MODEL REACTION FOR A
SYNTHESIS OF STREPTAMINE

by

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PREFACE

This thesis consists of two independent parts. Part I, which is the major part and is that to which the title refers, was undertaken in order to explore a new synthetic approach to aminocyclitols. Aminocyclitols are hydroxylated aminocyclohexanes. Many of them occur in nature as components of important antibiotics, streptamine being the best-known example. In the Introduction, a review of the naturally occurring aminocyclitols is followed by an outline of the general methods presently available for their chemical synthesis. It is then proposed that a reaction between ammonia and derivatives of nitrocyclohexane might offer a novel synthetic route into the field, and the history of pertinent interactions of ammonia and aliphatic nitro compounds is reviewed. The research work originating from this principle led the synthesis of a model compound of streptamine and to a first step in a new synthesis of streptamine itself.

The investigations described in Part II of this thesis were actually carried out prior to those of the main part. The intention was to contribute to the chemistry of compounds related to β-nitrostyrene and 2-nitroindanone, the specific goal at the outset being the synthesis of methyl 2-(2-nitrovinyl) benzoate. Unfortunately, the author at an early stage of the work developed a severe allergy apparently caused by some chemical, so that a radical change of field was advised. The results obtained up to this point, however fragmentary, are recorded in order to facilitate an eventual continuation of the project.

ACKNOWLEDGMENTS

I wish to express my sincere thanks to my research supervisor, Prof. Hans H. Baer, for his stimulating guidance, precious instructions and especially, his patience throughout the course of this research work and preparation of this thesis. I also wish to acknowledge the general scientific training which I received in the Department of Chemistry.

I am very much obliged to my father, whose encouragement has initiated my study in Canada. To Mr. K. S. Ong, I extend my deepest gratitude for moral support and constant assistance.

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Part I

trans,*trans*-1,3-Diacetamido-2-nitrocyclohexane (IV) was prepared from *trans*,*trans*-1,3-diacetoxy-2-nitrocyclohexane (II) by reaction with ammonia followed by acetylation. The configuration of IV was determined by studies of the n.m.r. spectra of two derivatives, *trans*,*trans*-2-amino-1,3-diacetamidocyclohexane (V) and *trans*,*trans*-1,2,3-triacetamidocyclohexane (VI). Permanganate oxidation of compound IV gave 2,6-diacetamidocyclohexanone (VII), whose 2,4-dinitrophenylhydrazone (VIII) was also prepared. The ketone VII was reduced by sodium borohydride and yielded *trans*,*trans*-2,6-diacetamidocyclohexanol (IX), whose configuration was confirmed by its n.m.r. spectrum and by that of its derivative, *trans*,*trans*-2,6-diacetamidocyclohexanol acetate (XI). The Clemmensen reduction of compound VII was investigated as a possible route to 1,3-diacetamidocyclohexane (XII). Action of ammonia followed by N-acetylation converted deoxynitro-*scyllo*-inositol pentaacetate (XIII) into 1,3-diacetamido-2-deoxy-2-nitro-*scyllo*-inositol (XIV).

Part II

3-Phthalidylnitromethane (XIII) was allowed to react with triethylamine in anhydrous methylene chloride to give 2-(2-nitrovinyl) benzoate ion (XIV) as suggested by the ultraviolet spectrum. Upon subsequent addition of diazomethane two products were isolated, neither of which had retained the nitro group and only one of which contained methoxyl. Possible molecular formulas for these products are discussed.

PART I

INTRODUCTION

I. Actinomycetes Antibiotics and Carbohydrates

Antibiotics are metabolic products of microorganisms which possess the capacity, in low concentration, of inhibiting the growth of other microorganisms. They are elaborated mainly by actinomycetes, fungi, and bacteria, although substances exhibiting antibiotic properties are also produced by some lichens, algae, insects, and higher plants. Certain antibiotics derived from the first three categories have attained extraordinary success during the past two decades as therapeutic agents: penicillin, streptomycin, and terramycin are well-known examples.

