Studies towards C-nucleosides and oxacepham derivatives.

AN APPROACH TO THE SYNTHESIS OF C-NUCLEOSIDES
AND
STUDIES TOWARDS AN OXACEPHAM DERIVATIVE

A thesis

by

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PREFACE

The content of this thesis, includes "An approach to the synthesis of C-nucleosides (part I) and "Studies towards an oxacepham derivative" (part II). Each part is indexed separately with a listing of sub-headings in the text, and has an independent numbering system.

Part I, describes the synthesis of a valuable key intermediate, a α-keto acid, which makes C-nucleosides accessible, an explanation of an unusual cleavage reaction, and an ozonide rearrangement to D,L-talofuranuric acid derivatives.

After successful conclusion of the above subject, our immediate interest was a study towards the total synthesis of an oxacepham derivative and these results are described in part II, page 158.

Part I

An approach to the Synthesis of C-Nucleosides

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Abstract

The synthesis of an α-keto-ester acid as key intermediate for the preparation of C-nucleosides was studied, starting from furan and methyl β-nitroacrylate. The reaction pathway of an unusual cleavage with sodium metaperiodate was investigated and an older misconception corrected. The rearrangement of the ozonide leading to a 2,5-anhydroallose derivative was studied. During the course of this investigation a novel synthesis of dimethyl 1-O-oxalyl-2,3-di-O-isopropylidene β-D,L-ribohexofuran 5-ulosuronate was developed. In addition, several new D,L-talofuranuric acid derivatives were prepared.

Partie I

Contribution à la synthèse des C-nucléosides

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La synthèse d'un acide ester α-cétonique, intermédiaire clef dans la préparation des C-nucléosides, est réalisée à partir du furan et du β-nitroacrylate de méthyle. Le schéma réactionnel de la singulière scission au métaperiodate de sodium est étudié; la correction d'une conception périmée en résulte. La transposition d'un ozonide aboutissant à l'anhydro-2,5 allose est décrite. Au cours de cette étude une nouvelle synthèse de 1'O-oxalyl-1 di-O-isopropylidene-2,3-D,L-ribohexofuran ulosuronate de méthyle est mise au point. De plus, divers dérivés de l'acide D,L-talofuranurique sont préparés.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. George Just for his valuable advice and encouragement throughout this work.

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My colleagues for their helpful discussions.

Mrs. Annemarie Thomas for recording the p.m.r. spectra;

Mr. Frank Rothwell, for recording some of the mass spectra.

Finally, I would like to thank Mrs. Inge Wulf for her help in typing this manuscript.

III

DEDICATION

This thesis is dedicated to my wife and my children.

Table of Contents

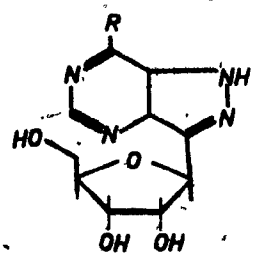
Chapter 1

a. Introduction

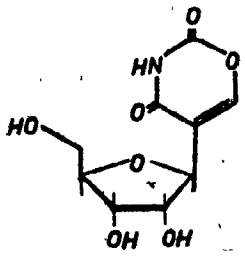
Among the relatively few naturally occurring nucleosides, which contain ribose bound to a carbon atom of the heterocyclic aglycone, some - the formycins (1)[1,2], oxazinomycin (2)[3], pyrazomycin (3)[4], and showdomycin (4)[5] - appear to act as antagonists to essential metabolites, whereas others - pseudouridine (5)[6], and formycin A (1a)[7,8] appear to resemble their respective counterparts - uridine and adenosine - to such degree as to be capable of functioning as metabolic substituents.

Recent studies[8,9] have focused on ribonucleoside phosphorylase, on the mode of action of C-nucleosides and their bio-synthesis. The observation of specific reversal of antiviral activity of pyrazomycin (3) by uridine alone points to pyrimidine biosynthetic pathways as a possible vulnerable site for growth inhibition[10].

The agricultural potential of formycin B (1b) against rice plant disease[11] and the inhibition of the multiplication of bromegrass mosaic virus in barley seedlings[12] has been noted, but no medical usefulness has thus far been demonstrated for members of the C-nucleoside class[11].



1a $R = NH_2$
1b $R = OH$



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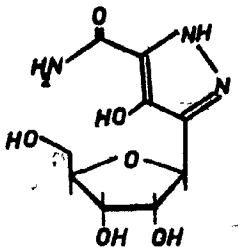

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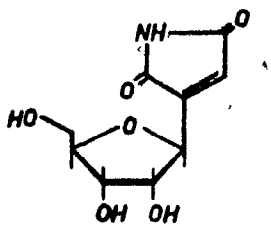

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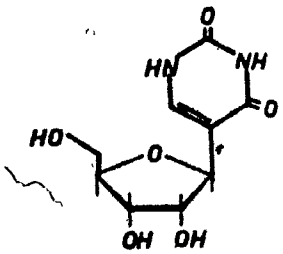


5

The preparation of additional C-nucleosides by synthesis or by modification of naturally available materials, together with a detailed understanding of structure - activity relationships, will assist in the realization of the therapeutic potential of this versatile group.

C-Nucleosides represent an important class of antibiotics due to their close analogy to the normal nucleoside metabolites. The varied effects of C-nucleosides on numerous enzymatic conversions render their further investigation as potential chemotherapeutic agents a worthwhile undertaking.

Recent surveys dealing with C-nucleoside research include a discussion of the relationship between nucleoside conformation and biological activity by Ward and Reich[13]. Suhadolnik has thoroughly reviewed the pertinent literature up to 1970[14]. The role of sugars in medicine, especially in chemotherapy, has been reviewed by Tronchet et al..[15] Structurally related compounds have been synthesized with the hope of enhancing biological activity. Parameters involved in "drug design" have been discussed[12-15] in detail.

b. Biological activity

Although broad-spectrum antibacterial agents and antibiotics have been developed to wide clinical usefulness over the period of the past 40 years, the comparable screening effort in the direction of the development of antiviral agents has yielded results so far short of the same degree of success[16-19].

This situation prevails despite the fact that respiratory conditions, especially those of viral origin, are responsible for more than half of all acute human illnesses[20-21].

In searching for a broad - spectrum antiviral agent, an effort was made to concentrate on the synthesis of compounds which have a potential effect on enzymatic processes which are common to all known viruses, such as virus-induced nucleic acid and protein synthesis. These processes are carried out by enzymes specifically coded for in the viral genome. Another common feature of all viruses is their lack of protein-synthesizing capability. It is conceivable that initiation of virus-specific protein and/or RNA synthesis may utilize unique viral enzymes which could be specifically inhibited.

A review by Wagner in 1971[23] gives details of nucleoside antimetabolites, which exert their activity by incorporation into DNA and RNA macromolecules, or by the inhibiton of enzymes, involved in nucleic acid synthesis.

Several C-nucleosides such as the ribofuranosyl nucleoside antibiotic pyrazomycin (3) (3β-D-ribofuranosyl-4-hydroxypyrazole-5-carboxamide) have been shown to have antiviral activity against rhinovirus, measels, herpes simplex, and vaccina viruses in tissue cultures[24-26]. Apparently inhibition of viral replication in vivo and toxicity to the host could be only partially separated in studies of (3)[10].

Another ribonucleoside antibiotic formycin (1) has also shown antiviral activity[27,28] in vitro.

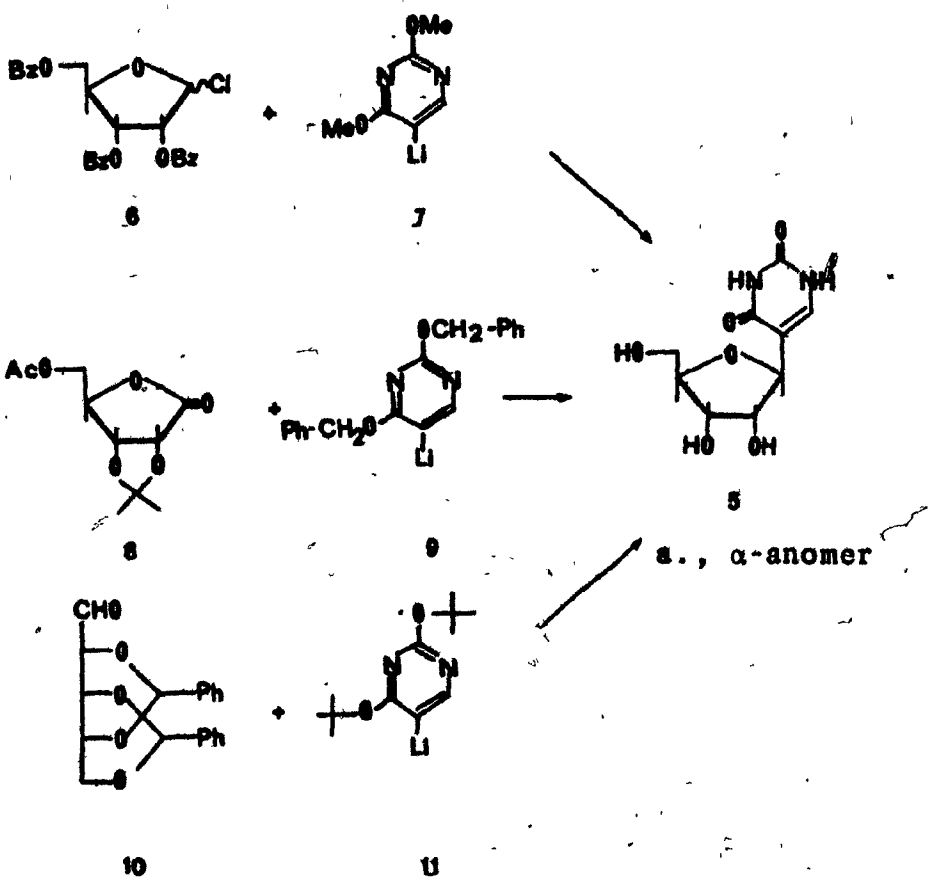
Showdomycin (4)[29] is an example of a biologically active C-nucleoside with the β-D-ribofuranose moiety attached to a 5-membered heterocyclic ring.
The glycosyl bond of C-nucleosides showed an increased stability towards chemical and enzymatic attacks, relative to their N-counterparts, where protonation on oxygen or nitrogen atom occurred, followed by C-N bond cleavage to give the free base and sugar. It is believed that the stability of the glycosyl bond is related to its activity in inhibiting the growth of bacteria or malignant cells[30]. Since C-nucleosides are considerably more stable in this respect, their activity should be more pronounced.

c. Synthesis of C-nucleosides

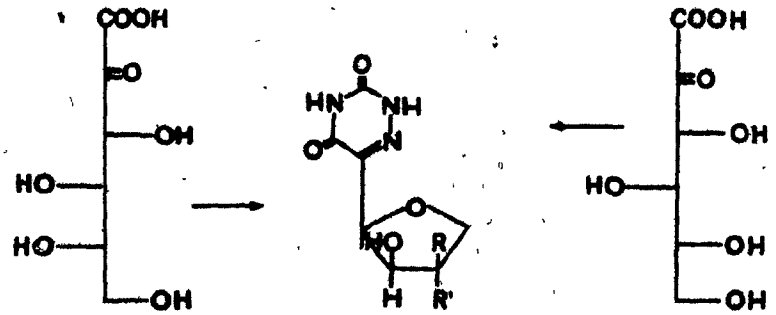
The first approach to the synthesis of C-nucleosides was derived from the one applied for N-nucleoside synthesis, that is, the sugar part was directly condensed to the heterocyclic base. The first synthesis of pseudouridine (5) was reported in 1961 by Asbun and Binkley[31] and Shapiro and Chambers[32]. They started from 1-chloro-2,3,5-tri-O-benzoyl-D-ribofuranose (6) and 2,4-dimethyoxy-5-lithio-pyrimidine (7), but the yield reported was low.

Asbun and Binkley reported in 1968[33] another synthesis of pseudouridine (5). 5-O-Acetyl-2,3-O-isopropylidene-D-ribolactone (8) was condensed with 2,4-dibenzyloxy-5-lithio-pyrimidine (9) followed by borohydride reduction and acid hydrolysis of the condensation product to give (5) in 10% yield.

In 1965, Brown and Burden[34,35] using the open chain carbohydrate (10) and 5-lithio-2,6-di-tert-butoxy-pyrimidine (11), isolated pseudouridine (5) in 18% yield. The α anomer (5a) was also obtained.

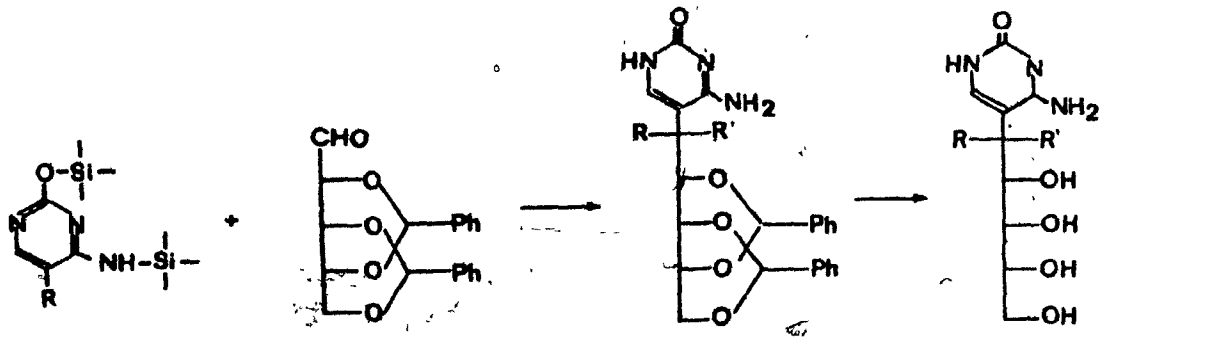


There are other reported syntheses of C-nucleosides using the open chain carbohydrate; examples of this type were shown by Šorm[16,17], who synthesized 5'-anhydro-6-azauracils (14) from L-xylo hexulosonic acid (12) and D-arabino hexulosonic acid (13) by alkali catalysed cyclisation of the corresponding thiosemicarbazones, followed by methylation and hydrolysis.



12 14, R=OH, R'=H
a, R=H , R'=OH 13

Recently pseudocytidine (22) and the anomeric 5-(α-D-ribofuranosyl) cytosine (23) were reported[38] by David and Lubineau. They protected 5-bromocytosine with hexamethyldisilane/trimethylchlorosilane to give (15), which was treated with Bu-Li to afford (16). Reaction of (16) with 2,4:3,5-di-O-benzylidene-D-ribose (17) produced (18) and (19); this mixture was hydrolyzed to (20) and (21) with acetic acid. These isomers were separated on Dowex 50 resin. Treatment of the mixture of (20) and (21) with $NaNO_2$/ HOAc furnished pseudouridine (5) and its α-anomer (5a), whilst cyclization of (20) and (21) with 1N-HCl formed (22) and (23).

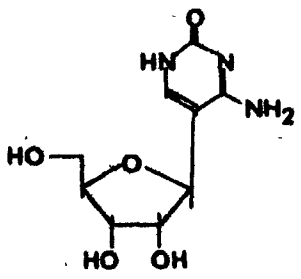


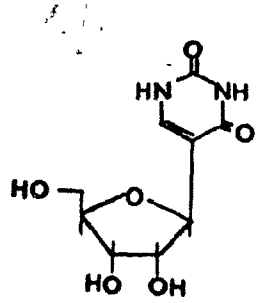
15, R = Br
16, R = Li

17

18, R = OH, R' = H
19, R = H, R' = OH

20, R = OH, R' = H
21, R = H, R' = OH

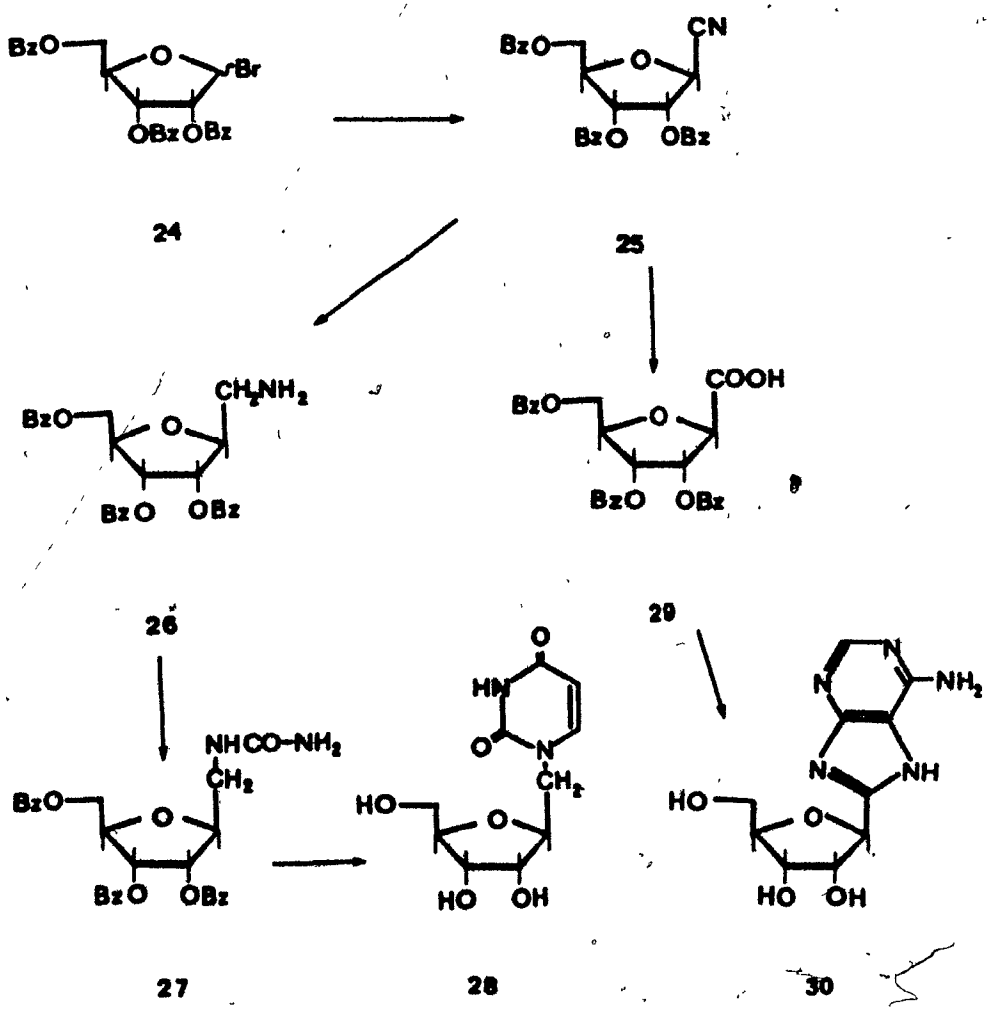




22
23 (α-anomer)

5,
5a, (α-anomer)

The next development was an attempt to introduce the correct stereochemistry at the anomeric centre. Farkaš and co-workers[39,40] prepared from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide (24) the corresponding cyano derivative (25).[41] The cyano group was reduced with lithium aluminum hydride to 1-deoxy-1-amino-2,5-anhydro-D-allitol (26), converted to the urea (27), which, after treatment with β-ethoxyacryl chloride followed by cyclization gave homouridine (28)[42].

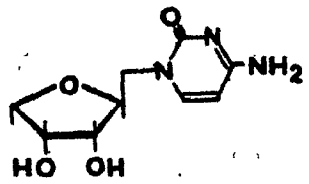


24 25 26 27 28 29 30

Farkaš also hydrolized the cyano group to 3,4,6-tri-O-benzoyl-2.5-anhydro-D-allonic acid (29), which upon condensation with 4,5,6-triaminopyrimidine afforded 8-β-D-ribofuranosyladenine (30) in several steps.

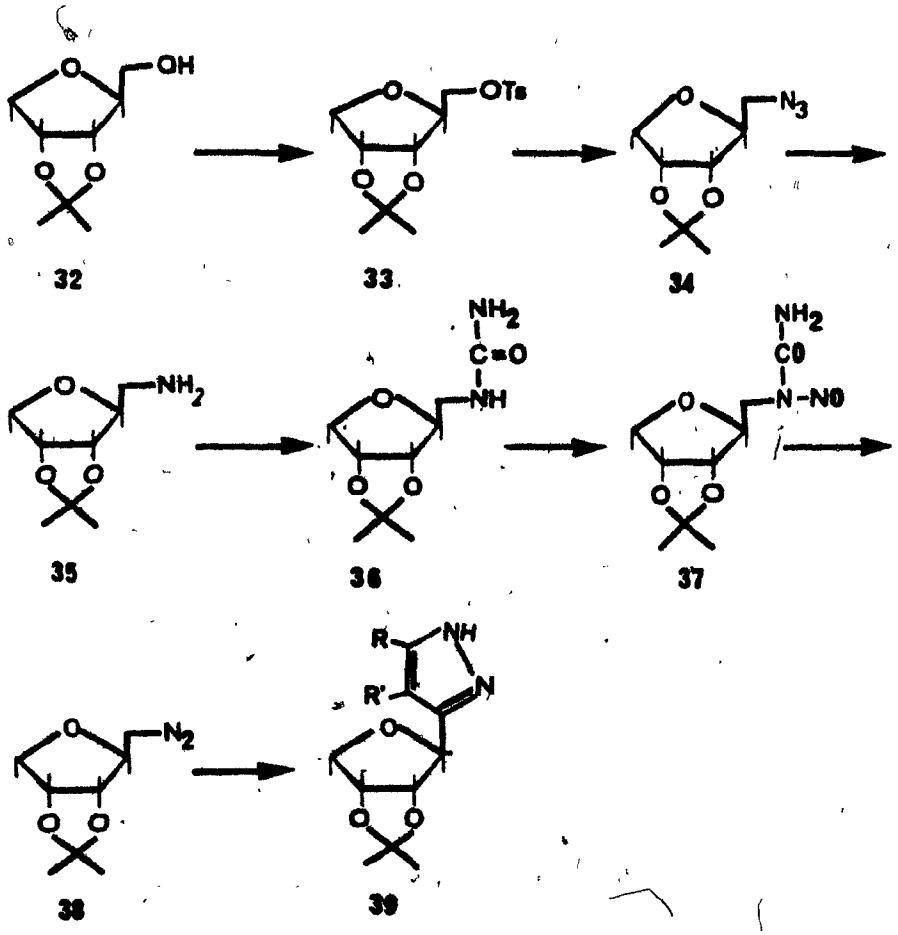
The cyano derivative (25) was also used to synthesize homocytidine (31)[43].

A general synthetic approach to C-nucleosides was shown by Acton et al.[44], using a 1-diazo-sugar[45], applying it in a synthetic sequence devised by Sprinzl, Farkaš and Šorm[39].



31

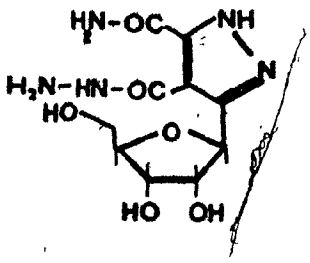
2,5-Anhydro-D,L-ribitol (32) was obtained from ribitol[47] and was converted via the 3,4-O-isopropylidene-1-O-tosylate (33), to the 1-azide (34). The azide was reduced with sodium borohydride to the primary amine (35), which was converted with potassium cyanate into the urea (36). Nitrosation and treatment in aqueous base generated the diazo-sugar (38).



a, R = R' = C00Me
b, R = C0-NH2 , R' = C02Me
c, R = C0-NH2 , R' = C0-NH-NH2

1,3-Dipolar addition of (38) and acetylene dicarboxylic ester gave a pyrazole-4,5-dicarboxylic ester (39a) with a sugar moiety attached at C-3.

Using a part of the reaction sequence described by Acton[44], Šorm et al.[48] synthesized oxoformycin (41) by Curtius rearrangement of (40), obtained from the corresponding (39a) via (39b).



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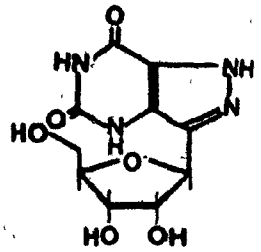
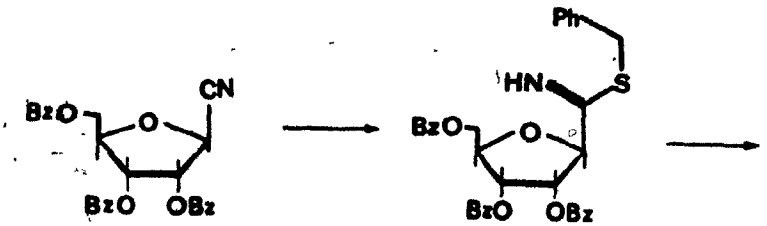
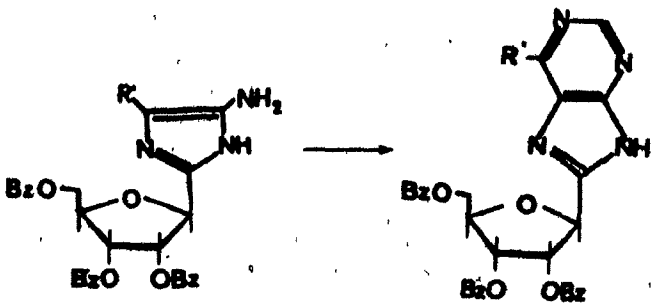


41

With slight modification of the above procedure Acton et al. reported the synthesis of formycin B (1b)[2,50]. The synthesis of C-nucleosides from 1-cyano-1-deoxyribose was also used by Igolen and Dinh[51]. They applied the Pinner reaction[45] to the nitrile (25), which gave the corresponding thioformimidite (42); ring closure in the presence of α-aminocyano-acetic acid derivatives gives (43a).



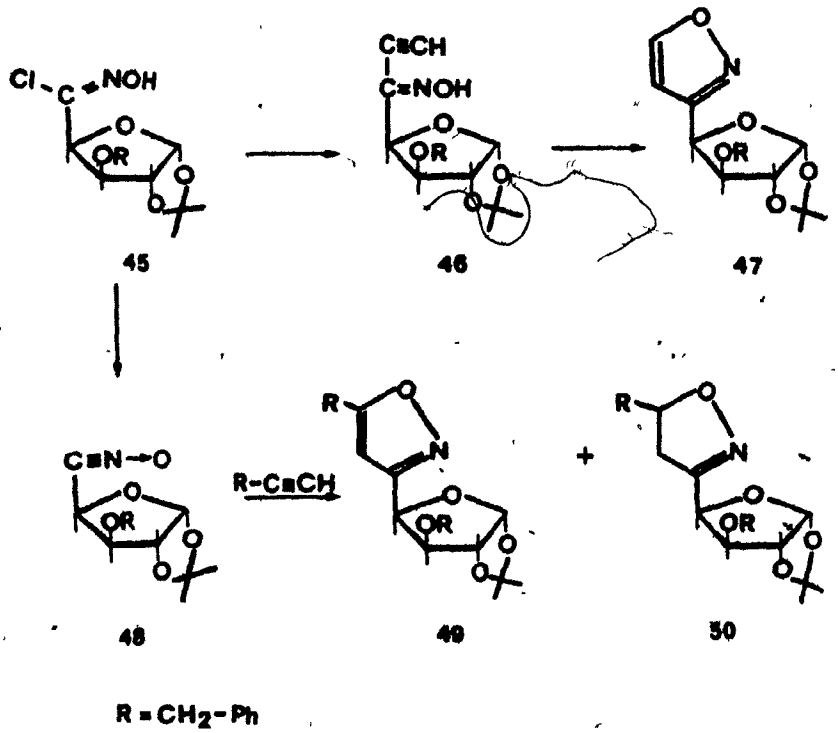
25 42



43a, R = CN
b. R = CO-NH2

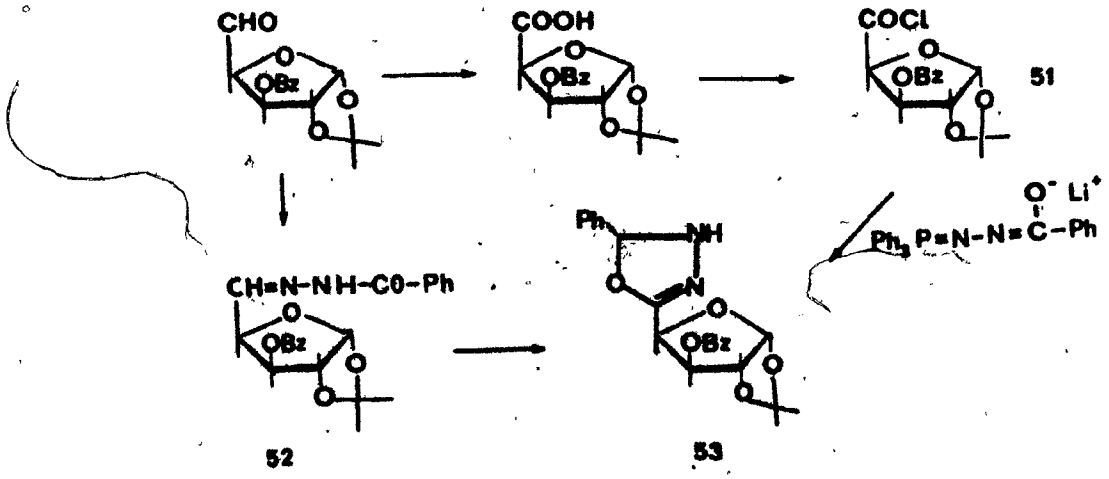
44, R' = NH2, OH

The corresponding 8-tri-O-benzoylribofuranosylpurines (44) were obtained by treatment of (43 a,b) with formamidine acetate or with diethoxymethyl acetate. A promising route was published in 1969 by Tronchet[52]. This involved the synthesis from sugar aldehydes such as 3-O-benzyl-1,2-O-isopropylidene-α-D-xylopenta-dialdehydo-furanose, which was transformed to the chloro oxime (45)[53]. Reaction with acetylene, followed by cyclization, gave the isoxazole derivative (47).

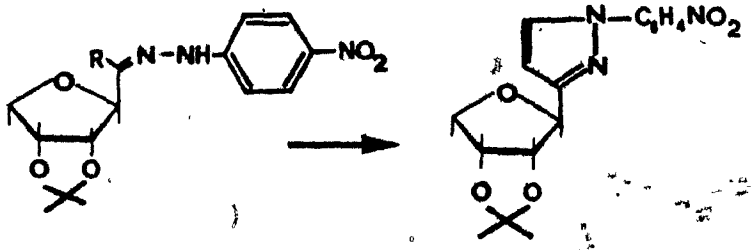


From the chloro oxime (45) the corresponding nitrile (48) was prepared, which after 1,3-dipolar addition with an acetylenic or ethylenic compound gave 3-glycosyl isoxazoles (49) or isoxazolines (50)[54].

Tronchet and co-workers also prepared in their series of "reversed" C-nucleosides[55-57] some 3,4-oxadiazoyl C-nucleosides. By treatment of an alduronic chloride (51) with N-benzoylamino-triphenylphosphinimine or by oxidation of aldehydo-dialdose benzoyl-phenylhydrazone (52)[56], they synthesized an oxadiazole (53).



Analogs of pyrazomycin were synthesized by Tronchet et al.[57] using the p-nitrophenylhydrazone derivative of 2,5-anhydroribose (54) followed by bromination. Displacement of the bromine with ethyne magnesium bromide afforded (55), which after cyclization gave 3-β-D-erythrofuranosyl-1-p-nitrophenyl-pyrazole (56).

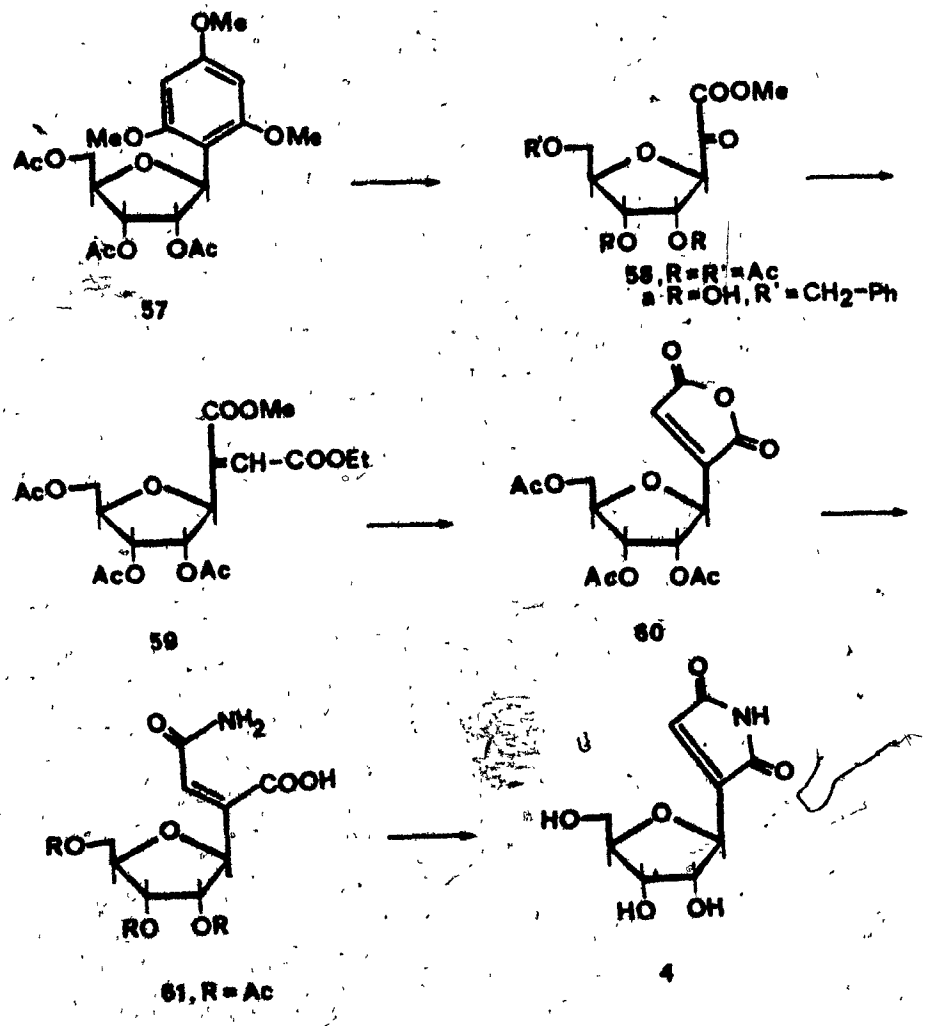


54, R = H
a, R = Br
55, R = C≡CH

56

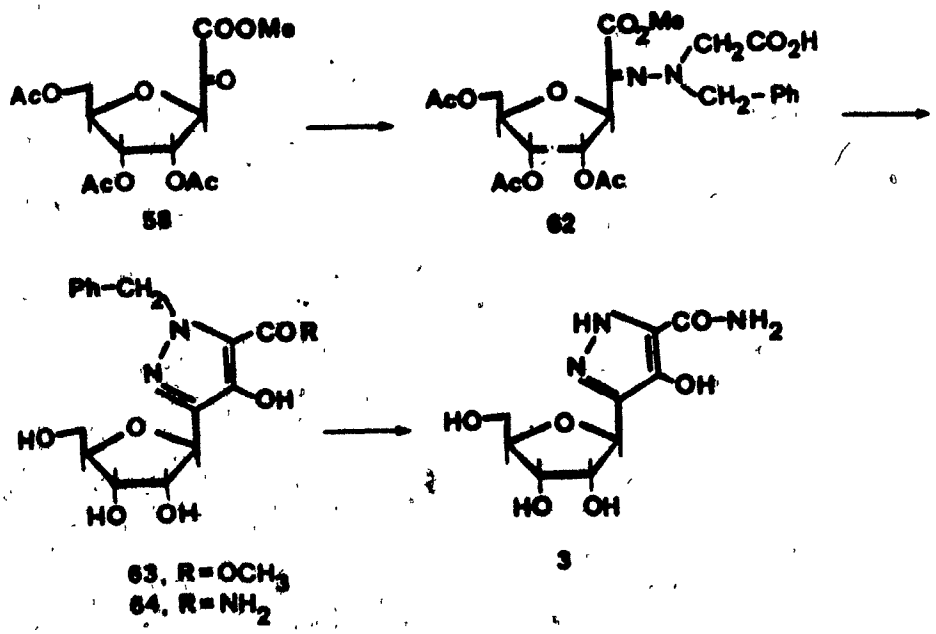
In a further extension of their nucleoside investigation Šorm, Farkaš and their associates in Prague, have achieved a first total synthesis of showdomycin (4) via the key intermediate (58)[58].

They proceeded from 1-(2,3,5-tri-O-benzoyl-β-ribofuranosyl)-2,4,6-trimethoxybenzene which is accessible by condensation of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide with 1,3,5-trimethoxybenzene in the presence of zinc oxide. Hydrolysis and acetylation gave (57). Ozonolysis and mild reduction with dimethyl sulfide[59] of the suitably protected 1-(β-D-ribofuranosyl)-2,4,6-trimethoxybenzene represented a critical step in producing the methyl furanosyl glyoxalate. The keto acid (58) was treated with carboethoxymethylene triphenylphosphorane to give the unsaturated ester (59), which was cyclized to the maleic anhydride derivative (60). Reaction of (60) with ammonia gave the maleamic acid derivative (61) which after cyclization and removal of the protecting groups afforded showdomycin (4).

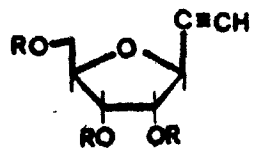

OMe
MeO
OMe
AcO
AcO
OAc
57
COOMe
RO
O
RO
OR
58, R=R'=Ac
a R=OH, R'=CH2-Ph
COOMe
CH-COOEt
AcO
AcO
OAc
59
O
AcO
AcO
OAc
60
NH2
O
COOH
RO
RO
OR
61, R=Ac
NH
HO
HO
OH
4

Pyrazomycin (3) was prepared by Farkaš et al.[60] using a procedure suggested previously[61] as a general route to 3-substituted 4-hydroxypyrazole-5-carboxylic acids.

The authors started from the α-keto acid ester (58) which on treatment with 1-benzylhydrazino-acetic acid gave (62); ring closure afforded (63). Subsequent treatment with methanolic ammonia gave (64), which was debenzylated by hydrogen over palladium to pyrazomycin (3).



Buchanan[62] described a synthesis of β-D-ribofuranosyl-ethyne (65) by reacting ethyne magnesium bromide with chloro ribose. This paved the way to certain 4-ribotriazoles[63].



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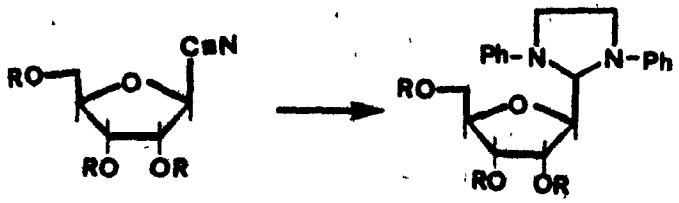
It is obvious that Šorm's key intermediate, the ketoester (58) has great potential for the synthesis of C-nucleosides and this was further confirmed by Moffatt et al., who in a series of papers[64,65] described the synthesis of (58). Starting with (25), they reduced the cyano group in the presence of N,N'-diphenylethylenediamine and obtained a stable crystalline 1,3-diphenylimidazolidine derivative (66).

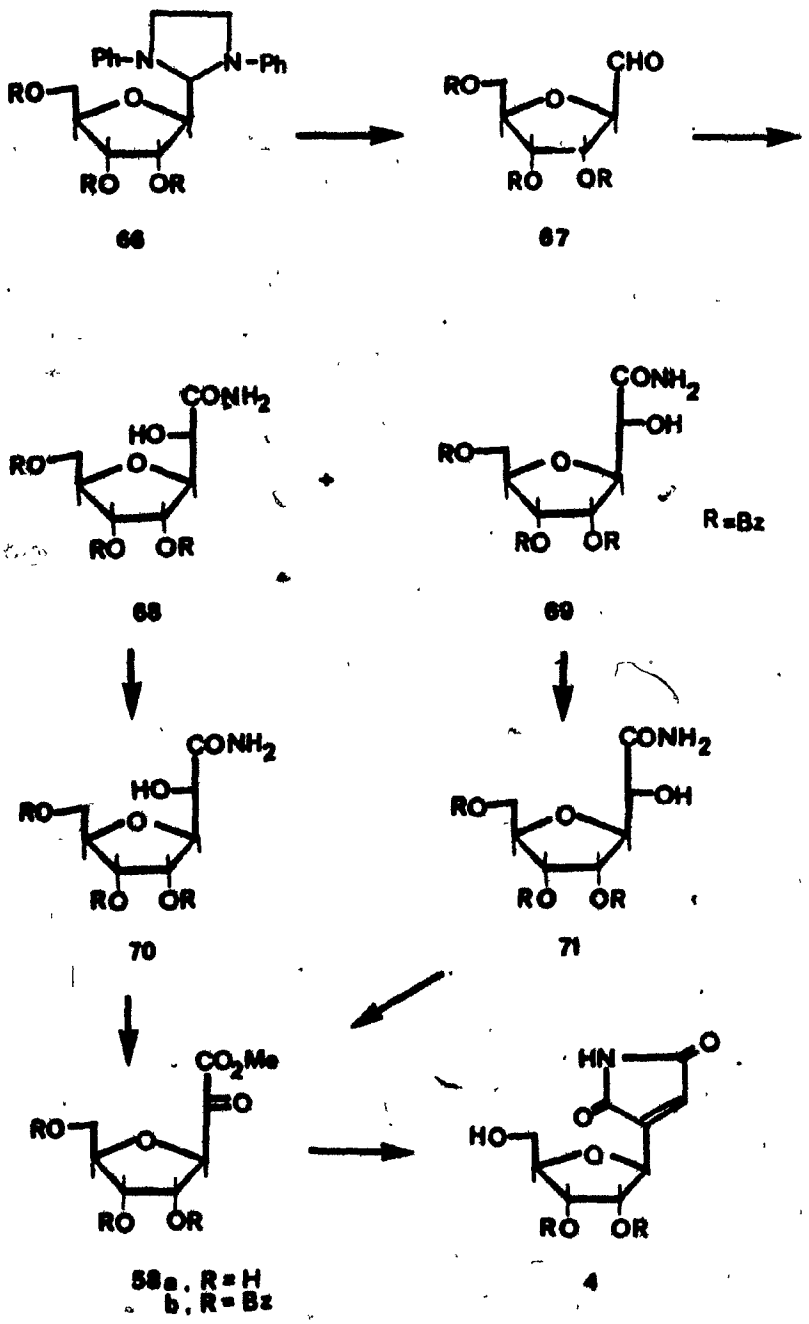


25 66

Regeneration of the free 3,4,6-trisubstituted 2,5-anhydro-D-allose (67) could be achieved by mild acidic treatment.

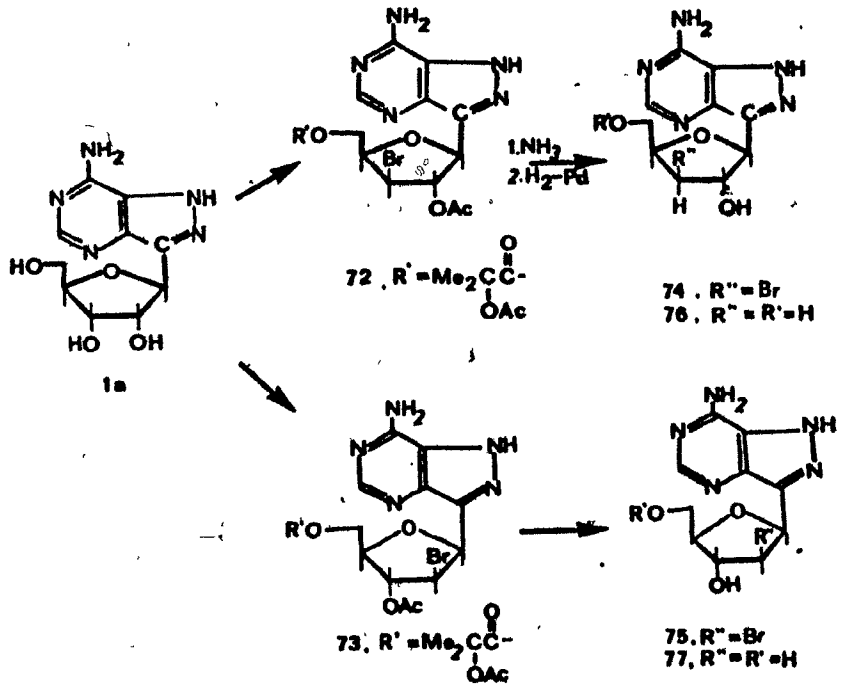
The reaction of the aldehyde with sodium cyanide and hydrogen peroxide gave 3,6-anhydro-4,5,7-tri-O-benzyl-D-glycero-D-allo heptonamide (68) and its D-glycero-D-altro isomer (69). Methanolysis of these substances gave the corresponding methyl heptonates which were oxidized using DMSO and DCC in the presence of dichloroacetic acid to the keto-ester (58b).

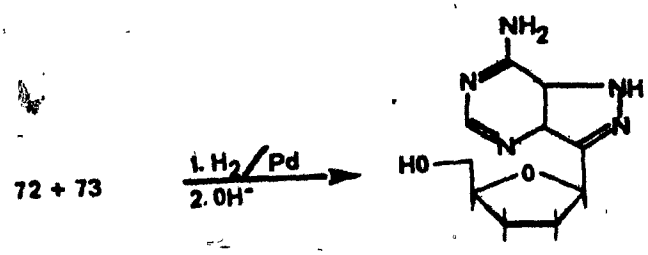
Reaction of (58b) with carbamoylmethylenetriphenylphosphorane afforded directly the tribenzyl ether of showdomycin (4)[65].


Ph-N
N-Ph
RO
OR
66
CHO
67
CONH2
HO
68
OH
R=Bz
69
CO2Me
=O
58a, R=H
b, R=Bz
HN
4
70
71

In addition to the total synthesis of C-nucleosides, chemical modificationson the sugar moiety have been reported[66,67] on formycin (1a).

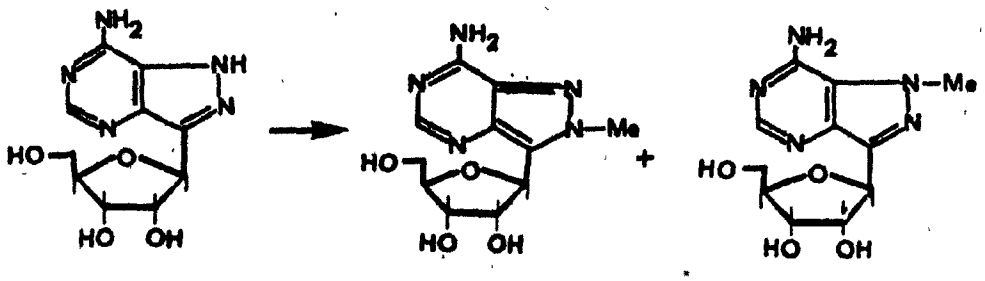
Formycin was reacted with 2-acetoxyisobutyryl bromide to give an inseparable mixture of 2'-O-acetyl-3'-bromo-3'-deoxy-β-D-xylofuranosyl and 3'-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl nucleosides (72, 73). Brief treatment with ammonia of the mixture of (72) and (73) removed the acetyl groups.The resulting isomeric trans-bromohydrins (74) and (75) could be separated. Palladium catalyzed hydrogenolysis gave the corresponding 3'-deoxyformycin (76) and 2'-deoxyformycin (77). Direct hydrogenolysis of the mixture of the fully blocked bromo acetates (72) and (73), followed by removal of the 5'-substituent gave 2',3'-dideoxyformycin (78).





