A Synthetic Studies of Precurors to Daunomycin

B Solvolysis Studies of Hydroxythioacetals and an Attempted Synthesis of Yashabushiketol

by

Raymond James Hill

A thesis submitted to the

Faculty of Graduate Studies and Research

of the University of Manitoba

In Partial Fulfillment of the Requirements

for the degree

Masters of Science

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To my loving wife,

Dorothy

"A SYNTHETIC STUDIES OF PRECURORS TO DAUNOMYCIN

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I would like to express my gratitude to my supervisor Dr. C.M. Wong for his guidance and time given so freely, but especially for his patience in allowing me to persue my own methods even if he felt they would not work.

My thanks is due Dr. Robert J. Schwenk for moral support in times of trouble and Dr. T.-L. Ho for taking me under his wing while Dr. Wong was away for a time.

Abstract

Part A

Butadiene was added to p-benzoquinone to give 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V. This Diels-Alder adduct was made aromatic, then methylated with K_2CO_3/dimethyl sulfate to give 5,8-dimethoxy-1,4-dihydronaphthalene VI. Hydrolysis of the double bond with B_2H_6/H_2O_2 followed by oxidation of the alcohol yielded 5,8-dimethoxy-2-tetralone IX. Conversion of IX to 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII was accomplished either by addition of an acetylene Grignard followed by hydrolysis with mercuric salts or by addition of HCN to the ketone, blockage of the alcohol and then addition of methyl lithium to the nitrile.

β-Propiolactone was stirred with $NaNO_2$ to give 3-nitropropionic acid XXVII. With the acid halide XXVIII of this compound was condensed methylvinylcarbinol to yield sec-butenyl 3-nitropropionate XXIX. Ozonolysis of the product afforded 1'-formylethyl 3-nitropropionate XXX which would not cyclize to 4-nitro-5-hydroxy-6-methyl-2-pyranone.

Part B

Several α-hydroxy thioacetals were synthesized, then hydrolized with $Tl(CF_3CO_2)_3$ to test the specificity of its solvolysis reaction.

Benzyl magnesium chloride was reacted with allyl bromide to give 4-phenyl-1-butene (XXXVIII) which was epoxidized to yield 1,2-epoxy-4-phenyl butane XXXIV. To this was added the anion of cinnamaldehyde thioacetal XLI giving yashabushiketol thioketal XLIII. Solvolysis yielded not racemic yashabushiketol XLIV as hoped, but cis and trans 2-phenyl-6-(2'-phenylethyl) tetrahydro-4-pyrone.

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PART A

INTRODUCTION

Daunomycin (fig. i), a new antibiotic isolated from Streptomyces peucetius[1], has been shown to inhibit DNA and RNA synthesis in vivo in bacterial cells[2] and animal cells[3-5] and to inhibit DNA-dependent RNA polymerase and DNA polymerase in vitro.[6] This inhibition results from the fact that daunomycin binds to the DNA Template; in the case of cells, to the DNA of the chromosome.[7] Thus, daunomycin is toxic and specific for animal tumor cells which have an accelerated rate of growth.

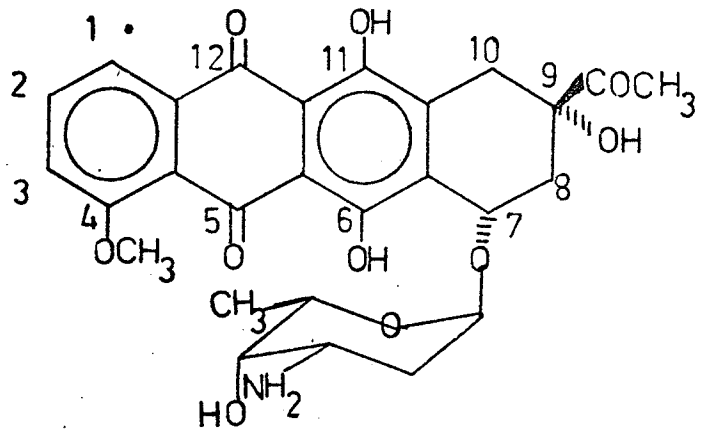
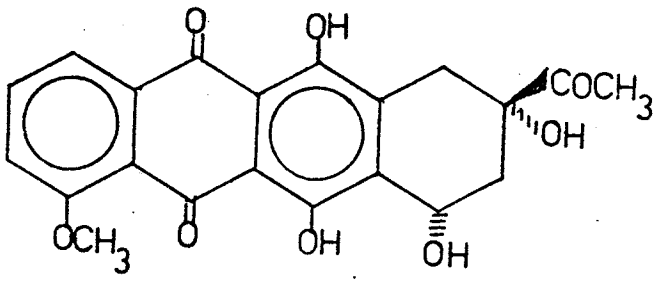


Figure i

In clinical applications, a dose of 1 mg/kg per day for 6 to 8 days produces complete or good partial remission in childhood leukemia with seemingly no accumulative bone marrow damage.[8]

Daunomycin consists of two moieties: daunomycinone (fig. ii a), an aglycone, the structure of which was finally elucidated by Mondeli et al.[9,10], and an amino sugar, daunosamine (fig. iib)[11],

which is attached to the aglycone via an α-linkage at C-7.