In addition to their medical importance, antibiotics are of great interest to organic chemistry - few areas of the natural products field have confronted chemists with equally novel, varied, and complex problems of structural elucidation and synthesis.

Until now, more than 600 antibiotics have been characterized and the largest number of them are produced by Actinomycetes, a large group of hardy microorganisms that occur widely in soils, air, dust, or associated with plants. It has been suggested that the Actinomycetes group be divided into four genera: Actinomyces, Nocardia, Micromonospora, and Streptomyces (1,2).

Many important antibiotics, especially from Streptomyces and Actinomyces species, became known to contain carbohydrate moieties; in fact, a considerable number are made up entirely of carbohydrate components (3). For the most part these carbohydrate components, which include branched-chain sugars, amino sugars, and aminocyclitols, had not been previously encountered elsewhere in nature or synthesized in the laboratory. Although great progress has been made during the past twenty years in the determination of structure and in the synthesis of antibiotics carbohydrates, work in these areas continues to be of urgency as many gaps still persist and as new antibiotics of potential usefulness are continually being discovered. The present thesis was intended to make a contribution to the chemistry of aminocyclitols. As a background for the experimental work undertaken, some chemical aspects of aminocyclitols relating to Actinomycetes antibiotics will be reviewed in the following sections.

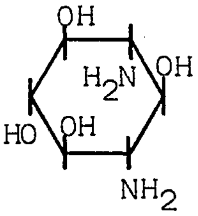
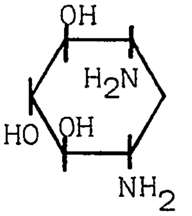
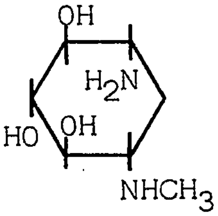
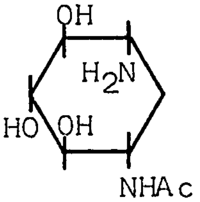
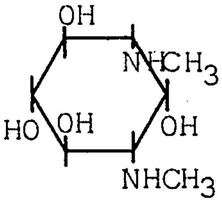
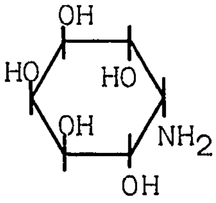
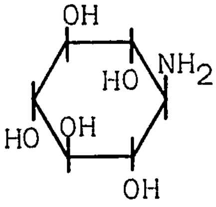
II. Aminocyclitols as Component of Actinomycetes Antibiotics

The aminocyclitols that have been found in Actinomycetes antibiotics are listed in Table I.

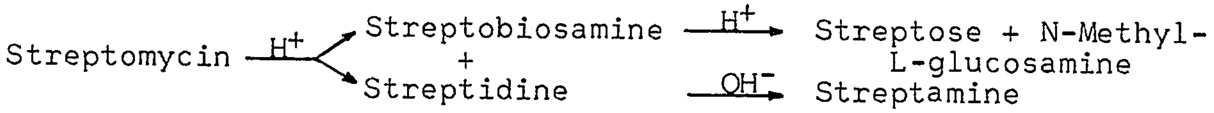
A. Streptamine

Streptamine was first obtained by the degradation of streptomycin. This important antibiotic was isolated in 1944 by Waksman and his co-workers (4) from cultures of