78

Other chemical transformations of formycin (1a), led to selenoformycin B and related derivatives[68], and selective alkylation[69] to the monomethyl derivatives 7-amino-2-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-d]pyrimidine (79) and 7-amino-1-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-d]pyrimidine (80).



1a 79 80

Chapter II

a) Aims of the project

This thesis is part of a project towards the development of a general synthesis of C-nucleosides. Previous studies concerning this subject include a thesis[70] and publication[71] by Alain Martel. Our efforts concentrated on three main areas:

Firstly, separation and identification of the Diels Alder reaction products at the beginning of the sequence (scheme I), subsequently found to be II and III.

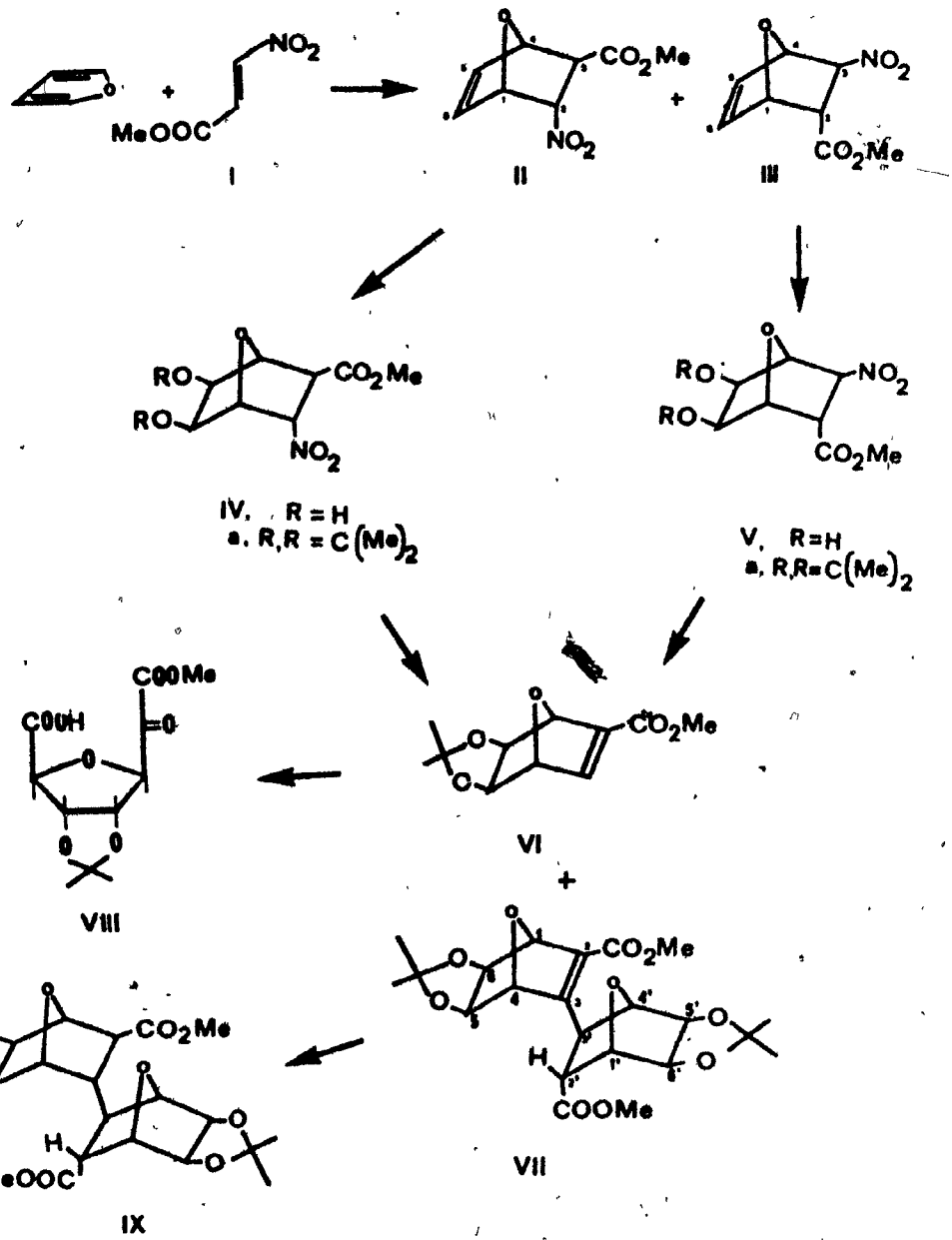
Secondly, the elimination of nitrous acid by means of 1,5-diazobicyclo[5.4.0]undec-5-ene from the endo nitro ester IVa, was reported to give a low yield of olefin VI. Experimental condition were to be modified in such a way that both isomers give high yields of the olefin VI.

Thirdly, since the α-keto ester acid VIII is a valuable intermediate which could make C-nucleosides[50,65] accessible, the synthesis conditions were to be optimized. The reported yield of 32% was increased to 84%[70] by working at optimum pH during extraction procedure.

b. Results and Discussions

Methyl β-nitroacrylate[73,74] was prepared from 2-iodo-3-nitropropionate, as described. Upon treatment of methyl-β-nitroacrylate (I) with 4 equivalents of furan at room temperature overnight, crystals separated out (17% yield), later identified to be the endo-nitro isomer II, m.p. 66-67°. Evaporation of the excess furan afforded the oily exo isomer III in 55% yield. The structural assignment of the isomers II and III was based on p.m.r. spectral data. Separation of the esters allowed for complete analysis of the p.m.r. spectra of the isomers. Considerable differences were noted (Table I). The signal most useful was the proton α to the carbomethoxy group observed as a doublet at 3.20 ppm ($J_{3,2}$= 2 Hz) for the endo 2-nitro ester II. Similarly, the corresponding proton H_2-exo at 3.90 ppm for the exo 3-nitro ester III shows a difference in chemical shift, with the exo proton being downfield, most likely an effect of the 7-oxygen atom producing a deshielding effect[76]. Chemical shifts and coupling constants for the isomers are given in table I.

Scheme 1


NO2
MeOOC
CO2Me
NO2
NO2
CO2Me
I
II
III
RO
RO
CO2Me
NO2
IV, R = H
a, R,R = C(Me)2
RO
RO
NO2
CO2Me
V, R=H
a, R,R=C(Me)2
COOMe
COOH
=O
O
O
O
VIII
CO2Me
O
O
VI
+
CO2Me
O
O
O
O
H
COOMe
VII
CO2Me
O
O
O
H
MeOOC
IX

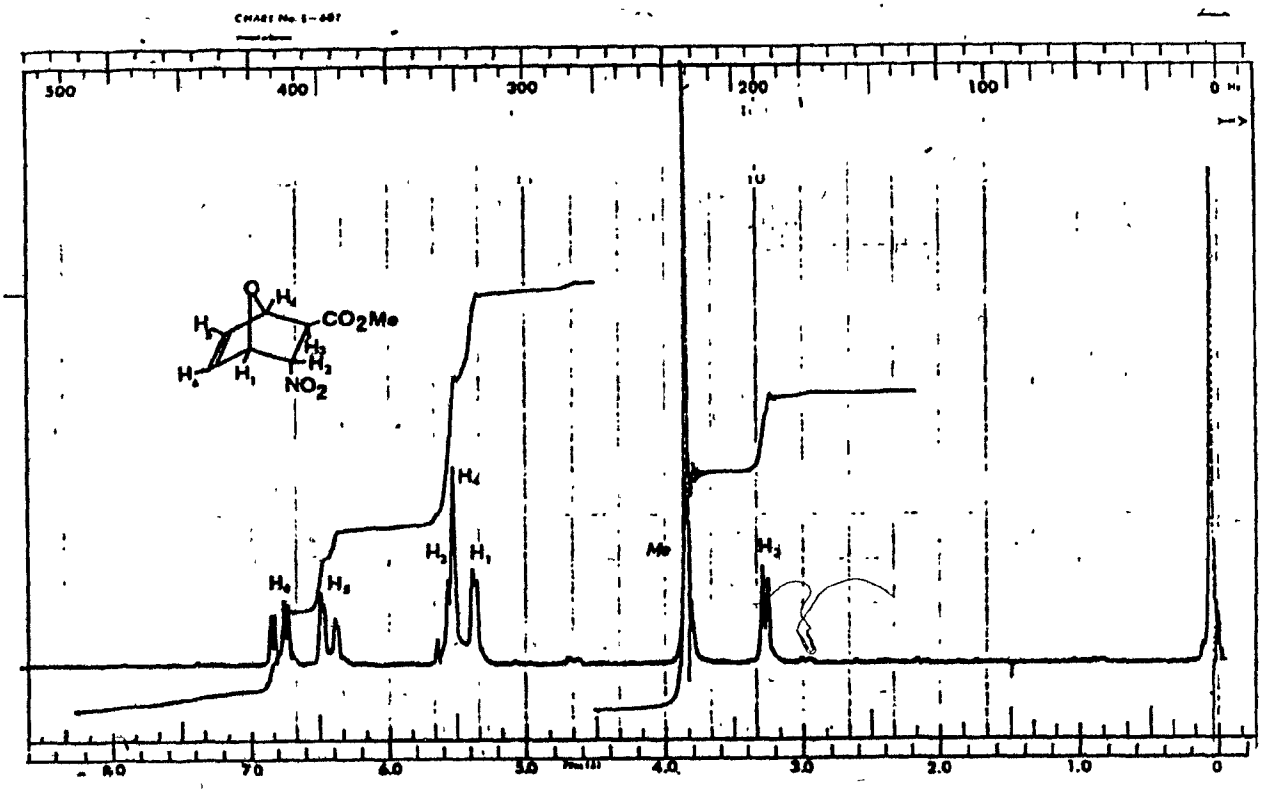


Fig. 1. The p.m.r. spectrum of Methyl trans-7-oxabicyclo-[2.2.1]hept-5-ene-2-endo-nitro-3-exo-carboxylate II in chloroform -D .

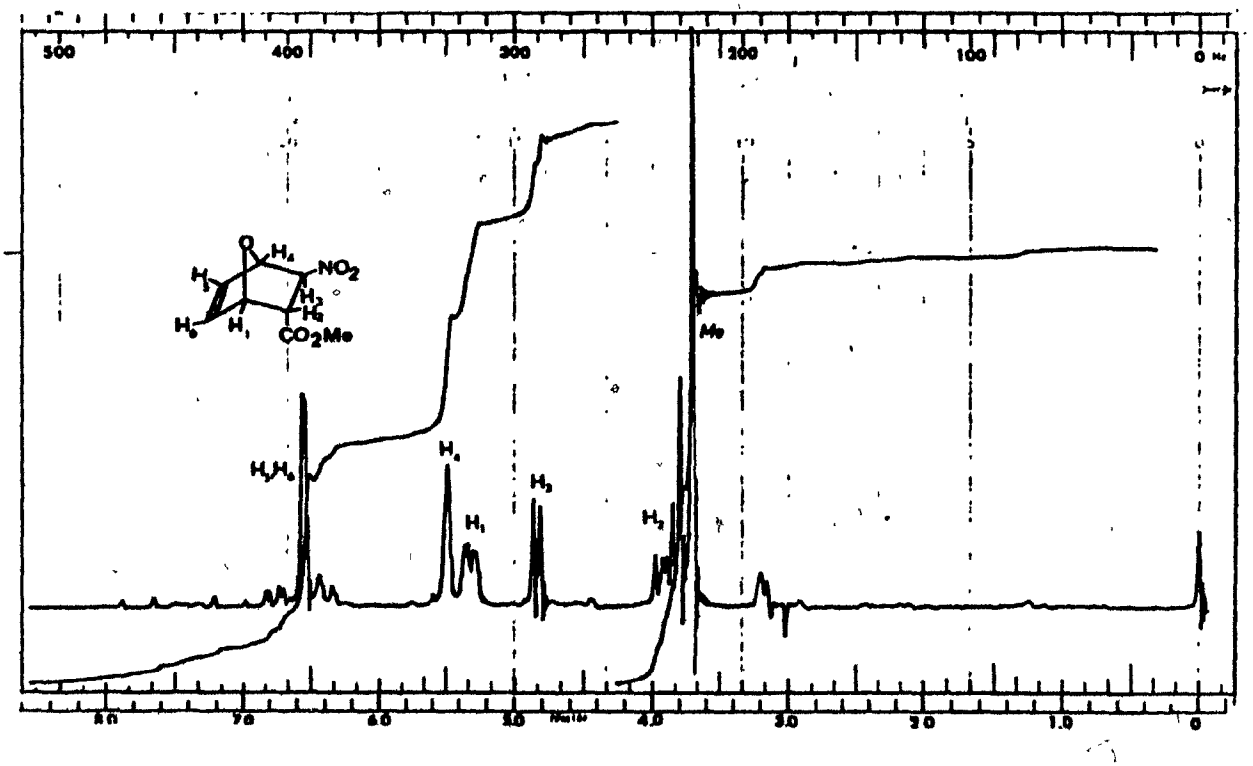


Fig. 2. The p.m.r. spectrum of Methyl trans-7-oxabicyclo-[2.2.1]hept-5-ene-3-exo-nitro-2-endo-carboxylate III in chloroform-D .

TABLE I

P.m.r. parameters for II and III

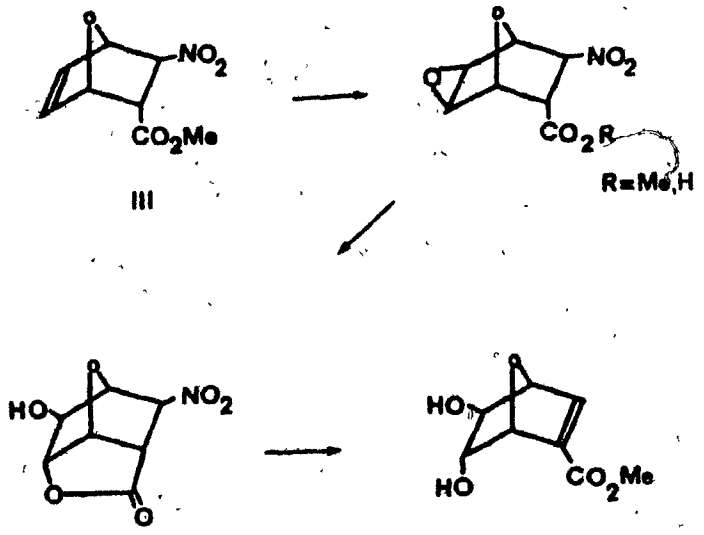
	Compound	Chemical shifts					
		OCH_3	H-1	H-2	H-3	H-4	H-5	H-6
II	(endo-2-nitro)	3.80 s	5.56 dd	5.47 dd	3.20 d	5.30 d	6.70 dd	6.35 dd
			$J_{1,6}$= 1	$J_{2,1}$= 3	$J_{3,4}$= 0	$J_{3,4}$= 0	$J_{5,6}$= 6	$J_{5,6}$= 6
			$J_{1,2}$= 3	$J_{2,3}$= 2	$J_{2,3}$= 2	$J_{4,5}$= 2	$J_{5,4}$= 2	$J_{6,1}$= 1
III	(exo-3-nitro)	3.72(s)	5.32 dd	3.90 dd	4.82 d	5.50 d broadened	6.55 d	6.55 d
			$J_{1,6}$= 1	$J_{1,2}$= 4	$J_{3,2}$= 3	$J_{4,5}$= 1	$J_{5,6}$=0	$J_{5,6}$=0
			$J_{1,2}$= 4	$J_{2,3}$= 3	$J_{3,4}$= 0	$J_{4,3}$= 0	$J_{5,4}$=1	$J_{6,1}$=1

Spectra are recorded in deuteriochloroform

Chemical shifts are given in δ, coupling constants in Hz.

The exo-nitro isomer III was used by Lim* as an intermediate in the arabinose series outlined in Scheme II, confirming the stereochemical assignment.

Scheme II



*M.I. Lim, Ph.D. Thesis, 1976.

Exo-cis-hydroxylation of the isomers II and III with hydrogen peroxide and a catalytic amount of osmium tetroxide[75] gave the crystalline diols IV, mp 168-170°, and V, mp 145-147°.

The assignment of the isomers was confirmed at this stage. It is known, that the coupling constant of endo protons with the bridge-head proton in bicyclo [2.2.1] heptane derivatives is close to zero[76], whereas the coupling constants of an exo proton should be of significant order of magnitute (J = 4 Hz). One would therefore expect that the low field proton α to the nitro group in V should appear as a doublet, and in IV as a doublet of doublets, or a triplet. We found that the low field proton α to the nitro-group appears as a doublet in V and as a triplet in IV.

Treatment of IV and V with acetone/dimethoxypropane in the presence of p-toluenesulfonic acid for several hours resulted in a good yield of the corresponding isopropylidene derivatives IVa and Va.

Elimination of nitrous acid by means of 1,5-diazabicyclo-[5.4.0]undec-5-ene in ether at 0° from the exo-nitro-ester Va gave 60% of olefin VI and 8% of dimer VII. The ratio olefin VI (28%) to dimer VII (45%) was less favourable, when nitrous acid was eliminated from the endo-nitro ester IVa.

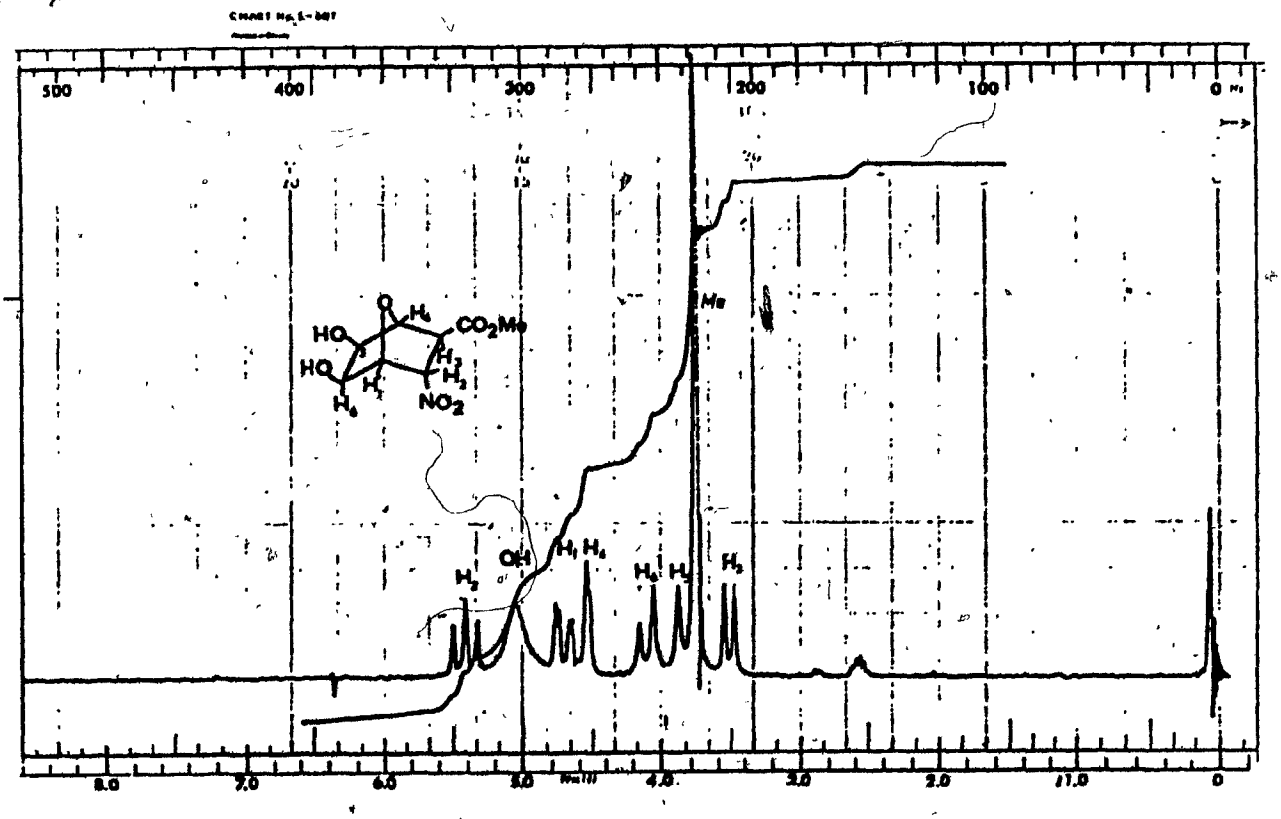


Fig. 3. The p.m.r. spectrum of Methyl exo-cis-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-trans-2-endo-nitro-3-exo-carboxylate IV in DMSO-D_6.

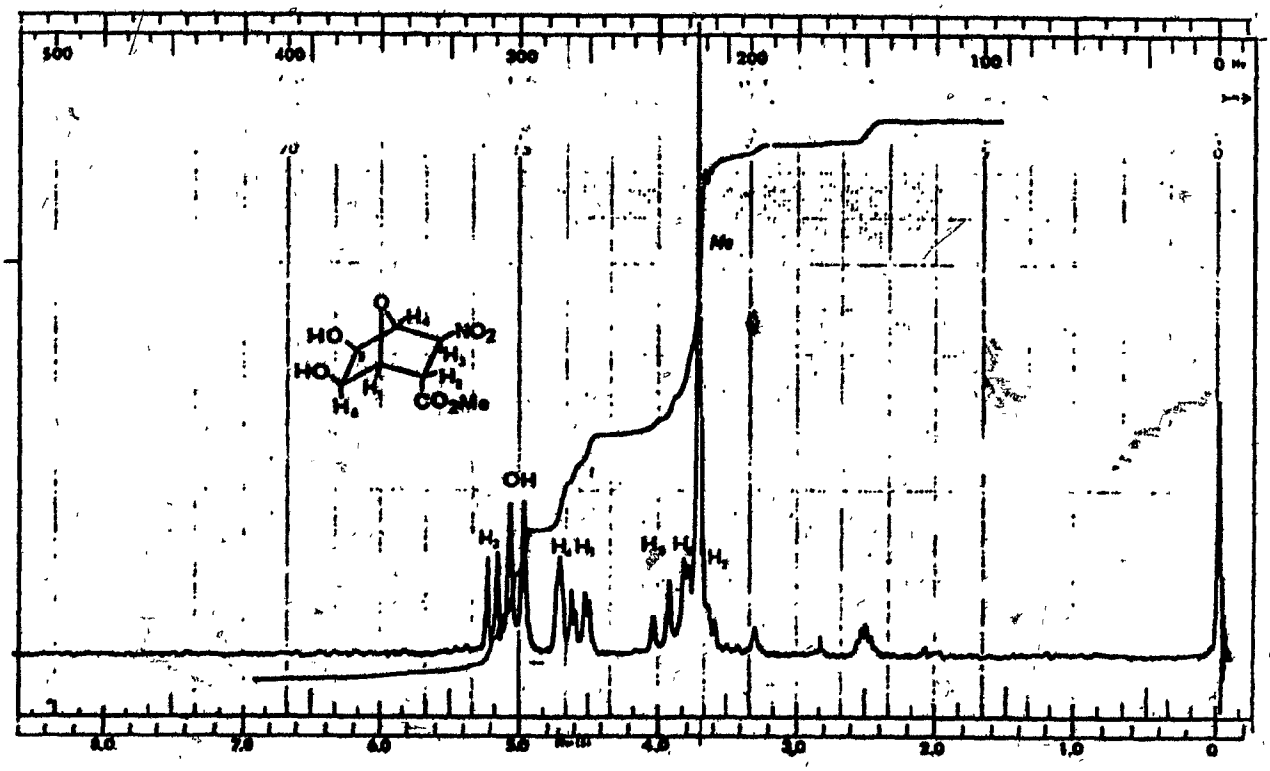


Fig. 4. The p.m.r. spectrum of Methyl exo-cis-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-trans-2-exo-nitro-3-endo-carboxylate V in DMSO-D_6.

TABLE II

P.m.r. parameters for IV and V

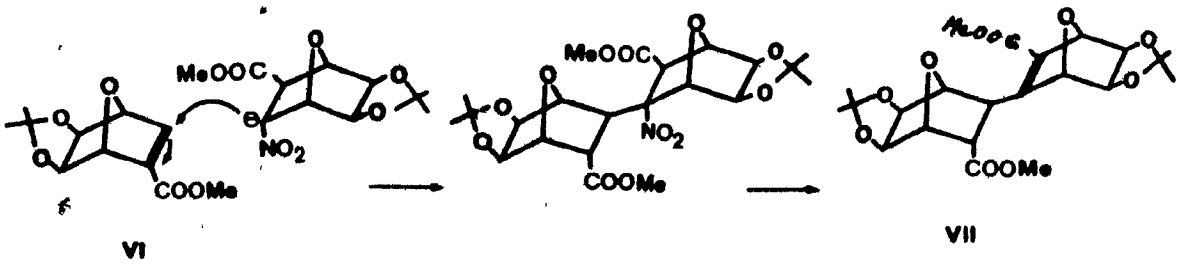
Compound		Chemical shifts						
		OCH_3	H-1	H-2	H-3	H-4	H-5	H-6
IV	(endo-2-nitro)	3.72(s)	4.55 dd	3.7-3.8 dd	5.18 d	4.72 d	3.98 d	3.78 d
			$J_{1,2}$= 6	$J_{2,3}$= 5	$J_{3,2}$= 5	$J_{4,5}$= 2	$J_{5,6}$=6	$J_{6,5}$=6
			$J_{1,6}$= 2	$J_{1,2}$= 2	$J_{3,4}$= 0	$J_{4,3}$= 0	$J_{5,4}$=0	$J_{6,1}$=0
V	(exo-2-nitro)	3.72(s)	4.65 dd	5.35 t	3.42 d	4.48 d	3.78 d	4.02 d
			$J_{1,2}$= 5	$J_{1,2}$= 6	$J_{3,2}$= 5	$J_{4,5}$= 2	$J_{5,6}$=8	$J_{6,5}$=8
			$J_{1,6}$= 2	$J_{2,3}$= 6	$J_{3,4}$= 0	$J_{4,3}$= 0	$J_{5,1}$=0	$J_{6,1}$=0

Spectra are recorded in DMSO-d_6

Chemical shifts are given in δ, coupling constants in Hz.

A variety of experimental conditions were studied, to improve the yields of olefin from both starting materials at the expense of the unwanted dimer formation. This was finally accomplished by adding the nitro-ester IVa and Va into a refluxing solution of DBU in ether. The yield of olefin then reached 80% (from IVa) and 72% (from Va). Only traces of dimer VII were identified by t.l.c.

The structure and stereochemistry of the dimer VII was determined by p.m.r. and chemical transformation, and probably arises in the following manner:



VI VII

It is known that protons α to a nitro group are more acidic than protons α to a carbomethoxy group. The fact that the exo nitro isomer (Va) form olefinic esters readily is probably due to the better accessibility of the exo proton α to the carboxymethyl group. In the case of the elimination of nitrous acid from the endo nitro isomer (IVa), it appears that some olefin ester (VI) is formed, but that it is consumed in dimer (VII) formation, because of the ready formation of of the carbanion α to the nitro group, since the hydrogen is the more acidic and more accessible one.

The protons of olefin VI were assigned on the basis of known bicyclo[2.2.1] systems[6]. The H-5 endo and H-6 endo protons gave a single signal at δ4.42; the bridgehead proton H-1 showed downfield at δ5.00 (s). The signal of the proton at C-4 (δ4.90) is split into a doublet (J = 2 Hz) due to coupling with the olefinic proton at C-3, δ7.02 (J = 2 Hz).

The protons H-5 and H-6 of dimer VII can readily be discerned from proton H-5' and H-6' of the saturated portion. One of these resonances occurs at a position very close to that of the unsaturated monomer and was assigned accordingly. The H-5-endo and H-6-endo protons resonate as a single peak at δ4.42 and the H-5' endo and H-6' endo at δ4.50 as equally sharp signals. The bridgehead protons H-1 and H-4 appear as a singlet at δ4.97 (J≈0).

The proton H-1' resonates downfield from H-4' due to the deshielding effect of the endo methoxycarbonyl group. H-1' is split into a doublet (J=6Hz) by H-2'-exo, δ4.70. The H-4' bridgehead proton occurs at a singlet at δ4.20 since the coupling constant of endo protons is close to zero. H-3'-endo is split into a doublet by H-2'-exo, the coupling constant is difficult to measure, since one signal occurs at about the same value as the methyl ester group, which can be

observed as two magnetically different groups having a small chemical shift (∿1 cps) which increases to 6 cps if benzene-d_6 is used as a solvent. H-2' exo, δ2.95 (t, J=6Hz) is at higher field than the other protons (except the gem-dimethyl) since it is not deshielded by the magnetically anisotropic double bond, which is approximately in the plane of the H-3' endo-proton. This absorption is split into a doublet. Coupling between three nonequivalent protons could give rise to an AMX spectra, which consists in theory of three quartets, or 12 lines[77,78]. Three coupling constants are involved in the spectrum, the interaction H-2' exo with H-1' and H-3' endo which gave rise to a triplet. The triplet observed for proton H-2' exo - an apparent AMX spectrum - is due to the fortuitous near identity of $J_{1',2'}$ and $J_{2',3'}$. Coupling constants $J_{1',2'}$ and $J_{2',3'}$ could be expected to be slightly different but the resolution of the instrument available was insufficient to separate the two central peaks.

If VII would have a different configuration at C-2', with the methoxycarbonyl group in the exo position, the p.m.r. spectrum should have shown two single peaks for the bridgehead protons C-1' and C-4', which was not observed. Similar reasoning may be applied for the assignment of the peaks of the isomer in which the groups at C-3' have been inverted.

The saturated dimer was prepared by catalytic reduction of VII with Pd on charcoal. The relative configuration at C-2 and C-3 can be assigned on the following basis. In the process of catalytic hydrogenation, absorption of a molecule on the catalyst occurs on the least hindered side, followed by delivery of hydrogen to that side[79]. Hence the C-2 and C-3 hydrogen atoms must have the cis relationship. The p.m.r. analysis of VII is simplified, since after reduction the protons of both rings have similar chemical shift values. The signals most useful were the carboxymethyl ester singlets observed at δ 3.60 and δ 3.65.

These methyl groups occur at different field strength, suggesting that after hydrogenation one of the ester groups is in the exo and the other in the endo position. Since we know the configuration of the ester group in the saturated part of the dimer VII to be in the endo position, it can be assumed that the C-2'-ester group of the saturated dimer is in the exo position as shown.

The remaining spectrum of IX can be analysed as follows: The protons at C-5 and C-6 and C-5' and C-6' are magnetically equivalent. The chemical shift values were essentially the same as the ones observed in the much simpler unsaturated dimer H-5' and H-6', δ4.50 (s) and H-5 and H-6, δ4.42 (s). The bridgehead protons H-1 and H-4 gave a single peak at δ4.65 and δ4.20. The bridgehead proton H-4' occurs downfield due to the vicinity of the 2-endo carboxyl group.

This interaction can not take place with the proton at C-4, since the exo methoxycarbonyl group at C-2' points away from the hydrogenated ring. H-2' exo is split into a doublet of doublets by H-1' ($J_{1',2'}$=6Hz) and by H-3' (J~5Hz), it occurs at lower frequency (δ3.0) than the remainder of the spectrum, which consists of a broad hump attributed to C-3', C-3 and C-2 endo protons. From the knowledge of the factors influencing chemical shifts it is not surprising that these hydrogens have similar chemical shifts, resonating in the 2.2-2.6 ppm region.

Large shifts of proton resonances may be observed on comparison of spectra which have been determined in non-aromatic solvents and aromatic solvents. These large shifts may be attributed to the anisotropy of the magnetic susceptibility of aromatic solvents.

When the spectra were determined in benzene d_6-solution, as opposed to the deuteriochloroform, essentially the same results were obtained, except that the C-5 and C-6 protons in VI, VII and IX form a symmetrical quartet of the easily recognizable AB type[90]. This shows that benzene can be a useful solvent in inducing chemical shifts between protons which otherwise have accidentally the same chemical shifts.

TABLE III

CHEMICAL SHIFTS FOR 7-OXABICYCLO [2.2.1] HEPT-2-CARBOXYLATES

	H_1	H_2	H_3	H_4	H_5	H_6	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	O-CH$_3$	gem(CH$_3$)
VI	5.10(s)	-	6.60(d) J=2Hz	4.60 J=2Hz	3.95(d)	4.25(d)	-	-	-	-	-	-	3.40(s)	1.25(s) 1.57(s)
VII	5.10(s)	-	-	5.00	4.57d	4.32d	4.57d J=5Hz	2.78t J=5Hz	3.97d J=5Hz	4.12	4.25(s)	4.25(s)	3.25(s) 3.35(s)	1.60(s) 1.30(s) 1.55(s) 1.28(s) 1.15(s)
IX	4.4-4.6*	2.3-2.5*		4.4-4.6*	4.72d	4.48d	4.32(s)	2.25-2.90m		4.4 ------ 2.3-2.5*		4.6*	3.30(s) 3.22(s)	1.60(s) 1.28(s)

NMR-Spectra were determined with a Varian A-60 spectrometer using TMS as internal standard, recorded in benzene-d_6

*estimated, since no individual values were observable.

TABLE IV

CHEMICAL SHIFTS FOR 7-OXABICYCLO [2.2.1] HEPT-2-CARBOXYLATES

	H_1	H_2	H_3	H_4	H_5*H_6	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$*$H_{6'}$	O-CH_3	$C(CH_3)_2$
VI	5.00(s)	-	7.05d $J_{3,4}$=2Hz	4.90d J=2 Hz	4.42(s)	-	-	-	-	-	3.78(s)	1.35(s) 1.50(s)
VII	4.97(s)	-	-	4.97(s)	4.42(s)	4.70d J=6 Hz	2.95t J=6 Hz	3.85d J=6Hz	4.20(s)	4.50(s)	3.99(s)	1.50(s) 1.35(s) 1.45(s) 1.30(s)
IX	4.65(s)	2.2-2.6*		4.20(s)	4.42(s)	4.75d J=6Hz	3.00(m)	2.2-2.6*	4.60(s)	4.50(s)	3.60(s) 3.70(s)	1.48(s) 1.50(s)

NMR-Spectra were determined with a Varian A-60 spectrometer using TMS as internal standard, recorded in deuteriochloroform.

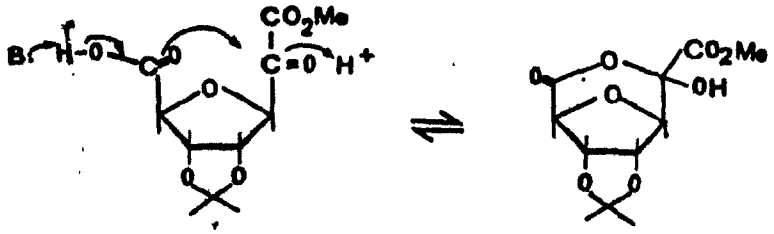
*estimated, since no individual values were observable.

Syntheses of showdomycin[58] and pyrazomycin[60] have been briefly reported by Farkaš et al., and involve as key intermediate the keto ester (58) (Chapter I). As yet details and yields of this process have not been disclosed but the conversion of 58 into showdomycin required a six step sequence.

Above we described an efficient route for the preparation of olefin VI in which the hydroxyl groups are protected as an isopropylidene ketal. At this point, we looked for an oxidative procedure to generate the structural features of a keto ester containing compound on which we could build a C-nucleoside ring system. The use of a modified ruthenium tetroxide catalysed oxidation[60,61] gave a crystalline product, m.p. 114-116°, in high yield (84%) after one recrystallization from acetone/hexane. The acid keto ester VIII met the stereochemical requirements as key intermediate for the synthesis of C-nucleosides, the acid group being cis to the α-keto ester.

As we were concerned with the total synthesis of C-nucleosides, we attempted the resolution of 3,4-O-isopropylidene tetrahydrofuran-3α,4α-diol-5β-carboxylic acid-2β (methyl glyoxalate) VIII. This was accomplished by recrystallization of the L-strychnine salt from isopropanol, as indicated by attainment of constant optical rotation $[\alpha]D_{20}$ -7.1°. Regeneration of the free acid by ion exchange column (Rexyn 101-H) gave an optical rotation of $[\alpha]D_{20}$ -3.2°.

However, the yield of the crystalline product was very low, possibly due to the presence of the bridged form X in solution. This was established by p.m.r. which showed in deuterated DMSO or acetone-d_6, two peaks in the region of absorption of the methyl ester, this indicated that the free acid was present to the extent of only 50%.



VIII X

The work that is detailed in the next chapter became of more immediate interest to us at the time and these studies were discontinued. However, the synthetic importance of an α-keto ester acid was shown by a colleague in this laboratory[110].

Chapter 2

Experimental

Melting points were determined on an electrothermal block and are corrected. P.m.r. spectra were recorded on a Varian Associates A-60 spectrometer. IR spectra were obtained on a Perkin-Elmer 237-B spectrometer. U.V.-spectra were recorded on a Bausch & Lomb 505 spectrophotometer. Micro-analyses were carried out by Micro-Tech. Laboratories Inc., Skokie, Ill., USA.

Methyl 3-nitro-2-iodopropionate[73]

A stirred solution containing 86 g (1 mole) methyl acrylate and 252 g (1 equiv) of iodine in 1 *l* of ether was cooled to 0°. The reaction system was protected with a Dry-ice/acetone condenser and a drying tube. Freshly condensed dinitrogen tetroxide (46 g, 0.5 mole) was added through a dropping funnel over a period of 1 hour. The reaction was stirred for an additional 2 hours at 0°. The ether solution was washed until colourless with a 15% sodium thiosulfate solution, subsequently washed with aqueous sodium bicarbonate, water and then dried over magnesium sulfate. The brown oil (140 g, 54.2%, lit.[73] 75%) obtained on evaporation of the ether at 20° was used without purification.

I.r. (film) 1740 cm^{-1} (C=O), 1560 cm^{-1} (NO_2) 1370, 1385 cm^{-1} (CH_3).

P.m.r. ($CDCl_3$) δ3.82 (s, 3H), 4.58 - 5.15 (m, 3H).

Methyl 3-nitroacrylate (I)[74]

Methyl 3-nitro-2-iodopropionate (250 g, 0.97 mole) was added dropwise to a stirred suspension of anhydrous sodium acetate (80 g, 0.985 mole) in ethyl ether (1 l) under a nitrogen atmosphere, at 0°. After the addition was completed, the mixture was stirred at room temperature for one hour, then refluxed for 3 hours. After cooling to 5°, the sodium iodide and sodium acetate were filtered off. The ether was washed with 2 N sodium bicarbonate, dried over sodium sulfate and concentrated to dryness. The residue solidified on cooling and gave 120 g (94.5%) yellow crystals, mp: 35-37°, lit.[74] mp: 38°.

I.r. (KBr): 1730 cm^{-1} (C=O), 1540 cm^{-1} (NO_2), 1645 cm^{-1} (C=C), 1360 cm^{-1} (CH_3).

P.m.r. ($CDCl_3$): δ 3.91 (s, 3H), 7.15 (d, 1H), 7.80 (d, 1H).

Methyl trans-7-oxabicyclo[2.2.1]hept-5-ene-2-endo-nitro-3-carboxylate (II) and Methyl trans-7-oxabicyclo[2.2.1]hept-5-ene-3-exo-nitro-2-carboxylate (III).

Methyl 3-nitroacrylate (I) (120 g, 0.91 mole) and an excess of furan (270 g, 4 moles) were stirred overnight at room temperature. The excess furan was evaporated under reduced pressure; addition of ether afforded II, 31 g (17%) mp: 66-67°.

I.r. (KBr): 1730 (C=O), 1540 (NO_2), 870 cm^{-1} (C-N).

P.m.r. ($CDCl_3$): δ 3.20 (d, J=3Hz, 1H), 3.80 (s, 3H), 5.30-5.60 (m, 3H), 6.30-6.78 (m, 2H).

Anal. Calcd. for $C_8H_9NO_5$ C; 48.24, H; 4.56, N; 7.03
Found: C; 48.33, H; 4.77, N; 7.35.

The filtrate was concentrated to dryness; chromatography on silicic acid with chloroform, gave 100 g (55%) almost pure III as a colorless oil.

I.r. (film): 1735 cm^{-1} (CO), 1525 (NO_2), 1375 (CH_3), 870 cm^{-1} (C-N).

P.m.r. ($CDCl_3$): δ 3.62 (s, 3H), 3.90 (dd, 1H), 4.82 (d, 1H), 5.32 (dd, 1H), 5.50 (s, 1H), 6.53 (s, 2H).

Methyl exo-cis-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-trans--2-endo-nitro-3-carboxylate (IV).

The Diels-Alder adduct II (31.0 g, 0.155 mole) was treated with osmium tetroxide (20 ml of a solution made from 1 g of osmium tetroxide in 200 ml of t-butanol) and 3 x 6 ml of hydrogen peroxide according to the procedure of Daniels[75]. From the reaction mixture, 18.3 g (50.5%) of IV, mp 168-170°, was filtered off. Upon further evaporation, 5.0 g of methyl 3-nitroacrylate, mp 35-37° was isolated.

I.r. (KBr): 3500-3200 (OH), 1740 (C=O), 1550 cm^{-1} (NO_2);

P.m.r. (DMSO-d_6): δ 3.42 (d, J = 5Hz, 1H), 3.70 (s, 3H), 3.78 (d, 1H), 4.02 (d, 1H), 4.48 (d, 1H), 4.65 (dd, 1H), 5.00, (s, ex.2H), 5.35 (t, J = 6Hz, 1H).

Anal. Calcd. for $C_8H_{11}NO_7$(233.18): C, 41.20; H, 4.76; N, 6.01.
Found : C, 41.22; H, 4.80; N, 6.00.

Methyl exo-cis-5,6-dihydroxy-O-isopropylidene-7-oxabicyclo [2.2.1]heptane-trans-2-endo-nitro-3-carboxylate (IVa).

The diol IV (18.3 g, 0.078 mole) was refluxed in a mixture of acetone and 2,2-dimethoxypropane containing a catalytic amount of p-toluenesulfonic acid with a Dean-Stark trap filled with molecular sieves. At the end of the reaction, which was followed by t.l.c., the mixture was evaporated and the residue obtained was dissolved in chloroform, washed with water and concentrated. The crude product was crystallized from ether, (20.5 g, 96%) mp: 90-92°.

I.r. (KBr): 1745 cm^{-1} (C=O), 1550 cm^{-1} (NO_2), 1380, 1390 (gem-dimethyl).

P.m.r. ($CDCl_3$): δ 1.30 (s, 3H), 1.47 (s, 3H, 3.35 (d, 1H), 3.82 (s, 3H), 4.42 (q, 2H), 4.82 (s, 1H), 4.87 (d, 1H), 5.40 (t, 1H).

Anal. Calcd. for $C_{11}H_{15}NO_7$ (273.24): C, 48.35; H, 5.53; N, 5.13
Found : C, 48.59; H, 5.49; N, 5.21.

Methyl exo-cis-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-trans-2-exo-nitro-3-carboxylate (V).

The Diels-Alder adduct III (50 g, 0.25 mole) was treated with osmium tetroxide (30 ml of a solution made from 1 g of osmium tetroxide in 200 ml of t-butanol) and 3x8 ml of hydrogen peroxide according to the procedure of Daniels[64]. From the reaction mixture, 24.5 g (42%) of V, mp: 145-147°, was filtered off.

I.r. (KBr): 3500-3200 cm^{-1} (OH), 1735 cm^{-1} (CO), 1560 cm^{-1} (NO_2), 1360, 1380 cm (gem-dimethyl).

P.m.r. (DMSO-d_6): δ 3.73 (s, 3H), 3.7-3.8 (dd, 1H), 3.98 (d, 1H), 3.78 (d, 1H), 4.55 (dd, 1H), 4.72 (s, 1H), 5.01 (d, 2H ex.), 5.18 (d, 1H).

Anal. Calcd. for $C_8H_{11}NO_7$ (233.18): C, 41.20; H, 4.76; N, 6.01.
Found : C, 41.14; H, 4.68; N, 6.06.

Methyl exo-cis-5,6-dihydroxy-O-isopropylidene-7-oxabicyclo [2.2.1]heptane-trans-2-exo-nitro-3-carboxylate (Va).

The diol V (24.5 g, 0.105 mole) was refluxed in a mixture of acetone and dimethoxypropane containing a catalytic amount of p-toluenesulfonic acid with a Dean-Stark trap filled with molecular sieves. At the end of the reaction, which was followed by t.l.c., the solvent was evaporated and the residue obtained was dissolved in chloroform, washed with water, dried and concentrated. The crude reaction product was recrystallized from ether/petroleum ether to give 26.4 g (92%), mp: 87-87°.

I.r. (KBr): 1725^{-1} (COC), 1560^{-1} (NO), 1375, 1380 cm^{-1} (gem-dimethyl).

P.m.r. ($CDCl_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 3.82 (s, 3H), 3.95 (m, 1H), 4.23 (d, 1H), 4.42 (d, 1H), 4.80 (d, 1H), 4.90 (d, 1H), 5.00 (s, 1H).

Anal. Calcd. $C_{11}H_{15}NO_7$ (273.24): C, 48.35; H, 5.53; N, 5.13.
Found : C, 48.19; H, 5.58; N, 5.06.

Methyl exo-cis-5,6-dihydroxy-O-isopropylidene-7-oxabicyclo [2.2.1]hept-2-ene-2-carboxylate (VI).

A solution of 26.4 g of Va in 100 ml ether was added dropwise to a stirred refluxing mixture of 29.3 g (1.93 mole) 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in 500 ml ether. After completed addition, the reaction mixture was cooled, filtered and the filtrate washed with 2N sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the crystalline product, obtained on evaporation, was crystallized twice from ether. Yield: 15.0 g (80%), mp: 118-119°.

I.r. (KBr): 1720 (C=O), 1610 (C=C), 1380, 1370 (gem-dimethyl) 1065 cm^{-1} (C-O-C);

P.m.r. ($CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 3.75 (s, 3H), 4.42 (s, 2H), 4.90 (m, 1H), 5.00 (m, 1H), 7.05 (d, J = 2Hz, 1H).

Mass spectrum 70 e.V. m/e 211 (M^+-CH_3) 126,100.

Anal. Calcd. for $C_{11}H_{14}O_5$ (226.23): C, 58.40; H, 6.24.
Found : C, 58.20; H, 6.39.

Dimethyl bis(7-oxabicyclo[2.2.1]hept-3,3'-yl)2-ene-trans 2'-endo-2-dicarboxylate (VII).

An ether solution of protected diol IVa (18.0 g, 0.066 mole) was treated with 1,5-diazobicyclo[5.4.0]undec-5-ene (14.5 g, 0.095 mole) at 0° for one hour. After work-up the crystalline residue was chromatographed on silicic acid using benzene/ethyl acetate (95:5) as an elution solvent. The first fraction 4.2 g (28%), was identified as olefin VI. The major product (VII), which eluted later, crystallized as colorless plates, mp: 169-171° (6.8 g, 45%).

Under the above reaction conditions using diol Va (exo-nitro ester), a mixture of olefin VI (60%) and dimer VII (8%) was obtained. The dimer proved to be identical in all respects with the sample obtained from the endo-nitro ester IVa.

I.r. (KBr): 1735, 1720 (C=O), 1640 (C=C), 1370, 1380 (gem-dimethyl), 1070, 1075 cm^{-1} (C-O-C).

P.m.r. ($CDCl_3$): see table III.

Anal. Calcd. for $C_{22}H_{28}O_{10}$ (452.44): C, 58.40; H, 6.24.

Found : C, 58.66; H, 6.27.

Hydrogenation of VII.