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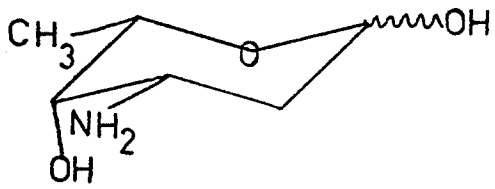


b

Figure ii

THE NATURE OF THE PROBLEM

Goodman et al.[12] have synthesized the amino sugar, daunosamine, while the synthesis of racemic daunomycinone has recently been accomplished in this laboratory.[13]

The first section of the work was devoted to finding a shorter, simpler synthesis of one of the intermediates of the daunomycinone synthesis, namely, 2-hydroxy-2-acetyl-5,8-dimethoxytetralin (fig. iii). The first section also involved an approach to the synthesis of the amino sugar, daunosamine, from a "non-sugar" starting material.

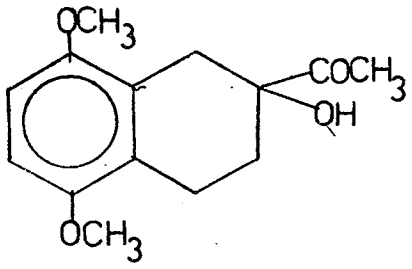


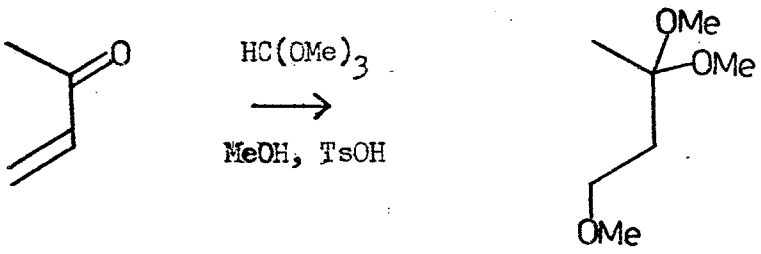
Figure iii

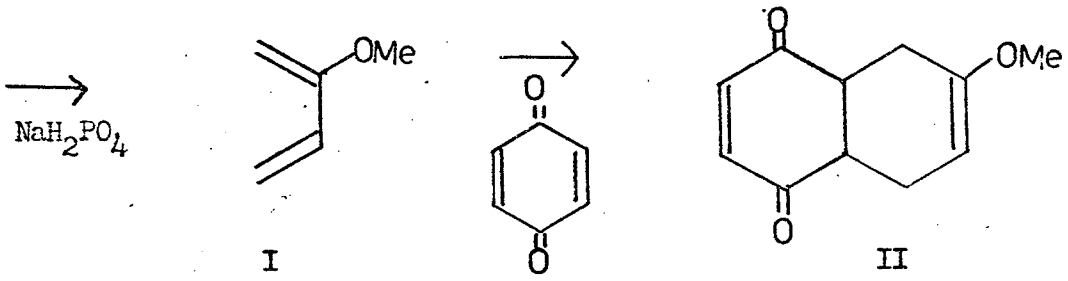
RESULTS AND DISCUSSION

5,8-dimethoxy-2-tetraline IX was prepared according to the procedure outlined by Grob and Jundt[14], scheme I, save for one small change. In lieu of sodium in methanol for enolization of the Diels-Alder adduct, II, to IIa, potassium carbonate in acetone was used. As a result, the yield from II to III was increased from 65% to 87%; otherwise, yields in scheme I were comparable to those of Grob and Jundt.

Due to the fact that the synthesis of the starting material, 2-methoxy-1,4-butadiene I, took two weeks to complete, the synthesis as outlined in scheme I was thought too lengthy and, therefore, an alternate synthesis of 5,8-dimethoxy-2-tetraline IV was devised (see scheme II).

p-Benzoquinone was reacted with butadiene in benzene at room temperature for one week to give 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V in 80% yield. The melting point, 51 - 53°C (all temperatures will be given in Celcius) corresponded to that given by Van Tamelen.[15] The infrared spectrum (i.r.), figure IR-I, gave the conjugated δ-diketone absorption at 1695 cm^{-1}; the nuclear magnetic resonance spectrum (n.m.r.), figure NMR-I, was as expected and the mass spectrum showed the required P = 162.





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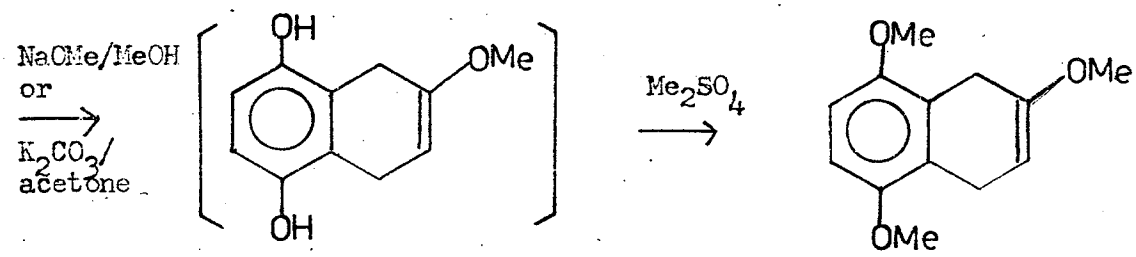

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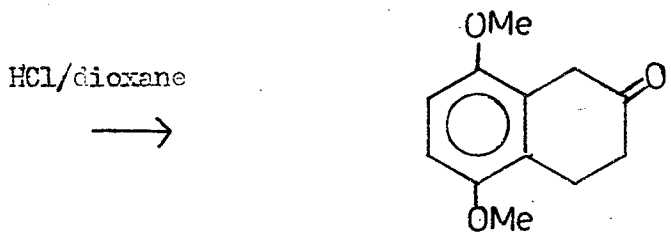