Table I Aminocyclitols Found in Actinomycetes Antibiotics

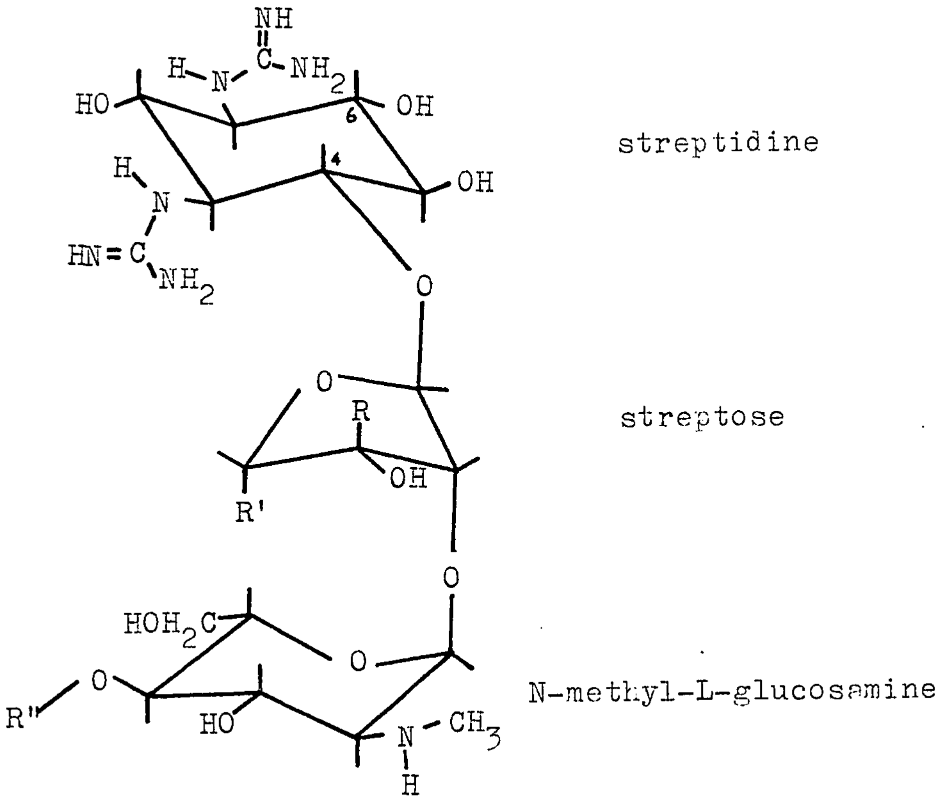
Aminocyclitols	Structure	Antibiotics	Ref.
Streptamine		Streptomycin	Fig. 1
		Hydroxystreptomycin	Fig. 1
		Mannosidostreptomycin	Fig. 1
		Dihydrostreptomycin	Fig. 1
		Zygomycin B	(16)
2-Deoxystreptamine		Neomycins	Fig. 2
		Paromomycins	Fig. 2
		Kanamycins	Fig. 3
		Gentamycins C_1 and C_2	(54)
Hyosamine		Hygromycin B	Fig. 4
Mono-N-acetyl-2-deoxystreptamine		Neomycins LP_B and LP_C	Fig. 5
Actinamine		Actinospectatine	Fig. 6
neo-Inosamine-2		Hygromycin	Fig. 7
scyllo-Inosamine		Bluensomycin	Fig. 8

Streptomyces griseus. It is fairly sensitive to the action of mineral acid which causes hydrolysis to two nitrogenous fragments, streptidine and streptobiosamine. Under more vigorous conditions, streptobiosamine is hydrolyzed to streptose (5) and an amino sugar (6). Studies on streptidine (7,8) revealed that it was converted by alkaline hydrolysis into streptamine, a new base.



The structure of streptidine and streptamine were finally established as 1,3-diguanidino- and 1,3-diaminotetrahydroxycyclohexane (7,9,10). In 1950, Wolfrom and associates (11) achieved the first synthesis of streptamine, and they suggested that the molecule has the *scyllo* configuration. This configuration was confirmed by Wintersteiner and Klingsberg (12). They subjected tetra-O-acetyl-N,N'-dicarbobenzoxystreptamine to catalytic hydrogenation and obtained a tri-O-acetyl-N-acetyl-streptamine, which was then deaminated and hydrolyzed to a known compound, *myo*-inosamine-4(6). The n.m.r. spectrum of N,N'-tetramethylstreptamine was later interpreted by Slomp and MacKellar (13) who found it to be in agreement with the accepted stereochemistry.