904.8 mg (2 mmole) of VII were dissolved in 50 ml of absolute ethanol and hydrogenated at atmospheric pressure over 100 mg of palladium on charcoal. After quantitative hydrogen uptake of 1 equiv. in 30 minutes, the catalyst was removed by filtration, and the solvent evaporated under reduced pressure to leave 900 mg of a crystalline solid. The crude product was purified by crystallization from ethanol. 800 mg (88%), mp: 188-189°.

I.r. (KBr): 1745 (C=O), 1380, 1375 (gem-dimethyl), 1060 cm^{-1} (C-O-C).

P.m.r. ($CDCl_3$): see Table IV.

Anal. Calcd. for $C_{22}H_{30}O_{10}$ (454.46): C, 58.14; H, 6.65.
Found : C, 57.91; H, 6.93.

Methyl 2-(4β-carboxy-2,3-O-isopropylidene tetrahydrofuran-3α,4α-diol 1β-yl)glyoxylate VIII.

Sodium metaperiodate (10.7 g, 0.05 mole) in 100 *ml* acetone-water (1:1) was added over a period of 3 hours to an acetone solution (100 *ml*) of the olefin V (4.5 g, 20 mmole) and 0.67 g, 5 mmole of ruthenium dioxide[82] with stirring at room temperature. The excess of ruthenium tetroxide was reduced with isopropyl alcohol and the reaction was worked up according to the procedure of *Piatak*[80,81] to give VIII in 83.5% yield. The compound was recrystallized from a mixture of acetone/hexane, mp: 114-116°.

I.r. (KBr): 3500, 3320, (OH), 1750 (C=O), 1390, 1380 cm^{-1} (gem-dimethyl);

P.m.r.($(CD_3)_2CO$): δ 1.35 (s, 3H), 1.55 (s, 3H), 3.82 (d, 3H), 4.50-4.70 (m, 2H), 4.90-5.35 (m, 2H), 6.67 (broad s, 3H, ex.);

Mass spectrum (70 e.V.) m/e 274 (M^+), 259 ($M^+ - CH_3$), 231 ($M^+ - CH_3$-CO).

Anal. Calcd. for $C_{11}H_{14}O_8 \cdot H_2O$ (292.24): C, 45.21; H, 5.52.
Found : C, 45.46; H, 5.54.

Resolution of the *l*-strychnine salt of Methyl 2-(4β-carboxy-2,3-isopropylidene tetrahydrofuran 3α, 4α-diol 1β-yl)glyoxylate.

A solution of this salt was prepared by dissolving 876.7 mg (3 mmole) of VIII and 1.003 g (3 mmole) of *l*-strychnine in 25 *ml* ethanol. Addition of 10 *ml* of ether deposited 520 mg of crystals, which were crystallized from isopropanol ($[\alpha]_D^{25}$ -6.6°, c = 1); recrystallization from isopropanol gave a rotation of $[\alpha]_D^{25}$ -7.1°, (c = 1, ethanol), which remained unchanged after further recrystallizations. Regeneration of the free acid by means of an ion-exchange column (Rexyn 101 (H)) left 200 mg of one antipode of VIII, (rotation $[\alpha]_D^{25}$ -3.2°, c = 2). In order to obtain the dextrorotating antipode, the mother liquor (30 *ml* of ethanol/ether) from the first crystallization of the *l*-strychnine salt was concentrated to 5 *ml*, left standing overnight at 5°C and filtered. The filtrate, after removal of *l*-strychnine, yielded 100 mg of resinous acid VIII, rotation $[\alpha]_D^{25}$ + 2.3°, c = 2 ethanol).

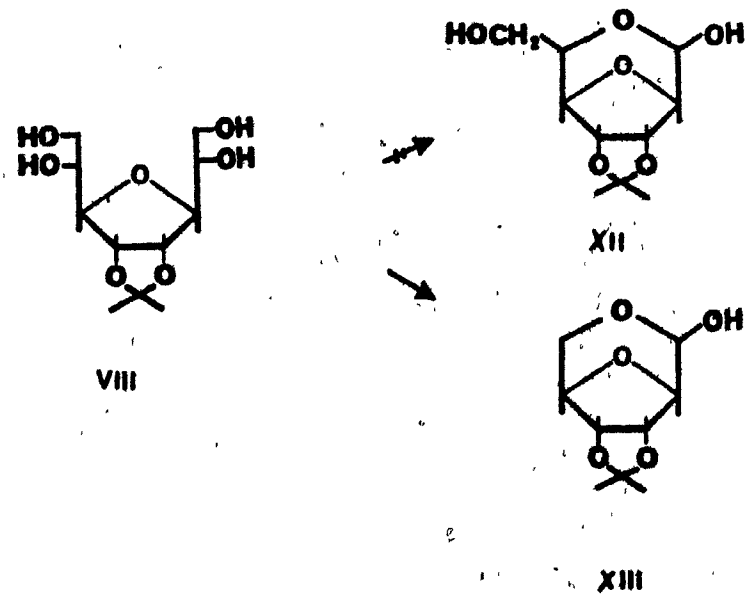
Chapter III

A reinvestigation on the periodate induced deformylation of 3,4-O-isopropylidene 2β, 5β-bis (1',2'-dihydroxyethyl) tetrahydrofuran-3α, 4α diol.

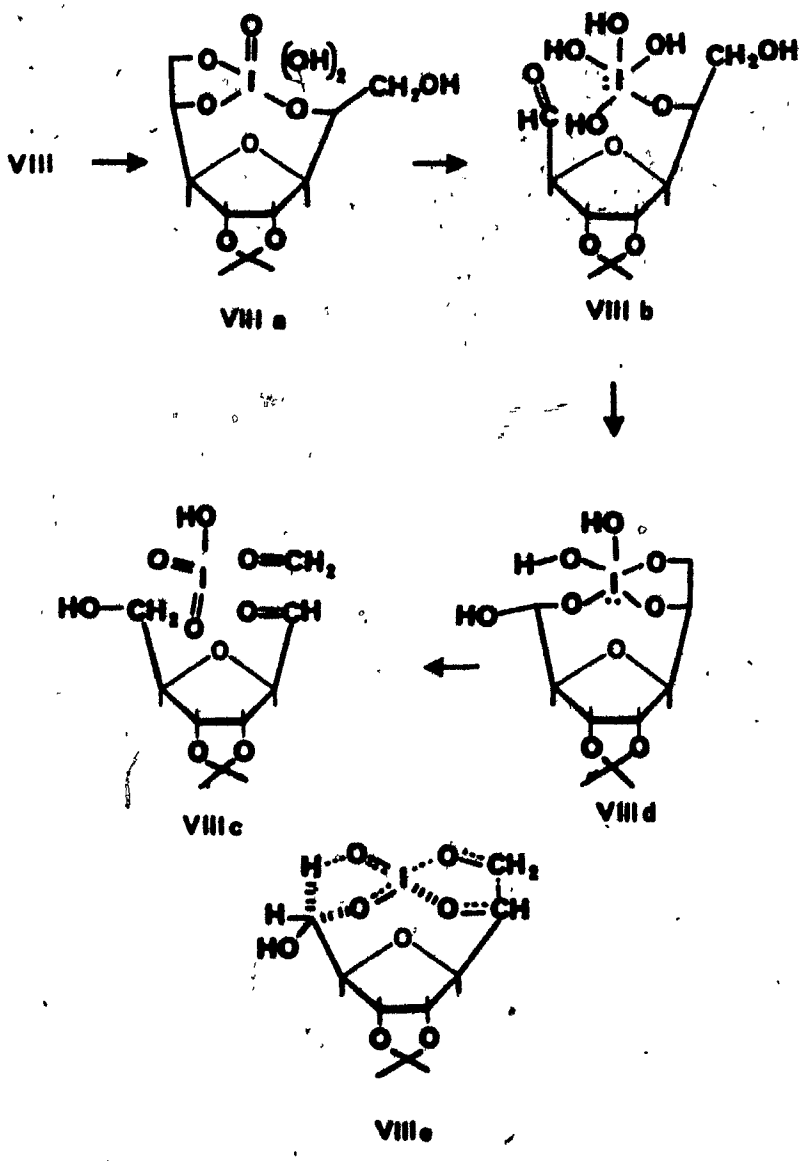
1. Aims of this project.
2. A reinvestigation of the published synthesis[70,71] of 3,4-O-isopropylidene-2,5-anhydro-D,L-allose.
3. New synthesis of the key intermediate 3,4-O-isopropylidene 2β,5β-bis(1',2'-dihydroxyethyl)-tetrahydrofuran-3α,4α-diol VIII.
4. An alternative synthesis of the expected periodate cleavage product: the diol aldehyde as hemiketal XIII.
5. Characterization of the lactones XV and XVI with special emphasis on stereochemistry by p.m.r.
6. Experimental Part.

1. Aims of this project.

Recently it was reported[70,71] that treatment of the tetraol (VIII) with sodium metaperiodate did not give the expected hydroxy aldehyde-hemiketal (XII) but instead, 3,4-O-isopropylidene-2,5-anhydroallose (XIII).



Since there is no precedent for this type of non oxidative olimination of formaldehyde from the tetraol VIII[70], a mechanism was postulated by Martel[70]. This mechanism is based on the formation of tridentate complexes of periodates.


VIII
VIII a
VIII b
VIII c
VIII d
VIII e

After a normal cleavage of formaldehyde to give VIIIb, the remaining free hydroxyl is then complexed with iodate (IO_3^-). Furthermore one hydroxyl group of the iodate may form a hemiketal with the aldehyde group to give a species of type VIIId, followed by an hydride shift of the hydrogen from the hydroxyl group to the hemiketal, as represented by VIIIe. Then the right-hand side would cleave in the normal fashion to give VIIIc.

The validity of this proposed mechanism could therefore be checked by exchanging the hydroxyl groups with deuterium, and repeating the elimination with sodium metaperiodate in deuterium oxide. The anhydroallose formed in the reaction should contain deuterium.

At this stage we felt that a more detailed investigation of the reaction pathway would be justified. A further proof of the validity of the above proposed mechanism could be accomplished by an unambiguous synthesis of the intermediate aldehyde-hemiketal (XII), followed by the treatment with IO_3^- (Step VIIIb via VIIId to VIIIc).

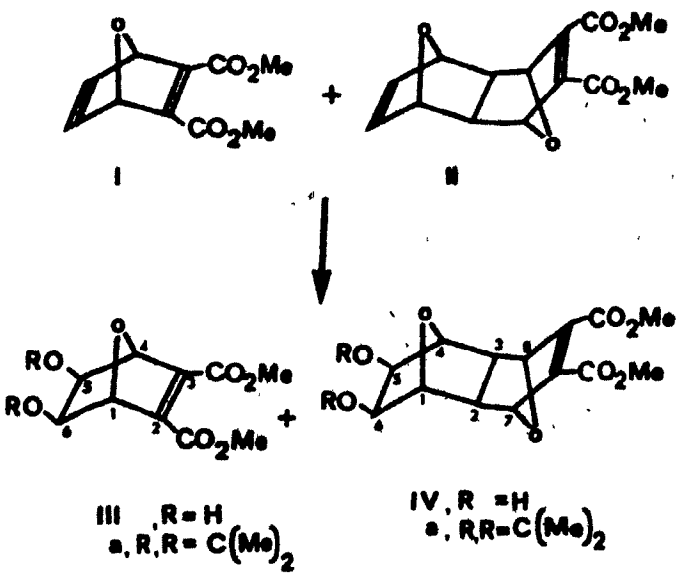
2. A reinvestigation of the synthesis of 3,4-O-isopropylidene 2,5-anhydro-D,L-allose XIII[70,71].

The olefin diester IIIa was prepared from the known adduct of furan and dimethyl acetylenedicarboxylate I as a starting material[83]. The mono-adduct I is well authenticated[84-86] and was obtained as an oily mixture with traces of a dimeric product II. Without separation the mixture was submitted to a catalytic osmylation reaction[75,87] to give the diol diester III and impurity IV. Treatment of III and IV with acetone/dimethoxypropane in the presence of p-toluenesulfonic acid gave the corresponding isopropylidene derivatives IIIa and IVa. The mixture was separated by chromatography on silicic acid and resulted in crystalline, analytically pure products.

The cis-hydroxylation with osmium tetroxide could give either exo or the endo products. However, there are several examples of this type of oxidation on similar systems[88,89] and the products have been identified by p.m.r. to have the hydroxyl groups in the exo configuration. The structural assignment of IIIa was readily established from the multiplicity of the signals by p.m.r. In the exo-hydroxylated product, the dihedral angles between the bridgehead (H_1, H_4) and the endo (H_5, H_6) protons are close to 90°, resulting in near absence of coupling[90,91,92].

In the endo-hydroxylated product, however, the bridgehead protons (H_1, H_4) and the exo-protons (H_5, H_6) require dihedral angles of approximately 45°. This would result in a significant coupling constant, $J_{1,6}$ $J_{4,5} \approx$ 4Hz..

Scheme 1



In the case of the dimer IVa, the endo-protons (H_5, H_6) and the bridgehead protons (H_1, H_4) appear as singlets.

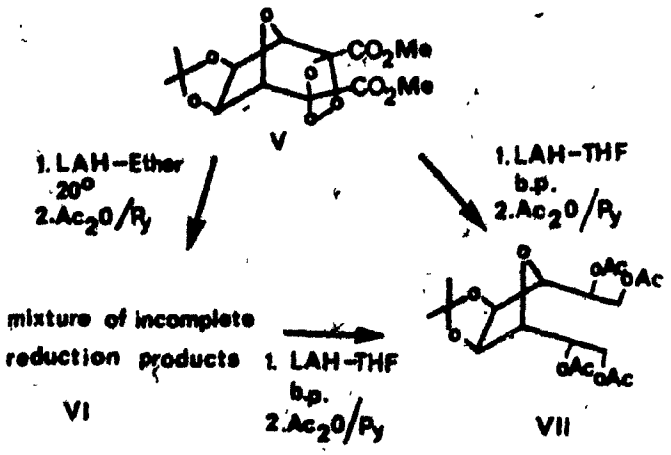
Absence of coupling between the bridgehead protons (H_1, H_4) and the ring juncture protons (H_2, H_3) confirms the ring juncture stereochemistry of IVa as having the endo-exo-configuration[93]. In contrast, the bridgehead and ring-juncture hydrogens H_2, H_7 and H_8, H_3 require a dihedral angle of approximately 45°, resulting in a significant coupling $J_{2,7}$ $J_{3,8}$= 4.9 Hz .

Subsequent to the completion of this research, a study of the influence of Lewis Acids on the Diels-Alder reactions of furan with dimethyl acetylenedicarboxylate was published by another group[93]. Dimer II was first identified by Slee and LeGoff[94].

Ozonolysis of IIIa gave a crystalline ozonide (mp: 79-81°), to which structure V was tentatively assigned, based on similar ozonides[70,95].

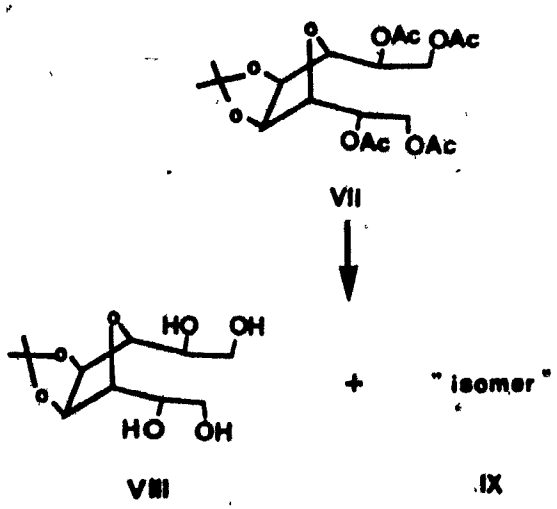
Reduction of the ozonide V using the condition described by Martel[70] gave a mixture of the required product (by mass-spectrometry) and unreduced ester as determined by its p.m.r.-spectrum, which showed a ratio of acetate to isopropylidene protons as 1:1 and a carboxy-methyl group at δ 3.80 typical for the starting material. The reduction of the ozonide was then carried out under more drastic conditions by refluxing in tetrahydrofuran and direct acetylation of the reaction mixture. This resulted in a 40% yield of the tetraacetate VII. Elemental analysis and spectra data agreed with the structure proposed by Martel[70].

Scheme 2.



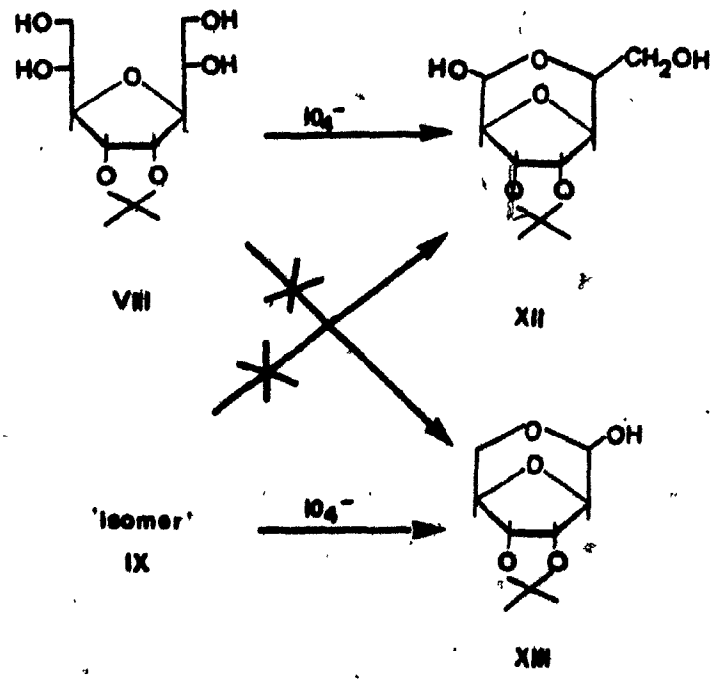
Cleavage of the tetraacetate VII with sodium methoxide in methanol resulted in two products VIII and IX, which were readily separated by column chromatography on silicic acid.

Scheme 3



Oxidation of tetraol VIII with one mole sodium periodate in aqueous solution gave the originally expected[70] dihydroxy aldehyde hemiacetal XII and one mole of formaldehyde (dimedone derivative). Thin-layer chromatography indicated the absence of 2,5-anhydroallose, prepared by an unambiguous route[72]. However, oxidative cleavage of the "isomer IX", using the above conditions, resulted in the formation of 2,5-anhydroallose in 80% yield, and the liberation of one mole of formaldehyde (dimedone derivative). The 2,5-anhydroallose was identical in all respects (p.m.r., i.r., m.p., m.m.p.) with the compound obtained from the allose prepared independently[72].

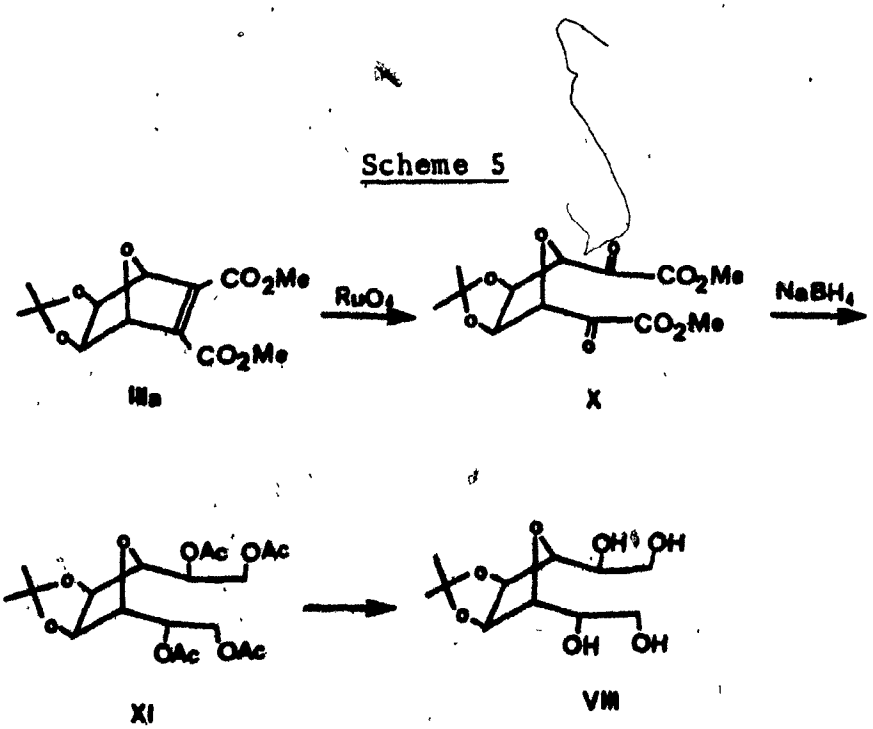
Scheme 4



3. New synthesis of the key intermediate tetraol VIII.

Since none of the steps described for the synthesis of VIII or "isomer IX" could be improved any further and since larger quantities were required to study the mechanism of the 2,5-anhydroallose (XIII) formation, we investigated a different route, as outlined in scheme 5.

Scheme 5



A ruthenium tetroxide catalysed oxidation[80,81] of the olefin diester IIIa gave an oily diketo ester X. Reduction of X with sodium borohydride in refluxing isopropanol and direct acetylation gave the tetraacetate XI in 58% yield, based on diketo ester X.

It was noted, however, that chromatographically homogeneous XI showed a slightly different p.m.r. signal pattern of the acetyl protons than the tetraacetate VII prepared according to scheme 2, (page 63).

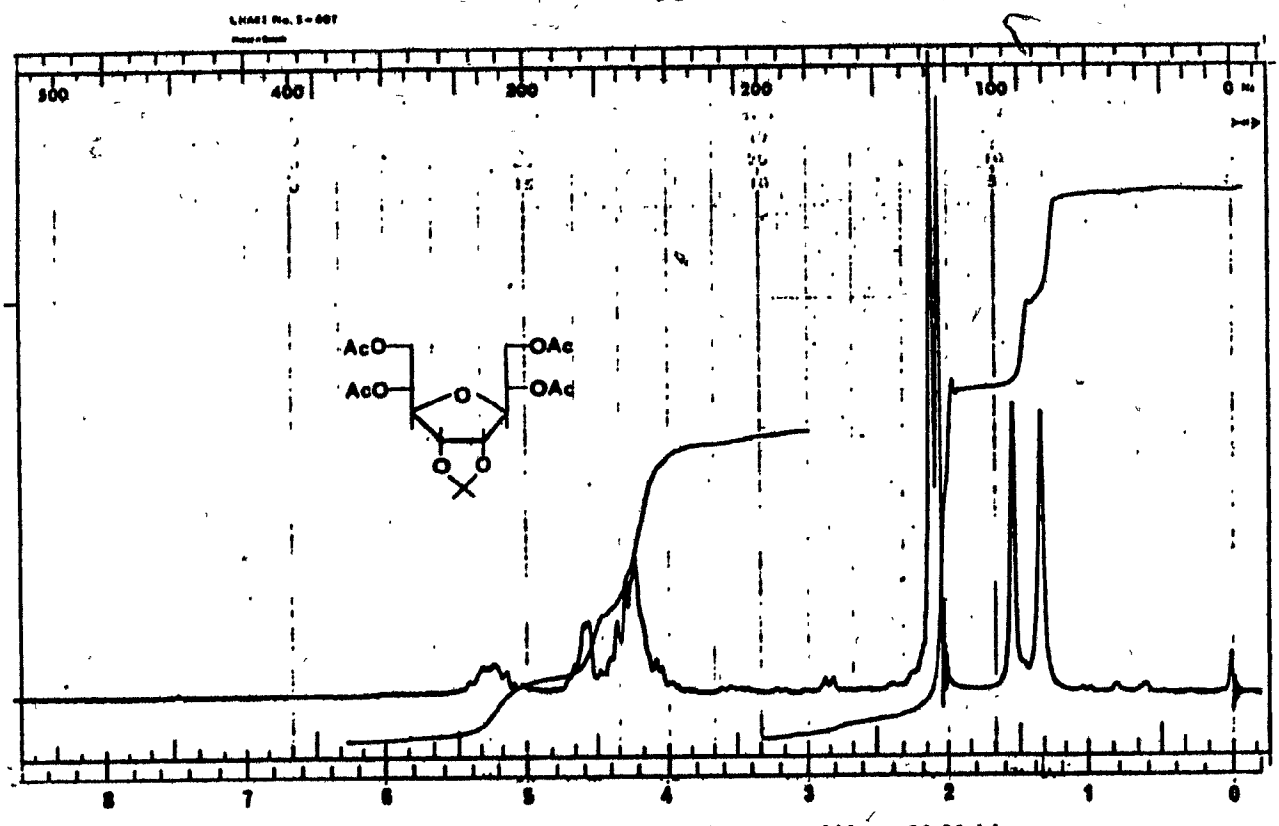


Fig. 1. The p.m.r. spectrum of 3,4-Isopropylidene 2β,5β-bis (1',2'-diacetoxy-ethyl) tetrahydrofuran -3α,4α-diol (XI) in chloroform-D .

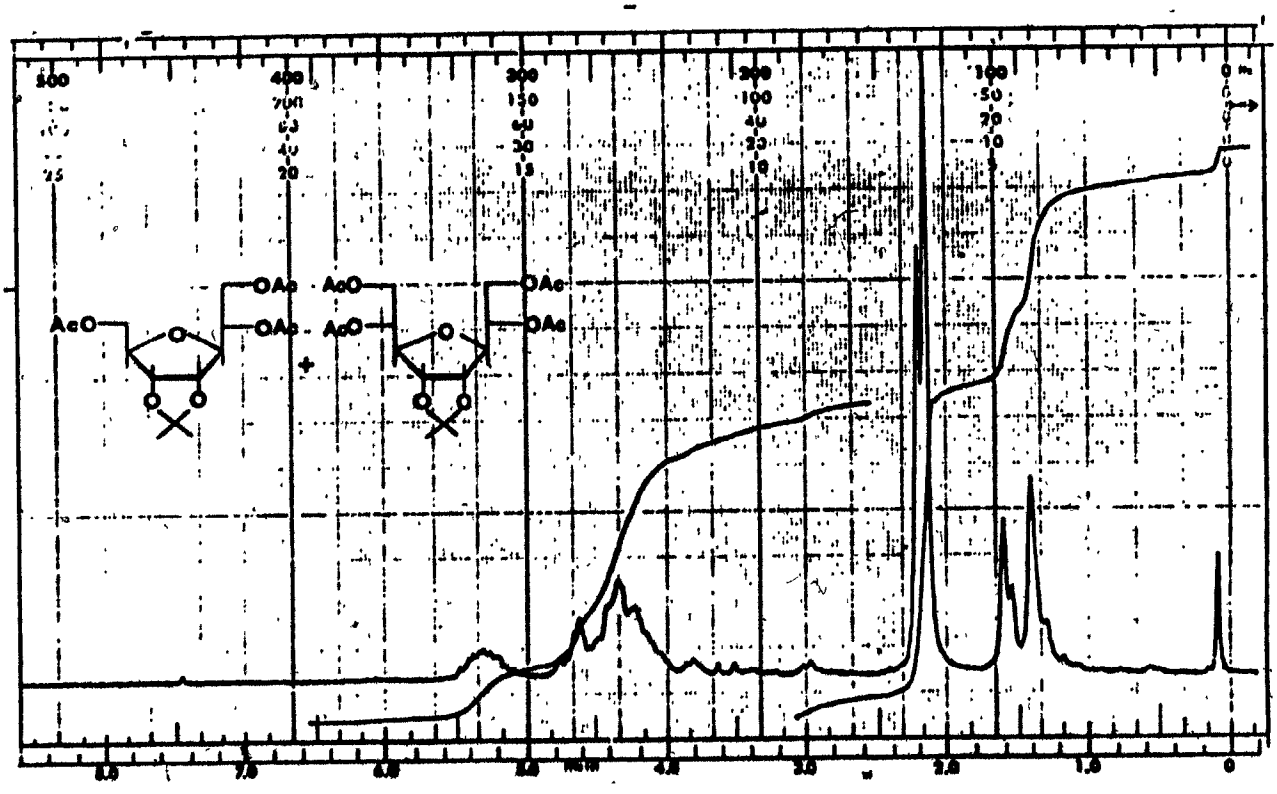


Fig.2. The p.m.r. spectrum of 3,4-Isopropylidene 2β,5β-bis (1',2'-diacetoxy-ethyl) tetrahydrofuran -3α,4α-diol (VI) in chloroform-D .

Treatment of tetraacetate XI with sodium methoxide in methanol resulted in only one product which was identical in all respects with VIII and not a trace of "isomer IX" was found in the reaction mixture. Consequently oxidation of VIII, prepared via scheme 5, did not give 2.5-anhydroallose XIII, but the expected diol aldehyde XII, as its hemiacetal m.p. 138-140°. Since at this stage, we did not know the structure of IX, we considered the possibility, that IX was some isomer of VIII, which gave rise to the unusual periodate reaction.

In any case it became necessary now, to modify the ozonide V reduction[59] in such a way, that sufficient quantities of IX could be isolated.

As first approach we employed milder conditions than lithium aluminium hydride:

Reduction of the ozonide V with sodium borohydride in refluxing isopropanol, followed by acetylation in pyridine resulted in formation of 69% tetraacetate which was identical in all respects to XI (p.m.r., mass-spectrum, t.l.c. and i.r.). A second compound was isolated in 15% yield, and was identified by i.r., t.l.c., p.m.r., m.p. and m.m.p. as the lactone XV prepared via scheme 8 (page 78).

Hydrolysis of the tetraacetate XI obtained with sodium borohydride reduction of ozonide V gave the tetraol VIII and oxidation with periodate again afforded solely the diol aldehyde as its hemiacetal XII as expected.

Obviously, either isopropanol or sodium borohydride could effect decarboxymethylation of V.

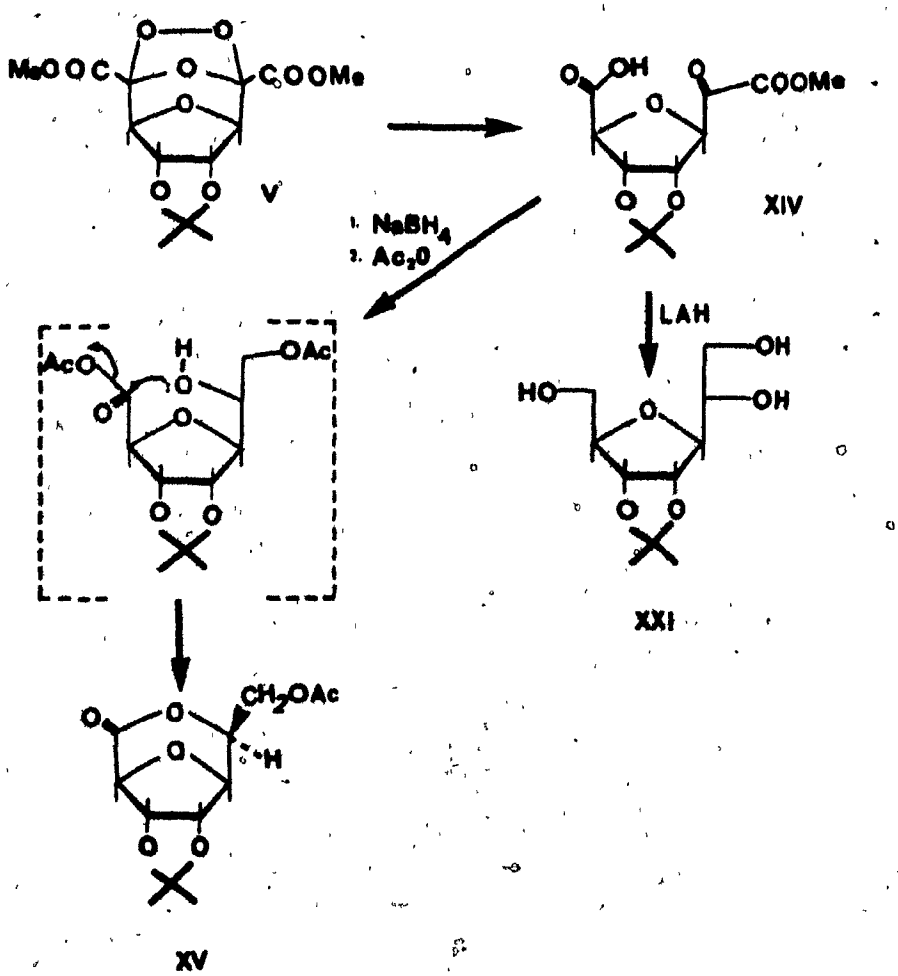
A possible mechanism for the ozonide reduction is outlined in scheme 6. The intermediate XIV could either - in the presence of sodium borohydride - give the lactone XV or - in case of the lithium aluminum hydride reduction - yield a triol XXI, which indeed may be postulated as the structure of our isomer IX (scheme 4). Thus, the sodium borohydride reduction by-product, even though it was not the desired IX, offered some clue for the important by-product IX.

Hydrolysis of the tetraacetate XI obtained with sodium borohydride reduction of ozonide V, gave the tetraol VIII and oxidation with periodate again afforded solely the diol aldehyde as its hemiacetal XII as expected.

Obviously, either isopropanol or sodium borohydride could effect decarboxymethylation of V.

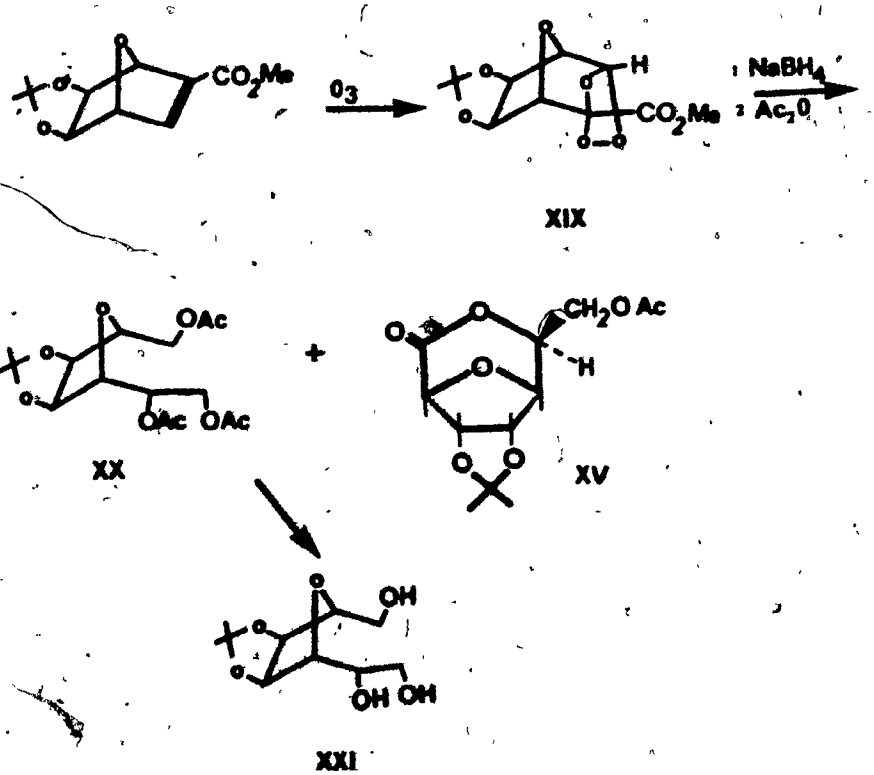
A possible mechanism for the ozonide reduction is outlined in scheme 6. The intermediate XIV could either - in the presence of sodium borohydride - give the lactone XV or - in case of the lithium aluminumhydride reduction - yield a triol XXI, which indeed may be postulated as the structure of our isomer IX (scheme 4). Thus, the sodium borohydride reduction by-product, even though it was not the desired IX, offered some clue for the important by-product IX.

Scheme 6


MeOOC
COOMe
V
COOMe
XIV
1. NaBH4
2. Ac2O
LAH
HO
OH
OH
XXI
AcO
OAc
CH2OAc
XV

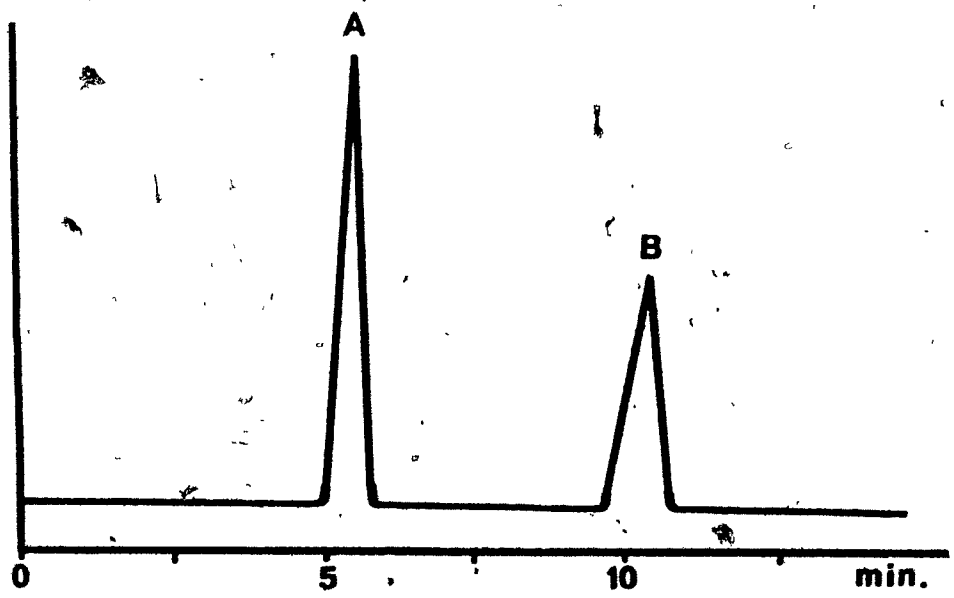
To prove the structure XXI (or IX) to be 3,4-O-isopropylidene 2β-(1',2'-dihydroxyethyl)-5β-hydroxymethyl-tetrahydrofuran 3α, 4α-diol we synthesized it independently according to scheme 7.

Scheme 7



Ozonolysis of methyl exo-cis-5,6-dihydroxy-O-isopropylidene-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (Chapter II) gave an oily ozonide XIX, which crystallized on standing. Sodium borohydride reduction and acetylation in situ, afforded the triacetate XX in 62% yield, and the lactone XV in 5% yield. The triacetate XX was indistinguishable in all t.l.c. systems tested from the tetraacetate VII (or XI) obtained via Scheme 3 (or 5). Hydrolysis of the triacetate XX with a trace of sodium in methanol gave a product XXI, which was indeed identical in all respects with the isomer IX. For further corroboration, the "isomer" IX (obtained via scheme 3) was acetylated and compared on gas liquid chromatography, (rubber silicon column, 4 ft length). It had an identical retention time with triacetate XX.

Gas-Liquid Chromatogram of VII



Chromatogram obtained in the analysis of VII.

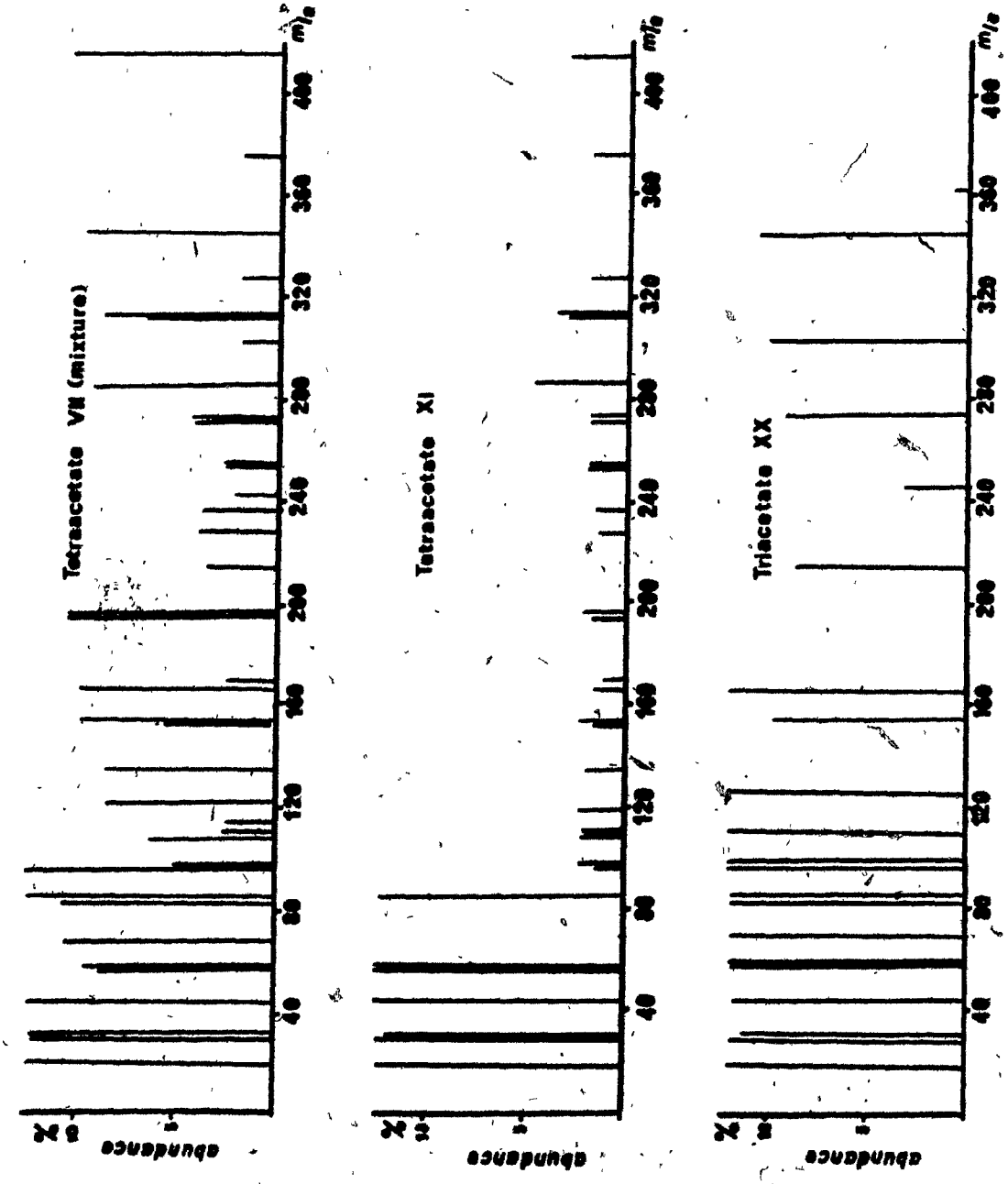
Peaks: A, 3,4-O-isoproylidene 2β-(1',2'-diacetoxyethyl) 5β acetoxymethyl tetrahydrofuran 3α, 4α-diol.

B, 3,4-O-isopropylidene 2β, 5β-bis(1',2'-diacetoxyethyl)-tetrahydrofuran 3α, 4α-diol.

The column was packed with silicon gum rubber SE 30; the temperature was 240°C and the flow rate was 50 ml helium/minute.

In this system, the tetraacetate VII of scheme 3 was clearly a mixture of tetra- and triacetate. It was clear now, that the formation of 2,3-anhydroallose XIII during the periodate cleavage of tetraol VIII was due to the presence of triol and not the result of a periodate oxidation. Furthermore, this also explains the different p.m.r. spectra observed for tetraacetate VII and XI (see page 67). From the relative intensities of the O-acetyl signals, the overall integral for VII suggest that the two signals δ2.03 and 2.11, account for a total of closer to nine protons rather than the value of twelve required for XI.

Mass spectrometry has been extensively employed for the confirmation of the constitution of structural analogs and related precursers and derivatives. The fragmentation pattern observed for tetraacetate VII, XI and triacetate XX is given below.

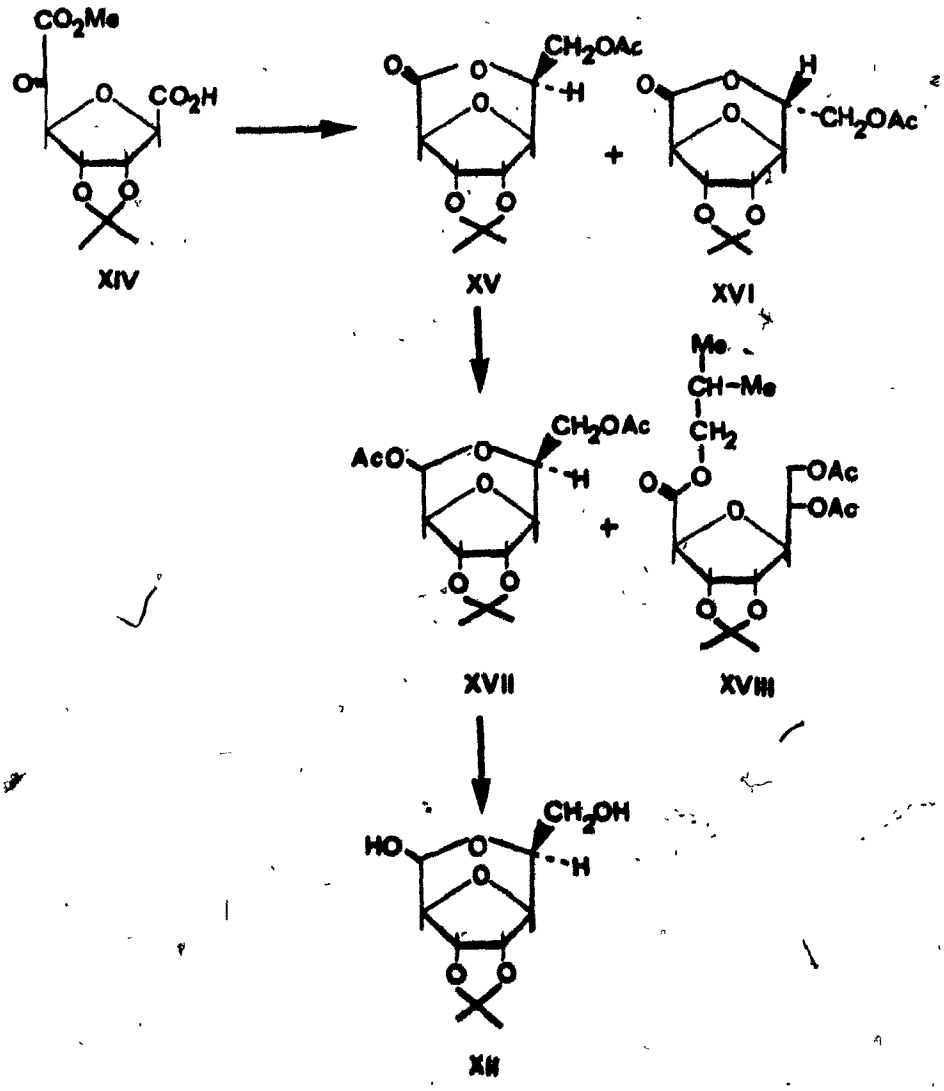

Tetraacetate VII (mixture)
Tetraacetate XI
Triacetate XX
abundance
m/e
40
80
120
160
200
240
280
320
360
400

4. An alternative synthesis of 3,4-O-isopropylidene 2β-(1',2'-dihydroxyethyl)tetrahydrofuran-3α, 4α diol-5β-aldehyde hemiketal XII.

Early in our investigation of the proposed reaction mechanism[70], we turned our attention to the preparation of the diol aldehyde XII, which was the suggested intermediate product in the oxidation of tetraol VIII or "isomer" IX. The proposed mechanism for the cleavage involved the complexation of the diol aldehyde XII with IO_3^-, followed by an hydride shift, (see page 58).

We, therefore, studied an independent, unambiguous synthesis of compound XII, which is outlined in scheme 8.