IX

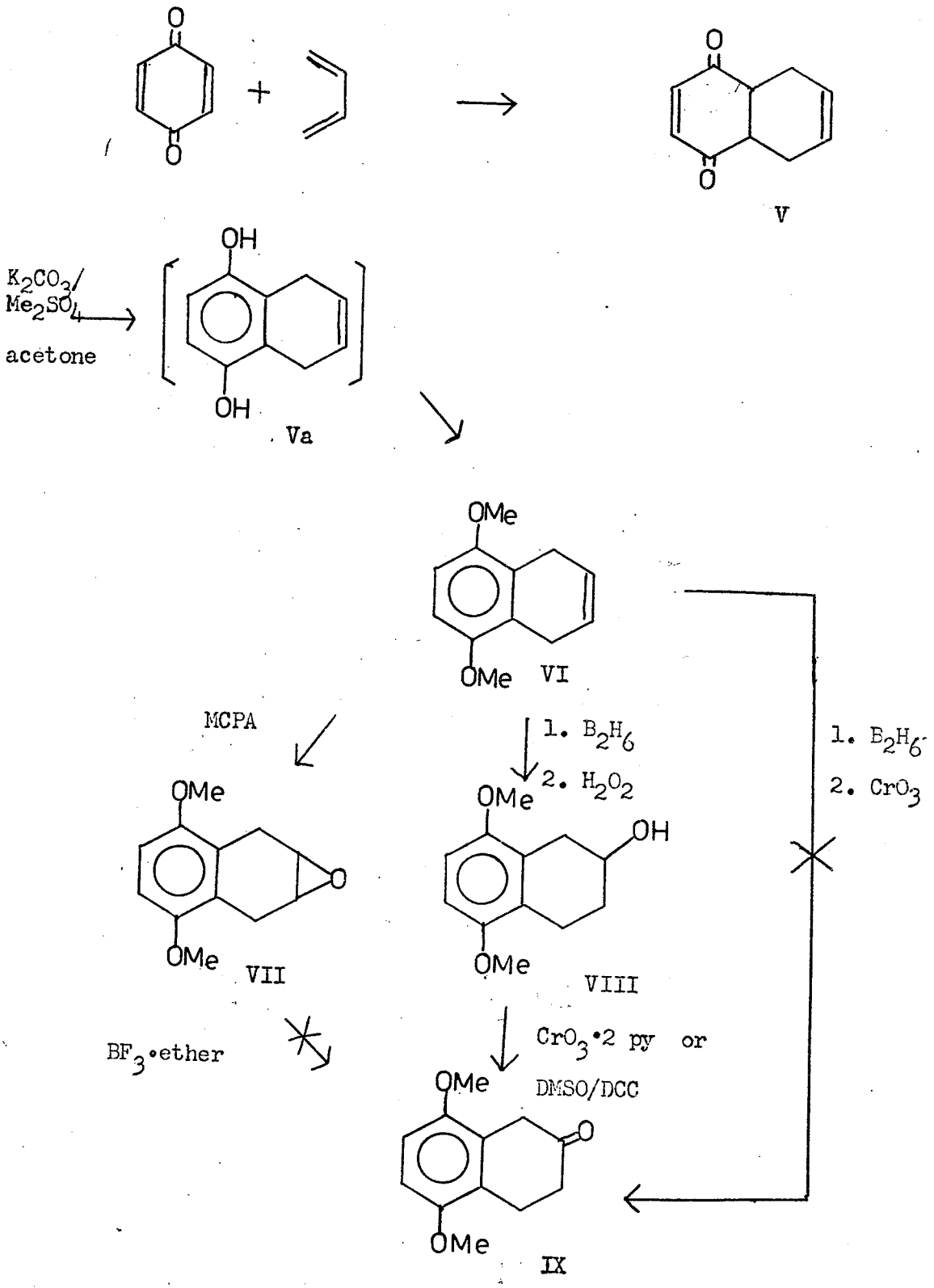
SCHEME I

The tetrahydronaphthoquinone V was then treated with K_2CO_3/Me_2SO_4 in acetone to give 5,8-dimethoxy-1,4-dihydronaphthalene VI, as a light brown oil which on distillation yielded a faintly yellow oil that crystallized on standing to a white solid m.p. 43 - 44° (Terent'ev[16] reports 50°). The i.r. (fig. IR-II) revealed no carbonyl absorption, but did show peaks corresponding to an aromatic double bond (1600 cm^{-1}), and ether linkages (1075, 1090 cm^{-1}). The n.m.r. (fig. NMR-II) was consistent with the structure VI and the mass spectrum again manifested the desired molecular ion at 190 amu.

At this point, several successful and unsuccessful attempts were made to convert the olefin VI to the tetralone IX.

One such attempt was to first convert the olefin VI to the epoxide VII, then to isomerize the epoxide to the ketone IX with BF_3 etherate. The epoxide formed smoothly at room temperature with MCPA (metachloroperbenzoic acid), giving a white crystalline solid in 75% yield, m.p. 131-132°. The i.r. (fig. IR-III) was similar to that of the olefin save for the appearance of a peak at 860 cm^{-1}, indicating the presence of the desired epoxide. The n.m.r. (fig. NMR-III) was now minus the olefinic proton absorptions and showed peaks at δ=6.61 (2H, s[singlet]) 3.75 (6H, s), ca 3.4 (4H, multiplet), and 2.5 - 3.0 (2H). The mass spectrum gave the desired P = 206. Attempts at isomerization, however, with BF_3 etherate in benzene or with acetic anhydride proved fruitless, with none of the desired ketone IX being isolated.