The complete structure of streptomycin is given in Fig. 1. However, one stereochemical detail still awaits settlement: the absolute configuration of the substituted



	R	R'	R"
Streptomycin	CHO	CH_3	H
Dihydrostreptomycin	CH_2OH	CH_3	H
Hydroxystreptomycin	CHO	CH_2OH	H
Mannosidostreptomycin	CHO	CH_3	$C_6H_{11}O_5$ (*)

(*) α-D-mannopyranosyl

Fig.1. Streptomycins

streptamine molecule, i.e. the question of the attachment of streptose to C-4 or C-6, has not yet been decided (14).

Three additional Streptomyces metabolites which are closely related to streptomycin and contain the streptidine moiety have been isolated. These are hydroxystreptomycin, dihydrostreptomycin, and mannosidostreptomycin (Fig. 1) (15).

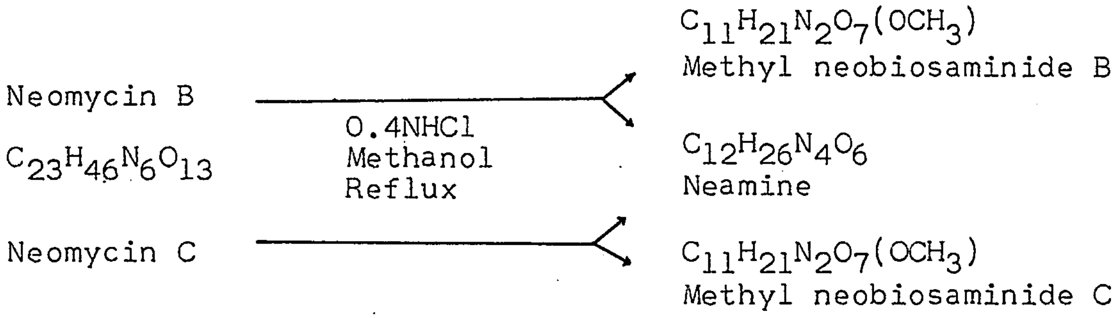
Another antibiotic reported to contain the guanidino group, zygomycin B, has been noted as a second component of the zygomycins (16).

B. 2-Deoxystreptamine

a. In the Neomycins

Neomycin constitutes a group of antibiotics produced by *Streptomyces fradiae* (17). From crude neomycin, three different substances (A, B, C) have been separated (18,19). The compound originally described as neomycin A (20) was subsequently recognized as a fragment of both neomycin B and neomycin C, rather than a genuine metabolite (21,22).

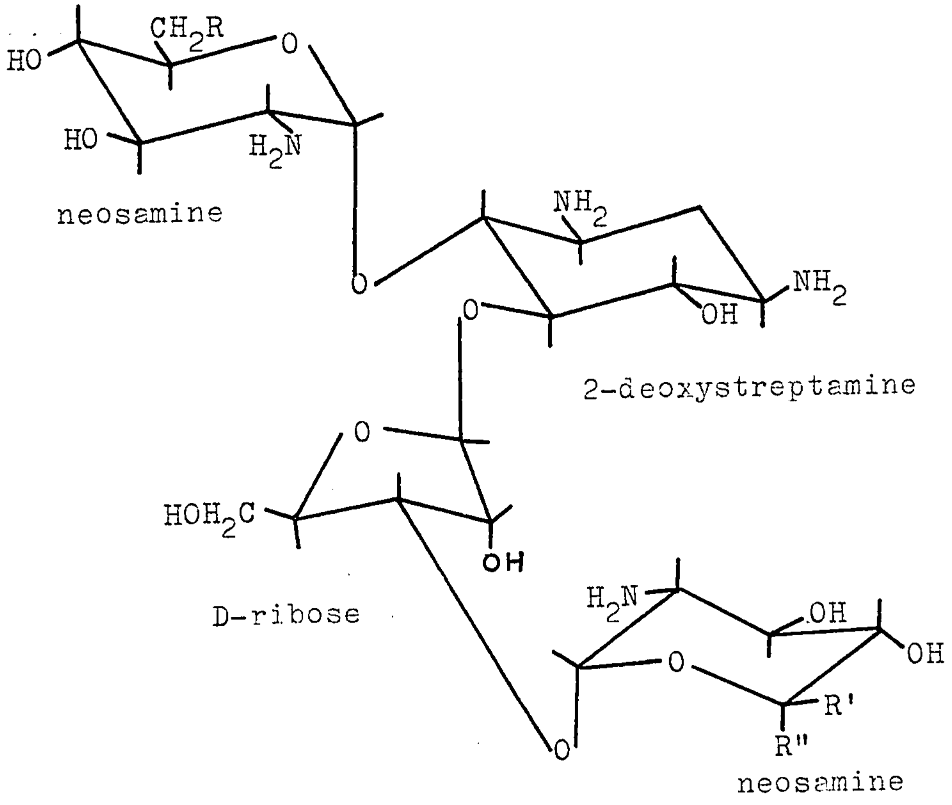
On mild methanolysis, the neomycins are cleaved to give two fragments, neamine and the methyl glycoside of neobiosamine (18).