Scheme 8



XIV XV XVI XVII XVIII XII

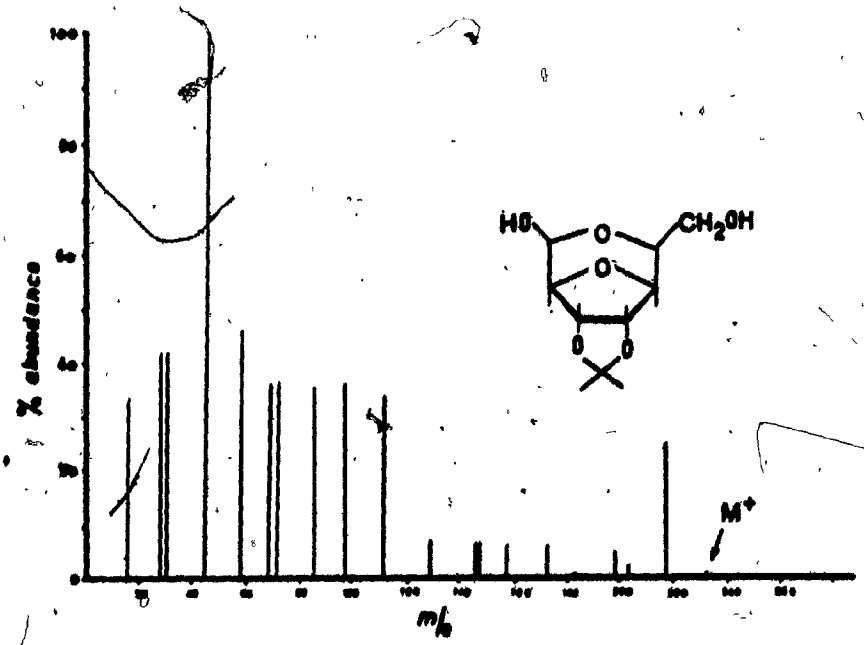
The first step consisted of the reduction of methyl 2-(5β-carboxy 3,4-O-isopropylidene tetrahydrofuran 3α,4α-diol-2β-yl) glyoxylate XIV (see Chapter II) with sodium borohydride in the presence of sodium bicarbonate. After acetylation 3,4-O-isopropylidene 2β(1',2'-dihydroxy-ethyl-2'-O-acetyl)tetrahydrofuran-3α,4α-diol-5β-carboxylic acid δ lactone XV, m.p. 156-157°, and its isomer XVI m.p. 102-103°, were obtained. Their different solubilities in ether provided a clean separation by fractional crystallization. Both isomers were obtained analytically pure.

Reduction of the lactone XV with diisobutyl aluminium hydride (2 eq.) in toluene at -78° according to the procedure of Corey[99] and acetylation of the reaction mixture afforded the corresponding lactol -diacetate XVII, and a minor impurity, which was identified as isobutyl ester XVIII. Hydrolysis of XVII in aqueous sodium bicarbonate gave the crystalline diol aldehyde hemiketal XII, identical with a sample obtained from oxidation of the tetraol VIII (Scheme 4, page 65).

As one might expect now - as the problem of the periodate reaction has been solved - treatment of hemiketal XII with potassium iodate in various buffer solutions resulted in quantitative recovery of starting material.

The mass spectrum of XII appears to retain the pattern observed for the 5,6-O-isopropylidene-7-oxabicyclo [2.2.1] derivatives. A molecular ion is still obtained (Figure 3). However, the base peak in the spectrum is M^+ -15, since cleavage of the methyl group of the acetonide is an important fragmentation process.

Figure 3



Mass spectrum of XII

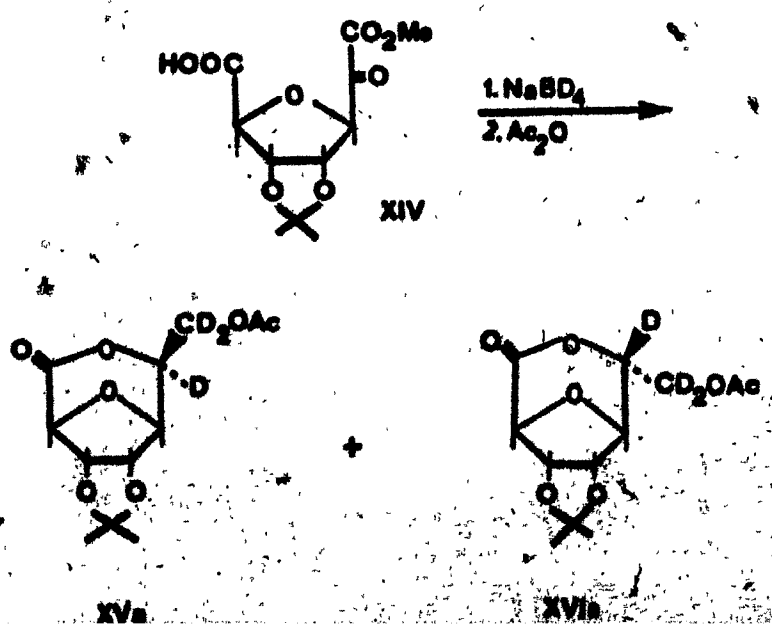
232*	⟶	217*	+	CH_3
217*	⟶	199*	+	H_2O
217*	⟶	182*		$m^* = \frac{182^2}{217}$
217*	⟶	157*	+	$OHC\text{-}CH_2OH$
217*	⟶	127*	+	$OHC\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$
232*	⟶	174*	+	$(CH_3)_2\text{-}CO$
174*	⟶	144*	+	$CH_2{=}O$
174*	⟶	113*	+	$O\text{-}CH_2\text{-}CH_2\text{-}OH$
174*	⟶	84*	+	$OHC\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$
232*	⟶	157*	+	$(CH_3)_2C{<}^{OH}_{O}$ H-transfer
157*	⟶	127*	+	CH_2O
157*	⟶	97*	+	$O{=}CH\text{-}CH_2\text{-}OH$

5. Characterization of the lactones XV and XVI.

Reduction of the acid keto ester XIV with sodium borohydride, followed by acetylation afforded a mixture of two isomeric lactones XV and XVI. Both were obtained in analytically pure form by crystallization in a ratio of 3:1. Reaction of lactone XV and XVI with diisobutyl aluminum hydride in toluene at -78° gave the corresponding lactol. However, only the lactol obtained from lactone XV corresponded with the diol aldehyde hemiketal obtained via the oxidation of the tetraol VIII (Scheme 4, page 65).

Stereochemical studies of various 7-oxabicyclo [2.2.1] heptanes in simple compounds, using the p.m.r. method, have been reviewed[76,97]. To find the chemical shift of the proton at C-1, we repeated the reduction of the acid keto ester XIV with sodium borodeuteride.

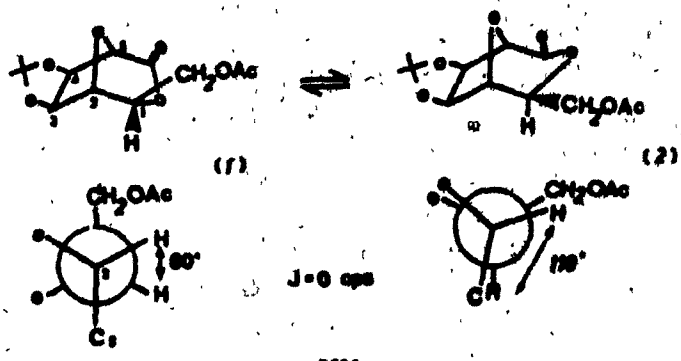
Scheme 9



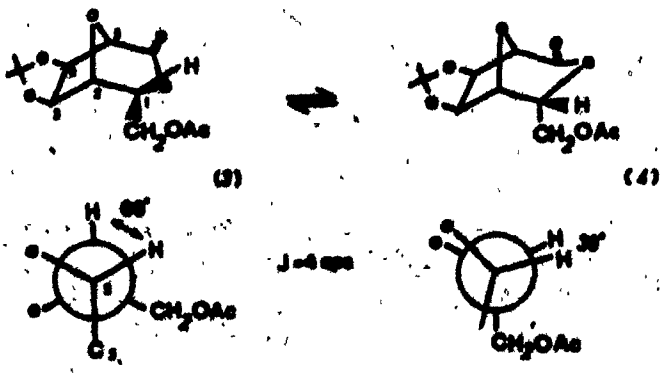
After isolating the pure deuterated lactones XVa and XVIa, we compared their relatively simple spectra with those of the non-deuterated products with regard to the coupling constants[92,98]. It is obvious that the coupling constants depend very markedly on the conformation(s) which the molecule adopts. If the coupling constants are known, it may become possible to deduce the conformation of such rings. Attempts to do this have already been made by Jardetzky[98] in the case of the ribose nucleosides and nucleotides. For each isomer XV or XVI, there are two conformations possible, (see scheme 10). If we assume conformation (1), (chair form) the dihedral angle of protons H_1, H_2, would be 60°, and assuming the other extreme, conformation (2), the angle would be about 110°. However, in each case the observed coupling constants may be averages of both conformations, possible due to non-bonded interactions of (1) by the acetoxy-methyl with the 7-oxygen, and the eclipsed form of the 7-oxygen with the lactone oxygen of conformation (2). Assuming this, the dihedral angle between the bridgehead proton H_1, H_2 is about 80°, and this would result in almost no coupling. Similar in isomer XVI, the average dihedral angle between the protons H_1, H_2 of conformations (3) and (4) is about 45°. The coupling constant for this angle is $J = 4$ c.p.s which is the observed value.

The dihedral angles were obtained by measurements made on Fieser molecular models. The exact values are uncertain, because it is not known exactly how the distortion is spread through the molecule. The uncertainties in dihedral bond angles are most unlikely to affect the conclusion made in this analysis. The good agreement between calculated and observed coupling constants found, supports the validity of the assignment made for XV and XVI.

Scheme 10



XV



XVI

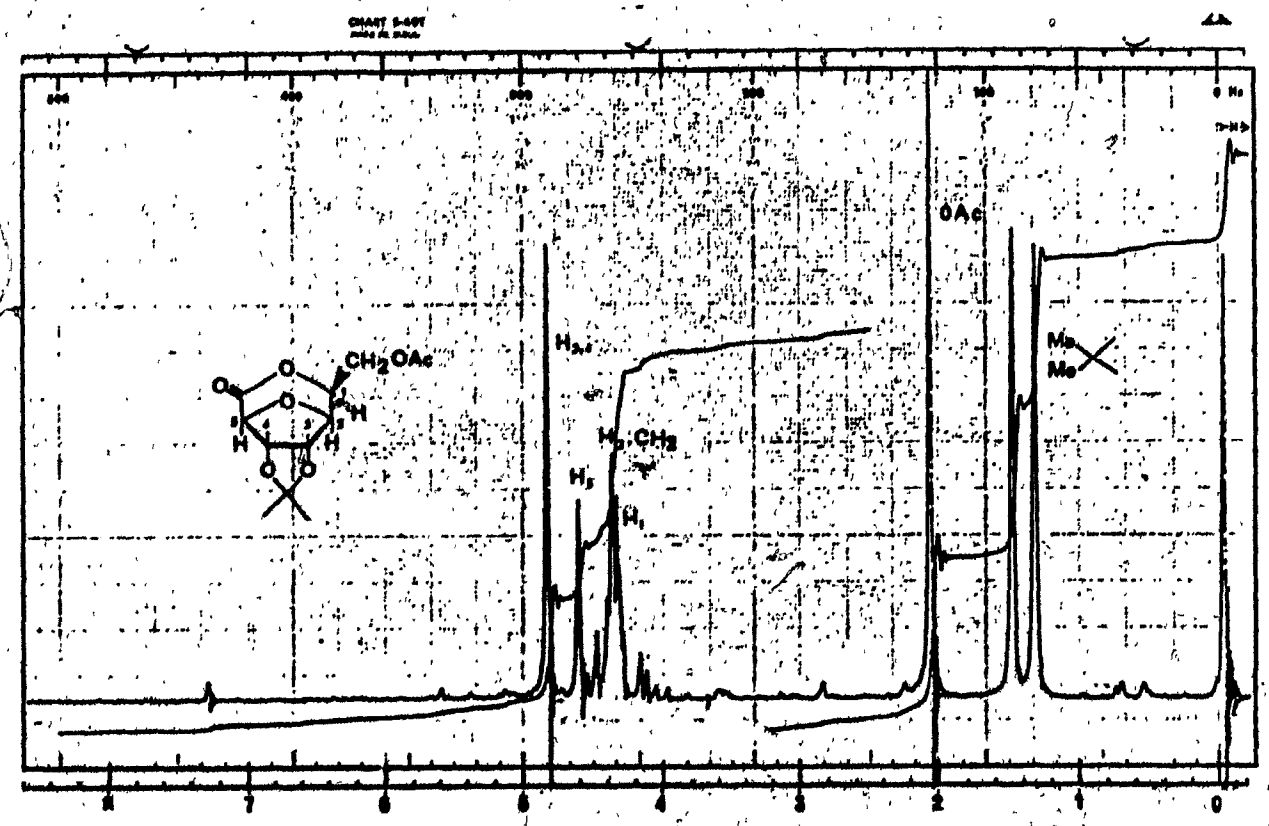


Fig. 4 The p.m.r. spectrum of 3,4-O-isopropylidene 2β(1',2'-dihydroxyethyl-2'-O-acetyl) tetrahydrofuran-3α,4α-diol-5β-carboxylic acid δ lactone XV in chloroform-D.

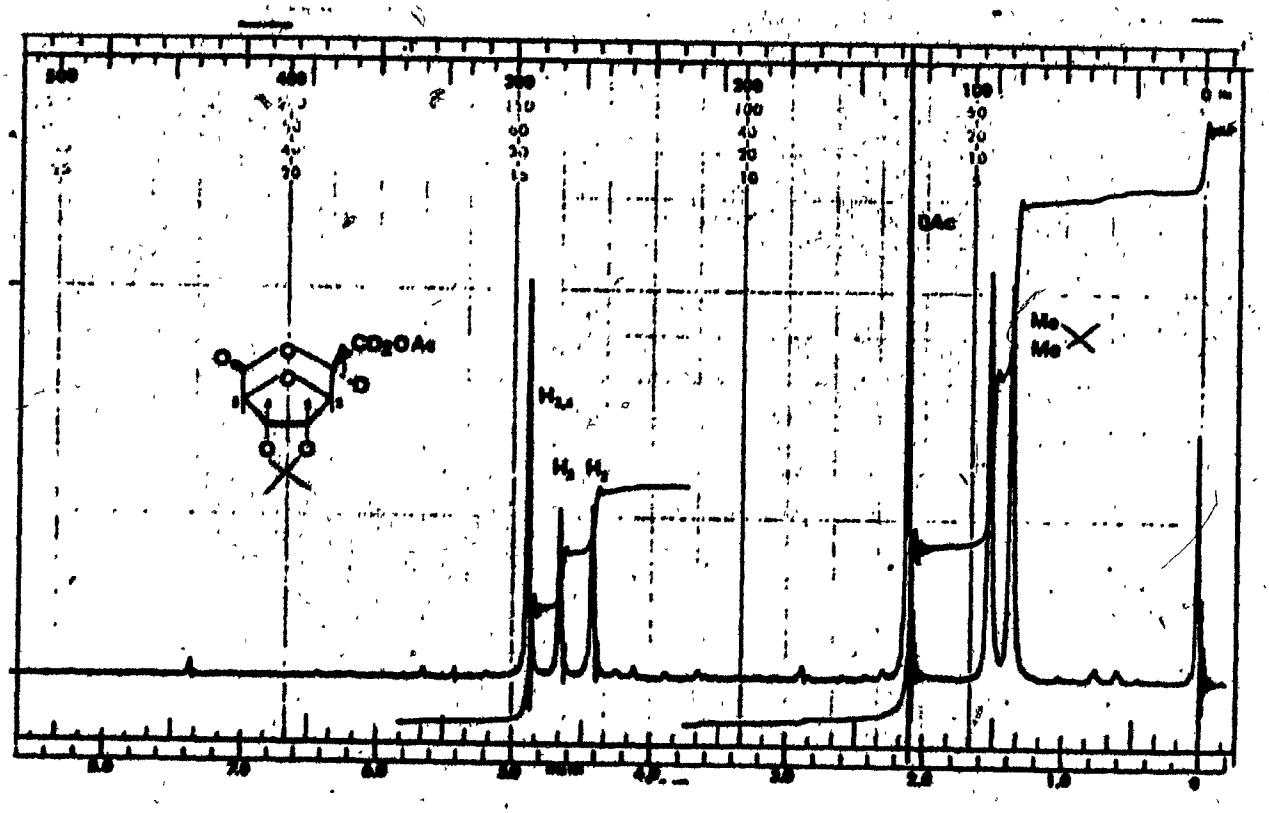


Fig. 5. The p.m.r. of deuterated lactone XVb in chloroform-D.

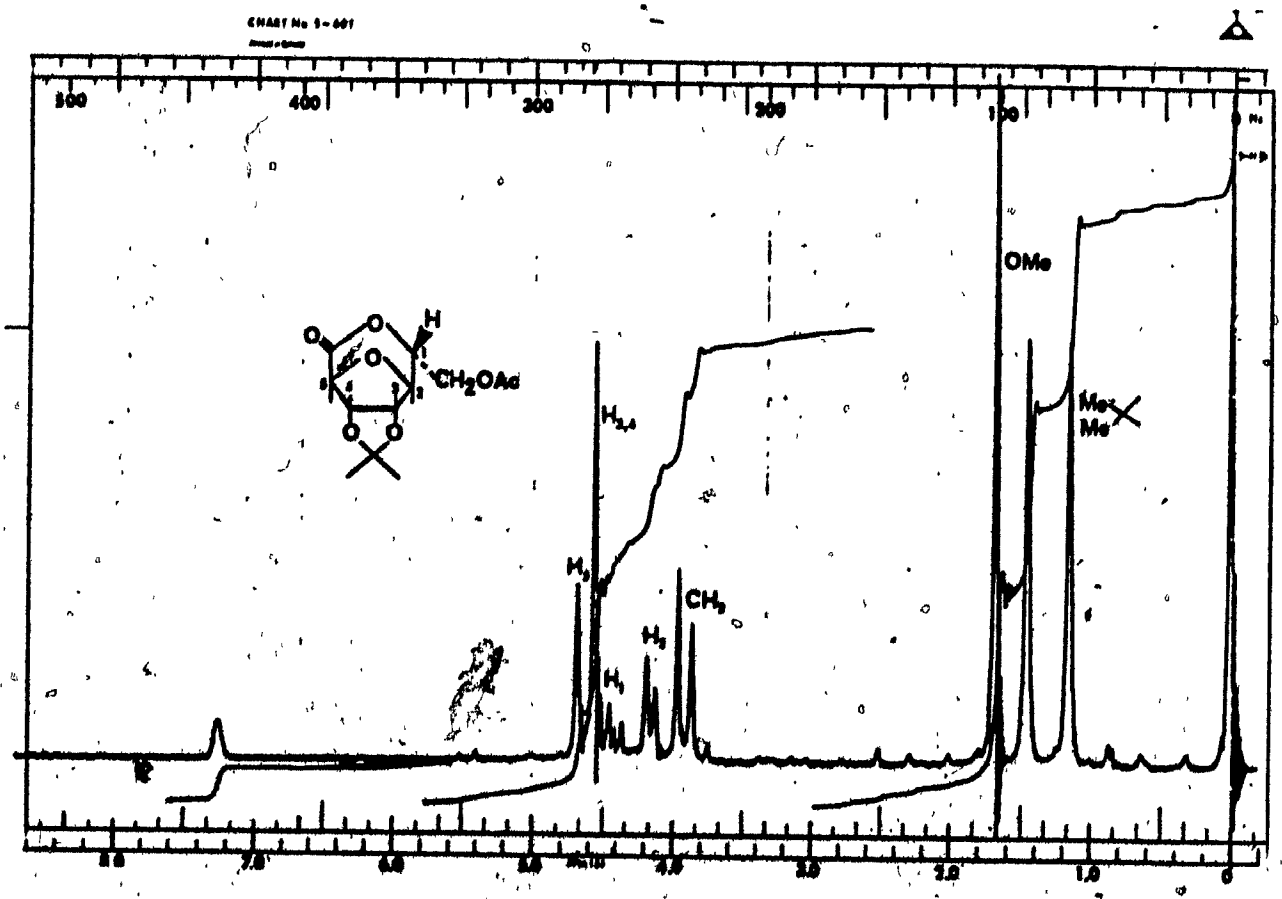


Fig. 6 The p.m.r. spectrum of 3,4-O-isopropylidene 2β(1',2'-dihydroxyethyl-2'-O-acetyl) tetrahydrofuran-3α,4α-diol-5β-carboxylic acid δ lactone XVI in benzene-D_6.

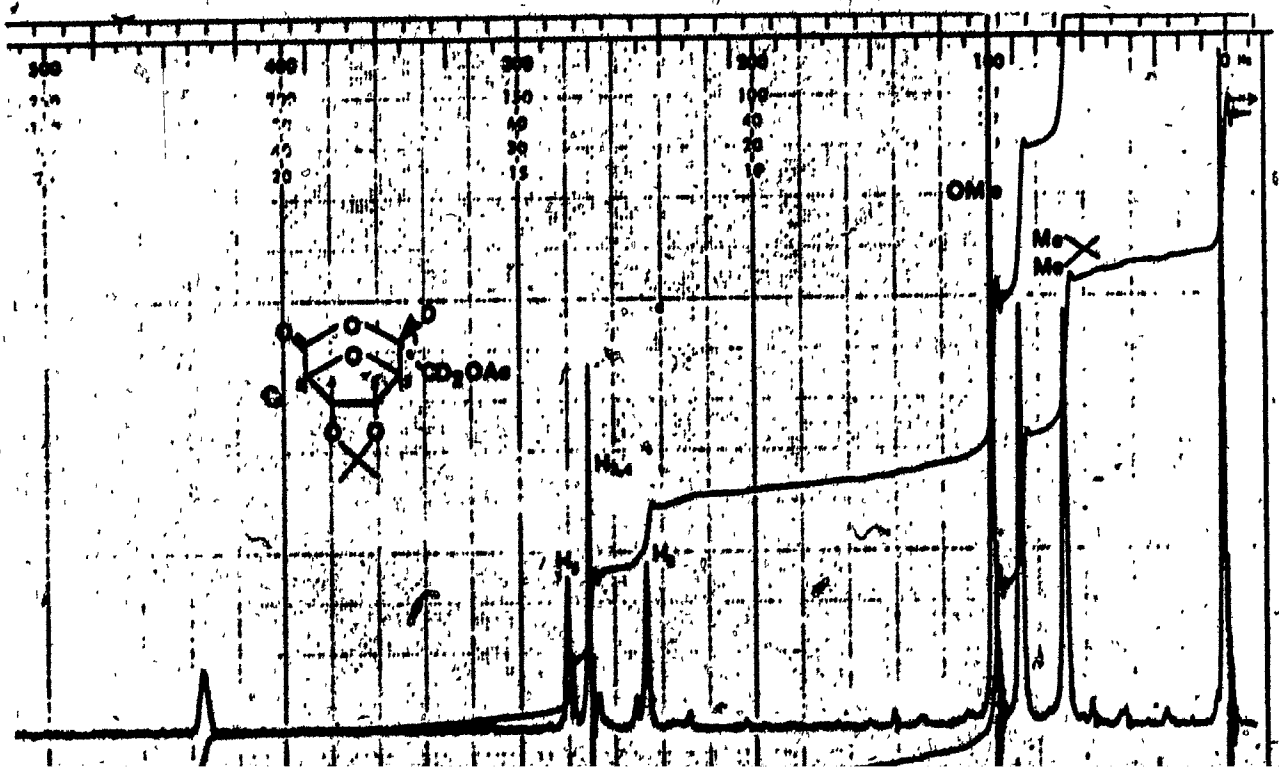


Table 1

P.m.r. parameters for XV and XVa in $CDCl_3$

(Chemical shifts in ppm)

Compound	gem-dimethyl		OCH_3	H_1	H_2	H_3, H_4	H_5	CH_2O
XV	1.37 (s)	1.51 (s)	2.10 (s)	4.1-4.5 (m)	4.38 (s)	4.90 (s)	4.62 (s)	4.1-4.5 (m)
XVa	1.37 (s)	1.51 (s)	2.10 (s)	-	4.38 (s)	4.90 (s)	4.62 (s)	-

P.m.r. parameters for XV and XV in benzene-d_6

Compound	gem-dimethyl		OCH_3	H_1	H_2	H_3, H_4	H_5	CH_2O
XV	1.03 (s)	1.40 (s)	1.59 (s)	4.21 (dd)	4.00 (s)	4.20 (q)	4.53 (s)	3.84 (dd)
XVa	1.03 (s)	1.40 (s)	1.59 (s)	-	4.00 (s)	4.20 (q)	4.53 (s)	-

Table 2

P.m.r. parameters for XVI and XVIa in $CDCl_3$

Compound	(Chemical shifts in ppm.)								
	gem-dimethyl		OCH_3	H_1	H_2	H_3	H_4	H_5	CH_2O
XVI	1.35 (s)	1.50 (s)	2.10 (s)	4.8-5.0 (m)	4.41 (d) J = 4 Hz	4.85 (q)		4.63 (s)	4.18 (d) 4.26 (s)
XVIa	1.35 (s)	1.50 (s)	2.10 (s)	-	4.44 (s)	4.87 (q)		4.63 (s)	-

P.m.r. parameters for XVI and XVIa in benzene-d_6

Compound	gem-dimethyl		OCH_3	H_1	H_2	H_3,H_4	H_5	CH_2O
XVI	1.11 (s)	1.42 (s)	1.63 (s)	4.45 (dd) J = 4 Hz	4.11 (d) J = 4 Hz	4.50 (s)	4.63 (s)	3.92 (d) J = 6 Hz
XVIa	1.11 (s)	1.42 (s)	1.63 (s)	-	4.10 (s)	4.50 (s)	4.63 (s)	-

In summary, the foregoing discussion showed that lithium aluminum hydride reduction of the ozonide V not only gave tetraol VIII but also triol XXI or IX and that the periodate cleavage of the mixture of VIII and XXI (or IX) gave 2,5-anhydroallose XIII, which was formed from triol XXI (or IX) rather than from tetraol VIII.

In order to explain the loss of a skeletal carbon atom upon heating ozonide V in the presence of hydride, the thermal reaction of ozonide V was studied and is described in chapter IV of this thesis.

The correction of "A novel periodate cleavage" [70,71] was published in 1974 [100].

6. Experimental Part.

a) General

In the experimental methods reported, the following general procedures were employed:

(i) All solution evaporations were conducted under diminished pressure on a rotatory evaporator, unless otherwise specified.

(ii) Melting points were determined on a electrothermal melting point apparatus, and are corrected to USP-samples.

(iii) Thin layer chromatography (t.l.c.) was carried out on Kieselgel F-504.

(iv) Column chromatographic separations were carried out using Silica Gel Fa. Herrmann, Köln, Germany. A ratio of one gram of substance to 50 grams of silica gel was generally employed.

(v) Vapor phase chromatographic (V.P.C.) analysis and separations were effected through the use of a FM Research Dual Column Gas Chromatograph, Model 810 employing a thermal conductivity detector.

(vi) Infrared (i.r.) absorption spectra were recorded on a Perkin-Elmer 237-B spectrometer. Potassium bromide discs were used. νmax. values were measured by reference to a polystyrene standard.

(vii) Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian A-60 Spectrometer.

(viii) Mass spectra were recorded on an AEI-MS-902 mass spectrometer using the direct sample inlet system with a 70 e.V. ionization energy.

Dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[83] (I).

Furan (16.5 g, 0.242 mole) and dimethyl acetylenedicarboxylate (30 g, 0.211 mole) were placed into a 100 ml stainless steel vessel of a "Parr" high pressure autoclave. The reaction temperature was maintained at approximately 100° for 20 h. The product was a highly viscous syrup. The crude reaction mixture was chromatographed on silicic acid; elution with chloroform/methanol (98:2) afforded the monoadduct I as a yellow oil (22.5 g, 62%, contaminated with traces of the endo-exo diadduct II. I.r. (film) 1710 (CO), 1635 (C=C), 1435 (C-H), p.m.r. ($CDCl_3$) δ = 3.81 (s, OCH_3) 5.67 (d, $J_{1.6} = J_{4.5}$ = 2Hz), 7.20 (d, $J_{6.1} = J_{5.4}$ = 2Hz).

Dimethyl 7-oxabicyclo[2.2.1]hept-2-ene-exo-5,6-diol-2,3-dicarboxylate (III).

40 ml of a solution made up from 1 g osmium tetroxide in 200 ml of t-butanol, followed by 40 ml of 30% hydrogen peroxide were added to a solution of 42 g of crude I in 80 ml of ether and 320 ml of acetone. After completion of the reaction as monitored by t.l.c. (chloroform - methanol 9:1) the excess H_2O_2 was decomposed by the addition of aqueous sodium bisulfite. Methylene chloride extraction gave III and impurity IV as an oily mixture (16 g, 35%). I.r. (film): 3425 (OH), 1710 (CO), 1620 cm^{-1} (C=C), p.m.r. ($CDCl_3$) δ = 3.84 (s, OCH_3), 4.02 (s, OH ex. H_5, H_6), 5.00 (s, H_2, H_4).

Dimethyl 5,6-O-isopropylidene-7-oxabicyclo[2.2.1]hept-2-ene-exo-5,6-diol-2,3-dicarboxylate (IIIa) (and dimer IVa).

The crude diol (21 g, 0.0915 mole) was dissolved in acetone (500 ml) and dimethoxypropane (160 ml) and heated to reflux with a catalytic amount of p-toluenesulfonic acid acid for 3 h. After evaporation of the solvent, the residue was dissolved in chloroform and washed with water (2 x 50 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silicic acid using chloroform as eluent. The first fraction 17.0g (64.5%) was identified as IIIa, recrystallization from isopropanol/petroleum ether gave colorless plates, m.p. 60.5-62°C. I.r. (KBr) 1710 (CO), 1623 (C=C), 1360, 1370 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$) δ = 1.32 (s, 3H), 1.50 (s, 3H), 2.50 (s, 3H), 3.83 (s, 3H), 4.60, (s, 2H), 5.08 (s, 2H).

Anal. calc. for $C_{13}H_{16}O_7$ (284.2): C, 54.93; H, 5.67.

Found : C, 54.82; H, 5.82.

The minor product IVa, which eluted later, crystallized from chloroform (350 mg, 0.4% based on furan), m.p. 222-224°C. I.r. (KBr) 1717, 1705 (CO), 1615 (C=C), 1360 cm^{-1} (gem-dimethyl). Mass spectrum (70 e.V.): m/e 353, 347 (M^+-CH_3), p.m.r. ($CDCl_3$) δ = 1.30 (s, 3H), 1.47 (s, 3H), 2.62-2.75 (m, 2H), 3.87 (s, 6H), 4.36-4.48 (m, 2H), 4.50 (s, 2H), 5.08 (s, 2H).

Anal. calc. for $C_{17}H_{20}O_8$ (352.3): C, 57.95; H, 5.72.

Found : C, 58.04; H, 5.87.

Dimethyl 6.7-O-isopropylidene-2.4-epidioxo-3,8-dioxabicyclo [3.2.1]octane-exo-6.7-diol-2,4-dicarboxylate V.

Olefin IIIa (2.5 g) was dissolved in 50 ml of ethyl-acetate, was ozonolyzed at -50°. Evaporation of the solvent afforded a crystalline ozonide (V) in quantitative yield, m.p.: 79-81°C. I.r. (KBr) 1780, 1745 (CO), 1380 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$) δ = 1.35 (s, 3H), 1.50 (s, 3H), 3.94 (s, 6H), 4.73 (s, 2H), 5.12 (s, 2H).

Mass spectrum (70 e.V.): m/e 303, 243, [no M^+ 332 or 317 (M^+-CH_3)].

Anal. Calc. for $C_{13}H_{16}O_{10}$ (332.2): C, 46.99; H, 4.85.

Found : C, 46.63; H, 5.06.

3,4-O-Isopropylidene 2β, 5β-bis (1',2'-diacetoxyethyl)-tetrahydrofuran-3α, 4α-diol (VII) via lithium aluminum hydride reduction of ozonide V.

The ozonide V (4.0 g, 10 mmole) was added to a slurry of lithium aluminum hydride (3.4 g, 90 mmol) in anhydrous tetrahydrofuran (150 ml) at 0° over 2 hours. The mixture was stirred overnight at room temperature, then refluxed for 2 hours. The reaction mixture was cooled to 0° and acetic anhydride (25 ml) was dropped in, followed by pyridine (20 ml). The reaction mixture was stirred at room temperature for 8 hours. Addition of water and filtration, followed by extraction with chloroform (3x) gave the crude tetraacetate VII. Column chromatography on silicic acid and elution with chloroform gave 1.75 g, 40.5% chromatographically pure VII. I.r. (film): 1740 (C=O), 1370, 1380 (gem-dimethyl), mass spectrum (70 e.V.): m/e 432 (M^+-CH_3), p.m.r.: ($CDCl_3$) δ = 1.35 (s, 3H), 1.54 (s, 3H), 2.03 (s, 6H), 2.11 (s, 6H), 4.0-4.4 (m, 6H), 4.60 (m, 2H), 5.25 (m, 2H).

Anal. Calcd. for $C_{19}H_{28}O_{11}$ (432.4): C, 52.77; H, 6.53.

Found : C, 52.81; H, 6.55.

3,4-O-Isopropylidene 2β, 5β-bis(1',2'-dihydroxyethyl)-tetrahydrofuran -3α, 4α-diol VIII and "Isomer" IX.

A methanolic solution of VII (1.3 g, 3 mmole) was treated overnight with a catalytic amount of sodium. After neutralization with anhydrous hydrochloric acid, the mixture was chromatographed on silicic acid, using chloroform/methanol (9:1). The less polar product gave 300 mg (41% based on triol) of IX, later identified as triol XXI. I.r. (film) 3360 (OH), 1375 cm^{-1} (gem-dimethyl), mass-spectrum (70 e.V.): m/e 235 (M+1), 234 M^+, 219 (M^+-CH_3), 203 (M^+-CH_2OH), 187 (219 - CH_3OH).

P.m.r.: (Acetone-d_6) δ 1.31 (s, 3H), 1.48 (s, 3H), 3.62 (b.s., 5H), 3.90-4.10 (m, 5H), 4.75 (m, 2H).

Anal. Calcd. for $C_{10}H_{18}O_6 \times \frac{1}{2}H_2O$ (243.2): C, 49.37; H, 7.87.
Found : C, 49.64; H, 7.81.

The more polar isomer VIII (240 mg, 29%) was obtained as a syrup that was homogenous and free of IX by t.l.c.

I.r. (film) 3360 (OH), 1370, 1375 cm^{-1} (gem-dimethyl), mass-spectrum (70 e.V.): m/e 265 (M + 1) 249 (M - CH_3) 233 (M - $CH_2.OH$) 231 (m/e 249 - H_2O) 215 (m/e 233 - H_2O).

P.m.r.; (Acetone-d_6) δ = 1.35 (s, 3H), 1.46 (s, 3H), 3.63 (b.s., 7H), 3.8-4.1 (m, 3H), 4.30-4.50 (m, 2H), 4.80 (d, 2H).

Anal.Calcd. for $C_{11}H_{20}O_7 \times \frac{1}{2}H_2O$ (273.3): C, 48.34; H, 7.74.
Found : C, 48.76; H, 7.57.

3,4-O-Isopropylidene-2β, 5β-bis(1',2'-diacetoxyethyl)-tetrahydrofuran-3α, 4α-diol XI and 3,4-O-isopropylidene 2β(2'-O-acetyl 1',2'-dihydroxyethyl)tetrahydrofuran 3α, 4α-diol-5β-carboxylic acid δ lactone XV via $NaBH_4$ reduction of ozonide V.

Sodium borohydride (1.9 g, 50 mmole) was added in portions to a mixture of ozonide V (1.66 g, 5 mmole) and sodium bicarbonate (4.2 g, 50 mmole) in isopropanol (100 ml) with stirring at room temperature. The mixture was refluxed for 15 hours. After evaporation of the solvent, the solid residue was treated with a mixture of acetic anhydride-pyridine (12:8 ml) overnight. The solution was evaporated to dryness, followed by addition of chloroform and filtration to remove all inorganic material. The filtrate was evaporated leaving a syrup that crystallized upon addition of ether, giving 200 mg (14.7%) of XV, m.p. 156-157°. This material was shown by p.m.r., i.r. and mass spectrometry to be identical with the product synthesized via keto ester acid XIV (see below).

The ether solution gave 1.5 g (69.5%) of XI as a chromatographically homogeneous clear syrup, identical in all respects (i.r., p.m.r., t.l.c., g.l.c.) with the tetraacetate XI obtained via scheme 5.

Dimethyl-2',2-(3,4-O-isopropylidene tetrahydrofuran 3α, 4α-diol-2β, 5β-)bis glyoxylate (X).

Sodium metaperiodate (10 g, 50 mmole) in 50 ml of water, was added over a period of 3 hours, to an acetone solution (100 ml) of the olefin IIIa (2.5 g, 9 mmole) and ruthenium tetroxide (330 mg, 2 mmole) with stirring at room temperature. After 12 hours, the excess of ruthenium tetroxide was reduced with isopropanol (5 ml). The insoluble material was removed by filtration through celite and the filtrate concentrated in vacuo. The crude product was purified by chromatography on a silica gel column. Elution with chloroform/methanol (98:2) gave a colorless oil.

I.r. (film): 3450 (H_2O), 1740 (ester), 1375 cm^{-1} (gem-dimethyl).

P.m.r. ($GDCl_3$): δ = 1.25 (m, 3H), 1.40 (m, 3H), 3.7-3.95 (m, 7H), 4.5-5.1 (m, 3H).

Anal. Calcd. for $C_{13}H_{16}O_9 \times H_2O$ (318.3): C, 49.06; H, 5.70.
Found : C, 49.32; H, 5.97.

3,4-O-Isopropylidene 2β, 5β-bis(1',2'-diacetoxyethyl)-tetrahydrofuran-3α, 4α-diol (XI).

The diketo ester X (1.9 g, 6 mmole) was treated with sodium borohydride (2.3 g, 60 mmole) in refluxing isopropanol for 4 hours. The reaction mixture was cooled to -30° and acidified with anhydrous hydrochloric acid. The mixture was concentrated to dryness. The solid residue was stirred with a mixture of 10 ml acetic anhydride and 15 ml pyridine overnight. After concentration to dryness the residue was extracted with methylene chloride and washed with 0.5 N hydrochloric acid to remove traces of pyridine. Evaporation of the solvent gave an oily residue which was chromatographed on 50 g of silicic acid using chloroform as an elution solvent. The desired product was eluted first and gave 1.5 g (58%) of a colorless oil.

I.r. (film) 1740 (C=O), 1370 cm^{-1} (gem-dimethyl).
Mass-spectrum (70 e.V.): m/e 432 M^+, 417 (M^+-CH_3).
P.m.r. ($CDCl_3$): δ = 1.34 (s, 3H), 1.55 (s, 3H), 2.05 (s, 6H), 2.10 (s, 6H), 4.0-4.2 (m, 6H), 4.5-4.7 (m, 2H), 5.1-5.4 (m, 2H).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53.
Found : C, 52.48; H, 6.77.

3,4-O-Isopropylidene 2β, 5β-bis(1', 2'-dihydroxyethyl)-tetrahydrofuran-3α, 4α-diol (VIII).

A solution of tetraacetate XI (1.51 g, 3.5 mmole) in 50 ml methanol was treated with a catalytic amount of sodium for 6 hours. After neutralization with gaseous hydrogen chloride and evaporation of the solvent the crude product was chromatographed on 50 g silicic acid using chloroform/methanol (9:1). The tetraol VIII (850 mg, 93%) was identical with the tetraol obtained by hydrolysis of VII, see above.

3,4-O-Isopropylidene 2β-(1',2'-dihydroxyethyl)tetrahydrofuran-3α, 4α-diol-5β-aldehyde hemiketal XII.

A stirred solution of tetraol VIII (200 mg, 0.76 mmole) in 5 ml of 50% aqueous methanol was treated with sodium metaperiodate (162 mg, 0.76 mmole) at room temperature for one hour. The reaction mixture was concentrated in vacuo to dryness, addition of acetone and filtration to remove the inorganic salts, gave colorless plates (155 mg, 88%), m.p. 139-140°, m.m.p. with authentical sample via reduction of XV, 139-140° (see page 110).

3,4-O-Isopropylidene-2,5-anhydro-D,L-allose (XIII)[72].

A stirred solution of 3,4-O-Isopropylidene-2β-(1',2'-dihydroxyethyl)-5β-hydroxymethyl-tetrahydrofuran-3α, 4α-diol ("isomer IX"), (132 mg, 0.5 mmole) in 4 ml of a 50% aqueous methanol was treated with sodium meta-periodate (107 mg, 0.5 mmole) at room temperature for one hour. A white precipitate formed, which was removed by filtration. The filtrate was extracted with four 25 ml portions of chloroform. The organic phase was dried and evaporated to dryness in vacuo. The crystalline residue was recrystallized once from acetone/hexane to give the hemiketal XIII m.p. 194-195°C (81 mg, 80%). A mixture of XIII, obtained by periodate cleavage via a different route[72] did not depress the m.p.. The t.l.c. ($CHCl_3$:CH_3OH 9:1) was identical with the authentic sample[72].

3,4-O-Isopropylidene-2β-(2'-O-acetyl-1',2'-dihydroxyethyl) tetrahydrofuran-3α, 4α-diol-5β-carboxylic acid δ lactone XV and XVI.

Sodium borohydride (1.52 g, 40 mmole) was added to a slurry of sodium bicarbonate (3.36 g, 40 mmole) and α-keto ester XIV (1.2 g, 4 mmole) in isopropanol (50 ml) at 0°. The reaction mixture was refluxed for 4 hours. The solution was cooled to 0° and neutralized with 2 n hydrochloric acid. After concentration to dryness and drying at room temperature in vacuo overnight, the mixture was acetylated with 8 ml acetic anhydride and 12 ml pyridine. The mixture was concentrated to dryness in vacuo, addition of chloroform, followed by filtration using celite, and concentration gave colorless crystals of lactone XV (600 mg, 53.5%), m.p. 156-157°C.

I.r. (KBr): 1760, 1740 (CO), 1360, 1370 cm^{-1} (gem-dimethyl).
Mass-spectrum (70 e.V.): 257 ($M-CH_3$), 229 ($M-COCH_3$).
P.m.r.: see table 1, Chapter 3, 5.

Anal. Calcd. for $C_{12}H_{16}O_7$ (272.2): C, 52.94; H, 5.92.
Found: C, 52.78; H, 5.91.

Evaporation of the filtrate gave 200 mg (18%) of isomer XVI, m.p. 102-103.

I.r. (KBr): 1765, 1750 (CO), 1375, 1380cm^{-1} (gem-dimethyl).

Mass-spectrum (70 e.V.): 257 (M-CH_3), 229 (M-$COCH_3$).

P.m.r. : see table 2, Chapter 3, 5.

Anal. Calcd. for $C_{12}H_{16}O_7$ (272.2): C, 52.94; H, 5.92.

Found: C, 52.72; H, 5.96.

3,4-O-Isopropylidene-2β-(2'-O-acetyl 1',2'-dihydroxy-1',2',2'-tridentero-ethyl)tetrahydrofuran-3α, 4α-diol-5 -carboxylic acid δ lactone XVa and XVI a.

These compounds were prepared exactly as XV and XVI using sodium borodeuteride instead.

Compound XVa : m.p. 154-156°C, i.r. (KBr): 1755, 1735 (CO), 1370, 1380 cm^{-1} (gem-dimethyl); p.m.r. data see table 1, Chapter 3,5.
Mass spectrum (70 e.V.): m/e 260 (M^+-CH_3), 232 (M^+-$COCH_3$).

Compound XVIa: m.p. 73-75°C, i.r. (KBr): 1758, 1745 1370, 1380 cm^{-1} (gem-dimethyl); p.m.r. data see table 2, Chapter 3,5.
Mass spectrum (70 e.V.): m/e 260 (M^+-CH_3), 232 (M^+-$COCH_3$).

6,7-O-Isopropylidene-exo-2-acetoxymethyl-4-O-acetyl-3,8-dioxabicyclo[3.2.1]octane-exo-6,7-diol XVII and isobutyl 3,4-O-isopropylidene-2β-(1',2'-diacetoxyethyl) tetrahydrofuran-3α, 4α-diol 5β-carboxylate XVIII.

Lactone XV (950 mg, 3.5 mmole) was treated with diisobutyl aluminum hydride (1.0 g, 7 mmole) in toluene (25 ml) at -78° for 10 min. The reaction was quenched by the addition of 2 ml of methanol. After evaporation of the solvent to dryness in vacuo, the solid residue was treated with a mixture of 20 ml acetic anhydride/ 30 ml pyridine overnight. After partial evaporation, the residue was extracted with ether. The crude lactol was chromatographed on silicic acid, using benzene-ethyl acetate (9:1). The separation of the less polar impurity XVIII was monitored by t.l.c.. This separation afforded (70 mg, 4.9%) of impurity XVIII, which was identified as isobutyl 3,4-O-isopropylidene-2β-(1',2'-diacetoxyethyl) tetrahydrofuran-3α, 4α-diol 5β-carboxylate, m.p. 79-80°.

I.r. (KBr): 2980, 2960 (C-H), 1740 (CO), 1370, 1380 cm^{-1} (gem-dimethyl). Mass spectrum (70 e.V.): m/e 388, (M^+), 373 ($M-CH_3$), 331 ($M-(CH_3)_2CH-CH_2^+$).

P.m.r. (benzene-d_6): δ= 0.74 (s, 3H), 0.82 (s, 3H), 1.17 (s, 3H), 1.44 (s, 3H), 1.62 (s, 3H), 1.75 (s, 3H), 1.5-1.7 (m, 1H), 3.76 (d, 1H), 3.95 (d, 1H), 4.37-4.70 (m, 5H), 5.1-5.3 (m, 2H).

Anal. Calcd. for $C_{18}H_{28}O_9$ (388.40): C, 55.66; H, 7.27.
Found : C, 56.03; H, 7.37.

The lactol-acetate XVII was eluted later, and afforded 560 mg (58.3%) of an oil.

I.r. (film): 2980, 2930 (C-H), 1740 (C=O), 1370 (gem-dimethyl), 1220, 1040 cm^{-1} (C-O).

P.m.r. ($CDCl_3$): δ = 1.35 (s, 3H), 1.55 (s, 3H), 2.03 (s, 6H), 3.80 (s, 2H), 4.3-4.6 (m, 4H), 5.0-5.3 (m, 2H).

Hydrolysis in methanol with a trace of sodium gave XII. The spectral data (i.r., p.m.r., m.s.) were identical with those of the product obtained without isolating the lactol-acetate.

3,4-O-Isopropylidene-2β-(1',2'-dihydroxyethyl)tetrahydrofuran-3α, 4α-diol-5β-aldehyde hemiketal (XII).

The lactone XV, 420 mg (1.54 mmole), was treated with diisobutyl aluminium hydride (4.36 mg, 3.08 mmole) in toluene (25 ml) at 78°, under nitrogen for 10 minutes. The reaction was quenched by the addition of methanol (2 ml). Addition of sodium bicarbonate (500 mg) and stirring at room temperature gave the pure aldehyde-hemiketal XII (240 mg, 67%), m.p.: 138-140°C.

I.r. (KBr): 3410, 3310 (OH), 1370, 1380 cm^{-1} (gem-dimethyl).
Mass spectrum (70 e.V.): m/e 232 (M^+), 217 ($M-CH_3$);
199 ($232-H_2O$), m* 182.5 ($199^2/217$).