A one step conversion of the olefin VI to the ketone IX


V
K_2CO_3/
Me_2SO_4
acetone
Va
VI
MCPA
1. B_2H_6
2. H_2O_2
1. B_2H_6
2. CrO_3
VII
VIII
BF_3•ether
CrO_3•2 py or
DMSO/DCC
IX

SCHEME II

involving hydroboration followed by chromic acid oxidation also failed. The crude product of this procedure showed a single carbonyl peak at 1670 cm^{-1} in the i.r. so purification of the oil was not attempted. It is believed that the chromic acid attacked the susceptible benzylic position rather than cleave the alkyl-boron bond.

The successful approach to compound IX proved to be hydroboration of the olefin VI with subsequent oxidation to the alcohol VIII by H_2O_2/NaOH followed by oxidation employing the CrO_3-pyridine complex in methylene chloride.

The hydroboration of the olefin was carried out at room temperature and subsequent addition of H_2O_2 gave a snow-white crystalline crude product (m.p. 131 - 132°, Lewis reports 130.5 - 132°[17]) in essentially quantitative yield. The i.r. (fig. IR-IV) exhibited an absorption at 3640 cm^{-1} (OH stretch), along with the now familiar peaks in this series: aromatic double bonds, 1600 cm^{-1}, and ether linkages, 1095 cm^{-1}. The n.m.r. (fig. NMR-IV) showed resonances corresponding to aromatic protons at δ = 6.62 (2H, s), O<u>H</u> and C<u>H</u>OH ca 4.1 (broad, 2H), aromatic OCH_3 at 3.75 (6H, s), benzylic protons ca 2.8 (4H, multiplet), and aliphatic protons ca 1.9 (2H, multiplet). The mass spectrum was also consistent with the structure, giving fragment masses at 208 (P), 190 (P - H_2O) and 175 (P - H_2O, $\cdot CH_3$).

It was found that oxidation by CrO_3 in acetic acid was too vigorous and that the benzylic position was attacked. The mild CrO_3.2 pyridine complex oxidation was successful, however, giving

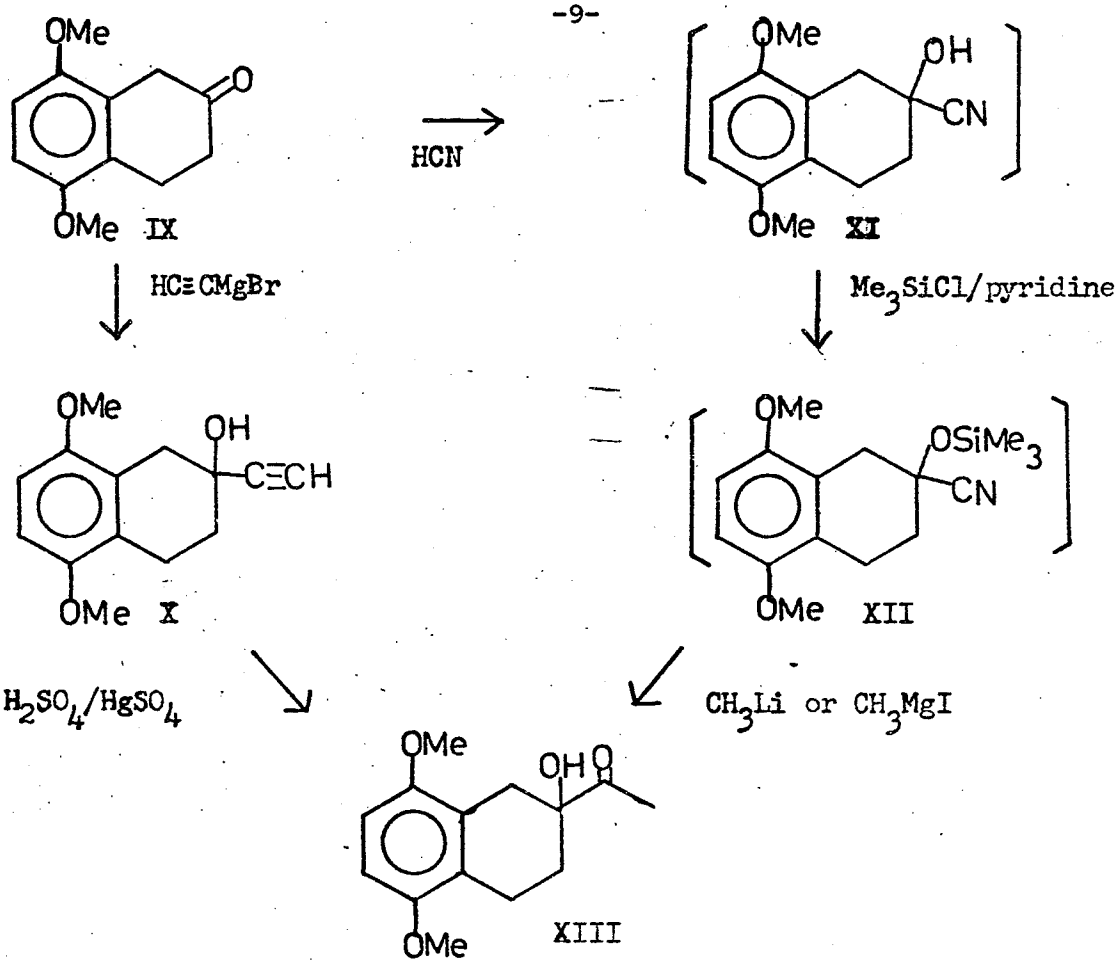
5,8-dimethoxy-2-tetraline IX in 84% yield as heavy white crystals (m.p. 98 - 99.5°).