By strong acid hydrolysis neamine is cleaved into two fragments. One is 2,6-diamino-2,6-dideoxy-D-glucose (neosamine) (23) and the other, an optically inactive base (24). This base was deduced by degradation to be a 1,3-diamino-4,5,6-cyclohexanetriol (2-deoxystreptamine). Its all-trans configuration was confirmed in 1963 by Lemieux and Cushly (25), who studied the n.m.r. spectrum of 5-O-methyl-1,3-di-N-methyl-4,6-di-O-acetyl-2-deoxystreptamine. Recently, 2-deoxystreptamine was synthesized by Nakajima et al.(26).

The structures of the neomycins were elucidated chiefly by Rinehart (15,27,28,29). They are the first carbohydrate antibiotics to be known in complete stereochemical detail.

Neomycin C (Fig. 2) is composed of two 2,6-diamino-2,6-dideoxy-D-glucose molecules, D-ribose, and 2-deoxystreptamine. In neomycin B (Fig. 2), a molecule of 2,6-diamino-2,6-dideoxy-L-idose is substituted for the diamino glucose in neobiosamine C. The two antibiotics are, therefore, identical except for an opposite configuration at a single



	R	R'	R"
Neomycin C	NH_2	CH_2NH_2	H
Neomycin B	NH_2	H	CH_2NH_2
Paromomycin II	OH	CH_2NH_2	H
Paromomycin I	OH	H	CH_2NH_2

Fig.2. Neomycins and Paromomycins

asymmetric center - the C-5 position of the neosamine moiety of neobiosamine.

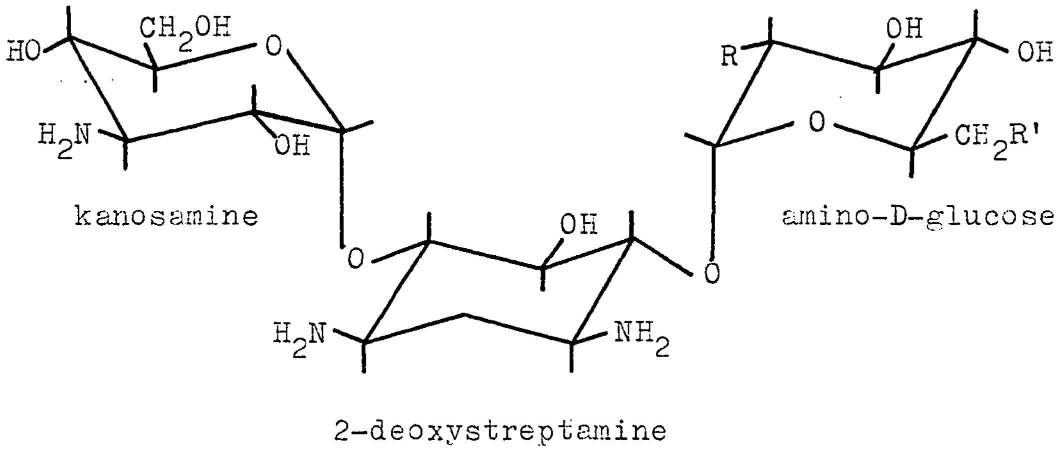
b. In the Paromomycins

Paromomycin, which was obtained in 1956 by Frohardt et al. (30) from culture filtrates of a strain of streptomyces, contains two isomers, the paromomycins I and II (31,32). The two compounds are a pair of epimers like the neomycins B and C, and they differ from these only in the substitution of a hydroxyl for an amino group as shown in Fig. 2 (29,33,34,35).