P.m.r. (DMSO): δ = 1.30 (s, 3H), 1.39 (s, 3H), 3.60-3.65 (m, 2H), 3.92 (s, 1H), 4.1-4.2 (m, 2H), 4.60 (OH, ex.), 4.60-5.0 (m, 3H), 6.49, 6.89 (dd,OH ex.).

Anal. Calcd. for $C_{10}H_{16}O_6$ (232.2): C, 51.72; H, 6.94.
Found : C, 52.04; H, 7.17.

3,4-O-Isopropylidene 2β-(1',2'-diacetoxyethyl)5β-acetoxymethyl-tetrahydrofuran-3α,4α-diol (XX).

The ozonide XIX[70,72] (2.7 g, 0.01 mole) was treated with sodium borohydride (3.8 g, 0.1 mole) in refluxing isopropanol (100 ml) for 4 hours. The reaction mixture was cooled to 0°, and hydrogen chloride was added until pH 4 was reached. After evaporation of the solvent, the solid residue was treated with a mixture of acetic anhydride-pyridine (30 ml:25 ml) overnight. After partial evaporation and addition of water, the product was extracted with chloroform, and dried over anhydrous sodium sulfate. The mixture was chromatographed on silicic acid with chloroform to effect a clean separation of the product. The least polar fraction gave 140 mg (5.1%) of lactone XV. The spectral data (i.r., p.m.r., m.s.) were identical with those of the product obtained before.

A second fraction (700 mg, 22%) gave a partially acetylated product (diacetate).

I.r. (film): 1740 (C=O), 1370 (C-CH_3), 1220, 1045 cm^{-1}, (C-O).

P.m.r. ($CDCl_3$): δ = 1.39 (s, 3H), 1.50 (s, 3H), 2.10 (m, 7H), 4.0-4.8 (m, 8H), 4.9-5.25 (m, 1H).

Mass spectrum (70 e.V.): m/e 318, 303 ($M-CH_3$), 260 (m/e 303-$COCH_3$).

Anal. Calcd. for $C_{14}H_{22}O_8$ (318.3): C, 52.82; H, 6.97.

Found : C, 52.24; H, 7.06.

The more polar and major product XX 1.55 g (42.5%) was obtained as a syrup that was homogeneous and free of the other products by t.l.c. using chloroform/methanol (98:2).

I.r. (film): 1740 (C=O), 1370 (gem-dimethyl), 1230 cm^{-1}, 1070 and 1040 cm^{-1} (C-O).

P.m.r. ($CDCl_3$): δ = 1.37 (s, 3H), 1.56 (s, 3H), 2.06 (s, 3H), 2.12 (s, 6H), 3.9-4.4 (m, 6H, 4.5-4.6 (m, 2H), 5.1-5.4 (m, 1H).

Mass spectrum (70 e.V.): m/e 361 (M+1), 345 ($M-CH_3$).

Anal. Calcd. for $C_{16}H_{24}O_9$ (360.3): C, 53.33, H, 6.71.

Found : C, 53.15; H, 6.70.

3,4-O-Isopropylidene 2β-(1',2'-dihydroxyethyl)-5β-hydroxymethyl-tetrahydrofuran -3α,4α-diol (XXI).

A solution of XX (0.2 g,0.55 mmole) in 30 ml methanol was treated with a catalytic amount of sodium overnight. After neutralization with hydrogen chloride, the mixture was concentrated and chromatographed on silicic acid using chloroform-methanol (9:1). Evaporation of the main fraction gave 120 mg (82%) of the triol XXI, identical in all respects with the "isomer IX".

3,4-O-Isopropylidene 2β-(1',2'-diacetoxyethyl)5β-acetoxymethyl-tetrahydrofuran-3α,4α-diol XX via acetylation of "isomer IX".

Treatment of "isomer IX" (48 mg) in a mixture of acetic anhydride (0.4 ml) and pyridine (0.6 ml) overnight at room temperature gave after usual workup 70.8 mg (95%) of XX. The triacetate was identical with the triacetate obtained via reduction of ozonide XIX, see above.

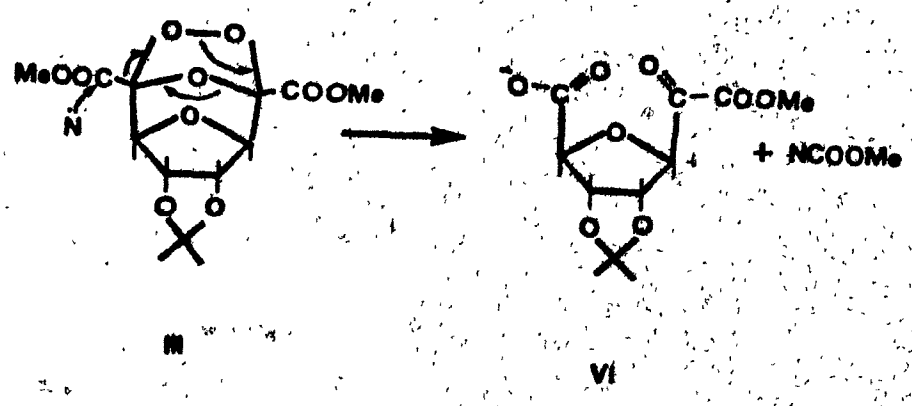
Chapter IV

An explanation of an unexpected reaction of an ozonide. A novel synthesis of D,L-talofuranuric acid derivatives.

1. Results and Discussion.

After careful reinvestigation we could show that lithium aluminium hydride reduction of the ozonide III gave a mixture of tetraol and triol (see chapter III).

In order to explain the loss of one skeletal carbon atom upon heating ozonide III in the presence of hydride, we first studied the reaction with several other nucleophiles (KCN, LiBr, NaN_3). However, the highly exothermic reaction led to unsatisfactory results and gave complex mixtures.



M VI

Our next step was to investigate a possible thermal rearrangement of ozonide III. Upon heating in various solvents, III rearranged predominantly to the stable oxalic ester V, m.p. 112-114°, and to the mixed anhydride VIa, which was not isolated[101] (Scheme 1). Hydrolysis of the mixed anhydride led to VI, m.p. 114-116°. The keto-ester VI was identified by comparison of its spectral data with those of an authentic sample described in Chapter II. There are many precedences for both types of rearrangements. For instance, addition of singlet oxygen to heterocycles leads to bicyclic systems which rearrange to Bayer-Villiger type products[102,103,104,105].

The results of the thermal rearrangement of the ozonide III in various solvents are summarized in table I. The yields refer to isolated products. There does not seem to be an obvious correlation between product distribution and solvent polarity or dielectric constants.

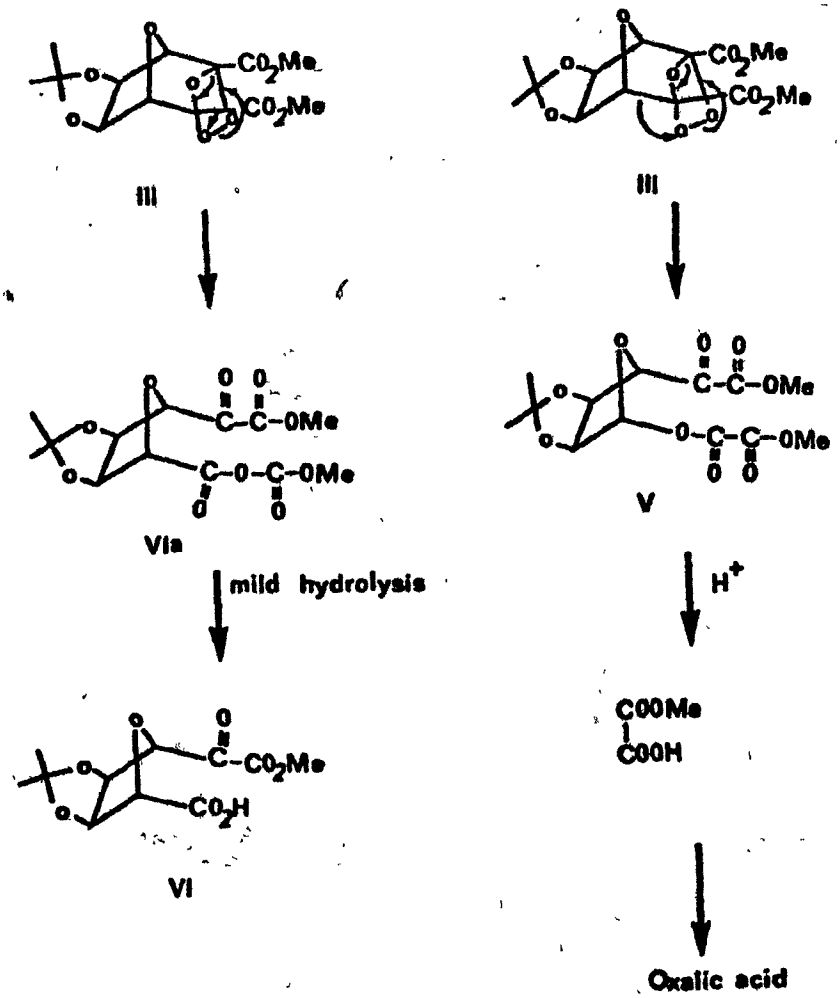
Table I

Solvent	% yield V	% yield VI
Ethyl acetate	93	0
Benzene	90	0
Acetone	90	0
Ether	10*	0
Isopropanol	60	10
Tetrahydrofuran	60	27
Water (phosphate buffer pH 6.0)	10**	20

* The balance consisted of recovered starting material.

** The balance consisted of unidentified products.

Scheme I



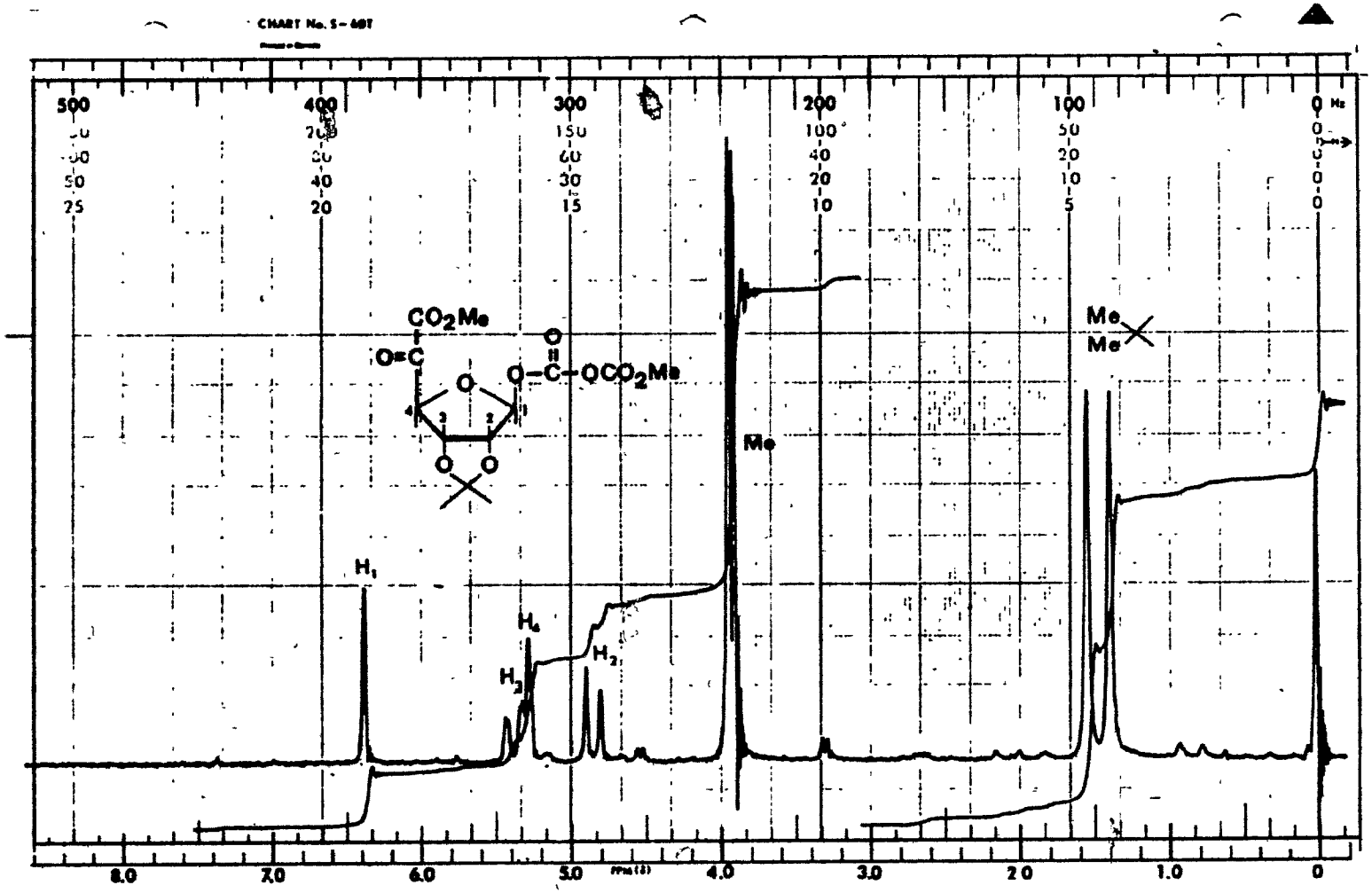


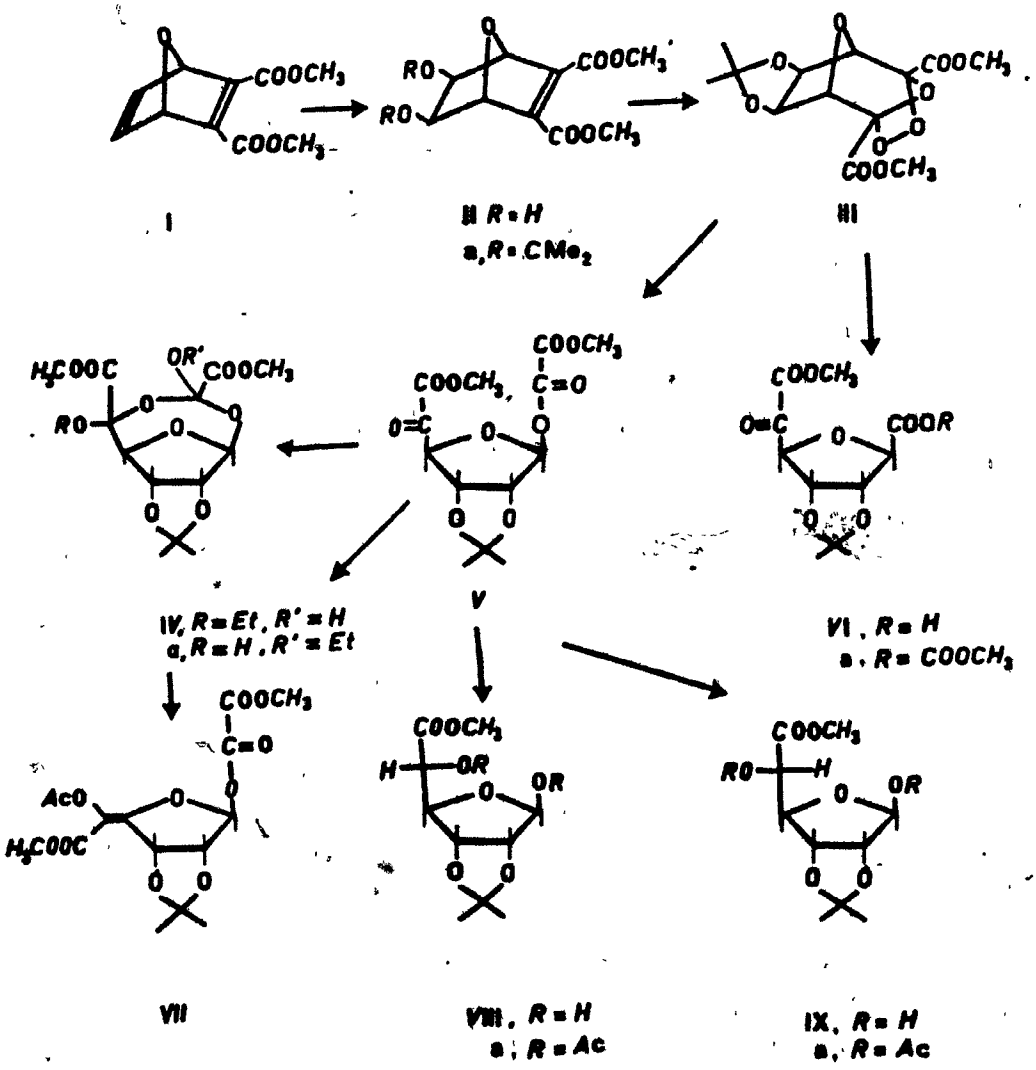
Fig. 1. The p.m.r. spectrum of Dimethyl 2,3-O-isopropylidene-1-O-oxalyl-β-D.L-ribo-hexofuran-5-ulosuronate V, in chloroform-D .

The p.m.r. spectrum of V (see Fig. 1) indicated the presence of two methoxy groups at 3.90 and 3.92 ppm., the anomeric proton as a singlet at 6.35 ppm., and an AB system corresponding to protons H_2 and H_3, centered at 5.09 ppm. The H_3 signal is split into a double doublet $J_{3,2}$ = 6 Hz, and $J_{3,4}$ = 1 Hz, H_4 appears as a doublet at 5.23 ppm.

Further proof for the structure of V was obtained through degradation reactions (Scheme 2, p. 120). Mild hydrolysis of V gave oxalic acid monomethyl ester which on further hydrolysis gave oxalic acid, isolated from the mixture by sublimation. When V was allowed to stand in ethanol containing palladium on charcoal, a new product crystallized out.

Spectral and analytical data indicated the new product, m.p. 94-95°, to be a ketal-hemiketal of formula IV or IVa. Although no rigorous proof is adduced, we prefer formula IV for mechanistic reasons. A slight modification of the procedure permitted the isolation of IV in 56% yield. On treatment with acetic anhydride IV was transformed to VII, m.p. 147-148°, in 92% yield. VII is also formed by direct acetylation of V. VII was identified on the basis of spectroscopic evidence. The u.v. spectrum exhibits a maximum at 232 nm. in ethanol, and the i.r. spectrum (KBr) showed absorptions at 1782, 1769, 1748,

Scheme 2


I
II R = H
a, R = CMe2
III
IV, R = Et, R' = H
a, R = H, R' = Et
V
VI, R = H
a, R = COOCH3
VII
VIII, R = H
a; R = Ac
IX, R = H
a, R = Ac

1725 and 1682 cm^{-1}, which is in accord with the ester and C=C double bond absorptions.

Catalytic hydrogenation of IV or V with palladium catalyst in ethanol gave two products, which were isolated by column chromatography on silica with ethyl acetate/benzene (3:7). The major product was shown to be methyl 2,3-O-isopropylidene-β-D,L-talofuranuronate VIII, m.p. 112-114°, (67%). It gave upon acetylation a diacetate VIIIa , m.p. 77-79°. The minor product isolated was identified as the allo isomer IX, m.p. 96-97°, (22%). Acetylation of IX gave the diacetate IXa, m.p. 133-134°. The p.m.r. spectra of these two isomers are shown in Fig. 2 and 3, (page 122).

The structures of the two furanuronates were established by the following reactions (Scheme 3): VIII was heated in methanol in the presence of a catalytic amount of sulfuric acid for two hours and the mixture separated on silica with ethyl acetate. The first product eluted was methyl (methyl 2,3-O-isopropylidene-β-D,L-talofuranosid) uronate X, m.p. 63-64° (25%). Acetylation gave the oily monoacetate Xa. A comparison of the chemical shifts closely resembles that of the reported[106] values of the allo isomer (see Table II). Because of the approximate nature a conclusion derived from these values is necessarily tentative.

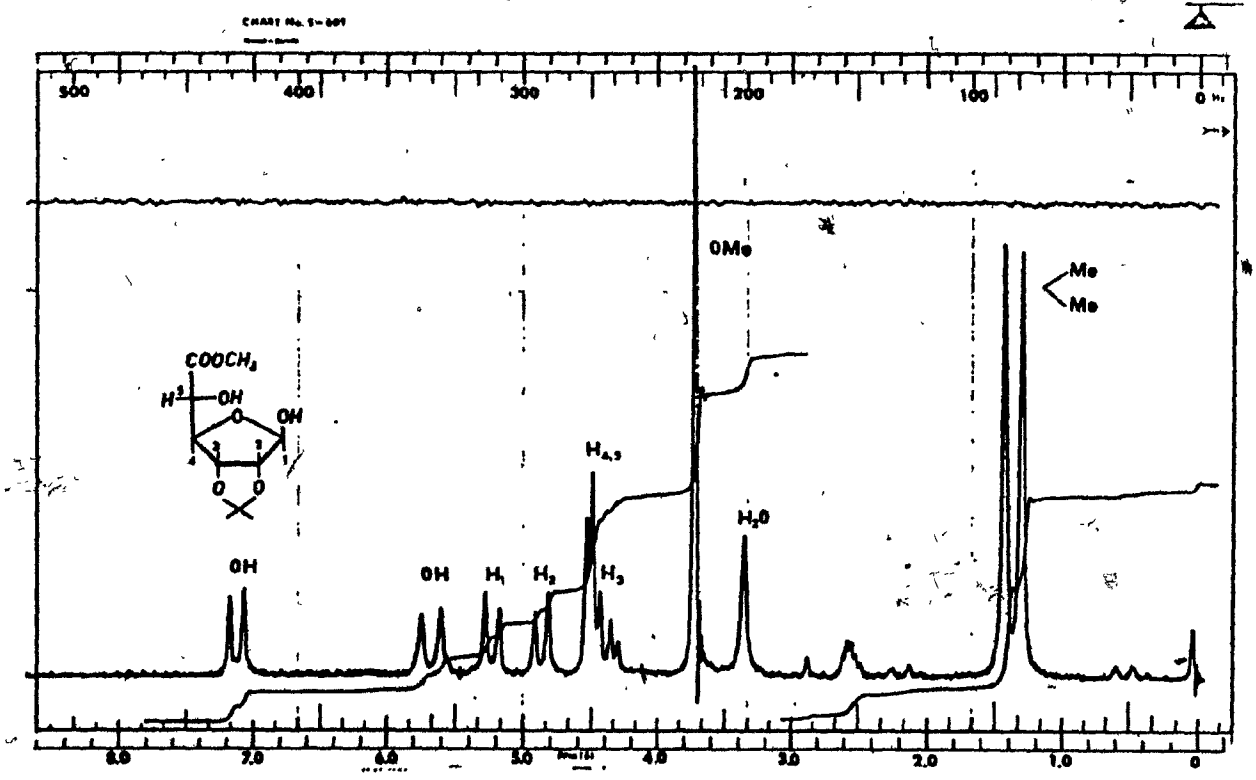


Fig. 2 The p.m.r. spectrum of Methyl 2,3-O-isopropylidene-β-D,L-talofuranuronate VIII in DMSO-D_6.

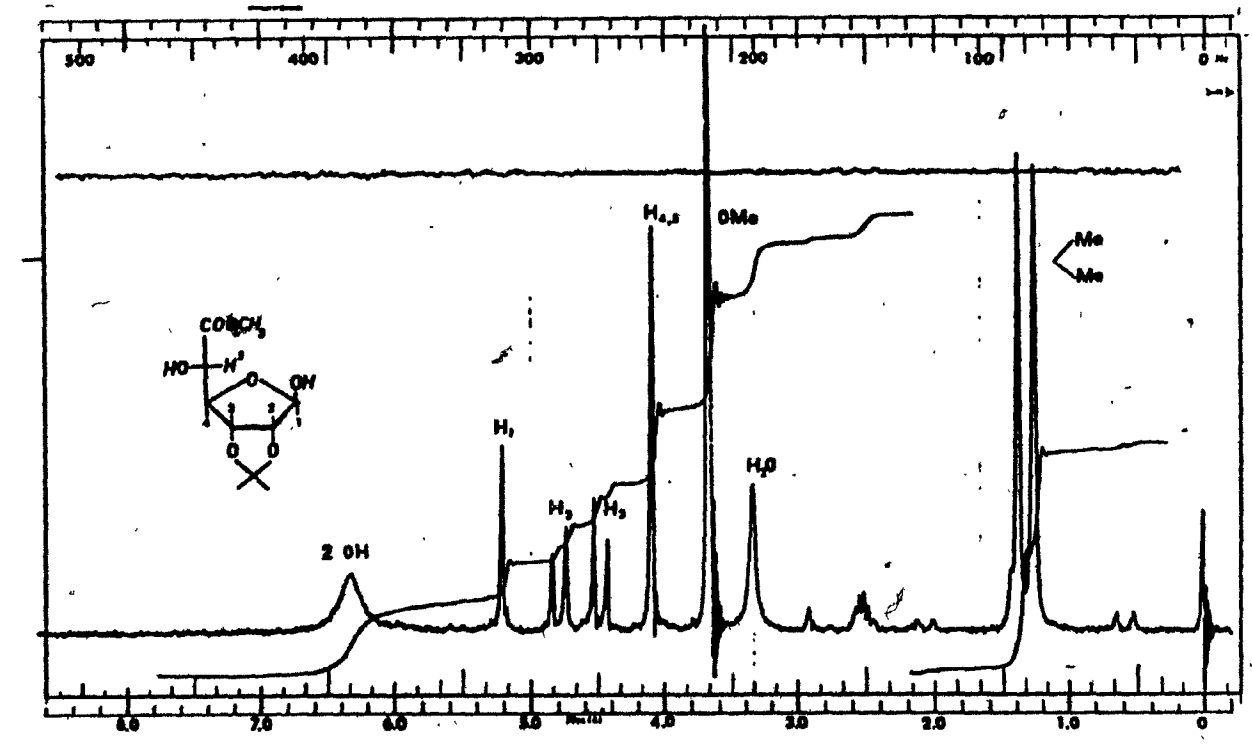


Fig. 3 The p.m.r. spectrum of Methyl 2,3-O-isopropylidene-β-D,L-allofuranuronate IX in DMSO-D_6.

Scheme 3

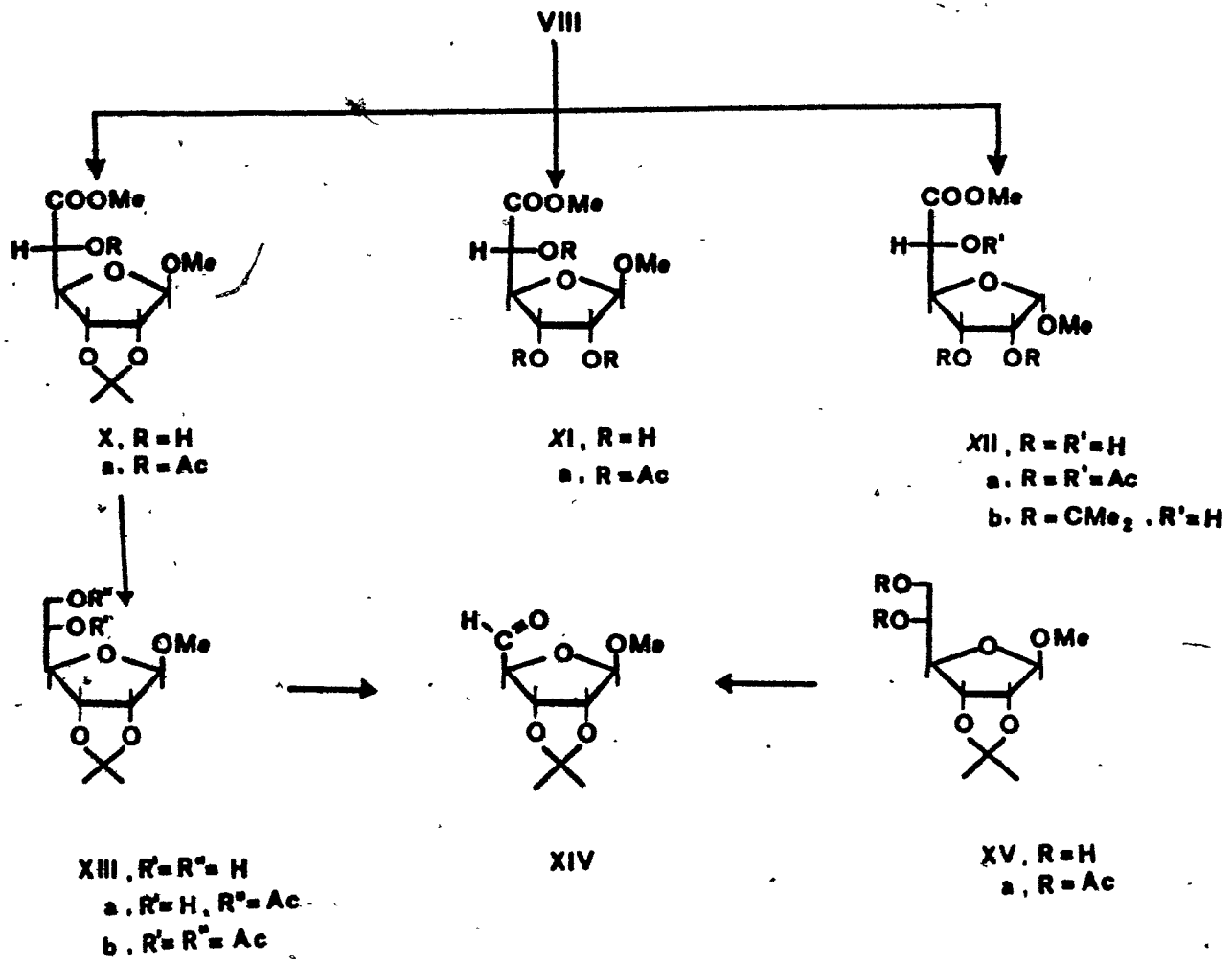

VIII
COOMe
H
OR
OMe
O
RO
OR
X, R = H
a, R = Ac
XI, R = H
a, R = Ac
OR'
XII, R = R' = H
a, R = R' = Ac
b, R = CMe2, R' = H
OR''
XIII, R' = R'' = H
a, R' = H, R'' = Ac
b, R' = R'' = Ac
C=O
XIV
RO
XV, R = H
a, R = Ac

Table II

P.m.r. ($CDCl_3$) in δ (ppm) of methyl (methyl 2,3-O-isopropylidene-5-O-acetyl-β-D,L-talofuranosid)uronate Xa and its allo-isomer[106].

Protons	allo-isomer literature values[106]	talo-isomer Xa
isopropylidene	1.40 (s), 1.50 (s)	1.34 (s), 1.50 (s)
O-acetyl	2.17 (s)	2.17 (s)
O-methyl	3.36 (s)	3.30 (s)
methyl ester	3.81 (s)	3.81 (s)
C-1	5.01 (s)	5.00 (s)
C-2		4.55 (d) $J_{2,3}$ = 6 Hz, $J_{2,1}$ = 0 Hz
C-3	not defined ring protons	4.86(dd) $J_{3,4}$ = 2 Hz, $J_{3,2}$ = 6 Hz
C-4		4.50(dd) $J_{4,5}$ = 8 Hz, $J_{4,3}$ = 2 Hz
C-5	5.13 (d) $J_{4,5}$ = 6 Hz	5.07 (d) $J_{4,5}$ = 8 Hz

The next product eluted (R_f 0.5) was the oily methyl (methyl β-D,L-talofuranosid)uronate XI (46%). Treatment of XI with acetone and 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid for several hours gave a high yield of X, identified by p.m.r., i.r., t.l.c., m.p. and mixture m.p.

Acetylation of XI gave the tri-acetate XIa, m.p. 105-107°. The p.m.r. proved to be slightly different from that of methyl (methyl 2,3,5-tri-O-acetyl-β-D,L-allofuranosid)uronate[106,108]. A sample of this compound, m.p. 103-104°, obtained from Prof. Fukami, showed a m.p. depression with XIa, and a different pattern in the i.r. (KBr) spectrum.

The third product of the methanol/sulfuric acid reaction proved to be the α-isomer XII. It was eluted last (R_f 0.2) in 29% yield. Treatment of XII with acetone/dimethoxypropane in the presence of p-toluenesulfonic acid gave XIIb, m.p. 112-113°. Fig. 4 and 5 show the p.m.r. spectra of the β-isomer X and α-isomer XIIb.

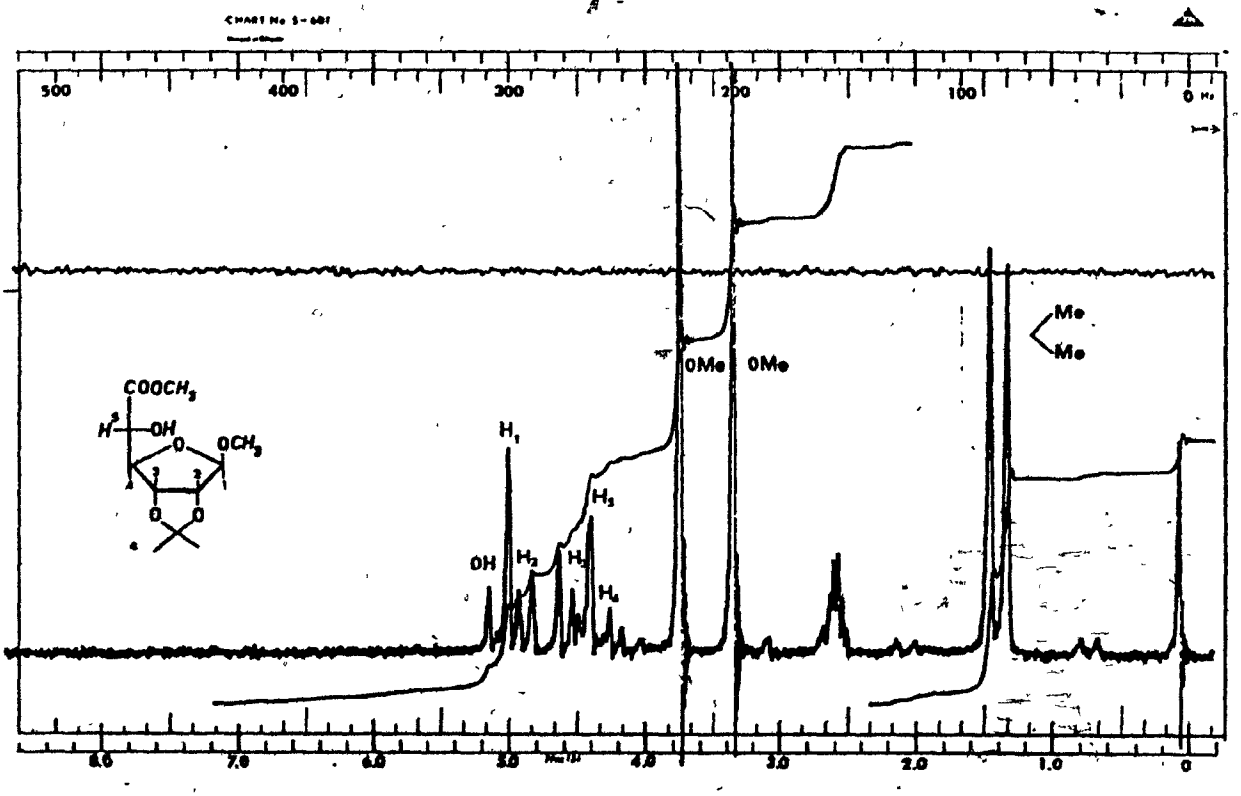


Fig. 4 The p.m.r. spectrum of Methyl (methyl 2,3-O-isopropylidene-β-D,L-talofuranosid) uronate X in DMSO-D_6.

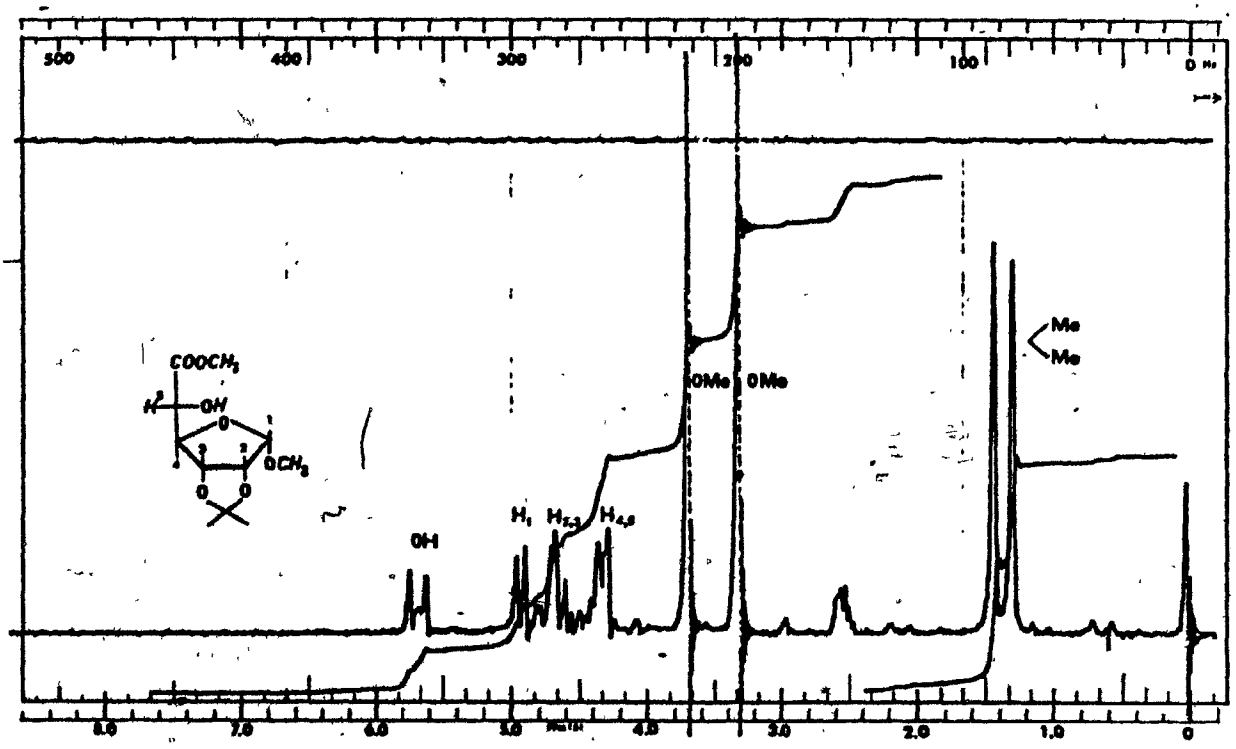


Fig. 5 The p.m.r. spectrum of Methyl (methyl 2,3-O-isopropylidene-α-D,L-talofuranosid) uronate XIIb in DMSO-D_6.

Reduction of the mono acetate Xa with lithium aluminum hydride in ether and direct acetylation of the reaction mixture, gave the mono acetate XIIIa, m.p. 64-65°, and the oily diacetate XIIIb. XIII was obtained by sodium methoxide catalyzed methanolysis of XIIIa or XIIIb. Here also, the analytical data were in complete agreement with the structures proposed.

A sample of methyl 2,3-O-isopropylidene-β-D-allofuranoside XV[107], m.p. 94-96°, was not identical with XIII, nor was the corresponding diacetate XVa identical with XIIIb. However, when XIII was subjected to oxidative cleavage with periodate, the aldehyde XIV, m.p. 94-95°, showed identical i.r. (in chloroform), p.m.r., t.l.c., and retention time on g.l.c. with the aldehyde obtained from oxidative cleavage of XV.

Conclusion:

From our experiments in Chapter III, lithium aluminum hydride reduction in tetrahydrofuran or sodium borohydride reduction in isopropanol gave higher yields of decarboxylated products (triol or lactone) than one would have expected from the thermal rearrangement alone (see table II, page 116). It would seem that there must also be some direct attack by the hydride ion (see page 114, Nu = H^-) during the reduction procedure.

In summary, we have elucidated the products of the thermal ozonide rearrangement, correlated the structures and stereochemistry of the reaction products and developed an interesting synthesis of talofuranoic acid derivatives. The total synthesis of dimethyl 1-O-oxalyl-2,3-O-isopropylidene β-D,L-ribohexofuran-5-ulosuronate V was published in the Can.J.Chem.[109]. It is dedicated to Professor C.A. Winkler of McGill University on the occasion of his sixty-fifth birthday.

2. Experimental

Melting points were determined on an electrothermal block and are corrected. NMR spectra were recorded on a Varian Associates A-60 spectrometer. I.r. spectra were obtained on a Perkin-Elmer 267B spectrometer. U.V.-spectra were recorded on a Bausch & Lomb 505 spectrophotometer. Micro-analyses were carried out by Micro-Tech. Laboratories Inc., Skokie, Ill., U.S.A.

Dimethyl 1-O-oxalyl-2,3-O-isopropylidene β-D,L ribohexofuran-5-ulosuronate (V).

An ethyl acetate (100 ml) solution of dimethyl 5,6-O-isopropylidene-7-oxabicyclo[2.2.1]hept-2-ene-exo-5,6-diol-2.3-dicarboxylate (IIa) (10 g, 0.035 mole) was cooled to -60°, and treated with ozone in oxygen at the rate of 7 mmoles of ozone per hour. The reaction was continued until the blue color, characteristic of ozone, persisted. The reaction mixture was flushed with nitrogen and the solvent was evaporated at room temperature under reduced pressure to about 20 ml. The semi-crystalline ozonide was heated in a water bath for 20 minutes until all the solvent evaporated. The product crystallized from ethylacetate and ether, yield 10.9 g (93.2%), m.p. 114-116°. I.r. (KBr) 1760 (Ester), 1720 (CO), 1380 cm^{-1} (gem. dimethyl), p.m.r. ($CDCl_3$) δ = 1.39 (s, 3H), 1.56 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.83 (d, $J_{2,3}$ = 6Hz,1H), 5.23 (d, $J_{4,3}$ = 1 Hz, 1H), 5.36 (d,d, $J_{2,3}$ = 6Hz,$J_{3,4}$ = 1 Hz, 1H), 6.35 (s, 1H).

Mass spectrum: m/e 332 (M^+), 317 ($M^+ - CH_3$)

Anal. Calc. for $C_{13}H_{16}O_{10}$ (332.2): C, 46.99; H, 4.85.
Found: C, 47.22; H, 4.85.

Alternatively, the ozonide (III), m.p. 79-81°, was isolated and the pure ozonide refluxed for 20 minutes (solvents see table I) and the residue after evaporation was crystallized from ethyl acetate-ether to give V.

Dimethyl 7,8-O-isopropylidene-2,4,9-trioxabicyclo[4.2.1] nonane exo-7,8-diol-3-hydroxy-5-ethoxy-3,5-dicarboxylate IV.

A solution of V (10.9 g, 0.033 mole) in ethanol (250 ml) was stirred with palladium (5%) on charcoal (2 g) for 8 hours. The suspension was filtered through celite, and the catalyst washed with ethanol (5 x 25 ml). The filtrate and washings were combined and evaporated to dryness. Addition of ether afforded 7.0 g (56%) of IV, m.p. 94-95°. I.r. (KBr) 3490 (OH), 1752, 1725 (Ester), 1378 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$) δ = 1.20 (t, J = 7 Hz, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 3.17 (q, 2H), 3.82 (s, 3H), 3.97 (s, 3H), 4.60 (s, 1H), 4.85 (d, $J_{2,3}$ = 6 Hz, 1H), 5.10 (d, $J_{2,3}$ = 6 Hz, 1H), 6.21 (s, 1H), 4.4-5.4 (broad OH).

Mass spectrum: (70 e.v.) m/e 362 (M^+-CH_3), 332 ($M^+-C_2H_5OH$), 317, 303.

Anal. Calc. for $C_{15}H_{22}O_{11}$ (378.3): C, 47.62; H, 5.86.
Found: C, 47.72; H, 5.91.

Treatment of dimethyl 1-O-oxalyl-2,3-O-isopropylidene-β-D,L-ribohexofuran-5-ulosuronate (V) with acetic anhydride.

A solution of V (166 mg, 0.5 mmole) in a mixture of acetic anhydride (1 ml) and pyridine (1 ml) was stirred for 12 h. After removal of the solvents, the oily residue was dissolved in chloroform, carefully washed with 1 N hydrochloric acid and dried over sodium sulfate. Evaporation and crystallization from ether-petroleum ether gave 150 mg (80%) of VII, m.p. 147-148°. I.r. (KBr): 1782, 1769, 1728 (ester, C=O), 1682 (C=C), 1437 (CH), 1389, 1370 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 1.43 (s, 3H), 1.45 (s, 3H), 2.20 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 4.81 (d, $J_{2,3}$ = 6Hz, 1H), 5.90 (d, $J_{2,3}$ = 6 Hz, 1H), 6.50 (s, 1H).

Mass spectrum: (70 e.V.) m/e 374 (M^+), 359 (M^+-CH_3), 343 (M^+-OCH_3), 315 ($M^+-COOCH_3$).

Anal. Calc. for $C_{15}H_{18}O_{11}$ (374.3): C, 48.13; H, 4.85.
Found: C, 48.32; H, 4.89.

Acetylation of IV

IV (500 mg, 1.34 mmole) was acetylated and purified as described above. 465 mg (92%) of VII m.p. 147-148°, were obtained. I.r. and p.m.r. spectra were identical with those of a sample obtained as above.

Methyl 2,3-O-isopropylidene-β-D,L-talofuranuronate (VIII), and Methyl 2,3-O-isopropylidene-β-D,L-allofuranuronate (IX) from (IV) or V.

A solution of IV (7.0 g, 18.5 mmole) (or V, 6.2 g, 18.5 mmole) in ethanol (250 ml) containing 5% palladium on charcoal (2 g) was hydrogenated for 16 h at 50 lbs/in^2. The suspension was filtered through celite, and the catalyst washed with ethanol. The filtrate and washings were combined and evaporated to a syrup. The crude mixture showed two products on t.l.c. Chromatography on a silica gel column (350 g) and elution with ethyl acetate benzene (3:7) gave successively 3.1 g of VIII (67.5%), m.p. 112-114° (from acetone petroleum ether), and 1.0 g of IX (29%), m.p. 96-97° (from ether petroleum ether).

VIII: I.r. (KBr) 3400 (OH), 1745 (Ester), 1442 (C-H), 1380, 1375 cm^{-1} (gem-dimethyl), p.m.r. (DMSO-d_6) δ = 1.22 (s, 3H), 1.40 (s, 3H), 3.71 (s, 3H), 4.35 (d, $J_{2,3}$ = 6 Hz, 1H), 4.3-4.4 (m, 2H), 4.83 (d, $J_{2,3}$ = 6 Hz, 1H), 5.20 (d, $J_{1,OH}$ = 6 Hz, 1H), 5.63 (d, J = 9 Hz, OH), 7.10 (d, J = 6 Hz, OH).

Mass spectrum (70 e.V.): m/e 248 (M^+), 233 (M^+-CH_3).

Analysis calc. for $C_{10}H_{16}O_7$ (248.2): C, 48.38; H, 6.50.
Found: C, 48.14; H, 6.50.

IX: I.r. (KBr): 3240 (OH), 1740 (Ester), 1470, 1440 (CH), 1380, 1370 cm^{-1} (gem-dimethyl), p.m.r. (DMSO-d_6) δ = 1.30 (s, 3H), 1.40 (s, 3H), 3.70 (s, 3H), 4.10 (s, 2H), 4.47 (d, $J_{2,3}$ = 6 Hz, 1H), 4.80 (d, $J_{2,3}$ = 6H, 1H), 5.20 (s, 1H), 6.23 (2 OH).

Mass spectrum (70 e.V.): m/e 248 (M^+), 233 (M^+-CH_3).

Anal.Calc. for $C_{10}H_{16}O_7$ (248.2): C, 48.38; H, 6.50.
Found: C, 48.49; H, 6.66.