The i.r. (fig. IR-V), n.m.r. (fig. NMR-V) and mass spectrum are identical to those given by the tetralone synthesized by Grob's method.[14] Oxidation of the alcohol VIII to the ketone IX employing dry dimethylsulphoxide (DMSO), Dicyclohexylcarbodiimide (DCC) was also successful. The yield was somewhat lower, but the method is amenable to conversion of larger quantities in a single reaction.

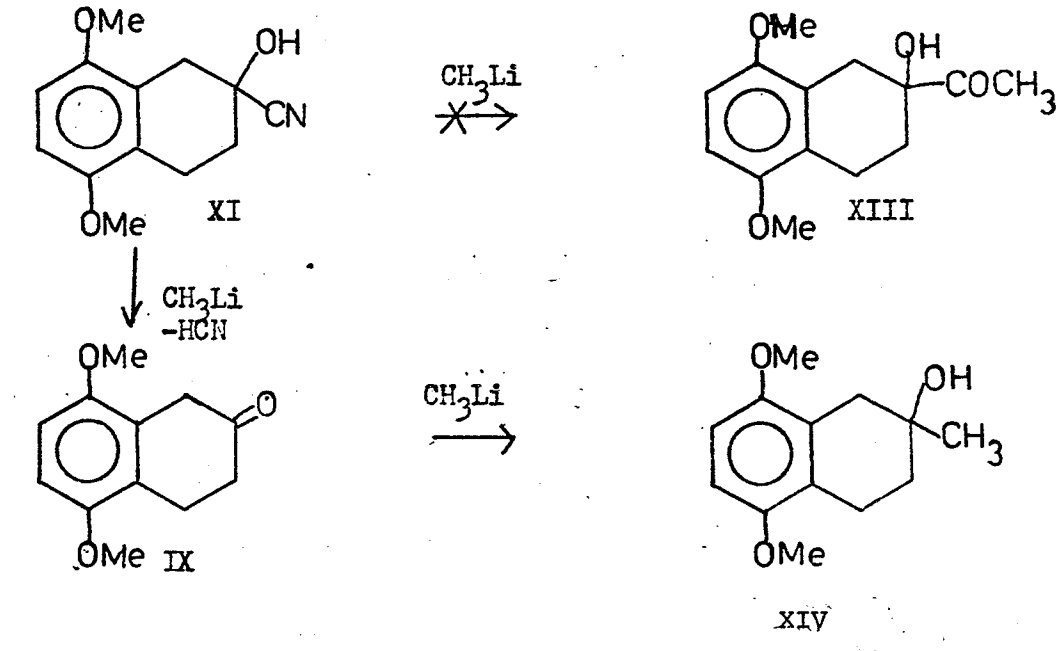
From the tetralone IX, two successful synthetic routes were found to the desired 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII (see scheme III).

The first route involved the conversion of the tetralone via an acetylene Grignard to 2-hydroxy-2-ethynyl-5,8-dimethoxytetralin X which could be isolated as a colorless oil in 83% yield. The i.r. (fig. IR-VI), now minus a carbonyl absorption, showed an absorption for an alcohol at 3630 cm^{-1} and the sharp acetylenic hydrogen stretch peak at 3340 cm^{-1}. The n.m.r. (fig. NMR-VI) was as expected; the mass spectrum also gave the desired molecular ion at 232 amu and P - H_2O at 214.

The hydroxyacetylene, compound X, which need not be isolated, was then hydrolysed with $HgSO_4/H_2SO_4$ in wet tetrahydrofuran (thf) to give 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII in 87% yield. The m.p., 102 - 102.5°, compared favourably to that reported by R.J. Schwenk[18] of 100 - 102°. The mixed m.p. with an authentic sample was unchanged and the i.r. (fig. IR-VII; compare IR-VIIA,



SHCEME III



SCHEME IIIA

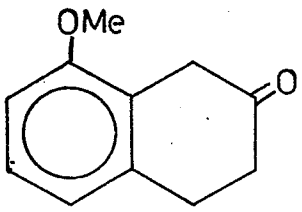
an authentic sample), n.m.r. (fig. NMR-VII) and mass spectrum were superimposable on those of the authentic sample.

The second successful approach involved: first, conversion of the ketone IX to its cyanohydrin XI (not isolated), blockage of the hydroxyl group with a trimethysilyl ether XII (also not isolated), and then the use of either methyl lithium or methyl magnesium iodide to convert the nitrile to a methyl ketone (see scheme III). Hydrolysis of the trimethylsilyl ether by dilute NH_4Cl/HCl afforded a product identical to the desired hydroxy ketone XIII.

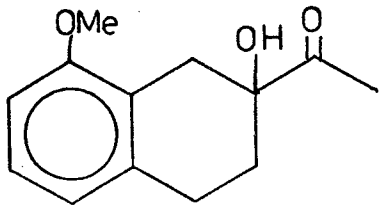
Addition of methyl lithium directly to cyanohydrins have been reported,[19] but in this case, the reaction of methyl lithium with the cyanohydrin XI gave a product which appears to have been compound XIV. The mass spectrum of the isolated product gave a molecular ion at 222 amu and the i.r. showed a hydroxyl group absorption but no carbonyl absorption. It seems that in basic medium, this cyanohydrin eliminates HCN to give the original ketone IX which then may add CH_3Li.

It might be mentioned at this point that 8-methoxy-2-tetralone XV[20] reacted analogously to the dimethoxytetraline IX, giving the hydroxyketone XVI through both the hydroxyacetylene and cyanohydrin intermediates. Since this was used as a model system, no data are reported excepting the i.r. (fig. IR-VIII) and n.m.r. (fig. NMR-VIII) of the hydroxyketone XVI.

