S.C.Wong and Sk.Asrof Ali, J. Am. Chem. Soc., 101, 2435(1979).

95. R.F.Borch, M.D.Berstein and D.H.Durst, J. Am. Chem. Soc., 93, 2897(1971).

96. W.Appel and J.R.Scheffer, unpublished results.

97. N.M.Yoon and H.C.Brown, J. Am. Chem. Soc., 90, 2927(1968).

98. (a). reference 89, p. 33-34.

(b). reference 91, p. 86-89.

99. D.J.Herbert, J.R.Scheffer, A.S.Secco and J.Trotter, Tetrahedron Lett., 22, 2941(1981).

100. S.Winstein, P.Carter, F.A.L.Anet and A.J.R.Bourn, J. Am. Chem. Soc., 87, 5247(1965).

101. A.Mandelbaum and M.Cais, J. Org. Chem., 27, 2243(1962).

102. H.Weingarten, J.P.Chupp and W.A.White, J. Org. Chem., 32, 3246(1967).

103. Gabrielle-Anne Craze and I.Watt, J. Chem. Soc. Chem. Comm., 147(1980).

104. W.C.Still, M. Kahn and A.Mitra, J. Org. Chem., 43, 2923(1978).