Methyl (2,3-O-isopropylidene-1,5-di-O-acetyl-β-D,L-allofuranosid)uronate (IXa).

A solution of IX (100 mg, 0.4 mmole) in acetic anhydride (3 ml) and pyridine (3 ml) was stirred for 18 h. at room temperature. After evaporation to dryness, the residue was dissolved in chloroform, the solution washed with dilute hydrochloric acid, dried (sodium sulfate), and evaporated to dryness. The residue was crystallized from ether and petroleum ether. Yield: 100 mg (74%), m.p. 133-134°: i.r. (KBr) 1745 (Ester), 1442 (C-H), 1380, 1360 cm^{-1} (gem-dimethyl); p.m.r. ($CDCl_3$): δ = 1.35 (s, 3H), 1.46 (s, 3H), 2.08 (s, 3H), 2.19 (s, 3H), 3.79 (s, 3H), 4.59 (d, $J_{2,3}$ = 7 Hz, 1H), 4.80 (d, 2H), 5.02 (d, $J_{2,3}$ = 7 Hz, 1H), 6.22 (s, 1H).

Mass spectrum (70 e.V.): m/e 332 (M^+), 317 (M^+-CH_3), 301 (M^+-OCH_3), 289 (M^+-CH_3CO), 273 (M^+-CH_3COO).

Anal. Calc. for $C_{14}H_{20}O_9$ (332.3): C, 50.60; H, 6.07.

Found : C, 50.51; H, 6.14.

Methyl (2,3-O-isopropylidene-1,5-di-O-acetyl-β-D,L-talofuranosid)uronate (VIIIa).

Treatment of VIII (100 mg, 0.4 mmole) with a mixture of acetic anhydride and pyridine (1:1), under conditions identical to those described for the preparation of IXa, gave 125 mg (93%) of VIIIa, m.p.: 77-79°. I.r. (KBr) 1770, 1755, 1742 (Ester), 1433 (CH), 1378 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 1.36 (s, 3H), 1.50 (s, 3H), 2.05 (s, 3H), 2.17 (s, 3H), 3.80 (s, 3H), 4.70 (dd, $J_{2,3}$ = 6.5 Hz, $J_{3,4}$ = 1 Hz, 1H), 4.75 (d, $J_{4,5}$ = 6.5 Hz, 1H), 4.94 (dd, $J_{4,5}$ = 6.5 Hz, $J_{3,4}$ = 1 Hz, 1H), 5.21 (d, $J_{2,3}$ = 6.5 Hz, 1H), 6.20 (s, 1H).

Mass spectrum (70 e.V.): m/e 332 (M^+), 317 (M^+-CH_3).

Anal. Calc. for $C_{14}H_{20}O_9$ (332.3): C, 50.60; H, 6.07.
Found : C, 50.61; H, 6.17.

Methyl (methyl 2,3-O-isopropylidene-β-D,L-talofuranosid) uronate (X), Methyl (methyl -β-D,L-talofuranosid)uronate (XI) and Methyl (methyl -α-D,L-talofuranosid)uronate (XII).

A solution of 2.3 g (9.3 mmole) of VIII in methanol (100 ml) and a catalytic amount of sulfuric acid was heated under reflux for 2 h., and evaporated to dryness. The residue was chromatographed on silicic acid with ethyl acetate as eluent. Fractions (15 ml each) were collected and examined by t.l.c.. Fractions 6-18 were combined and evaporated. Crystallization from hot petroleum ether yielded 610 mg (24%) of X, m.p.: 63-64°. I.r. (KBr) 3435 (OH), 1743 (Ester), 1455, 1442 (C-H), 1382, 1375 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 1.35 (s, 3H), 1.45 (s, 3H), 3.45 (s, 3H), 3.82 (s, 3H), 4.21 (s, 1 ex, 2H), 4.60 (d, $J_{2,3}$ = 6 Hz, 1H), 4.80 (d, $J_{4,5}$ = 2 Hz, 1H), 4.90 (d, $J_{2,3}$ = 6 Hz, 1H), 4.96 (s, 1H).

Mass spectrum (70 e.V.): m/e = 262 (M^+), 261 (M^+-1), 247 (M^+-CH_3).

Anal. Calc. for $C_{11}H_{18}O_7$ (262.2): C, 50.37; H, 6.92.
Found: C, 50.41; H, 6.97.

Fractions 22-32 were combined and evaporated to give 950 mg (46%) of XI as a syrup. I.r. (KBr): 3400 (OH), 1735 (Ester), 1437 cm^{-1} (CH); p.m.r. [$(CD_3)_2CO$]: δ = 2.92 (s, 1H), 3.30 (s, 3H), 3.72 (s, 4H), 3.95 (d, 1H), 4.1-4.4 (m, 4H), 4.70 (s, 1H).

Mass spectrum (70 e.V.): 222 (M^+), 190 (M^+-CH_3OH), 132 ($M^+-OH-CH_2-COOCH_3$).

Analytical data were obtained on the acetate XIa.

The more polar product XII was collected from fractions 35-43; yield: 600 mg (29%). I.r. (film): 3400 (OH), 1745 (Ester), 1437 (C-H), p.m.r. [$(CD_3)_2CO$]: δ 2.84 (s, 1H), 3.32 (s, 3H), 3.75 (s, 3H), 3.65 (d, J = 9 Hz, 1H), 3.9-4.5 (m, 5H), 4.82 (dd, $J_{1,2}$ = 4 Hz, 1H).

Mass spectrum (70 e.V.): m/e 221 (M^+-1), 190 (M^+-CH_3OH), 163 ($M^+-COOCH_3$).

Anal. Calc. for $C_8H_{14}O_7$ (222.2): C, 43.24; H, 6.35.
Found: C, 42.73; H, 6.48.

Methyl (methyl 2,3-O-isopropylidene-β-D,L-talofuranosid) uronate (X) from XI.

A solution of XI (500 mg, 2.25 mmole) in acetone (3 ml), 2,2-dimethoxypropane (5 ml) and a catalytic amount of p-toluenesulfonic acid was refluxed for 3 h. After concentration to dryness, the residue was dissolved in chloroform, washed with water, dried and evaporated. Crystallization from hot petroleum ether (b.p. 30-60°) gave 520 mg (88%) of X, m.p.: 64-65°. The spectral data (i.r., p.m.r., m.s.) were identical with those of the product obtained directly from VIII.

Methyl (methyl-2,3-O-isopropylidene-5-O-acetyl-β-D,L-talofuranosid)uronate (Xa).

Compound X (400 mg, 1.52 mmole) was acetylated with acetic anhydride (4 ml) and pyridine (4 ml) in the usual manner. Chloroform extraction and column chromatography, using benzene/isopropanol (98:2) as eluent, gave 450 mg (97%) of Xa. I.r. (film): 1747 (Ester), 1435 (CH), 1372 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 1.33 (s, 3H), 1.50 (s, 3H), 2.17 (s, 3H), 3.35 (s, 3H), 3.81 (s, 3H), 4.55 (dd, $J_{4,5}$ = 8 Hz, $J_{4,3}$ = 1 Hz, 1H), 4.60 (d, $J_{2,3}$ = 6 Hz, 1H), 4.90 (dd, $J_{3,4}$ = 1 Hz, $J_{3,2}$ = 6 Hz, 1H), 5.00 (s, 1H), 5.12 (d, $J_{5,4}$ = 8 Hz, 1H).

Mass spectrum (70 e.V.): m/e = 304 (M^+), 289 (M^+-CH_3), 273 (M^+-OCH_3).

Anal. Calc. for $C_{13}H_{20}O_8$ (304.3): C, 51.31; H, 6.63.
Found : C, 51.67; H, 6.75.

Methyl (methyl 2,3,5-tri-O-acetyl-β-D,L-talofuranosid) uronate (XIa).

Compound XI (450 mg, 2 mmole) was acetylated with acetic acid (4 ml) and pyridine (4 ml) in the usual manner. Chloroform extraction and crystallization from chloroform/petroleum ether, gave 550 mg (78%), m.p. 105-107°. I.r. (KBr) 1763, 1740 (Ester), 1440 (CH), 1375, 1368 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 2.07 (s, 3H), 2.12 (s, 3H), 2.21 (s, 3H), 3.41 (s, 3H), 3.82 (s, 3H), 4.60 (q, 1H), 4.90 (s, 1H), 5.19 (d, $J_{4,5}$ = 3.6 Hz, 1H), 5.22 (d, $J_{2,3}$ = 4.6 Hz, 1H), 5.44 (q, 1H).

Mass spectrum (70 e.V.): m/e = 348 (M^+), 347 (M^+-1), 288[(M^+-1)-$COOCH_3$].

Anal. Calc. for $C_{14}H_{20}O_{10}$ (348.3): C, 48.27; H, 5.79.
Found: C, 48.26; H, 5.88.

Methyl (methyl 2,3,5-tri-O-acetyl-α-D,L-talofuranosid) uronate (XIIa).

A solution of XII (100 mg, 0.45 mmole) in acetic anhydride (2 ml) and pyridine (2 ml) was stirred at room temperature for 20 h. After evaporation, the residue was purified on a silicic acid column using benzene/methanol (95:5) as eluent. The band of R_f=0.5, gave the triacetate XIIa, 90 mg (57%). I.r. (film) 1750 (Ester), 1435 (CH), 1370 (CH_3), p.m.r. ($CDCl_3$): δ = 2.15 (s, 6H), 2.20 (s, 3H), 3.42 (s, 3H), 3.80 (s, 3H), 4.60 (m, 1H), 5.0-5.3 (m, 3H), 5.40 (d, $J_{1,2}$ = 2.5 Hz, 1H).

Mass spectrum (70 e.V.): m/e = 317 (M^+-OCH_3), 289 (M^+-$COOCH_3$).

Anal. Calc. for $C_{14}H_{20}O_{10}$ (348.3): C, 48.27; H, 5.79. Found: C, 48.60; H, 5.87.

Methyl (methyl 2,3-O-isopropylidene-α-D,L-talofuranosid) uronate (XIIb).

A solution of XII (350 mg, 1.57 mmole) in acetone (5 ml) and 2,2-dimethoxypropane (10 ml), containing a catalytic amount of p-toluenesulfonic acid, was refluxed for 2 h. Chloroform extraction and purification on a silicic acid column gave 345 mg (84%) of XIIb, m.p. 111-112° as colorless needles. I.r. (KBr) 3435 (OH), 1745 (Ester), 1450, 1431 (CH), 1380, 1370 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ = 1.38 (s, 3H), 1.58 (s, 3H), 3.05 (d, 1 OH), 3.45 (s, 3H), 3.84 (s, 3H), 4.30 (d, J = 1 Hz, 1H), 4.50 (dd, 1H), 4.6-4.8 (m, 2H), 4.93 (d, $J_{1,2}$ = 4 Hz, 1H).

Mass spectrum (60 e.V.): m/e = 262 (M^+), 247 (M^+-CH_3), 231 (M^+-OCH_3), 203 ($M^+-COOCH_3$).

Anal. Calc. for $C_{11}H_{18}O_7$ (262.2): C, 50.37; H, 6.92.
Found: C, 50.49; H, 6.97.

Methyl 2,3-O-isopropylidene-5,6-di-O-acetyl-β-D,L-talofuranoside (XIIIb) and mono-acetate (XIIIa).

A solution of Xa (455 mg, 1.5 mmole) in ether (5 ml) was added dropwise at 20° to a slurry of lithium aluminum hydride (114 mg, 3 mmole) in anhydrous ether (50 ml). The mixture was refluxed for 3 h, cooled to 5°, and a mixture of pyridine-acetic anhydride (1:1, 10 ml) was slowly added. The reaction mixture was kept at room temperature for 20 h, poured on crushed ice, stirred for 15 min., and then extracted with three portions of chloroform. The extracts were combined, dried (sodium sulfate), and evaporated to a syrup. The residue was chromatographed on silicic acid with chloroform-methanol (98:2) for elution. Fractions (10 ml each) were collected and examined by t.l.c. The less polar oily diacetate XIIIb was eluted first. Yield of XIIIb: 180 mg (38%).
I.r. (film): 1740 (Ester), 1437 (CH), 1370 (CH_3), p.m.r. ($CDCl_3$): δ = 1.34 (s, 3H), 1.50 (s, 3H), 2.07 (s, 3H), 2.10 (s, 3H), 3.34 (s, 3H), 4.02 (dd, 1H), 4.23 (d, 1H), 4.35 (d, 1H), 4.55 (d, J = 6 Hz, 1H), 4.75 (dd, $J_{3,2}$ = 2 Hz, 1H), 5.00 (s, 1H), 5.20 (m, 1H).

Mass spectrum (70 e.V.): m/e 318 (M^+), 317 (M^+-1), 303 (M^+-CH_3), 287 (M^+-OCH_3), 275 (M^+-COCH_3).

Anal. Calc. for $C_{14}H_{22}O_8$ (318.3): C, 52.82; H, 6.97.
Found : C, 52.96; H, 7.03.

The more polar mono acetate XIIIa was eluted next, and crystallized from hot petroleum ether (b.p. 30-60°). Yield: 180 mg (43%), m.p.: 64-65°. I.r. (KBr): 3380 (OH), 1742 (Ester), 1462, 1437 (CH), 1375, 1365 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 2.09 (s, 3H), 3.50 (s, 3H), 3.60 (s, OH, 1H), 3.80 (m, 1H), 4.0-4.3 (m, 2H), 4.50 (s, 1H), 4.59 (d, $J_{2,3}$ = 6 Hz, 1H), 4.85 (d, $J_{2,3}$ = 6 Hz, 1H), 5.00 (s, 1H).

Mass spectrum (70 e.V.): m/e 276 (M^+), 261 (M^+-CH_3), 245 (M^+-OCH_3), 233 (M^+-COCH_3).

Anal. Calc. for $C_{12}H_{20}O_7$ (276.3): C, 52.16; H, 7.30.
Found: C, 52.27; H, 7.32.

Methyl 2,3-O-isopropylidene-β-D,L-talofuranoside (XIII).

A catalytic amount of sodium was added with stirring to a solution of XIIIb (180 mg, 0.56 mmole) in ethanol (20 ml). After 18 h at room temperature, the mixture was neutralized with anhydrous hydrogen chloride in ether, and concentrated under reduced pressure to dryness. The residue was purified by filtration through a silica gel column using chloroform/methanol (98:2) as eluent. After combining the main fractions, XIII was obtained as a colorless syrup. Yield: 100 mg (75%). I.r. (film) 3420 (OH), 1372 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$) δ = 1.32 (s, 3H), 1.50 (s, 3H), 2.90 (broad s, 2 OH), 3.48 (s, 3H), 3.65 (s, 3H), 4.50 (broad s, 1H), 4.60 (d, $J_{3,2}$ = 6 Hz, 1H), 4.85 d, $J_{2,3}$ = 6 Hz, 1H), 5.00 (s, 1H).

Mass spectrum (60 e.V.): m/e 234 (M^+), 219 (M^+-CH_3), 203 (M^+-OCH_3), 173 (M^+-HO-CH_2-CH-OH).

Anal. Calc. for $C_{10}H_{18}O_6$ (234.2): C, 51.27; H, 7.75.
Found: C, 51.17; H, 7.81.

Treatment of XIIIa under conditions identical with those described above, gave pure XIII in 45% yield.

Methyl 2,3-O-isopropylidene-β-D,L-ribo-pentodialdo-1,4-furanoside (XIV) from XIII.

A solution of sodium metaperiodate (22 mg, 0.2 mmole) in water (1 ml) was added to a solution of XIII (46 mg, 0.2 mmole) in methanol (1 ml) and phosphate buffer pH 7.0 (0.2 ml). The mixture was stirred for 2 h at 20°. Evaporation, ether extraction, and partial evaporation of the ether gave 35 mg (89%) of XIV, m.p. 94-95°. I.r. ($CHCl_3$): 1730 (CO), 1372 cm^{-1} (gem-dimethyl, p.m.r. ($CDCl_3$): δ = 1.35 (s, 3H), 1.50 (s, 3H), 3.37 (s, 3H), 4.50 (s, 1H), 4.55 (d, $J_{3,2}$ = 6 Hz, 1H), 5.05 (d, $J_{2,3}$ = 6 Hz, 1H), 5.10 (s, 1H), 9.95 (s, 1H).

Mass spectrum (70 e.V.): m/e 203 (M^++1), 187 (M^+-CH_3), 173 (M^+-CHO).

Anal. Calc. for $C_9H_{14}O_5$ (202.2): C, 53.46; H, 6.98.
Found: C, 53.24; H, 7.12.

Methyl (2,3-O-isopropylidene-5,6-di-O-acetyl)-β-D-allofuranoside (XVa).

Acetylation of XV[107] (117 mg, 0.5 mmole) in the usual manner gave 150 mg (94%), of XVa as a syrup. I.r. ($CHCl_3$): 1745 (CO), 1440 (CH), 1370 cm^{-1} (gem-dimethyl), p.m.r. ($CDCl_3$). δ = 1.27 (s, 3H), 1.45 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 3.35 (s, 3H), 4.0-4.5 (m, 3H), 4.60 (s, 2H), 4.98 (s, OH), 5.01 (dd, 1H).

Methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (XIV) from XV.

XV, m.p. 94-95°, was oxidized with sodium meta periodate in methanol at pH 7 as described previously. The aldehyde XIV had identical i.r. and p.m.r. spectra, and g.l.c. and t.l.c. behaviour as D,L-XIV, obtained from XIII.

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Part II

SYNTHETIC STUDIES TOWARDS OXACEPHAM DERIVATIVES

Abstract

Several synthetic sequences for the synthesis of an oxacepham derivative were investigated in detail and the resulting products were characterized. The Ugi-reaction using an aldehyde-acid with ammonia was studied and the reaction products identified.

A number of β,β,β-trichloroethylesters was prepared as a protecting group, which was to be removed without attacking the sensitive -C=N- group. This resulted in the development of a particularly mild cleavage method for these esters, with potential applications to peptide chemistry and similar synthetic problems.

Partie II

Contribution à la synthèse de dérivés de l'oxacéphame

Divers essais de synthèse de dérivés de l'oxacéphame sont examinés de près et les produits obtenus sont caractérisés. La réaction de Ugi avec un aldehyde-acide et l'ammoniac est étudiée et les produits de la réaction identifiés.

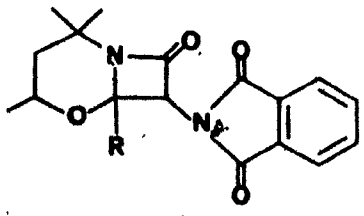
Quelques esters β,β,β-tricholoéthyl sont préparés comme groupe protecteur propres à être déplacés sans affecter la fonction instable -C=N-. Une méthode de clivage particulièrement efficace pour ces esters est alors élaborée. Cette méthode pourrait s'appliquer également à la chimie des peptides ou autres domaines connexes.

TABLE OF CONTENTS

INTRODUCTION

1. Oxygen analogs of cephalosporin antibiotics

Several total syntheses of penicillin-cephalosporin antibiotics have been completed[1-6], but to our knowledge only three[7-9], were achieved for the oxygen analogs of the cepham ring system (1).



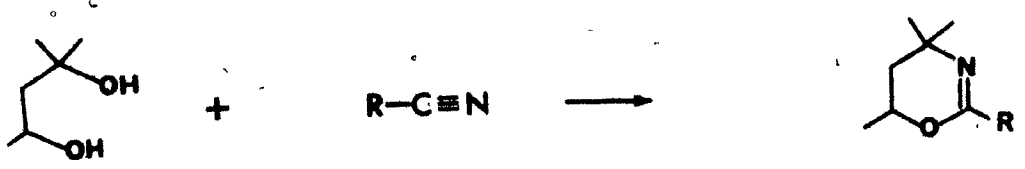
1

R = C_6H_5

$CH_2—C_6H_5$

C_6H_4-m-NO_2

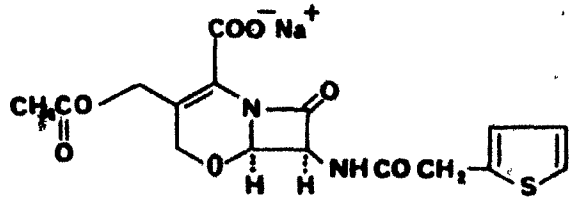
Sheehan[7] prepared the 2-aryl-5,6-dihydro-1,3-oxazines (4) by condensation of a nitrile (3) with 2-methyl-2,4-pentanediol (2) in the presence of sulfuric acid[10]. The reaction of these oxazines (4) with phthaloylglycyl chloride and triethylamine gave the β-lactam, 2,4,4-trimethyl-6-aryl-7-phthalimido-oxacepham (1).



2 + 3 → 4

Christensen[8] prepared (±)-1-oxacephalothin (12). Treatment of benzyl α-aminodiethylphosphonoacetate[5] (5) with ethyl thionoformate resulted in benzyl α-thioforamido-diethyl-phosphonoacetate (6). Treatment of 6 with methyl iodide and potassium carbonate gave benzyl α(S-methyl-thioimidato)diethylphosphonoacetate (7), which was condensed with azidoacetyl chloride to give the β-lactam (8). Chlorination of 8 gave the isomeric chloro compounds (9). The chloroazetidinone (9) was dissolved in 1-hydroxy-3-acetoxy-propanone and treated with $AgBF_4$ and Ag_2O to give (10) which was cyclized to (11).

Reduction of the azide with Pd/C and acylation with thienylacetyl chloride gave 7β-(thienylacetamide)-1-oxadethiacephalosporanic acid (12).



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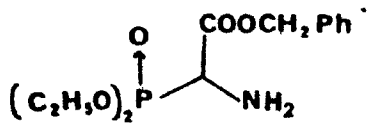

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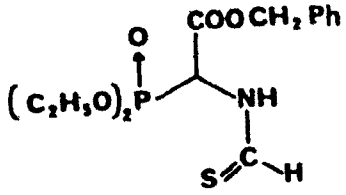

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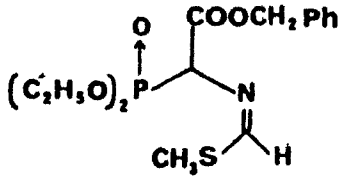

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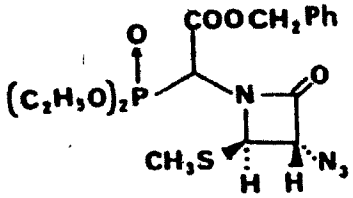

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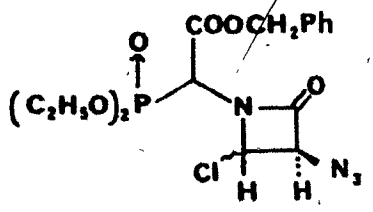

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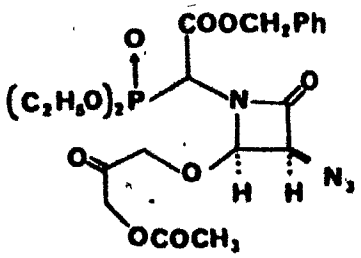

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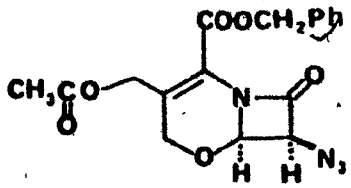
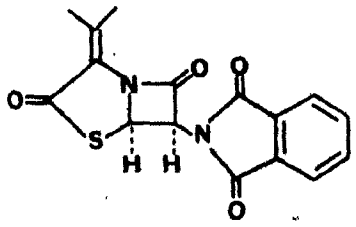


11

The third oxacepham synthesis was reported by Wolfe[9]. The crucial step was the transformation of the thiazolidine ring of the penicillin nucleus into a dihydro oxazine ring to form the oxygen analog (14) of Δ^3-cephem.



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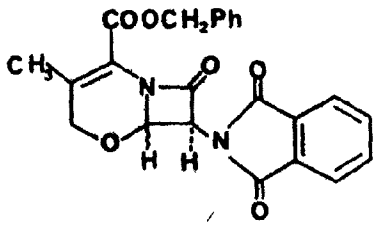


14

2. Biological activity of Penicillin and Cephalosporins

The penicillin and cephalosporin derivatives prevent cell wall formation in bacteria[11,12]. Specifically, they are thought to prevent cross-linkage of the peptidoglycan peptide chains, the terminal reaction in cell wall biosynthesis. These drugs are assumed to inactivate irreversibly the as yet unisolated membrane-bound transpeptidase enzyme[13]. The active penicillins are all derivatives of 6-aminopenicillanic acid and the active cephalosporins of Δ^3-7-aminocephalosporic acid[11,12]. Both series of drugs are remarkably nontoxic as a consequence of their great specificity.

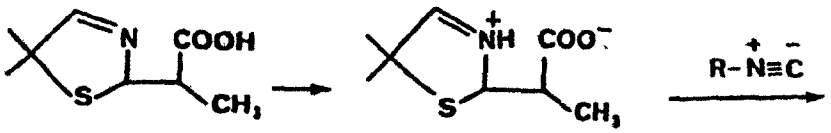
Early attempts to explain this specificity were based on the idea that penicillin is isosteric with the terminal D-alanyl-D-alanine dipeptide[14]. The strained β-lactam portion of the antibiotics are presumably the site of the chemical reactions. Thus in this scheme penicillin would be considered to be an affinity-labeling agent[15].

The enzyme binds penicillin to its active site in a conformation that approximates the dipeptide conformation. Penicillin is already a strained molecule, having the β-lactam ring; the rings are strongly puckered. If the rings get flattened out (i.e., ring N-hybridization goes from sp^3 to sp^2) at the active site of the enzyme, penicillin would mimic the dipeptide substrate. If penicillin is distorted in this way by the enzyme, its chemical reactivity would be increased manifold, thereby greatly increasing the probability of a chemical reaction with an active-site residue.

Aside from the nitrogen atom, the cephalosporins and penicillin nuclei have sulphur as the only other heteroatom. Since the sulphur atom could possibly bind to an electrophilic site on the enzyme, it was of interest to determine whether sulphur is necessary for the biological activity of these compounds. Substitution of sulphur in the bicyclic system by a smaller atom could also result in higher strain in the system and, hence, a more reactive β-lactam moiety and therefore an antibiotic with increased activity.

3. Outline of the Project.

A novel synthesis of β-lactams (18) was reported in 1962 by Ugi and Wischöffer[16] who allowed isocyanides to react with Schiff bases of aldehydes with β-amino acids (15). The reaction was carried out in a two phase system of water and petroleum ether. In aqueous solution the imine acid (15) is in equilibrium with the zwitterion (16), which reacts by α addition to the isonitrile to form the adduct (17). This rearranges by means of trans-annular acyl migration to (18). With this mechanism a cis configuration of the carbamide and β-lactam is expected.



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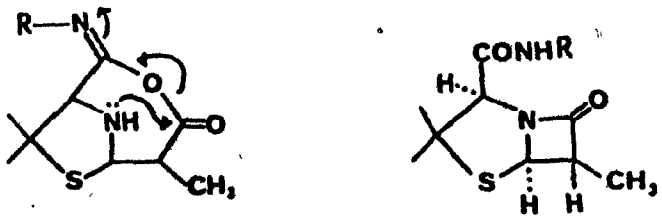
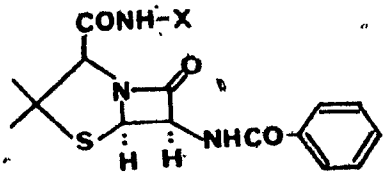


17 18

1965 Sjöberg[17] claimed in a dissertation to have synthesized cis-6-phenylacetamido penicillan alkylamide (19) using this Ugi-reaction.



19

These approaches suggested to synthesize a cepham derivative in a similar manner.

Previous studies by this research group[18,19,20] seem to have come very close to the envisaged objective and paved the way to the important intermediates 37a (Rossy and Roseberry)[18,19] or 40 (Chung)[20] respectively (Scheme 1, page 171).

The purpose of this study was twofold:

a) to improve the synthetic pathways (see scheme 1, page 171) to a degree, that sufficient quantities of 40 became available for

b) demonstration beyond doubt, whether it is possible or not to obtain an oxacepham derivative with this method.

In the course of these studies it became necessary, to devise a very mild method for ester cleavage which will be dealt with in chapter 4.

The synthetic routes existing at the beginning of this project are outlined below:

Rossy, Roseberry and Chung[18,19] started with D-mannitol (20) which was converted to the glyceraldehyde acetonide (22) via 21. 22 was reacted with formaldehyde to 23. This dioxane (23) was treated with either N-methylethanolamine[18,19] (27) or N- methylaminoethanethiol[20,28] (29) in refluxing benzene to give oxazolidine alcohol (24) or thiazolidine alcohol (24a). Treatment with methanesulfonyl chloride at -50° gave the crystalline oxazolidine mesylate (25) or thiazolidine mesylate (25a).

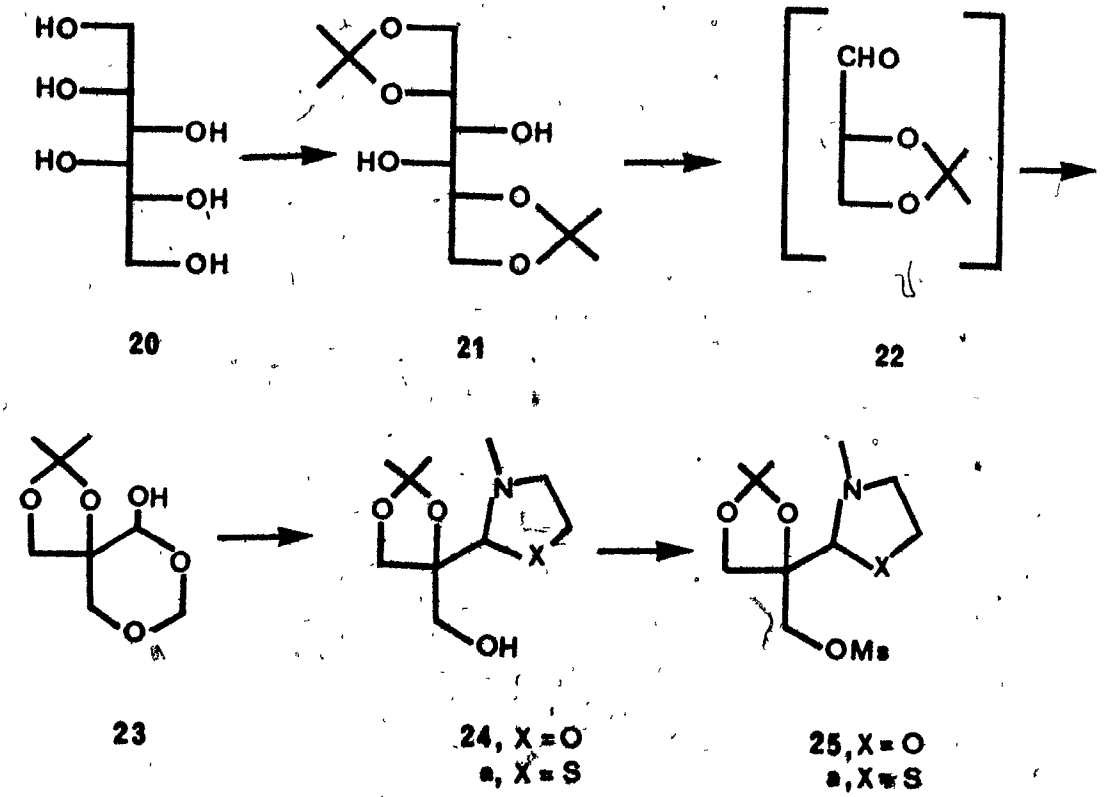
Condensation of the oxazolidine mesylate (25) with the sodium salt of thiol (31d) (derived from 2-phenyl-4-ethoxymethylene-5-oxazolone[24] (31)) in DMSO at 75° gave (33) in low yield[19]. At this stage Rossy hydrolyzed the oxazolidine protecting group to the aldehyde (34), followed by treatment with 2N- sodium hydroxide to give the aldehyde acid (35).

Roseberry on the other hand formed the methyl ester (36) by ring opening of the oxazolidine-oxazolone with methanol. Cleavage of the aldehyde protecting group followed by treatment with ammonia gave (37a), which was hydrolyzed by treatment with lithium n-propyl mercaptide in HMPT[21] to yield (37, page 171).

Building on the experience of these studies, Chung[20] pushed the scheme further and came closest to the desired synthesis of a new class of antibiotics, the oxacepham derivative (41). He formed the β,β,β-trichloroethylester by ring opening of the oxazolone (31a), followed by condensation with the thiazolidine mesylate (25a), since he found that the oxazolidine group reacted with oxygen nucleophiles. Hydrolysis of the thiazolidine group, followed by treatment with ammonia gave the ester (40). Cleavage of the β,β,β-trichloroethyl ester with zinc dust in 90% acetic acid at 0° yielded the crucial second-last intermediate (40a).

Unfortunately, the yields leading to 40a or 37 by either route were so low, that the eventual success of the final Ugi-reaction leading to (41) could only be judged by the infrared and mass spectra of the reaction products.

Scheme 1

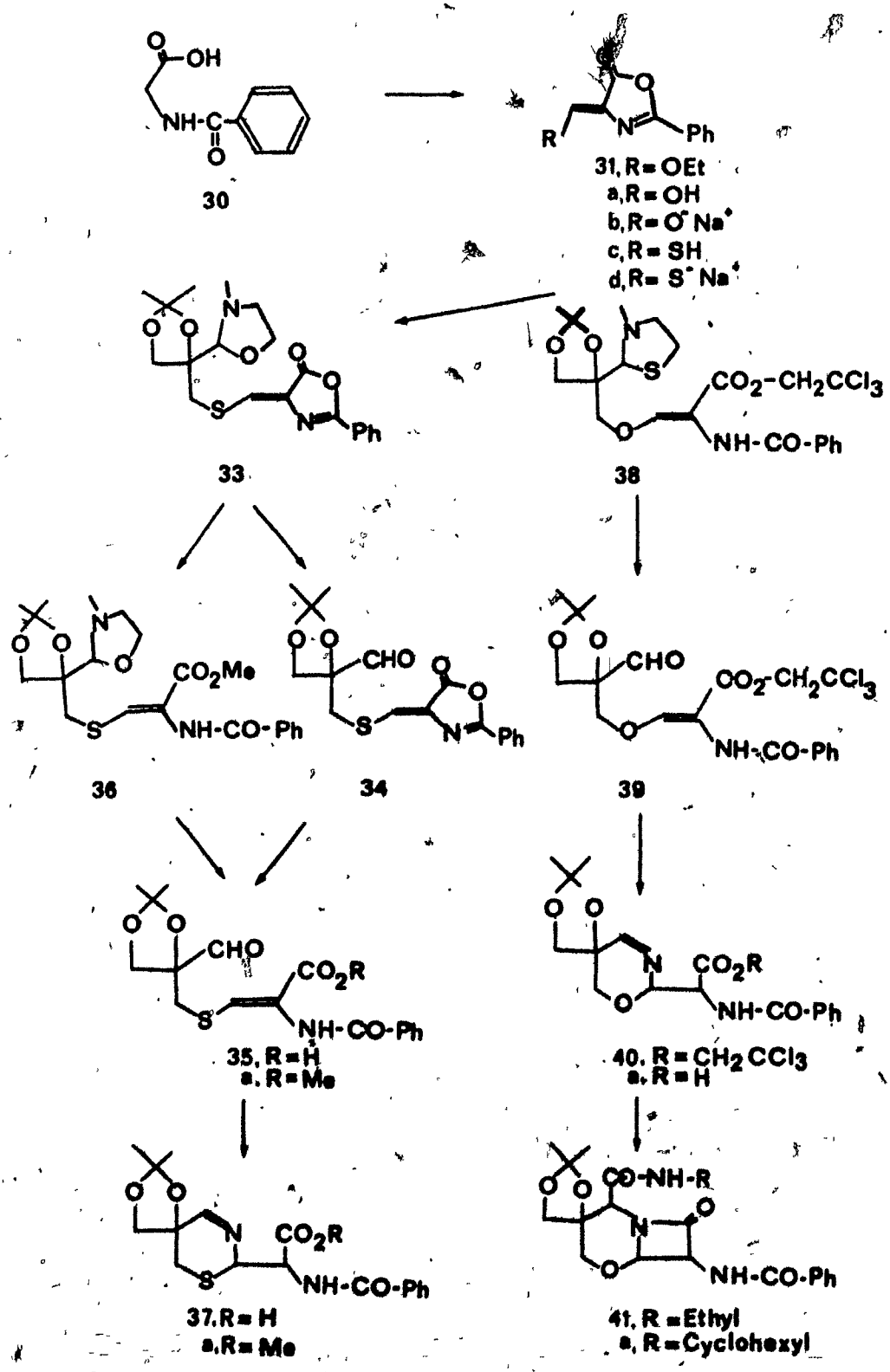


20 21 22

23 24, X = O
a, X = S
25, X = O
a, X = S

27 28 29

Scheme 1 (continued).



CHAPTER 1

Preliminary studies toward the synthesis of the imine acid, using benzyl and p-methoxybenzyl esters as acid protection groups.

Since Chung[20] had little success in hydrolyzing the β,β,β-trichloroethyl ester (40) to prepare the necessary precurser imine-acid (40a) in reasonable yields, we turned our attention to esters which are readily cleaved under mild (preferably anhydrous) conditions. Two of such esters were investigated, the p-methoxybenzyl and the benzyl esters.

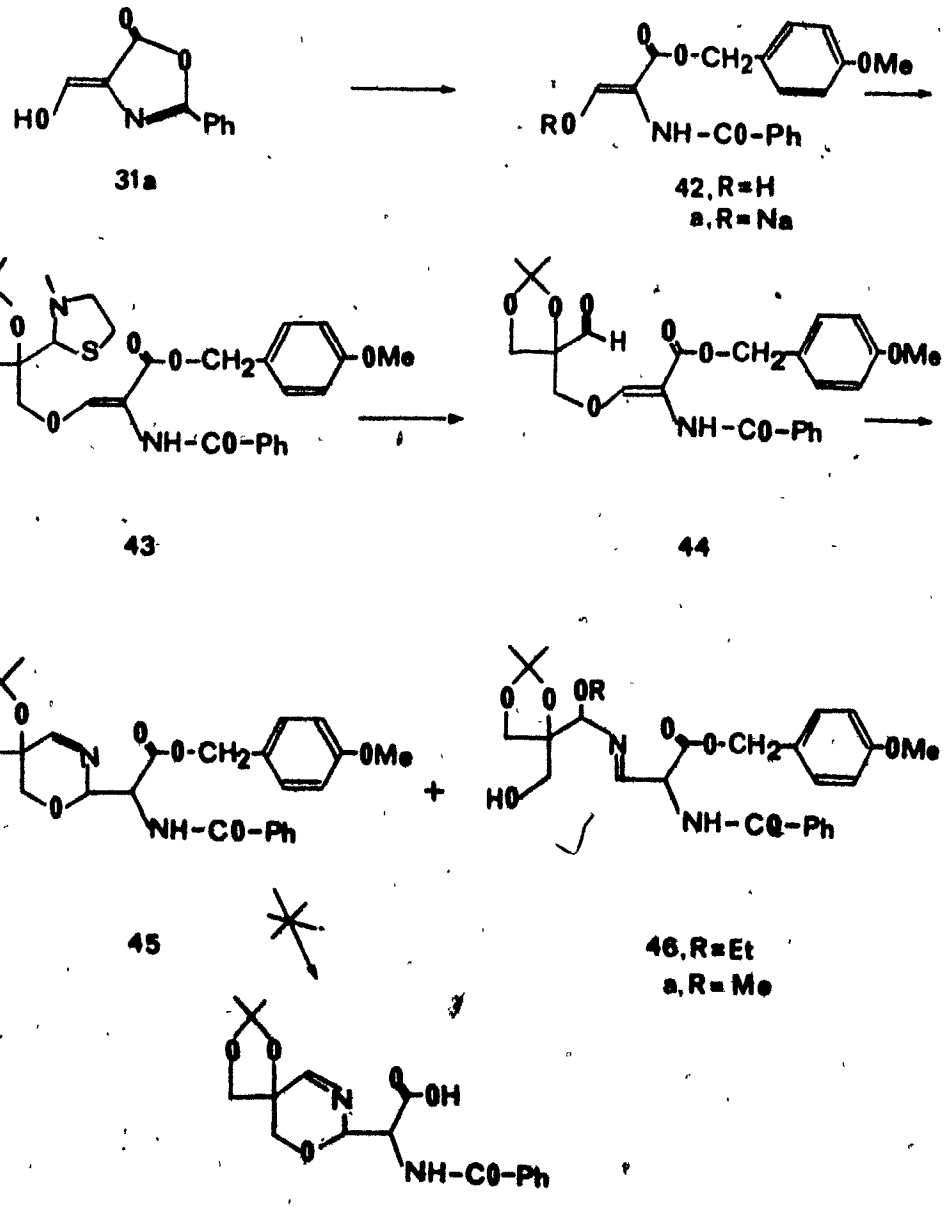
Benzyl esters and a variety of substituted benzyl esters, may be removed as toluene, or the corresponding substituted toluene, by hydrogenolysis. Several methods have been employed to bring about debenzylation[22].

Scheme 2 illustrates our approach to 45. 2-Benzamido-3-hydroxyacrylic acid p-methoxy-benzyl ester (42) was prepared from the reaction of 4-hydroxymethylene-2-phenyl-5-oxazolone (31a) with p-methoxybenzyl alcohol; the sodium salt (42a) was prepared with sodium ethoxide in ethanol.

Condensation of the thiazolidine mesylate (25a) (scheme 1) with the sodium salt (42a) in 2-butanone at 80° gave a 95% yield of the thiazolidine ester (43). Hydrolysis of the aldehyde protecting group was carried out using mercuric chloride[20] in aqueous tetrahydrofuran. Treatment of the aldehyde ester (44) with ammonia in THF gave the imine-ester, which was purified by column chromatography using ether as eluent. The imine ester (45), m.p. 114-117° was eluted first followed by a second fraction, which was identified as the reaction product (46) of ethanol with the imine ester (45). The p.m.r. spectrum of 46 shows a triplet at δ 1.20, coupled with a methylene group at δ 3.32 ppm (J = 7 Hz), indicating the presence of an ethyl group. An exchangeable triplet at δ 2.80 ppm, coupled with a methylene group at δ 3.67 ppm (J = 6 Hz) confirms the presence of a hydroxymethylene group. Furthermore there are 11 protons downfield, with one representing a CH=N group. The rest of the remaining spectrum is similar to that of the required product, the imine ester (45). The mass spectrum of 46 shows a molecular ion peak at m/e 514. The base peak at m/e 499 represents

the loss of a methyl group. Figures 1 and 2, page 176 show the p.m.r. spectrum in deuterated chloroform of 46 and 46a. The origin of the ethanol was traced back to the ether which was used for chromatography. That in fact the imine is very reactive toward alcohol was demonstrated by reacting (45) with one equivalent of methanol in tetrahydrofuran; an almost quantitative yield of (46a) was isolated. The above results exclude all alcohols for the hydrogenolysis of the imine-ester and also demonstrate the sensitivity of this group.