An attempt to synthesize 2-hydroxy-2-(1'-oxo-2'-hydroxyethyl)-5,8-dimethoxytetralin XIX (which might be a useful intermediate in the



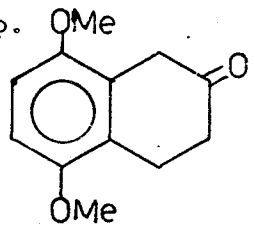
XV



XVI

proposed synthesis of adriamycinone XX,[21] the aglycone of another potent antitumor antibiotic, adriamycin) via scheme IV was a failure. The vinyl Grignard reacted in good yield with the dimethoxyketone IX to give the hydroxy olefin XVII, but subsequent attempts to epoxidize the double bond, varying reagents, conditions and blocking groups for the hydroxyl group gave at best 5% yields of compound XVIII.

Since radical conversions of α-hydroxyketones to α,α'-dihydroxyketones are already known [21, 22a, 22b] and are fairly efficient, this scheme was abandoned without attempting the final step.



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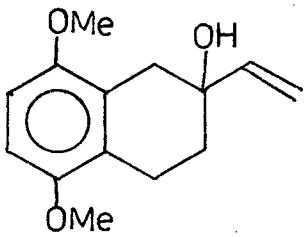
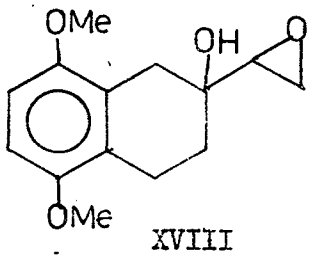
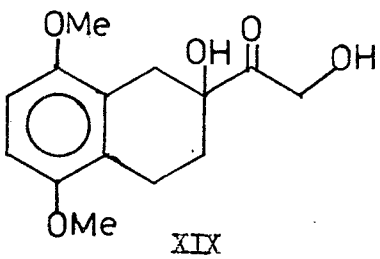


XVII

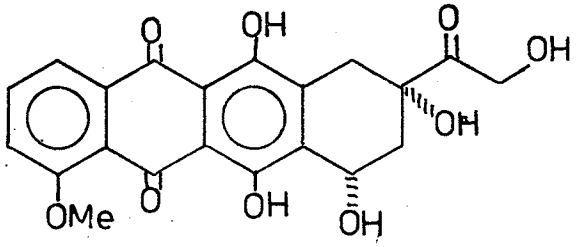


XVIII



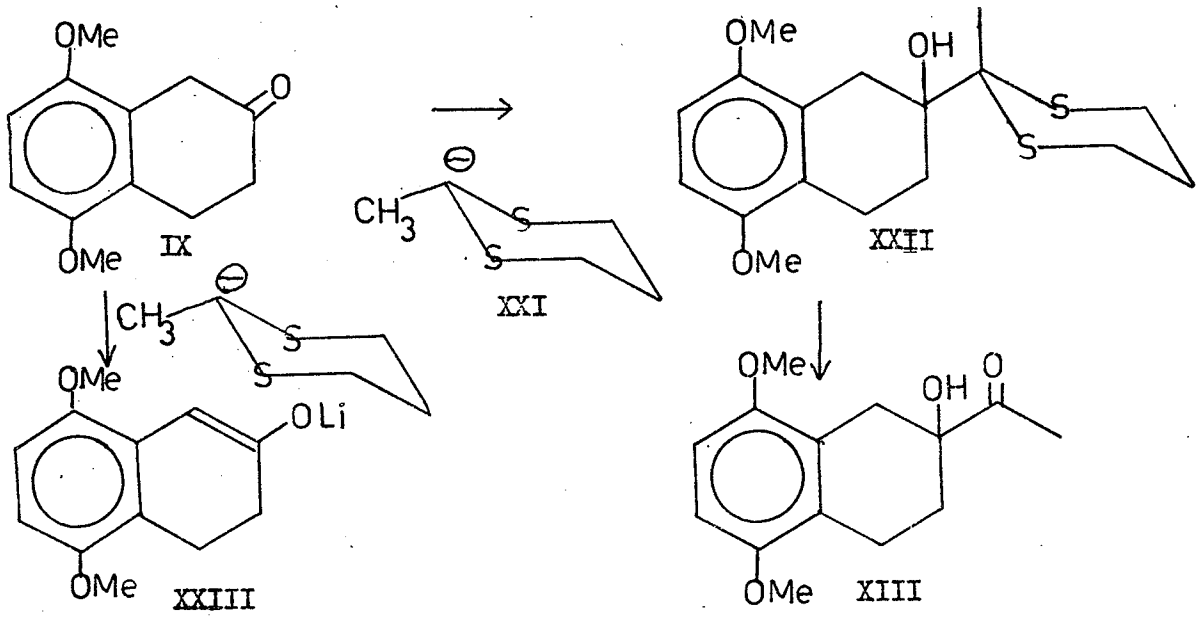
XIX

SCHEME IV



XX

Following this, the attempt to react the 2-methyldithiane anion XXI with the dimethoxytetralone IX (scheme V) also failed, giving compound XXII in yields of the order of 10% at best.