c. In the Kanamycins

Umezawa et al. (36) isolated kanamycin from cultures of Streptomyces kanamyceticus in 1957. It was later separated into two components, kanamycin A and B (37). A closely related substance, kanamycin C, was recently isolated and studied (38,39).

The gross structure of kanamycin A was largely elucidated by Lemieux and associates at the University of Ottawa and in collaboration with Bristol Laboratories (40) and, independently, by Umezawa et al. in Japan (41). It contains 2-deoxystreptamine (42), 3-amino-3-deoxy-D-glucose (kanosamine) (43), and 6-amino-6-deoxy-D-glucose (44). The detailed structure was determined (45) to be that shown in Fig. 3.



	R	R'
Kanamycin A	OH	NH_2
Kanamycin B	NH_2	NH_2
Kanamycin C	NH_2	OH

Fig.3. Kanamycins

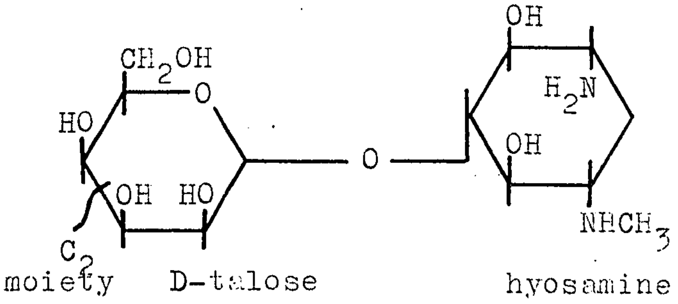


Fig.4. Hygromycin B

Kanamycin C (Fig. 3) (35,45) also contains deoxystreptamine and kanosamine, but 2-amino-2-deoxy-D-glucose instead of the 6-amino isomer, while kanamycin B has been shown to contain deoxystreptamine, kanosamine, and 2,6-diamino-2,6-dideoxy-D-glucose (37,46) (Fig. 3).

d. In the Gentamycins C_1 and C_2

In 1963, the gentamycin complex was isolated from micromonospora species (47). The two isomers, gentamycin C_1 and C_2, gave deoxystreptamine on acid hydrolysis, but otherwise they appeared to belong to a group distinctly separate from the members of the deoxystreptamine family listed above.

e. Derivatives of 2-deoxystreptamine

i. Hyosamine in Hygromycin B

Hygromycin B, an antibiotic produced by *Streptomyces hygroscopicus*, yielded on hydrolysis, in addition to the rare sugar D-talose and an unidentified C_2 moiety, a base named hyosamine (Fig. 4). Hyosamine is N-methyl-2-deoxystreptamine (48) and was synthesized recently (49).

ii. Neomycins LP_B and LP_C

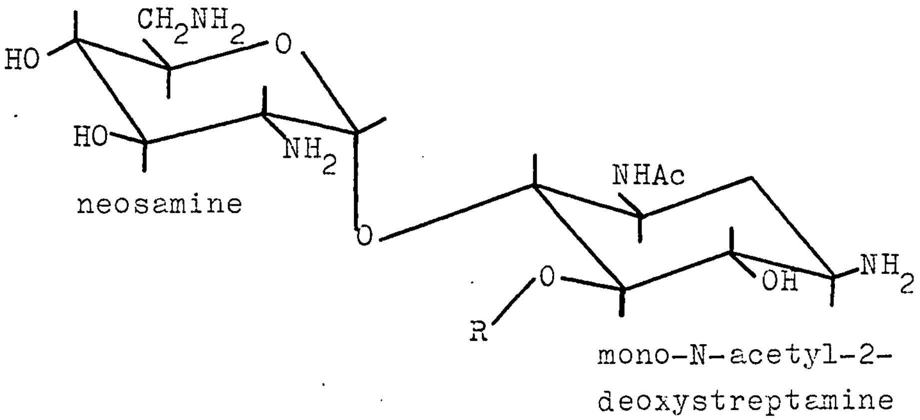
These two neomycins (34,50) were isolated from cultures of *Streptomyces fradiae*. They are the mono-N-acetylated neomycins B and C, carrying the acetyl group on the deoxystreptamine moiety adjacent to the glycosidic link to 2,6-diaminoglucose (Fig. 5).