Scheme 2


HO
N
Ph
31a
RO
O-CH2
OMe
NH-CO-Ph
42, R=H
a, R=Na
S
43
H
44
45
HO
OR
46, R=Et
a, R=Me
OH
37

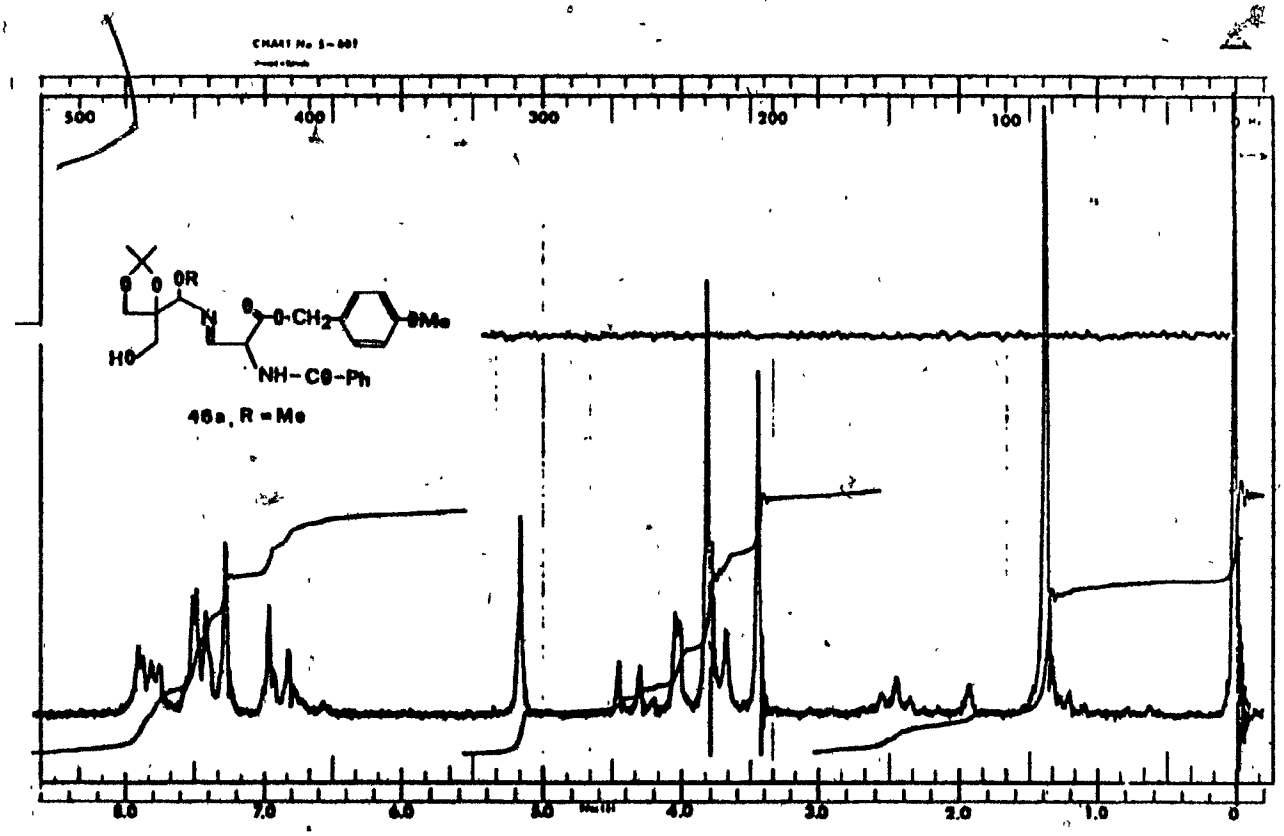


FIGURE 1

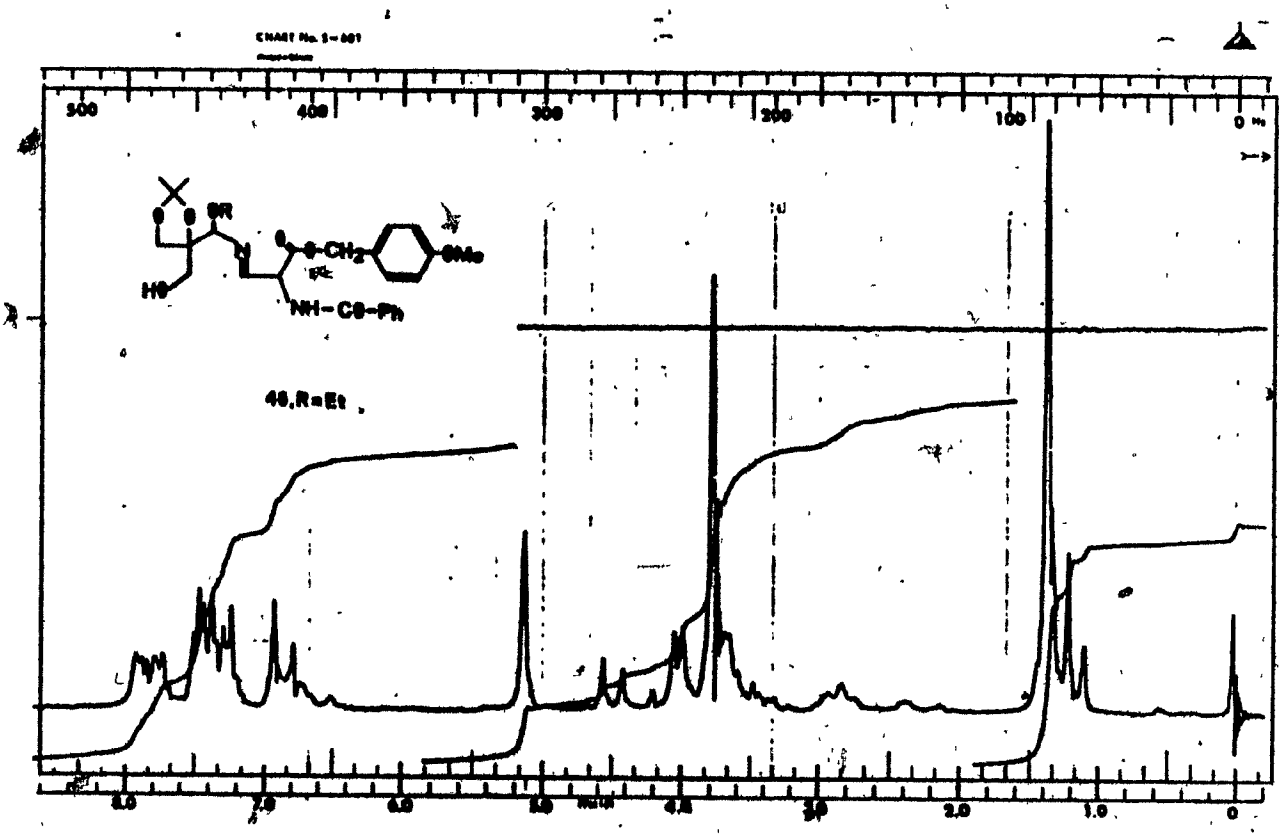


FIGURE 2

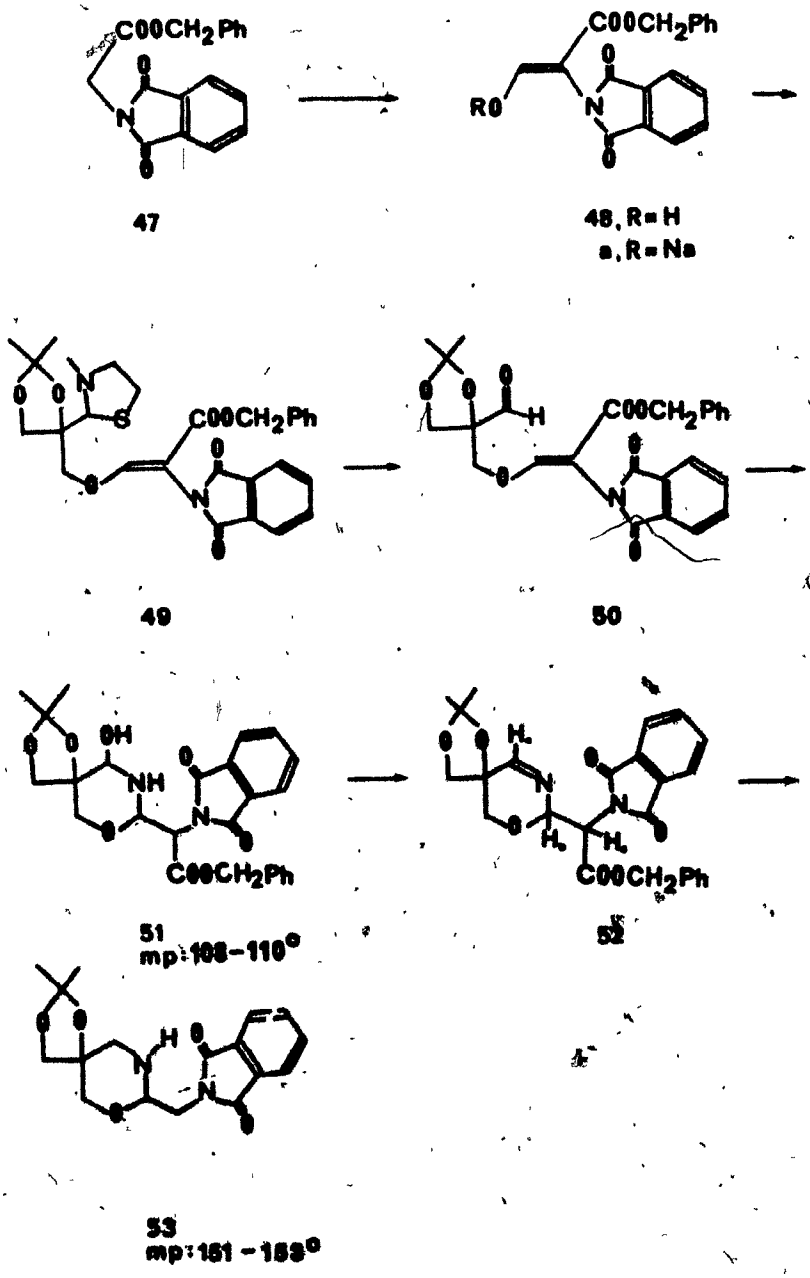
Before we proceeded with the hydrogenolysis we tested the stability of the imine-ester. Thus, the ester (45) was dissolved in a number of solvents such as ether, dioxane, ethyl acetate and chloroform. The solutions were stirred with and without Pd-C in the absence of hydrogen. It was found that the imine-ester (45) was not stable long enough to permit hydrogenolysis of the ester group.

In a parallel series, we prepared the benzyl ester using the phthaloyl group as outlined in scheme 3 (page 178) The phthaloyl derivatives had the advantage that they were highly crystalline.

Phthaloylglycine benzyl ester (47) was formylated with benzyl formate and sodium benzyloxide in refluxing toluene to benzyl 2-phthalimido-3-hydroxyacrylate (48)[23], and its sodium salt (48a) was prepared by treatment of (48) with sodium ethoxide. Condensation of the thiazolidine mesylate with 48a gave 49 in 89% yield. Hydrolysis of the thiazolidine group and treatment with ammonia in ether gave crystalline carbinolamine (51), m.p. 108-110° C, in 40% yield. P.m.r studies in DMSO-D_6 of the carbinolamine (51) showed that immediately after dissolving and deuterium exchange, CH-OD absorbed at δ4.28 ppm and ND-CH-O showed a doublet at δ5.43 ppm. After 20 hours, the CH=N absorption at δ7.72 ppm appeared, and H_b resonated downfield at

δ 5.68 ppm as a double doublet, coupled with H_c ($J_{b,c}$ = 3Hz), indicating that elimination of water took place to form the imine (52). Mild hydrogenolysis of (52) at atm. pressure in ethyl acetate at 20° gave the decarboxylated product (53) m.p. 151-153°C, in 50% yield.

Scheme 3



The p.m.r. spectrum was consistent with the proposed structure 53. The two protons, H_a and H_c, which had appeared at δ 7.72 ppm and δ 4.97 ppm respectively in the imine ester 52, disappeared. Eight protons appeared as multiplets at δ 2.98-4.05 ppm and one exchangeable proton at 1.90 ppm. Also, a double doublet at δ 4.35 ppm was assigned to the N-CH-O proton.

The mass spectrum of the product showed a molecular ion ($M^+ + 1 = 333$) and a base peak at m/e 317, indicating cleavage of the methyl group of the acetonide, which is an important fragmentation process.

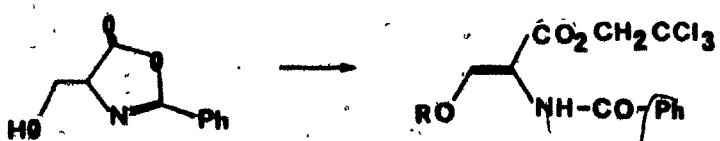
It is known that β-imino acids of type (52) are easily decarboxylated, and there is some experimental evidence[16,24] that similar imine acids lost carbon dioxide even on standing at room temperature. We concluded that, on the basis of the spectral data of 53, the hydrogenolysis produced the desired imine acid, but that the C=N bond was reduced equally rapidly. Further studies using different catalysts gave essentially the same results, and it was not possible to hydrogenolyze the benzyl esters without reducing the C=N bond.

Since we were unable to hydrogenolyze the imine-esters 45 or 51 to the imine acid (37) or to the corresponding phthaloyl derivative, we returned to the use of β,β,β-trichloroethyl esters as acid protecting groups in spite of the low yield reported by Chung[20], hoping to improve the reaction conditions. This is discussed in the next chapter.

CHAPTER 2

Studies towards the preparation of the oxacepham derivative using the aldehyde-acid (55) as intermediate.

Treatment of 4-hydroxymethylene-5-oxazolone (31a) with β,β,β-trichloroethanol gave (32), m.p. 87-88°C. The sodium salt (32a) was prepared by treatment of (32) with sodium ethoxide in ethanol.



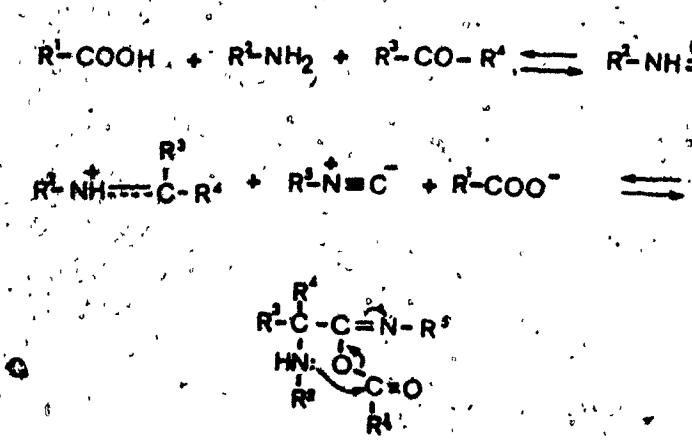
31a

32, R = H
a, R = Na

Condensation of the thiazolidine mesylate (25a) with the sodium salt of the benzamido acrylate (32a) gave (38)[20], which we obtained for the first time as crystalline material, m.p. 126-128°, in 68% yield. Treatment of the thiazolidine ester (38) with zinc dust in 90% aqueous acetic acid afforded the thiazolidine acid (54) in 53% yield, m.p. 159-160°. The aldehyde group was again liberated by treatment of (54) with mercuric chloride in aqueous tetrahydrofuran, yielding 55 in 90% yield. However, the aldehyde-acid (55), which was

initially soluble in ether, decomposed on standing at room temperature within 30 minutes, and the resulting product was insoluble in ether. The p.m.r. spectrum showed immediately after dissolving of the aldehyde-acid the required protons. However, after some time, a broad p.m.r. spectrum was obtained, indicating that the compound was unstable.

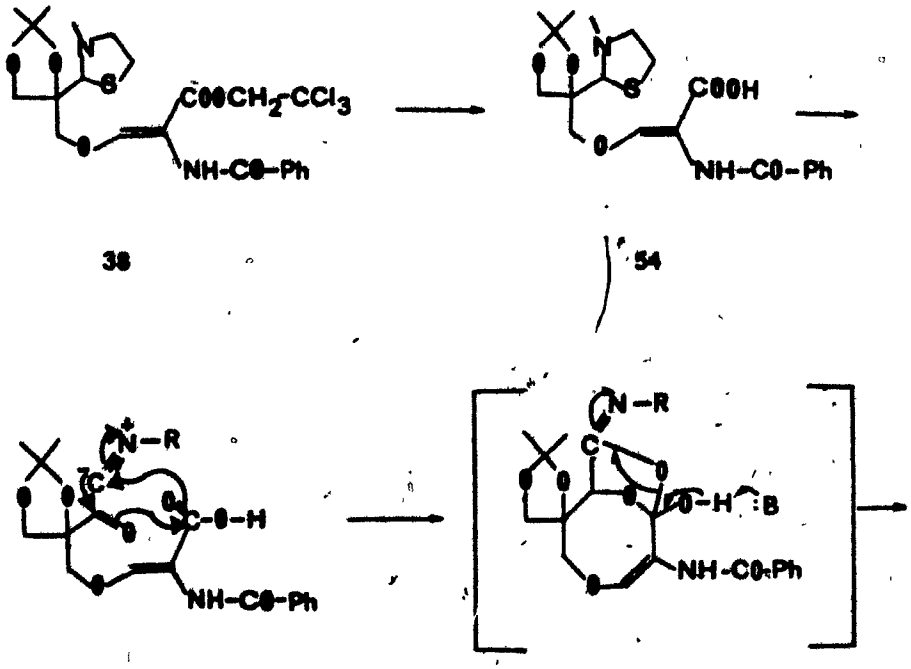
Since the above results showed that the aldehyde acid (55) is unstable, we attempted a four component condensation using the aldehyde-acid (55) in situ. It is known[33] that ammonia, primary and secondary amines, as well as hydrazine derivatives can be used as amine component in the Ugi-reaction.



The combination of ammonia or primary amines and aldehydes or ketones reacts with carboxylic acids and isonitriles to form the intermediate α-adducts. These undergo O→N acyl

transfer by a cyclic mechanism yielding β-acylaminocarbonamides. The formation of the two carbonamide groups in the final product provides the reaction with a strong driving force (see arrows). In our example, the aldehyde-acid (55) functions simultaneously as the aldehyde and acid component. Furthermore the reaction with the isonitrile takes place in the aqueous phase[16,33] and "under dilution conditions", otherwise the formation of resins predominates. For this reason we used aqueous ammonium hydroxyde. 0.9 Equivalents of ammonium hydroxide and cyclohexyl isonitrile and phosphate buffer (pH 6) were added to freshly prepared aldehyde-acid (55). The two-phase system was vigorously stirred for 24 hours. After workup, the mixture was purified by chromatography and the major fraction recrystallized from ether. The product showed an absorption at 1730 cm^{-1}, initially thought to be the β-lactam, and the mass spectrum showed a (M^+ +1) at m/e 458, the cleavage of the methyl group at m/e 443, and the loss of acetone at m/e 400. The rest of the fragmentation was characteristic for the required product (41a, page 184). Although the p.m.r. spectrum was consistent with structure (41a, $C_{24}H_{31}N_3O_6$) microanalysis pointed to $C_{24}H_{30}N_2O_7$, indicating that the isonitrile reacted with the aldehyde in a Passerini-like reaction (see scheme 4). The i.r. absorption at 1730 cm^{-1} could now be explained as a α,β-unsaturated ester and the peak at m/e 458 as the molecular ion peak.

Scheme 4

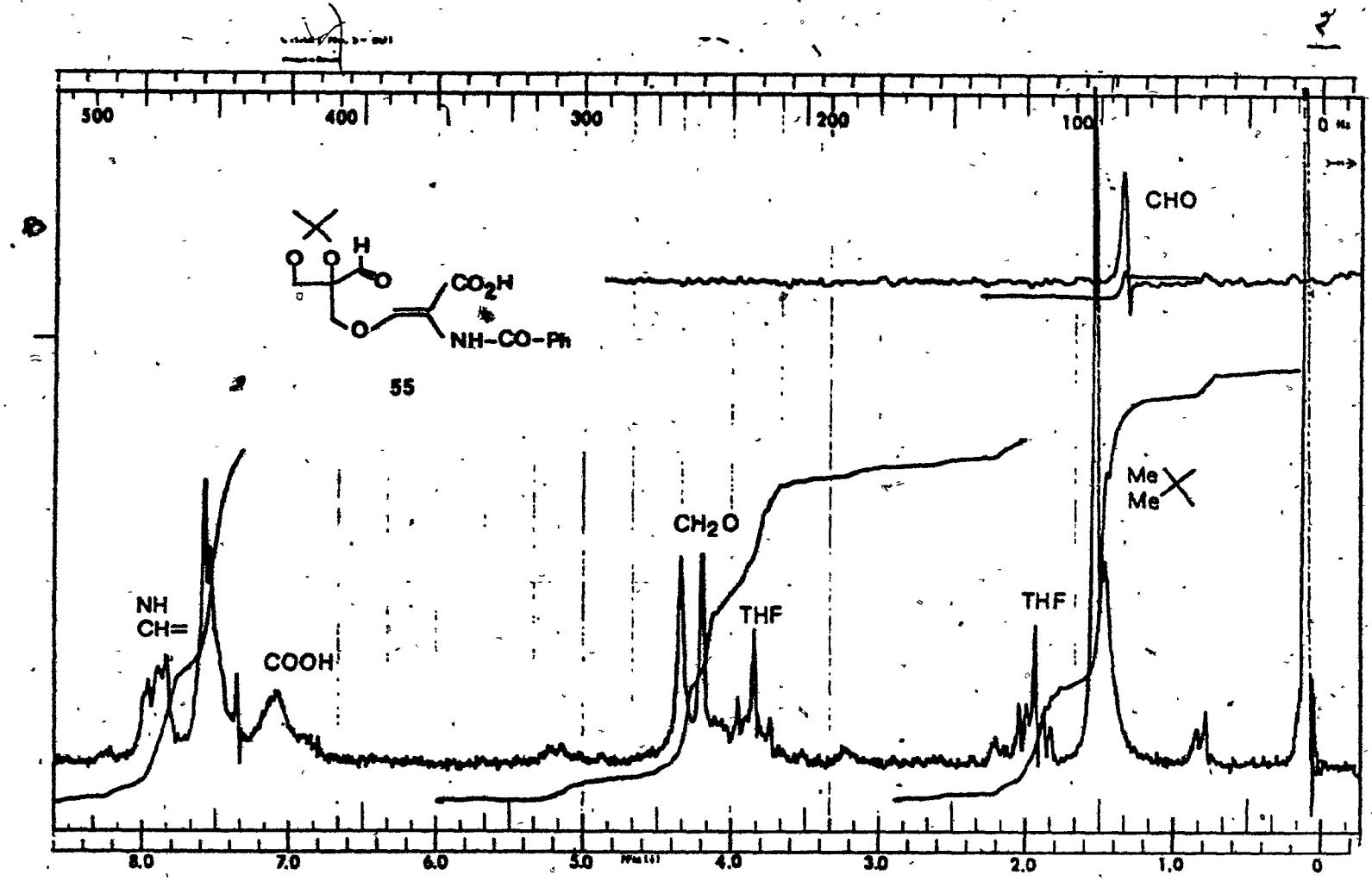


38 54

55 56

41, R = Ethyl
a, R = Cyclohexyl

57, R = C_6H_{11}
mp: 254-256



2-Benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylic acid (55) in chloroform-d.

CHAPTER 3

Attempts to develop a suitable acid protection group for the synthesis of a oxacepham derivative.

As a result of the foregoing studies it became evident that an acid protection group was needed, which fulfilled the following criteria:

a) Stability to aqueous tetrahydrofuran, which is the solvent required to liberate the free aldehyde function.

b) Stability towards ammonia in dry ether, necessary to form the imine.

c) Particularly mild cleavage prior to or during the Ugi reaction in order not to interfere with the sensitive aldimine.

Chung[20] found that t-butyldimethylsilyl ester of model compounds are stable to ammonia in methylene chloride for 24 hours, but solvolyzed within 40 minutes in aqueous tetrahydrofuran. This ruled out the possibility of cleaving the thiazolidine group with mercuric chloride in tetrahydrofuran. He also discovered that the thiazolidine group in 25a (page 170) could be cleaved using m-chloroperbenzoic acid without solvolysis of the silyl ester.

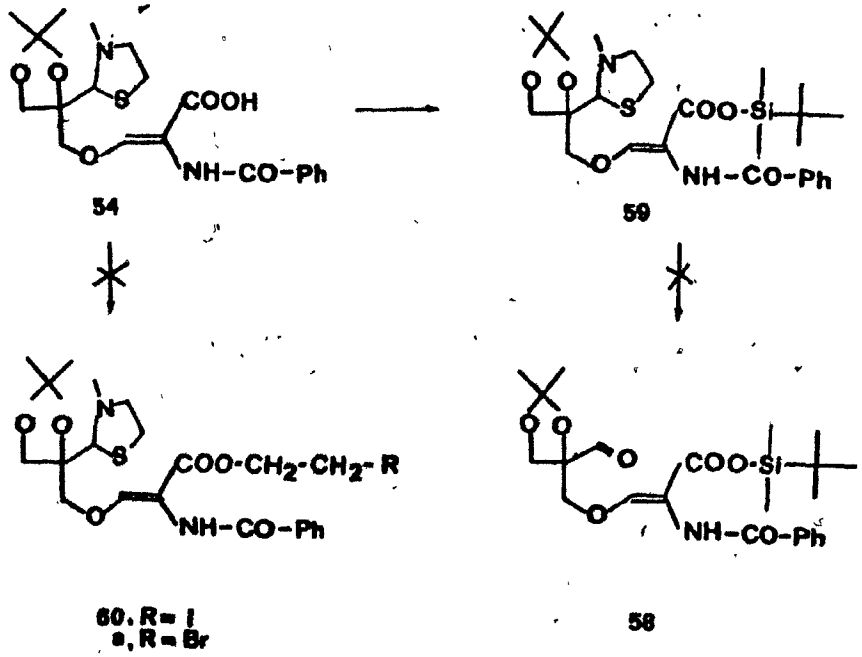
Treatment of thiazolidinesilyl ester(59) with m-chloroperbenzoic acid gave, however, a complicated mixture and no aldehyde silyl ester (58,page 188) could be isolated.

To try to circumvent the use of m-chloroperbenzoic acid, we studied acid protective groups stable to aqueous tetrahydrofuran. Triphenylsilyl esters are known to be stable towards ammonia and aqueous conditions, but formation of the triphenylsilyl ester from (54) using the condition described by Corey[31] for the preparation of dimethyl-t-butylsilyl esters, were unsuccessful, probably due to steric hindrance.

At this time a new mild procedure for the cleavage of an acid protection group, involving the iodoethyl ester was brought to our attention[25]. This ester is easily hydrolyzed by zinc dust and aqueous tetrahydrofuran at room temperature within 30 minutes. Using hippuric acid 2-iodoethyl ester, m.p. 78-80°C, as model, prepared via the 2-bromoethyl ester with potassium iodide in acetone, we could show that the iodoethyl group is stable to aqueous tetrahydrofuran and mercuric chloride, under similar condition which are used to cleave the thiazolidine group. It also proved to be stable to excess ammonia in ether for more than 24 hours.

Attempts to esterify the thiazolidine acid (54) (scheme 5) with 2-bromoethanol in refluxing toluene and p-toluenesulfonic acid, or excess 2-bromoethanol and boron trifluoride[26] at 110°; or dicyclohexylcarbodimide in methylene chloride containing pyridine at 25° for 15 minutes[32], failed. With all methods a reaction did occur; however, none of the expected ester (60) could be found. Instead, the thiazolidine alcohol (24a; page 170) was obtained.

Scheme 5



Consequently, we reinvestigated the hydrolysis of the trichloroethyl ester (38), using aqueous tetrahydrofuran and zinc dust at room temperature. Indeed, (54) m.p. 159-160° C, was obtained within 5 minutes. The t.l.c. was identical with the product obtained using 90% acetic acid. Using the sequence, which was already reported by Chung[20], (scheme 1) we prepared a supply of the imine trichlorbethyl ester (40, page 171) by treatment of the aldehyde ester with ammonia in ether. Now, with larger amounts at hand, the imine-ester could be purified by crystallization from benzene, m.p. 157-159° C.

Thin layer chromatography of the mother liquors indicated two by-products. These were separated by column chromatography and identified by p.m.r., i.r., mix-m.p. and t.l.c. as the acrylate ester (32, see page 181) and hippuric acid β,β,β-trichloroethyl ester (65). Their formation will be explained after additional experimental results are described (see page 191).

We were certain that the imine-acid (40a, page 171) generated from this reaction, could not be isolated due to the decarboxylation mentioned earlier. Hence, we performed the hydrolysis and Ugi-reaction without isolation of this intermediate (40a).

We used cyclohexylisonitrile and phosphate buffer solutions at pH 4.5, 6.0 or ammonium acetate at pH 7.0 under conditions described in chapter 4, which removed the β,β,β-trichloroethyl ester group in all models studied. But under these reaction conditions we found no trace of the oxacephalosporin derivative (41a) either by mass spectroscopy (m/e 457), or by infrared spectroscopy (υ 1750-1780 cm^{-1}).

All attempted cleavage methods of the β,β,β-trichloroethyl ester (40), benzyl esters 45 and 52 to the key intermediate imine acid failed, because of decarboxylation discussed earlier. We believed a possible reason for the instability of the imine-acids could be the presence of the spiro moiety. Consequently, our next approach was the removal of the isopropylidene group from (38), with 80% trifluoroacetic acid to the diol (61) (Scheme 6). Acetylation with acetic anhydride in pyridine afforded a crystalline mono acetate, m.p. 121-122 °C (62a). The p.m.r. of the obtained product was quite different from the expected one. Although the isopropylidene group was no longer present, the spectrum showed only one acetyl group at δ 1.85 ppm. Furthermore, the olefinic proton at δ7.66 ppm was not present. Two protons, H_a, doublet at 5.55 ppm ($J_{a,b}$ = 2.5 Hz) and H_b, dd at 5.16 ppm ($J_{a,b}$ = 2.5 Hz and $J_{b,NH}$ = 8 Hz) appeared, indicating that one of the hydroxyl

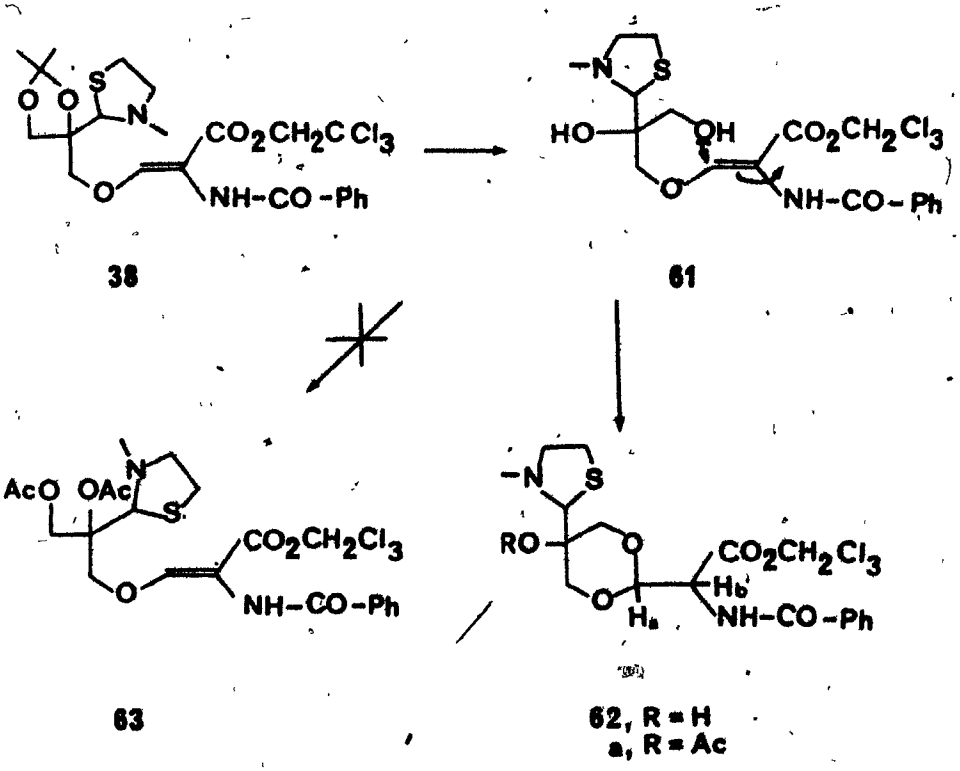
group reacted with the carbon double bond to form a six-membered ring compound (62) (Scheme 6, page 192). The alternative five-membered ring structure could be excluded because it would demand a primary acetate, with δCH_2-OAc at lower field than 5 ppm. The p.m.r. spectrum is shown on page 193 (figure 3).

This discouraging but rather interesting result helped to explain the low yields of imine ester (40), obtained from a mixture of hydrated and free aldehyde (39) with anhydrous ammonia in ether. 39 contained approximately 50-60% of free aldehyde as determined by p.m.r.

The formation of acrylate ester (32) and hippuric acid β,β,β-trichloroethyl ester (65) which were obtained after hydrolysis of the aldehyde protecting group with THF/H_2O and mercuric chloride (see page 189) could now be explained, and probably resulted from the reaction of the hydrated aldehyde (63) via (64) (Scheme 7 ,page 196).

Consideration of the above results caused us to re-investigate the Ugi-reaction with imine acid (40a, see page 171) and cyclohexyl isonitrile. These types of reactions are carried out in the two-phase mixture of water and petroleum ether. The reaction with the isonitrile presumably takes

Scheme 6



38 61

63

62, R = H
a, R = Ac

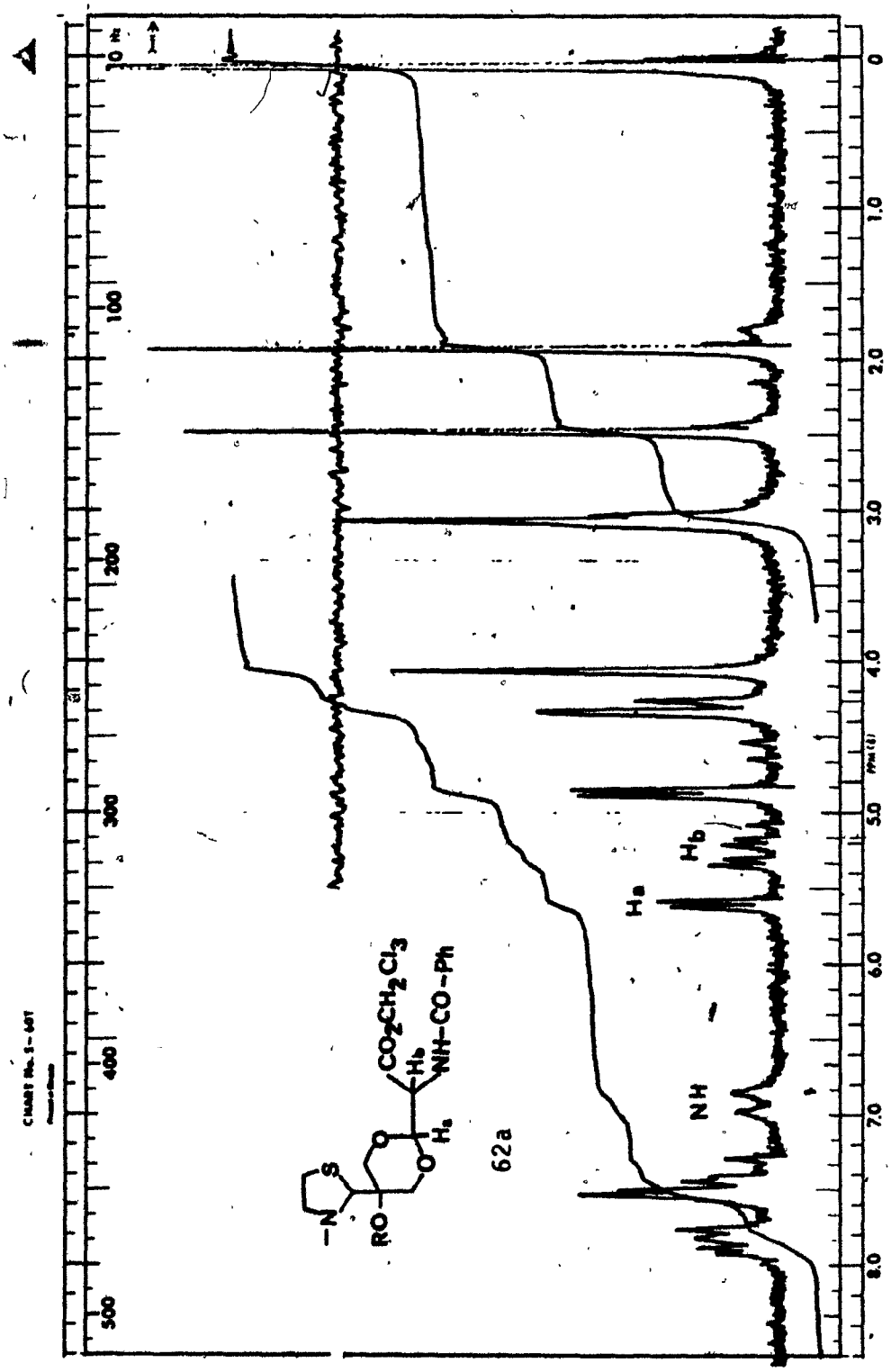

10 Hz
500
400
300
200
100
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
δ (ppm)
$CO_2CH_2Cl_3$
H_b
NH-CO-Ph
H_a
RO
62a
H_a
H_b
NH

FIGURE 3

place in the aqueous phase. If the reaction is carried out in a single organic phase, the formation of resin predominates[16,33]. An earlier attempt to reduce polymerization by variation of petroleum ether/water or tetrahydrofuran/water ratios failed. Since we were unable to isolate the imine acid (40a, page 171) we decided to hydrolyse the β,β,β-trichloroethyl ester of imine (40), with $Zn/H_2O/THF$ in the presence of cyclohexyl isonitrile. Careful workup of the reaction mixture failed to reveal the presence of an oxacephalosporin derivative, but showed a strong peak at 1730 cm^{-1} similar to that of 57 (page 184).

It seems that addition of water to the imine is very rapid and that no imino acid (40) is present in significant concentration

Support for this explanation came from the fact that a small amount of hippuric acid β,β,β-trichloroethyl ester (65) was isolated from the reaction mixture of imine ester (40) with THF/H_2O without zinc dust (Scheme 8, page 197).

In summary, the failure of these approaches can be attributed to three factors, all of which became evident as the results of the above studies:

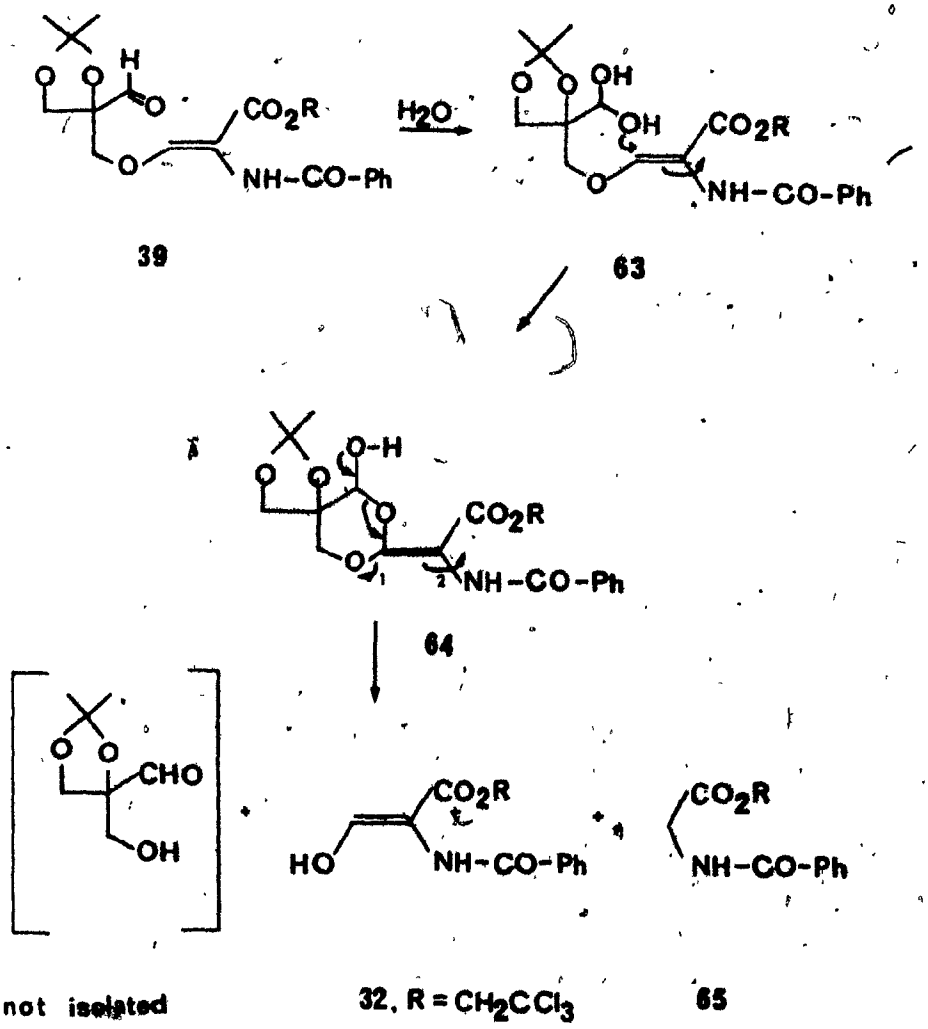
1) Reaction of the imine ester (40) with water;

2) Isomerisation of the imine acid (40a), followed by decarboxylation and

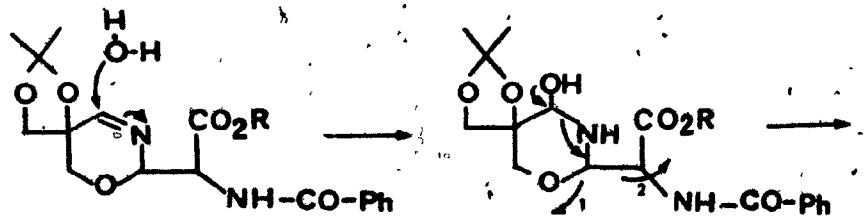
3) Polymerisation of the imine acid (40a) with isonitrile during the Ugi-reaction[33].

Consequently, this scheme had to be abandoned in its present form.

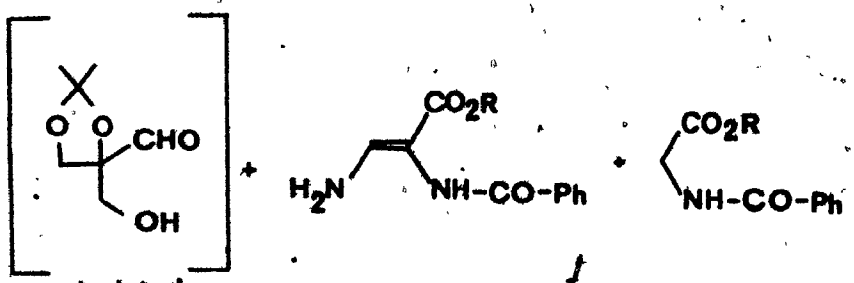
Scheme 7


H
O
CO2R
NH-CO-Ph
H2O
OH
OH
CO2R
NH-CO-Ph
39
63
O-H
CO2R
NH-CO-Ph
64
CHO
OH
CO2R
HO
NH-CO-Ph
CO2R
NH-CO-Ph
not isolated
32, R = CH2CCl3
65

Scheme 8



40



66 , R = CH_2CCl_3 65

Chapter 4

A new mild cleavage of β,β,β-trichloroethyl esters and β,β,β-trichloroethoxycarbonyl groups.

During the course of work described in the foregoing chapters, it became necessary to protect carboxylic acids with a protecting group that could be easily introduced and that could be removed under extremely mild, preferably neutral conditions.

Iodoethyl esters[25,41] fulfill the latter condition, in that these esters can be cleaved with zinc in organic solvents; they are difficult to prepare, however, and particularly unsuitable in cases, where the bromine-iodine exchange interferes with other sensitive functions of the molecule. Furthermore, iodoethanol is physiologically active, and great care has to be exercised when handling it and its derivatives.

β,β,β-Trichloroethyl esters on the other hand are easily prepared by esterification. Their cleavage with zinc dust, however, was believed to proceed only under acidic[3,34,35] conditions or at elevated temperatures[36,37].

We developed a method, by which β,β,β-trichloroethyl esters can be cleaved at room temperatures with zinc dust in aqueous tetrahydrofuran within 10 minutes.

In addition to the complicated imine ester of chapter 3, we studied several examples of carboxylic acids or urethanes. The results are listed in table 1.

Table 1

Acid, phenol or amine	β,β,β-trichloroethyl ester				% Recovery (time required for cleavage)		
	yield %	m.b./b.p.	lit.	Method	pH 4.2	pH 5.5	pH 7.2
(54) Scheme 5, Chapter 3	92	oil	-	see chapter 3	74 (10 min.)	70 (10 min.)	72(10 min.)
Hippuric acid	98	125-126	-	B	76 (10 min.)	83 (10 min.)	66 (10 min)
m. Ansic acid	74	115/20μ	-	A	84 (10 min.)	80 (15 min.)	76 (10 min.)
Cinnamic acid	89	112-115°/15μ		A	83 (10 min.)	75 (10 min.)	77 (30 min).
1-Amino-adamantan	97	122-124°	123-124°	lit.[36]	86 (30 min.)	96 (18 hr.)	96 (18 hrs.)
Estrone	87	139-141°	140-141°	lit.[36]	97 (6 hr.)	12 (24 hr.)	16 (24 hr.)

Several methods for the preparation of β,β,β-trichloroethyl esters have been reported. We used either boron-trifluoride-etherate alcohol[38] (Method A), or refluxing the alcohol in toluene in the presence of p-toluenesulfonic acid[39] (Method B). The urethane and carbonate esters were prepared with excess β,β,β-trichloroethoxycarbonyl chloride in pyridine and stirring for 2 hours at room temperatures[40], or under Schotten Baumann conditions[36].

A successful cleavage was accomplished at room temperature, by dissolving the esters in THF, addition of a several fold molar excess of zinc-dust, followed by a 1 molar KH_2PO_4 (pH 4.2), $KH_2PO_4/NaHPO_4$ (pH 5.5) or ammonium acetate (pH 7.2) solution. The ratio of THF vs. aqueous buffer solution was critical and it is necessary for complete reaction to maintain a homogeneous mixture.

The unmasked products were characterized by i.r., t.l.c., m.p. and m.m.p. .

This work could be extended to the selctive cleavage of trichloroethyl ester in the presence of trichloro urethanes and trichloro carbonate esters, since esters cleave within 10 minutes, whereas urethanes and carbonate esters require considerable more time (see table 1).

The results of Chapter 4, are reported in a forthcoming publication[42].

EXPERIMENTAL

Melting points were determined on an electrothermal block and are corrected.

Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 e.V. using a direct insertion probe. P.m.r. spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard. Doublets, triplets, and quartets in the p.m.r. spectral data were recorded as the center of the peaks and multiplets as their range of absorption. I.r. spectra were obtained on a Perkin-Elmer 267B infrared spectrophotometer.

Analytical thin layer chromatography was performed on silica gel coated plates and on a preparative scale on silica gel (Merck $UV_{254,366}$) coated glass plates.

Microanalyses were carried out by Micro-Tech. Laboratories Inc. and C. Daessle, Montreal.

Mannitol diacetonide (21)

D-Mannitol (182 g) was suspended in a mixture of acetone (1500 ml) and dimethoxypropane (180 g). p-Toluenesulfonic acid (1 g) was added and the suspension was stirred at room temperature for one hour. Unreacted mannitol (90 - 100 g) was filtered off and the filtrate shaken with anhydrous potassium carbonate (50 g) until it was colorless. Potassium carbonate was filtered off and the filtrate evaporated to dryness in vacuo. The semi-solid residue was transferred to an Erlenmeyer flask containing petroleum ether (60 - 80°C) (3500 ml) and heated to boiling with good stirring until almost all the solid had been dissolved. The undissolved material was immediately filtered and the filtrate heated to boiling. The solution was cooled and the product collected by filtration, washed with cold petroleum ether and allowed to dry.

Yield: 30 g, m.p.: 119-121°C. (lit.[19,20] m.p. 119-121°C).

P.m.r. ($CDCl_3$): δ 1.37, 1.42, (each s, 6H, acetonide), 2.70 (broad s, 2H, OH), 3.6-4.25 ppm. (m, 8H).

I.r. (KBr): 3400, 3280, 3000, 2946, 2900, 1427, 1396, 1385, 1374, 1169, 1135, 1078, 1050 cm^{-1}.

2,2-Dimethyl-1,3,7,9-tetraoxaspiro[4.5]10-decanol (23)

Mannitol diacetonide (21) (24 g) was dissolved in a pH 6 buffer solution (400 ml) and sodium periodate (20.4 g) was added. After the mixture was stirred for 30 minutes, 40% formaldehyde (74 ml) and a solution of potassium carbonate (23.1 g) in water (70 ml) were added. The mixture was stirred overnight at room temperature and extracted three times with methylene chloride. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crystalline product was pure enough for further use.

Yield: 28.3 g (81%), m.p.: 89-90°C. (lit.[20] m.p. 89-90°C).

P.m.r. (Acetone-d_6): δ 1.49 (s, 6H, acetonide), 3.9 (ABq, J=10 Hz, 2H, OCH_2), 4.2 (ABq, J=10 Hz, 2H, OCH_2), 4.02-5.97 (broad, 1H, OH), 5.0 (ABq, J=7 Hz, 2H, O-CH_2-O), 5.12 ppm (s, 1H, O-CH-O).

I.r. (KBr): 3405, 3100-2910, 1470, 1396, 1384, 1220, 1162, 1090, 1080 cm^{-1}.

1,2-O-Isopropylidene-2(3'-methylthiazolidine-2'yl)propanetriol (24a)[20].

The dioxan (23) (123.5 g) and N-metylaminoethanethiol (29) (150 g) were dissolved in dry benzene (7.5 *l*) and the mixture heated until benzene distilled slowly. After 5 *l* of benzene had been collected, the remaining benzene was evaporated in vacuo. The residue was twice distilled under high vacuum and the fraction, boiling at 109-111°C/0.02 mmHg was collected.

Yield: 116.0 g (77 %)

P.m.r. ($CDCl_3$): δ 1.47 (s, 6H, acetonide), 2.50, 2.58 (each s, 3H, $N-CH_3$), 2.87-3.23 (m, 4H, $N-CH_2-CH_2-S$), 3.8 (q, J=5Hz, 2H, OCH_2-C), 3.93 (q, 2H, OCH_2), 4.1 (s, 1H, OH), 4.48, 5.57 ppm (each s, 1H, N-CH-S)

I.r. (neat): 3460 (broad, OH), 3000-2800, 1470, 1390, 1379, 1300, 1216, 1071, 1000 cm^{-1}.

Mass spectrum (70 e.V.): m/e = 233 (M^+)

Anal.Calc. for $C_{10}H_{19}NO_3S$: C, 51.49; H, 8.21; N, 6.01; S, 13.72.

Found : C, 51.53; H, 8.17, N, 6.13; S, 13.63.

1,2-O-Isopropylidene-3-O-methanesulfonyl-2(3'-methylthiazolidine-2'yl)propanetriol (25a).

A solution of the thiazolidine alcohol (24a) (116 g) and triethylamine (76 g) in methylene chloride (2 l) was cooled to -78°C in a dry ice/acetone bath and freshly distilled mesyl chloride (63 g = 1.1 equivalent) in methylene chloride (500 ml) was added dropwise over a period of 4 hours. The mixture was poured into water (3 l) and the organic layer washed twice with cold water. The methylene chloride solution was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The oily residue was dissolved in ethyl ether (200 ml) and kept overnight in the refrigerator. The white crystalline product was collected by filtration, washed with cold ethyl ether and dried in vacuo.

Yield: 146 g, (94%), m.p.: 65-66°C.