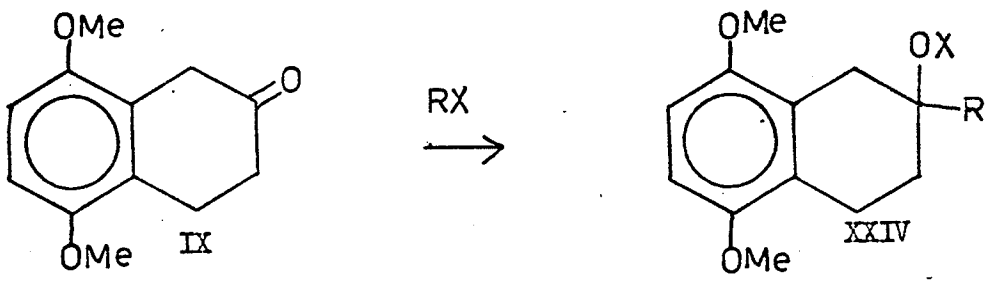
SCHEME V

Although unsuccessful in attaining the desired goals, these last two results would seem to be in agreement with an hypothesis promulgated by Pearson[23] denoting the reactivities of species in terms of hard/soft acids and bases (HSAB). He says that "hard" acids tend to react with "hard" bases and "soft" acids tend to

react with "soft" bases. The more localized the charge is, the harder the acid or base.

In this case, the C_2-carbon atom of the tetralone IX, being doubly bonded to the oxygen, would be quite electron deficient making it a much harder Lewis acid than the benzylic hydrogen.

The hard acetylene and vinyl Grignards (scheme VI), being sp and sp^2 hybridized anions respectively, preferentially attack the C_2-carbon atom while the soft lithium dithiane and ethyl Grignard (private communication from Dr. T.-L. Ho), being sp^3 anions, react with the benzylic hydrogen giving the anion XXIII (see table I)



SCHEME VI

TABLE I

Yields (%) of products of carbonyl addition of sp, sp^2, and sp^3 anions to compound XI

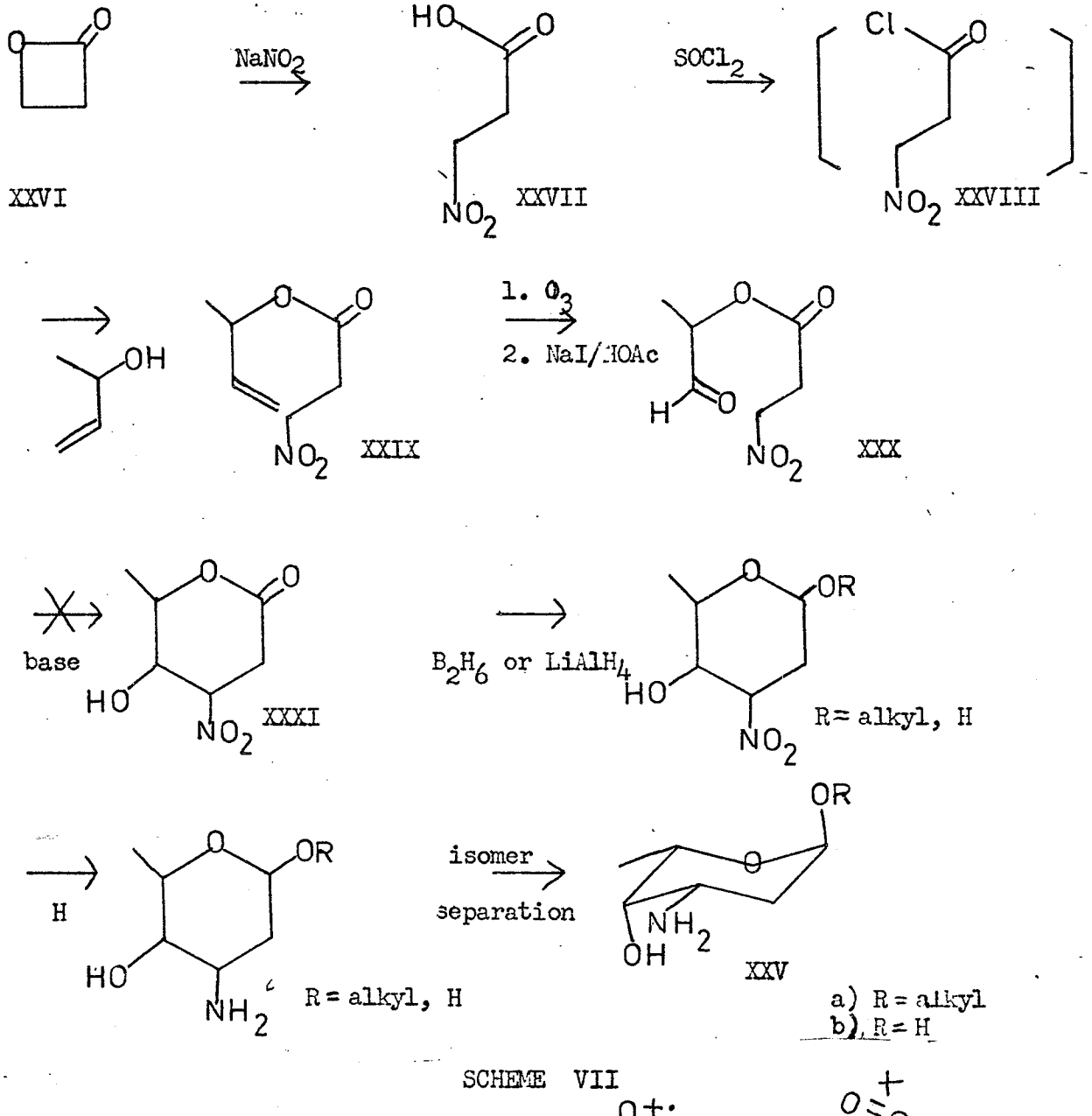
R	X	% XXIV
HC≡C	MgBr	83
H_2C=CH	MgCl	75
H_3C-CH_2	MgBr	10
$CH_3C(S)(S-(CH_2)_3)$	Li	10

In concluding this series, the synthesis of 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII, an intermediate in the laboratory prepration of daunomycinone iia, has been shortened with some improvements in yields.