C. <u>Actinamine in Actinospectatine</u>

Actinospectatine is an antibiotic that is produced by the actinomycete, <u>Streptomyces spectabilis</u>. On acid hydrolysis the antibiotic yielded a base, actinamine, which from chemical studies (25,51) and n.m.r. evidence (52) was found to be 1,3-deoxy-1,3-bis-methylamino-<u>myo</u>-inositol (Fig. 6). Its synthesis has also been reported (53,54). The complete structure assigned to actinospectatine (55) is shown in Fig. 6.

D. <u>neo-Inosamine-2 in Hygromycin</u>

Hygromycin is an antibiotic produced by <u>Streptomyces hygroscopicus</u>. Its main structural features were established by Mann and Woolf (56) (Fig. 7). On acid hydrolysis it gave an inosamine which was present also in another antibiotic, provisionally designated 1703-18B (57). This inosamine was determined to possess the <u>neo</u> configuration, which has also been confirmed by synthesis (58).



	R
Neomycin LP_B	neobiosamine B
Neomycin LP_C	neobiosamine C

Fig.5. Neomycins LP_B and LP_C

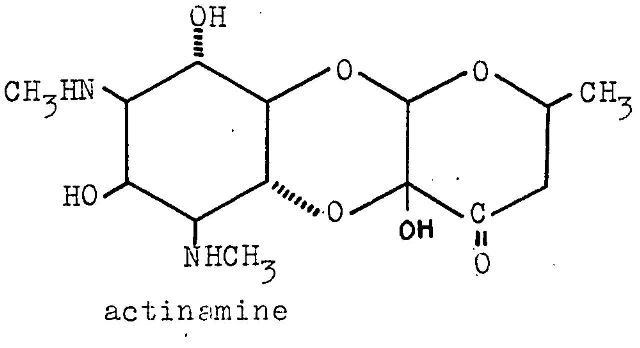


Fig.6. Actinospectatine

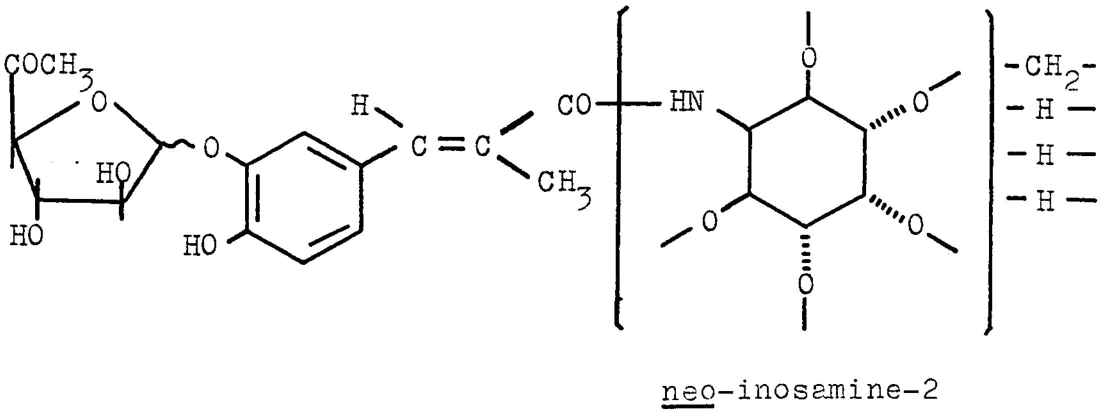
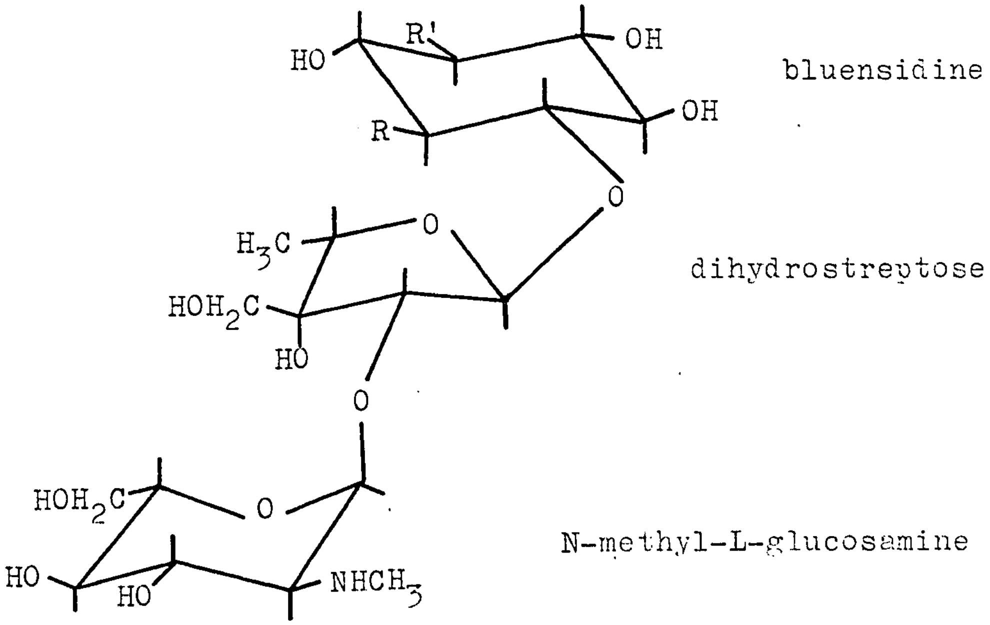


Fig.7. Hygromycin



$R=NH-\underset{\underset{NH}{\|}}{C}-NH_2$, $R'=OCONH_2$ or vice versa

Fig.8. Bluensomycin

E. scyllo-Inosamine in Bluensomycin