P.m.r. ($CDCl_3$): δ 1.44 (s, 6H, acetonide), 2.37, 2.42 (each s, N-CH_3), 2.8-3.18 (m, 4H, N-CH_2-CH_2-S), 3.06 (s, 3H, SO_2-CH_3), 3.95 (q, 2H, CH_2-O), 4.20, 4.25 (each s, 1H, S-CH-N), 4.30 ppm (s, 2H, CH_2-OSO_2)

I.r. (KBr): 3030-2810, 1455, 1391, 1380, 1361, 1339, 1300 1252, 1220, 1200, 1180 cm^{-1}.

Anal.Calc. for $C_{11}H_{21}NO_5S_2$: C, 42.45; H, 6.75; N, 4.50; S, 20.58.

Found: C, 42.25; H, 6.59; N, 4.62; S, 20.32.

2,3-O-Isopropylidene-2-hydroxymethyl glyceraldehyde mesylate*.

The thiazolidine mesylate (25a) (311 mg) was dissolved in 80% aqueous acetonitrile or tetrahydrofuran (10 ml) and mercuric chloride (975 mg = 1.2 equiv.) was added. The white milky suspension was refluxed for 30 min. and then filtered. The filtrate was evaporated in vacuo and the residue extracted with methylene chloride. The methylene chloride solution was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness in vacuo, giving a colorless oil.

Yield: 620 mg (87%)

P.m.r. ($CDCl_3$): δ 1.55 (s, 6H, acetonide), 3.10 (s, 3H, SO_2-CH_3), 4.12 (d, J = 3 Hz, 2H, CH_2-O-C), 4.42, s, 2H, SO_2-O-CH_2), 9.60 ppm (s, 1H, H-C=O).

I.r. (neat) : 3475, 2997, 2945, 2900, 1725 (aldehyde).

Anal.Calc. for $C_8H_{14}SO_6$: C, 40.34; H, 5.88; S, 13.46.

Found: C, 40.10; H, 6.11; S, 13.35.

*Model reaction

N-Methylaziridine (28)

A mixture of N-methylethanolamine (27) (150 g) and concentrated sulfuric acid (210 g) was heated slowly to 130°C and water was slowly distilled off. When all the water had been removed, the temperature was raised to 250°C and the mixture cooled immediately. The black solid was dissolved in water (700 ml) and a sodium hydroxide solution (400 g in 500 ml of water) was added. The mixture was slowly distilled with vigorous stirring and 400 ml of distillate consisting of aziridine and water was collected in an ice bath. Potassium hydroxide (100 g) was added in portions to the distillate with cooling, and the separated organic layer collected and distilled. The fraction boiling at 27-31°C (lit.[27] 26-30°C) was collected.

Yield: 45.6 g (40%)

P.m.r. ($CDCl_3$): δ 0.95 and 1.65 (each t, 4H, CH_2-CH_2), 2.27 ppm (s, 3H, N-CH_3)

I.r. ($CHCl_3$) : 3100-2800, 2500, 1670, 1470, 1309, 1100, 995 cm^{-1}.

N-Methylaminoethanethiol (29)

Dry methanol (750 ml) was cooled in a dry ice/acetone bath and saturated with hydrogen sulfide. A solution of N-methylaziridine (28) (160 g) in dry methanol (800 ml) was added dropwise to this mixture with slow bubbling of hydrogen sulfide for 2 hours. The mixture was then brought to room temperature and stirred overnight under dry nitrogen. The methanol was evaporated in vacuo and the resulting white solid was collected by filtration, washed with cold pentane. The product was very hygroscopic, and was kept in the refrigerator under nitrogen.

Yield: 150 g (58%), m.p.: 50-53°C (lit.[28] 48-54°C)

P.m.r. ($CDCl_3$): δ 1.82 (s, 1H, SH), 2.23 (s, 1H, NH), 2.59 (s, 3H, CH_3), 2.46-2.78 ppm (m, 4H, $N-CH_2-CH_2-S$)

I.r. ($CHCl_3$): 3340 (NH), 3060-2800, 2520 (SH), 1680, 1485, 1120 cm^{-1}.

4-Ethoxymethylene-2-phenyl-5-oxazolone (31)

Hippuric acid (360 g) and triethyl orthoformate (300 g) were heated for one hour under reflux with acetic anhydride (400 g), (bath temp. = 140-150°C). Low boiling material was then removed at reduced pressure. The dark red residue solidified on cooling. Treatment of the solid with charcoal and recrystallization from petroleum ether (60 - 80°) gave pink needles.

Yield: 195 g (45%) m.p. 95-97° (lit.[29] 97-98°C).

P.m.r. ($CDCl_3$): δ 1.47 (t, J = 7 Hz, 3H, CH_3), 4.46 (q, J = 7 Hz, 2H, CH_2), 7.40 (s, 1H, C=CH), 7.45-8.20 ppm (m, 5H, phenyl).

I.r. (KBr) : 1785 C=O, 1673 cm^{-1} (C=N).

4-Hydroxymethylene-2-phenyl-5-oxazolone (31a)

4-Ethoxymethylene-2-phenyl-5-oxazolone (31) (195 g, 0.9 mole) was suspended in 18 ℓ of a 0.1 N sodium hydroxide solution and stirred vigorously until everything dissolved. The reddish solution was filtered, and the filtrate acidified with cold dilute hydrochloric acid. The precipitate was immediately collected by filtration, and dried at r.t. in vacuo.

Yield: 125 g (67%), m.p.: 142-144° (lit.[30] 152°C).

P.m.r. (DMSO-d_6): δ 7.50-8.10 (m, 6H, phenyl, C=CH), 10.10 ppm (s, 1H, OH).

I.r. (KBr): 3500 (broad), 1795 (oxazolone), 1613, 1585, 1500, 1380, 1300, 1118 cm^{-1}.

β,β,β-Trichloroethyl 2-benzamido-3-hydroxy-acrylate (32).

4-Hydroxymethylene-2-phenyl-5-oxazolone (31a) (69.3 g, 0.365 mole) was suspended in dry benzene (3.5 l) and β,β,β-trichloroethanol (109 g, 0.73 mole) was added. The suspension was stirred under reflux for 6 hours and the clear solution evaporated. The oily residue was triturated with petroleum ether (30-60°C) and kept overnight in the refrigerator. The red solid was collected by filtration and recrystallized from petroleum ether (60-80°C). Treatment with charcoal gave pink needles.

Yield: 95 g, (76.6%), m.p. 87-88°C.

P.m.r. ($CDCl_3$): δ 4.98 (s, 2H, CH_2-CCl_3), 7.57-8.15 (m, 6H, phenyl and C=CH), 8.6 (broad, 1H, NH), 12.7 ppm (broad, 1H, OH).

I.r. (KBr): 3380, 1725 (ester), 1665 (amide and C=C), 1615, 1554, 1505, 1463, 1390, 1357, 1325, 1312, 1280, 1268, 1240, 1162, 1115 cm^{-1}.

Analysis: Calc. for $C_{12}H_{10}NO_4Cl_3$: C, 42.57; H, 2.98; N, 4.14; Cl, 31.61. Found: C, 42.83; H, 2.74; N, 4.27; Cl, 31.29.

β,β,β-Trichloroethyl 2-benzamido-3-hydroxy-acrylate sodium salt (32a).

β,β,β-Trichloroethyl 2-benzamido-3-hydroxyacrylate (32) (91 g, 0.27 mole) was added to an ethanolic solution of sodium ethoxide (4.6 g of sodium in 200 ml of ethanol). The mixture was shaken for 10 minutes and ethyl ether (1 Liter) added. The precipitated sodium salt was collected by filtration, washed several times with ethyl ether and dried in vacuo.

Yield: 70 g (72%), m.p. 200-202°C (decomp.)

P.m.r. (DMSO-d_6): δ 4.74 (s, 2H, CH_2-CCl_3), 7.3-8.1 (m, 5H, phenyl), 8.42 (s, 1H, NH), 9.12 ppm (s, 1H, C=CH).

I.r. (KBr): 3300(broad, salt), 3070, 2960, 1675, 1640, 1592, 1540, 1500, 1373, 1287, 1160 cm^{-1}.

Anal. Calc. for $C_{12}H_9NO_4Cl_3Na$:

C, 39.87; H, 2.52; N, 3.89; Cl, 29.50.

Found : C, 39.90; H, 2.63; N, 4.13; Cl, 29.74.

β,β,β-Trichloroethyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (38).

The sodium salt (32a) (70 g, 0.195 mole) was suspended in a solution of the thiazolidine mesylate (25a) (40 g, 0.130 mole) in dry 2-butanone (1ℓ) and the mixture stirred at 80-85°C (bath temperature) for 12 hours. The salt was filtered off and the filtrate evaporated. The red residue was dissolved in ethyl ether (50 ml), treated with charcoal, filtered and evaporated. The yellow oil was further purified by passing through a silica gel column using benzene/ethyl acetate (9:1) as eluent. Evaporation of the solvent gave colorless crystals. On recrystallization from ether, a pure sample was obtained.

Yield: 48.8 g, (68.5%), m.p.: 126-128°C.

P.m.r. ($CDCl_3$): δ 1.35, 1.46 (each s, 6H, acetonide), 2.37)s, 3H, N-CH_3), 2.8-3.2 (m, 4H, N-CH_2-CH_2-S), 3.93 (q, J = 10 Hz, 2H, OCH_2), 4.24 (s, 2H, OCH_2), 4.46 (s, 1H, N-CH-S), 4.84 (s, 2H, CH_2-CCl_3), 7.33-8.0 ppm (m, 7H, phenyl, NH and C=CH).

I.r. (CCl_4): 2990-2800, 1730 (ester), 1698 (amide), 1660 (C=C), 1503, 1480, 1381, 1369, 1210 cm^{-1}.

Mass spectrum (70 e.V.): m/e = 554 (M^+).

Anal. Calc. for $C_{22}H_{27}N_2O_6SCl_3$:
C, 47.71; H, 4.91; N, 5.06; S, 5.79; Cl, 19.20.
Found: C, 47.99; H, 5.10; N, 5.26; S, 5.50; Cl, 19.41.

β,β,β-Trichloroethyl 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (39).

Mercuric chloride (9.7 g, 35 mmole), was added to a solution of the thiazolidine ester (38) (19.8 g, 35 mmole), in tetrahydrofuran (200 ml) and water (20 ml); the resulting suspension was stirred for 5 minutes (t.l.c. benzene/ethyl acetate showed absence of thiazolidine ester). The reaction mixture was filtered and the filtrate evaporated. The residue was chromatographed on silicic acid, first eluted with benzene/ether (9:1), to remove all the mercuric salts, then with benzene/ether (1:1). The main fraction containing the aldehyde ester was concentrated to give a yellowish foamy solid. Yield: 13.5 g, (77%).

P.m.r. ($CDCl_3$): δ 1.39, 1.45 (6H, each s, acetonide), 4.10, 4.25 (4H, each s, two CH_2O), 4.80 (2H, s, CH_2CCl_3), 7.2-7.9 (m, 7H, phenyl, NH, C=CH), 9.63 ppm (s, 1H,CHO).

I.r. (KBr): 3340 (broad, NH, hydrated form), 1730 (ester, aldehyde), 1650 (amide), 1600 (phenyl), 1380, 1370 cm^{-1} (gem-dimethyl).

Mass spectrum (70 e.V.): m/e 481 [M^+, (Cl^{37})], 479 [M^+ Cl^{35}], 466 [$M^+(Cl^{37})-CH_3$], 464 [$M^+(Cl^{35})-CH_3$].

Anal.Calc.for $C_{19}H_{20}NO_7Cl_3$: C, 47.47; H, 4.19; N, 2.90; Cl, 22.12.

Found: C, 47.20; H, 4.26; N, 3.15; Cl, 21.98.

α-Benzamido-2,2-dimethyl-1,3,7-trioxa-9-aza(spiro)[4.5] dec-9-ene-8-acetic acid β,β,β-trichloroethyl ester (40).

A solution of the aldehyde ester (39) (15.2 g, 33 mmole) in ether (250 ml) was treated at room temperature with anhydrous ammonia for one minute (pH ∿8). After standing for 30 minutes, the ether was evaporated and the residue chromatographed on silicic acid using ether/benzene (1:1) as eluent. The product first eluted was identified as the imine ester (40). Yield: 10.0 g, (66.2%), m.p.: 157-159°C.

P.m.r. ($CDCl_3$): δ 1.42 (s, 6H, acetonide), 3.80 (q, 2H, CH_2O), 4.06 (t, 2H, CH_2O), 4.82 (q, 2H, $CH_2.CCl_3$), 5.43-5.62 (m, 2H, CO-CH-NH, N-CH-O), 6.77 (d, J = 9 Hz, 1H, NH), 7.3-7.9 ppm (m, 6H, phenyl, CH=N).

I.r. (KBr): 3280 (NH), 3060, 2960, 2870 (CH), 1760 (ester), 1650 (amide), 1600 (aromatic C-H), 1378 cm^{-1} (gem-dimethyl).

Mass spectrum (70 e.V.): m/e 478 [$M^+(Cl^{35})$], 480 [$M^+(Cl^{37})$], 464, 463 (M^+-CH_3), 422, 420 (M^+-acetone).

Anal.Calc. for $C_{19}H_{21}N_2O_6Cl_3$:

C, 47.57; H, 4.41; N, 5.84; Cl, 22.17.

Found: C, 47.46; H, 4.61; N, 6.02; Cl, 22.24.

Attempted preparations of the oxacepham derivative (41a).

Imine ester (40) (958 mg, 2.0 mmole) was dissolved in tetrahydrofuran (10 ml) and cyclohexyl isonitrile[33] (655 mg, 6 mmole) added with stirring*. After 10 minutes zinc dust (2 g) and a 1 molar phosphate buffer** solution (2 ml) was added***, the mixture stirred at room temperature for 24 h. Water was added and the product extracted with ether. The ether layer was dried over sodium sulfate and concentrated to a light yellow oil, which was subjected to careful chromatography on silicic acid using ether/benzene (1:1) as eluent. Every fraction was analysed for the presence of the oxacepham derivative by infrared (β-lactam) and mass spectrometry (m/e 457).

* in some experiments, the isonitrile was added 5, 10 and 30 minutes after removal of the zinc.

** KH_2PO_4, pH 4.2; KH_2PO_4/Na_2HPO_4, pH 5.5; Ammonium acetate, pH 7.2 .

*** in other experiments, EDTA (2.5 mmole) was added after the zinc was filtered off.

p-Methoxybenzyl 2-benzamido-3-hydroxy-acrylate (42)

4-Hydroxymethylene-2-phenyl-5-oxazolone (31a) (18.9 g, 0.1 mole) was suspended in benzene (400 ml) and p-methoxybenzyl alcohol (15.2 g, 0.11 mole) was added. The mixture was refluxed for 16 hours, evaporated and the residue recrystallized from benzene/petroleum ether.

Yield: 24.2 g (74%) m.p. 101-102°C.

P.m.r. ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.20 (s, 2H, O-CH_2), 7.15 (q, 4H, p-subst.phenyl), 7.4-8.0 (m, 6H, phenyl; CH=C), 8.50, (s, 1H, NHCO), 12.32 ppm (d, J = 12 Hz, 1H, OH).

I.r. (KBr) : 3335 (OH), 1688, 1650, 1600, 1540, 1510, 1388 cm^{-1}.

Mass spectrum (70 e.V.): m/e 327 (M^+), 310 (M^+-OH).

Anal.Calc. for $C_{18}H_{17}NO_5$ (327.3): C, 66.05; H, 5.24; N, 4.28.
Found : C, 66.10; H, 5.33; N, 4.25.

p-Methoxybenzyl 2-benzamido-3-hydroxyacrylate sodium salt (42a)

p-Methoxybenzyl 2-benzamido-3-hydroxyacrylate (42), (23 g, 0.07 mole), was suspended in ethanol (200 ml) and an ethanolic solution of sodium ethoxide (1.55 g, 0.075 mole of sodium) was added with vigorous stirring. The suspension dissolved immediately and the sodium salt precipitated. Ethyl ether (200 ml) was added and the white salt collected by filtration, washed with ether and dried in vacuo.

Yield: 22 g (90%), m.p. 225-226°C.

I.r. (KBr): 3400, 3200, 1635, 1600, 1555, 1515, 1485, 1460, 1400, 1358, 1310 cm^{-1}.

Mass spectrum (70 e.V.): m/e 349 (M^+), 300, 243, and 228 ($M^+ - CH_2 - p\text{-}OMeC_6H_4$).

Anal.Calc. for $C_{18}H_{16}NO_5Na$ (349.33): C, 61.88; H, 4.61; N, 4.00.

Found : C, 61.46; H, 4.54; N, 4.11.

p-Methoxybenzyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan 4-yl) methyl)oxy)acrylate (43).

The sodium salt (42a) (22g, 0.063 mole) was suspended in a solution of the thiazolidine mesylate (25a) (12 g, 0.0386 mole) in 2-butanone (300 ml) and the mixture refluxed for 16 hours. The salt was filtered off and the filtrate evaporated in vacuo. The residue was chromatographed on a silica gel column, eluted with chloroform/methanol (98:2). Evaporation of the solvent gave a colorless oil.

Yield: 20 g (95%).

P.m.r. ($CDCl_3$): δ 1.35, 1.42 (each s, 6H acetonide), 2.28, 2.38 (each s, 3H, N-CH_3), 2.8-3.1 (m, 4H, N-CH_2-CH_2-S), 3.80 (s, 3H, OCH_3), 3.8-4.2 (m, 4H, 2CH_2-O), 4.39, 4.49 (each s, 1H, N-CH-S), 5.18 (2H, CH_2), 7.20 (q, 4H, p-methoxyphenyl), 7.29-7.92, ppm (m, 7H, phenyl, NH, C=CH).

I.r. ($CHCl_3$): 3420 (NH), 2980 (CH), 1670 (ester, 1368, 1378 cm^{-1} (gem-dimethyl).

Anal.Calc.for $C_{28}H_{34}N_2O_7S \times \frac{1}{2}H_2O$:

C, 60.96; H, 6.39; N, 5.07; S, 5.81

Found: C, 60.59; H, 6.14; N, 4.95; S, 6.05.

p-Methoxybenzyl 2-benzamido-3-((4'formyl-2', 2'-dimethyl-1',3'-dioxolan-4'-yl)methoxy)acrylate (44).

The thiazolidine ester (43), (20 g, 0.037 mole) was dissolved in acetonitrile (240 ml) and water (60 ml). Mercuric chloride (12 g, 0.0445 mole) was added to this solution. The immediately formed milky suspension was refluxed for 30 min. The fine precipitate was filtered and the filtrate evaporated. The residue was extracted twice with methylene chloride, the extracts were washed with dilute hydrochloric acid and water and dried. After evaporation of the solvent, the residue was passed through a silica gel column using ether as eluent.

Yield: 14.5 g (84%) oily residue.

P.m.r. ($CDCl_3$): δ 1.38, 1.40 (each s, 6H, acetonide), 3.80 (s, 3H, OCH_3), 3.95-4.30 (m, 2H), 4.10, 4.21 (each s, 2H), 5.15 (s, 2H, CH_2-O), 7.10 (q, 4H, p-OCH_3-phenyl), 7.3-7.9 (m, 7H, phenyl, C=CH, NH), 9.70 ppm (s, 1H, CHO).

I.r. ($CHCl_3$): 3410 (NH), 2980 (CH_2), 1700 (ester), 1670 (CO), 1608 (phenyl), 1370 cm^{-1} (gem.dimethyl).

Mass spectrum (70 e.V.): m/e = 469 (M^+).

Analysis calc. for $C_{25}H_{27}NO_8xH_2O$: C, 61.59; H, 6.00; N, 2.87.

Found : C, 60.99; H, 5.99; N, 2.91.

α-Benzamido-2.2-dimethyl-1,3,7-trioxa-9-aza(spiro)[4,5]dec-9-ene-8-acetic acid p-methoxybenzyl ester (45) and by-product (46).

The aldehyde ester (44) (14 g, 0.03 mole) was dissolved in dry tetrahydrofuran (75 ml) and 1.1 equivalents of gaseous ammonia in tetrahydrofuran were added. The mixture was kept at room temperature overnight, and then evaporated in vacuo. The residue was chromatographed on a silica gel column using ether as eluent.

The first product eluted was crystallized from ether-petroleum ether and its spectral data indicated it to be the required product (45).

Yield: 3.0 g (22%), m.p.: 114-117°C.

P.m.r. ($CDCl_3$): δ 1.40 (s, 6H, acetonide), 3.62, 3.75 (each s, 2H, CH_2O), 3.80 (s, 3H, OCH_3), 3.92-4.10 (m, 2H, OCH_2), 5.18 (s, 2H, CH_2-O), 5.3-5.5 (m, 2H), 6.95 (s, 1H, NH), 7.10 (q, 4H, p-methoxyphenyl), 7.4-7.9 ppm (m, 6H, phenyl, C=CH).

I.r. (KBr): 3408 (NH), 2983, 2937, 2865 (CH), 1745 (ester), 1659 (amide), 1611 (phenyl), 1578, 1514, 1484, 1379, 1372 cm^{-1}.

Mass spectrum (70 e.V.): 468 (M^+), 453 (M^+-CH_3), 410 ($M^+-(CH_3)_2CO$), 347 (M^+-CH_2-p'-methoxyphenyl), 303 ($M^+-COOCH_2$-p-methoxyphenyl).

Analysis calc. for $C_{25}H_{28}N_2O_7 \times \frac{1}{2}H_2O$: C, 62.88; H, 6.12; N, 5.86. Found: C, 62.38; H, 6.12; N, 5.42.

The second fraction eluted gave (46) as a colorless oil.

Yield: 2.3 g (15%).

P.m.r. ($CDCl_3$): δ 1.20 (t, J = 7 Hz, 3H, $\underline{CH_3}$-CH_2), 1.28 (s, 6H, acetonide), 2.80 (t, J = 6 Hz, 1H, OH), 3.32 (q, J = 7 Hz, 2H, $\underline{CH_2}$-CH_3), 3.67 (d, J = 6 Hz, 2H, $\underline{CH_2}$-OH), 3.77 (s, 3H, OCH_3), 3.6-3.8 (m, 1H, CH-N=), 4.00 (d, 2H, CH_2O), 4.48 (d, J = 9 Hz, 1H, N-CH-CO), 5.12 (s, 2H, CH_2-phenyl), 6.7-8.0 ppm (m, 11H, phenyl, p-methoxyphenyl, NH, N=CH).

I.r. ($CHCl_3$): 3390 (OH), 2970 (CH_2), 1650 (ester, amide) 1370/1380 cm^{-1} (gem.dimethyl).

U.V. (EtOH): max. λ 231, 279 n.m.

Mass spectrum (70 e.V.): m/e 514 (M^+), 499 (M^+-CH_3), 484 (M^+-CH_2=O), 469 (M^+-OEt), 468 (M^+-EtOH).

Analysis calc. for $C_{27}H_{34}N_2O_8$: C, 63.02; H, 6.66; N, 5.44. Found: C, 62.92; H, 6.68; N, 5.32.

Treatment of α-Benzamide-2,2-dimethyl-1,3,7-trioxa-9-aza (spiro)[4,5] dec-9-ene-8-acetic acid p-methoxybenzyl ester with methanol: (46a).

An excess of methanol (1 ml) was added to a solution of the imine-p-methoxybenzyl ester (45) (468 mg, 1 mmole), in 50 ml of methylene chloride. The reaction mixture was stirred at room temperature for 3 hours. Evaporation of the solvent and purification by chromatography on silicic acid using ether as eluent gave 422 mg (84%) of (46a).

P.m.r. ($CDCl_3$): δ 1.37 (s, 6H, acetonide), 2.42 (t, J = 6 Hz, 1H, OH), 3.42 (s, 3H, OCH_3) 3.70 (d, J = 6 Hz, 2H, CH_2O), 3.80 (s, 3H, OCH_3), 3.7-3.9 (m, 1H, C-CH-NH), 4.00 (m, 2H, OCH_2), 4.35 (d, 1H, N-CH-O), 5.14 (s, 2H, CH_2-p-methoxy), 6.8-8.0 ppm. (m, 11H, phenyl, p-methoxy-phenyl, NH).

I.r. ($CHCl_3$): 3390 (OH), 2970 (CH_2), 1650 (ester, amide, C=N), 1370, 1380 cm^{-1} (gem-dimethyl).

U.V. (EtOH): max. λ 231, 279 nm.

Mass spectrum (70 e.V.): m/e 500 (M^+), 485 (M^+-CH_3), 468 (M^+-CH_3OH), 453 (468-CH_3).

Analysis calc. for $C_{26}H_{32}N_2O_8 \times \frac{1}{2}H_2O$: C, 61.28; H, 6.52; N, 5.49. Found : C, 61.50; H, 6.44; N, 5.52.

Benzyl 2-phthalimido-3-hydroxyacrylate (48)

The procedure of Sheehan and Johnson[23] was followed, and the white crystals recrystallized from ethanol-water.

Yield: 42% m.p. 130-131°C (lit.[23] 137-138°C).

P.m.r. (DMSO-d_6): δ 5.17 (s, 2H, CH_2), 7.34 (s, 5H, phenyl), 7.90 (s, 4H, phthalimido), 8.03 (s, 1H, C=CH), 8.5-9.5 ppm (broad, 1H, OH).

I.r. (KBr): 3240, 1800, 1730 (phthalimido), 1730 (ester), 1680 cm^{-1} (C=C).

Benzyl 2-phthalimido-3-hydroxyacrylate sodium salt (48a).

Benzyl 2-phthalimido-3-hydroxyacrylate (48), (12.8 g, 0.04 mole), was suspended in ethanol (25 ml) and an ethanolic solution of sodium ethoxide (from 0.88 g of sodium) was added with vigorous stirring. The suspension dissolved immediately and the sodium salt was precipitated by the addition of ether. The product was collected by filtration, washed with ether and dried in vacuo.

Yield: 13.0 g (94%), m.p. 200°C dec.

P.m.r. (DMSO-d_6): δ 5.06 (s, 2H, CH_2), 7.37 (s, 7H, phenyl, phthalimido), 7.80 (s, 2H, phthalimido), 8.80 ppm (s, 1H, CH=C).

I.r. (KBr): 3400, 1710 (ester), 1650 (amide), 1560 (C-O), 1400 (gem-dimethyl).

Benzyl 2-phthalimido-3-(((2',2'-dimethyl-4'-(3"-methyl-thiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy) acrylate (49)

The sodium salt (48a) (13 g, 0.038 mole) was suspended in a solution of the thiazolidine mesylate (25a) (7.8 g, 0.025 mole) in 2-butanone (300 ml) and the mixture refluxed for 16 hours. The salt was filtered off and the filtrate evaporated in vacuo. The residue was chromatographed on a silica gel column using chloroform/methanol (98:2) as eluent. Evaporation of the solvent gave white crystals.

Yield: 12.0 g (89%), m.p. 143-145°C.

P.m.r. ($CDCl_3$): δ 1.28, 1.37 (each s, 6H, acetonide), 2.25, 2.35 (each s, 3H, $N-CH_3$), 2.8-3.12 (m, 4H, $N-CH_2-CH_2-S$), 3.6-4.37 (m, 5H, two OCH_2 and N-CH-S), 5.1 (s, 2H, CH_2), 7.23 (s, 5H, $CH_2-C_6H_5$), 7.52-8.0 ppm (m, 5H, phthalimido and C=CH).

I.r. (KBr): 1785/1725 (phthalimido), 1700 (ester), 1658 (C=C), 1465, 1450, 1442, 1410, 1380, 1367 cm^{-1}.

Mass spectrum (70 e.V.): m/e = 538 (M^+)

Anal.Calc.for $C_{28}H_{30}N_2O_7S$: C, 62.44; H, 5.62; N, 5.20; S, 5.94.

Found: C, 62.59; H, 5.51; N, 5.40; S, 6.02.

Benzyl 2-phthalimido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (50).

The thiazolidine ester (49) (8.6 g, 0.016 mole) was dissolved in tetrahydrofuran/water (4:1) (100 ml) and mercuric chloride (1.2 g) was added. The immediately formed milky suspension was stirred at room temperature for 1 hour. The fine suspension was filtered off and the filtrate evaporated. The residue was extracted three times with benzene and the combined extracts were washed with dilute hydrochloric acid and water, and dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crude product was passed through a silica gel column using methylene chloride/ether (9:1) as eluent. Evaporation of the solvent gave a white foamy solid.

Yield: 6.7 g (90 %).

P.m.r. ($CDCl_3$): δ 1.38 (s, 6H, acetonide), 3.9-4.0 (m, 2H, OCH_2), 4.20 (m, 2H, OCH_2), 5.10 (s, 2H, $C\underline{H}_2$-C_6H_5), 7.34 (s, 5H, phenyl), 7.6-8.1 (m, 5H, phthalimido,=C-H), 9.73 ppm (s, 1H, CHO).

I.r. (KBr): 3480, 3072-2900, 1800/1735 (phthalimido), 1735 (ester), 1720 (aldehyde), 1665 (amide and C=C), 1430, 1395, 1382, 1290, 1100 cm^{-1}.

Mass spectrum (70 e.V.): m/e = 465 (M^+).

Analysis calc. for $C_{25}H_{23}NO_8$: C, 64.51; H, 4.98; N, 3.01.

Found: C, 64.34; H, 5.01; N, 3.25.

α-Phthalimido-2,2-dimethyl-10-hydroxy-1,3,7-trioxa-9-aza (spiro)[4,5]decane-8-acetic acid benzyl ester (51) and imine (52).

The aldehyde ester (50) (6.0 g, 0.013 mole) was dissolved in benzene (50 ml) and refluxed for 30 minutes using a Dean Stark trap. The solvent was concentrated and the residue dissolved in anhydrous ether (50 ml). Ammonia was passed through the clear solution for 5 min. at room temperature. Then it was kept overnight. White crystals (51) were colleted by filtration.

Yield: 2.5 g (40%), m.p. 108-110°C.

P.m.r. (DMSO-d_6): δ 1.34 (s, 6H acetonide), 3.33-4.00 (m, 5H, two OCH_2, OH), 4.28 (broad s, 1H, C<u>H</u>-NH), 4.95-5.40 (m, 2H, CH-CH), 5.17 (s, 2H, CH_2-phenyl), 5.95 (d, 1H, J = 4 Hz, NH), 7.28 (s, 5H, phenyl), 7.88 ppm (s, 4H, phthalimido).

I.r. (KBr): 3450, 3330, 3270 (NH, OH), 1780, 1720 (phthalimido), 1740 (ester), 1470,1450, 1380 cm^{-1}.

Mass-spectrum (70 e.V.): 464 (M^+-H_2O), 449 (464-CH_3), 421 (449-CO), 406 (421-CH_3/or 464- $(CH_3)_2CO$).

Anal.Calc.for $C_{25}H_{26}N_2O_8$ (482.5): C, 62.23; H, 5.43; N, 5.80.
Found : C, 62.44; H, 5.45; N, 5.81.

The filtrate was chromatographed on a silica gel column using methylene chloride / ether (95:5) as eluent. Evaporation of the major product gave a colorless oil, identified as the imine (52).

Yield: 2.0 g (33%).

P.m.r. ($CDCl_3$): δ 1.40 (s, 6H, acetonide), 3.4-4.3 (m, 4H, two OCH_2), 4.97 (d, 1H, N-CH-COO), 5.21 (s, 2H, CH_2-phenyl), 5.70 (dd, 1H, N-CH-O), 7.30 (s, 5H, phenyl), 7.6-8.0 ppm (m, 5H, phthalimido and N=CH).

I.r. (KBr): 3500, 3995-2880, 1800,1730 (phthalimido), 1760 (ester), 1660 (amide and C=N).

Mass spectrum (70 e.V.): m/e 464 (M^+).

Analysis calc. for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.21; N, 6.03.

Found: C, 64.43; H, 5.31; N, 6.18.

2,2-Dimethyl-8-phthalimidomethyl-1,3,7-trioxa-9-aza-spiro [4.5]decane (53).

The carbinolamine ester (51) or (52, 464 mg, 1 mmole) (482 mg, 1 mmole) was suspended in 25 ml of ethyl acetate and added to 240 mg of palladium on charcoal (10%) in 25 ml of ethyl acetate, previously prehydrogenated with hydrogen. The mixture was hydrogenated at atmospheric pressure, until 24 ml of hydrogen were consumed (6 hours). The catalyst was filtered off and the filtrate evaporated to dryness. Addition of ether gave white crystals, recrystallized once from ethyl acetate/ether. 191 mg (50%) m.p.: 151-153°C.

P.m.r. ($CDCl_3$): δ 1.37 (s, 6H, acetonide), 1.90 (broad s, 1H NH), 2.98 (s, 2H, CH_2), 3.45-3.90 (m, 4H, two CH_2), 4.05 (d, 2H, CH_2O), 4.35 (dd, 1H, N-CH-O), 7.6-8.0 ppm (m,4H, phthalimido).

I.r. (KBr): 3200 (NH), 2980-2860 (CH), 1770, 1705 (phthalimido, amide), 1610 (phenyl), 1460, 1430, 1400 cm^{-1}.

Mass spectrum (70 e.V.): m/e 333 (M^++1), 317 (M^+-CH_3).

Analysis calc. for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43.

Found : C, 61.67; H, 6.04; N, 8.19.

2-Benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1'-3'-dioxolan-4'-yl)methyl)oxy)acrylic acid (54).

Zinc dust (2 g) was added at room temperature to a stirred solution of thiazolidine ester (38) (1.0 g, 1.8 mmole) in tetrahydrofuran (10 ml) and a 1 molar potassium dihydrogen phosphate solution pH 4.2 (2 ml). The acid liberation was followed by t.l.c. (benzene-EtOAc 9:1). After 15 minutes the mixture was filtered and the tetrahydrofuran was evaporated. The residue was diluted with water (100 ml) and extracted with ether. The organic solution was dried over sodium sulfate, and evaporated in vacuo to give 580 mg (74%) of pure thiazolidine acid (54), m.p.: 159-160°C.

P.m.r. ($CDCl_3$): δ 1.40 (s, 6H, acetonide), 2.31, 2.40 (each s, 3H, N-CH_3), 2.90-3.10 (m, 4H, N-CH_2-CH_2-S), 3.65-4.48 (m, 5H, two OCH_2 and N-CH-S), 7.30-7.90 (m, 7H, phenyl, NH and C=CH), 10.23 ppm (s, 1H, COOH).

I.r. (KBr): 3250 (broad), 2980, 2940 (CH_2), 1650 (broad, amide), 1575, 1510, 1380 cm^{-1}.

Mass spectrum (70 e.V.): m/e 422 (M^+).

Anal. Calc. for $C_{20}H_{26}N_2O_6S$:

C, 56.86; H, 6.20; N, 6.63; S, 7.58.

Found: C, 56.75; H, 6.42; N, 6.45; S, 7.79.

2-Benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)oxy)acrylic acid (55).

The thiazolidine acid (54) (844 mg, 2 mmole), was dissolved in tetrahydrofuran/water (9:1) (10 ml) and mercuric chloride was added. The immediately formed precipitate was stirred for 30 minutes. The solid was filtered off and the filtrate was dried over sodium sulfate. Filtration and evaporation of the solvent gave a white solid.

Yield: 650 mg (93%), m.p. 55-58°C. (50% hydrated form).

P.m.r. ($CDCl_3$): δ 1.43 (s, 6H, acetonide), 3.6-4.2 (m, 4H, two CH_2-O), 5.05 (½ H, 50% hydrated aldehyde) 6.95 (1H, COOH), 7.5-7.9 (m, 7H, phenyl, NH, C=CH), 9.80 ppm (½ H, CH=O).

I.r. ($CHCl_3$): 3410 (OH), 2970, 2870 (CH_2), 1670 (CO), 1600 (phenyl), 1372, 1380 (gem.dimethyl).

Mass spectrum (70 e.V.): 349 (M^+), 334 (M^+-CH_3), 305 (M^+-CO_2) 290 (305 $-CH_3$), 273 ($M^+-C_6H_6$), 244 ($M^+-C_6H_5CO$).

Microanalysis was not performed because of instability.

2,2-Dimethyl-9-benzamido-1,3,7,11-tetraoxaspiro[4.7]- dodec-8-ene-10-one-12-carboxycyclohexylamide (57).

The thiazolidine acid (54) (844 mg, 2 mmole), was dissolved in tetrahydrofuran/water (9:1) (10 ml) and mercuric chloride was added. The reaction mixture was stirred at room temperature for 30 minutes. The solid was filtered off and ammonium hydroxide (1.5 mmole) was added. The pH was adjusted to 6.5 by adding phosphate buffer (2 ml). Cyclohexyl isonitrile (655 mg, 6 mmole) was added and the two phases mixed with vigorous stirring for 20 hours. The reaction mixture was diluted with water (100 ml) and the aqueous phase extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was washed with petroleum ether to remove the unreacted isonitrile. The residue was purified by chromatography on silica gel using chloroform/methanol (9:1) as eluent, to give 316 mg (36%) of white crystals, m.p.: 254-256°C.

P.m.r. (DMSO-d_6): δ 1.32, 1.40 (each s, 6H, acetonide), 1.0-1.9 (broad m, 10H, cyclohexane), 3.20 (s, 1H, CH-N), 4.1-4.4 (m, 4H, two CH_2O), 5.00 (s, 1H, CH-O), 7.45-8.00 ppm (m, 8H, phenyl, 2 NH, CH=C).

I.r. (KBr): 3330, 2280 (NH), 2925, 2850 (CH_2), 1732 (lactone), 1637 (amide), 1600 (phenyl), 1370, 1380 cm^{-1} (gem-dimethyl).

Mass spectrum (70 e.V.): 458 (M^+), 443-CH_3), 400 (M^+-$(CH_3)_2CO$). 383 (M^+-$(CH_3)_2C(OH)H$, H transfer), 360 (M^+-C_6H_6N).

Anal. Calc. for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.60; N, 6.11.

Found : C, 62.21; H, 6.84; N, 5.94.

t-Butyldimethylsilyl 2-benzamido-3-(((2',2'-dimethyl-4'-(3"-methylthiazolidine-2"-yl)-1',3'-dioxolan-4'-yl)methyl)oxy)acrylate (59).

The thiazolidine acid (54) (3.0 g, 7.1 mmole), tert-butyldimethyl-chlorosilane (1.6 g, 10.7 mmole) and imidazole (1.2 g, 17.7 mmole) were dissolved in dry dimethylformamide (10 ml); the mixture was stirred for 24 hours at room temperature. The reaction mixture was poured into chloroform (100 ml) and the resulting solution washed with sodium bicarbonate solution and water. The chloroform solution was dried over anhydrous sodium sulfate, filtered and the solvent evaporated. The residue was chromatographed on silicic acid (500 g), and the fraction containing the silyl ester was concentrated and dried in vacuo, to leave a colorless oil.

Yield: 1.4 g (22%).

P.m.r. ($CHCl_3$): δ 0.0 (s, 6H, CH_3-Si-CH_3), 0.82 (d, 3H, CH_3), 1.2-1.5 (m, 12H, acetonide, two CH_3), 2.24, 2.34 (each s, 3H, NCH_3), 2.7-3.1 (m, 4H, N-CH_2-CH_2-S), 3.6-4.2 (m, 4H, two OCH_2), 4.33 (d, 1H, N-CH-S), 7.2-7.9 ppm (m, 7H, phenyl, NH and C=CH).

I.r.: 3400, 3060-2800, 1730-1660 (intense broad peaks, ester, amide and C=C), 1518, 1486, 1385, 1370, 1310, 1226, 1145 cm^{-1}.

Anal. Calc. for $C_{26}H_{40}N_2O_6SSi \times \frac{1}{2}H_2O$: C, 57.22; H, 7.57; N, 5.13.
Found : C, 57.50; H, 6.96; N, 5.47.

β,β,β-Trichloroethyl α-benzamido-5-acetoxy-5-(3'-methyl-thiazolidine-2'yl)-1,3-dioxacyclohex-2-yl-acetic acid (62a).

Thiazolidine ester (38) (2.2 g, 4 mmole) was added at room temperature to a solution of trifluoroacetic acid (8 ml) and water (2 ml) and the mixture subsequently evaporated to dryness. The residue was neutralized with 2N sodium bicarbonate and extracted with chloroform and the extracts dried over sodium sulfate. Solvent removal left an oil which was treated with a mixture of acetic anhydride (5 ml) and pyridine (5 ml) overnight. Purification on a silica gel column, eluting with chloroform/methanol gave 1.3 g, (59%) of a colorless oil. The product was crystallized from ether, m.p. 117-119°C.

I.r. (KBr): 3392 (NH), 1770, 1740 (ester), 1655 (amide), 1522 cm^{-1}.

P.m.r. ($CDCl_3$): δ 1.85 (s, 3H, OCH_3), 2.40 (s, 3H, NCH_3), 3.00 (s, 4H, N-CH_2-CH_2-S), 4.00 (s, 2H, OCH_2), 4.20 (s, 1H, N-CH-S), 4.27 (s, 2H, CH_2O), 4.80 (d, 2H, CH_2CCl_3), 5.16 (dd, J = 2 Hz, J = 4 Hz, 1H, C-CH-N), 5.54 (d, J = 2 Hz, 1H, O-CH-O), 6.85 (d, J = 8 Hz, 1H, NH), 7.2-7.9 ppm (m, 5H, phenyl).

Mass spectrum (70 e.V.): m/e 556/554 (Cl^{37}/Cl^{35}), 541/539 (M-CH_3), 497/495 (M^+-$OCOCH_3$), 407 (M -OCH_2CCl_3), 379 (M^+ - $COOCH_2CCl_3$).

Anal.Calc.for $C_{21}H_{25}Cl_3N_2O_7S$: C, 45.37; H, 4.53; Cl, 19.13; N, 5.03.
Found : C, 45.38; H, 4.49; Cl, 19.32; N, 5.01.

Hippuric acid β,β,β-trichloroethylester (65).

A solution of 17.9 g (0.1 mole) of hippuric acid, (30 g, 0.2 mole) of β,β,β-trichloroethanol, and 500 mg p-toluenesulfonic acid in 150 ml of toluene was stirred and refluxed using a Dean Stark trap, for 20 hours. After cooling, 150 ml of a 1N sodium bicarbonate solution was added. The organic phase was separated and dried over sodium sulfate, concentrated under reduced pressure, and crystallized from chloroform/ether to yield 30.5 g (98%), m.p.: 125-126°C.

I.r. (KBr): 3300 (NH), 1770 (ester), 1640 (CO), 1600 (phenyl), 1545 cm^{-1}.

P.m.r. (DMSO-d_6): δ 4.22 (d, J = 6 Hz, 2H, CH_2), 4.95 (s, 2H, CH_2CCl_3), 7.4-8.0 (m, 5H, phenyl), 9.05 ppm (t, J = 6 Hz, 1H, NH).

Anal.Calc. for $C_{11}H_{10}Cl_3NO_3$: C, 42.54; H, 3.24; N, 4.51; Cl, 34.24.

Found: C, 42.76; H, 3.21; N, 4.59; Cl, 34.38.

N-(β,β,β-Trichloroethoxycarbonyl)-adamantanamine[36].

1-Adamamtanamine (1 g, 6.5 mmole) was dissolved in pyridine (20 ml), cooled in ice, and 2.2.2-trichloroethoxycarbonyl chloride (2.74 g, 13 mmole) was added with stirring. After 2 hours, the solution was diluted with water and then acidified with 2N hydrochloric acid and extracted with ether. The ether extract was dried (Na_2SO_4), and the solvent evaporated. The TrOC-adamantanamine crystallized from ether/light petroleum as needles (2.0 g, 97%), m.p.: 122-124°C, lit.[36] 123-124°C.

I.r. (KBr): 3270, 3140 (NH), 2900, 2823 (CH), 1710 cm^{-1} (CO).

P.m.r. ($CDCl_3$): δ 1.66-2.10 (m, 17H, CH_2, CH), 4.66 ppm (s, 2H, CH_2CCl_3).

m-Methoxybenzoic acid β,β,β-trichloroethyl ester.

A solution of 7.6 g (0.05 mole) of m-methoxybenzoic acid, 7.1 g (0.1 mole) of boron trifluoride-etherate, and 30.0 g (0.2 mole) of β,β,β-trichloroethanol was stirred and heated to 150° for 2 hours. After cooling, 200 ml of water was added, and the resulting mixture extracted with three 100 ml portions of ether. The combined ethereal phases were washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, concentrated under reduced pressure, and distilled to yield 10.5 g (74%), bp. 115° (0.02 mm Hg).

I.r. (film): 3000, 2950, 2835 (CH), 1730 (CO), 1600 (benzene ring), 1482, 1450, 1430 (CH), 1365 cm^{-1} (CH_3).

P.m.r. ($CDCl_3$): δ 3.86 (s, 3H, CH_3), 4.95 (s, 2H, CH_2CCl_3), 7.0-7.8 ppm (m, 4H, phenyl).

Anal.calc.for $C_{10}H_9Cl_3O_3$: C, 42.35; H, 3.19; Cl, 37.51.

Found : C, 42.29; H, 3.43; Cl, 36.98.

trans-Cinnamic acid β,β,β-trichloroethyl ester.

A solution of 7.4 g (0.05 mole) of trans-cinnamic acid, 7.1 g (0.1 mole) of boron trifluoride - etherate, and 30.0 g (0.2 mole) of β,β,β-trichloroethanol was stirred and heated to 150° for 3 hours. After cooling, 200 ml of water was added, and the resulting mixture was extracted with three 100 ml portions of ether. The combined ethereal phases were washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, concentrated under reduced pressure, and distilled to yield 12 g (89%), bp 112° (0.012 mm Hg).

I.r. (film): 3060, 3025, 2945 (CH), 1725 (CO), 1630 (C=C), 1575 (phenyl), 1450 cm^{-1} (CH).

P.m.r. ($CDCl_3$): δ 4.86 (s, 2H, CH_2CCl_3), 6.47 (d, J = 16 Hz, 1H, CH=CH), 7.2-7.6 (m, 5H, aromatic), 7.80 ppm (d, J = 16 Hz, 1H, CH=CH).

Anal.Calc. for $C_{11}H_9Cl_3O_2$: C, 47.25; H, 3.24; Cl, 38.04.

Found : C, 47.23; H, 3.31; Cl, 37.93.

3-(β,β,β-Trichloroethoxycarbonyl)-estrone[36].

β,β,β-Trichloroethoxycarbonyl chloride (2.74 g, 13 mmole) was added to a stirred mixture of 20 ml of pyridine and 1g (3.7 mmole) estrone. The reaction was stirred at 20° for 2 hours. Then water was added, followed by acidification with hydrochloric acid and extracted with ether. The ether extract was dried with sodium sulfate and evaporated to dryness. The ester was crystallized from ether to yield 1.40 g, (87%), m.p.: 139-141°C, lit.[36] 140-141°C.

I.r. (KBr): 2940, 2880, 2830 (CH), 1760 (ester), 1735 (CO), 1605 cm^{-1} (phenyl).

P.m.r. ($CDCl_3$): δ 0.90 (s, 3H, CH_3), 1.4-3.1 (m, 15H, CH, CH_2), 4.83 (s, 2H, CH_2-CCl_3), 6.87-7.37 ppm (m, 3H, aromatic).

General Procedure for the removal of the β,β,β-trichloroethoxy group.

2 g of the trichloroethyl ester was stirred for the time indicated in table 1, chapter 4, in 10 ml tetrahydrofuran with 2 g zinc dust and 2 ml of a 1 molar buffer* solution. Zinc was filtered off, and the filtrate was stirred with Rexyn 101 (H) for 5 minutes. The ion exchange resin was filtered off and the filtrate concentrated, addition of ether gave the unmasked acid or phenol**.

* KH_2PO_4 (pH 4.2) or a mixture of KH_2PO_4 with Na_2HPO_4 up to pH 6.5 or ammonium acetate (pH 7.2) was used.

** A slight modification of the work-up procedure permitted the isolation of the amines.

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