An attempt at the racemic synthesis of a second intermediate of daunomycin, its sugar moiety, daunosamine XXVb, was not nearly as successful. The limitation was placed on the project (scheme VII) that the starting materials would not be sugars, which Goodman et al.[12] had used with success in his synthesis.

β-Propiolactone XXVI was reacted with aqueous sodium nitrite[24] to give the white crystalline 3-nitropropionic acid XXVII in 22% yield (m.p. 63 - 65°). The n.m.r. (NMR-X) and i.r. (IR-X) verified the results.

3-Nitropropionic acid was converted to its acid halide XXVIII with thionyl chloride, then, without isolation, was reacted with methylvinyl-carbinol to give sec-butenyl 3-nitropropionate XXIX, as a colorless oil, in 61% yield. The n.m.r. (NMR-XI) was in agreement with the structure, the vinyl and allyl protons (deshielded by the oxygen) showing as a four proton multiplet (δ = 5.0 to 6.1), the four methylene protons as broadened triplets at δ = 4.56 (2H) and δ = 2.90 (2H), and the methyl protons as a doublet at δ = 1.31 (3H). The i.r. (IR-XI) showed an ester carbonyl absorption at 1735 cm^{-1} and peaks corresponding to a nitro group at 1560 cm^{-1} and 1380 cm^{-1}. Although the mass spectrum showed no molecular ion at 173 amu, it did show expected fragments at 55, 71, and 102 amu (fig. iv). The elemental analysis made it quite certain that the



SCHEME VII

Figure iv

isolated ester was the expected compound XXIX.

The next step was an ozonolysis to convert the olefin XXIX to the aldehyde XXX. This step provided the aldehyde ester in 77% yield. The compound was found to be unstable on silica gel and several other solid supports so could not be purified by thin layer chromatography (t.l.c.) nor by column chromatography. Further, it was found to decompose when heated, even under high vacuum distillation. Because of this, its analysis was virtually impossible so the structure of compound XXX had to be confirmed primarily by its infrared spectrum and its n.m.r.

The i.r. (IR-XII) still had the nitro and ester peaks except that the ester peak was shifted to higher wave number by 5 cm^{-1} and also, that it had become quite broad, indicating the probability of the presence of another overlapping carbonyl frequency. There was great variance in the fingerprint regions between the olefin ester XXIX i.r. (IR-XI) and the aldehyde ester XXX i.r. (IR-XII), with several notable peaks (olefin, 1647 cm^{-1}; terminal methylidene, 935 cm^{-1}) absent in the latter.

The best evidence that the assignment is correct, however, comes from the n.m.r. (NMR-XII). The complex vinyl-allyl multiplet has been replaced by a clean quartet arising from the methine proton resonance. The two sets of broad triplets from the methylene protons are still in evidence as is the methyl doublet (although now flanked by impurities). The aldehyde peak at $\delta = 9.50$ would also seem to verify the structural assignment.

The fact that the aldehyde proton is not a doublet is

not anomalous. Karabatsos and Hsi[25] showed that because of a stable conformation, the coupling constants of α-substituted aldehydes commonly fall below 2 Hz (Hertz = cycles per second). At 50 Hz sweep width, The coupling shows only as a slight broadening, indicating a coupling constant (J) of 0.5 Hz or less.

There was no molecular ion at 175 amu in the mass spectrum. Beyond this, mass spectroscopy was not used as a tool for identification since small amounts of impurities may give prominent peaks at positions incongruous with the structure.

This series ended abruptly when the aldehyde XXX refused to cyclize to compound XXXI under the influence of basic catalysts including NaH, KOtBu and NaOtBu with solvents including thf, ether, benzene and tertiary butanol.

PART B

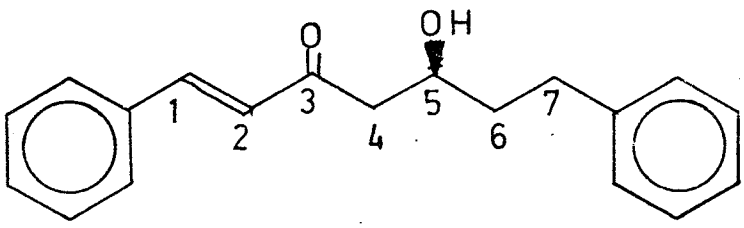
INTRODUCTION

Since the introduction of the addition of thioacetal anions to various electrophilic compounds by Corey and Seebach, there has been a flurry of activity to discover simple methods for hydrolysis of the resulting thioketals and thioacetals to their respective ketones and aldehydes. Some of these reagent-methods are: chloramine T,[26] ceric ammonium nitrate (CAN),[27] S-alkylation,[28, 29, 30] "soft" acid oxidation (Hg^{2+}, Cu^{2+}),[31, 32, 33, 34] concentrated sulphuric acid,[40] methylfluorosulphonate,[41] silver salts,[42, 43] N-halosuccinimide[44] and Tl $(CF_3CO_2)_3$[35].

THE NATURE OF THE PROBLEM

The attempted synthesis of the hydroxyketone XIII (section A) by scheme V as well as previous studies in this laboratory by T.-L. Ho and C.M.S. Wong[27, 35] prompted the study of the solvolysis of dithianes leading to α-hydroxyketones and α-hydroxyaldehydes.

The extension of this study was to carry out the racemic synthesis of the newly isolated yashabushiketol XXXIII,[36] a C_6-C_7-C_6 natural product from the male flowers of Alnus firma Sieb.



XXXIII