The antibiotic bluensomycin, whose structure had been established by Bannister and Argoudelis (59) in 1963 and by Rinehart in 1965 (14) (Fig. 8), represents a bridge between the streptomycin-type antibiotics and those containing an inosamine residue. It is very similar to a streptomycin: it contains dihydrostreptobiosamine (with dihydrostreptose and N-methyl-L-glucosamine), but instead of streptidine as the third component a different base is present. This base, bluensidine, is 1-guanidino-3-O-carbamoyl-*scyllo*-inositol. Bluensidine is converted to *scyllo*-inosamine by alkaline hydrolysis.

III. General Methods for the Synthesis of Aminocyclitols

Aminocyclitols have been synthesized by the following methods:

A. Hydrogenation of inosose phenylhydrazones or oximes.
B. Hydrogenation of nitrocyclitols.
C. Action of ammonia on bromocyclitols.
D. Action of ammonia on anhydrocyclitols.
E. Hydrogenation of aromatic derivatives.
F. Hydrogenation of azidocyclitols.

A. Hydrogenation of inosose phenylhydrazones or oximes

Inososes are pentahydroxycyclohexanones. The carbon-nitrogen double bond of their phenylhydrazones or oximes undergoes hydrogenation, either catalytic or with sodium amalgam, to give the amine function. The orientation of the amino group introduced in this way is, in general, the same as that of the hydroxyl group formed by hydrogenation under the same conditions of the starting inosose. This orientation is essentially axial when catalytic hydrogenation is employed. With sodium amalgam (60), on the other hand, a mixture of axial and equatorial epimers is usually obtained, with the latter predominating.

a. myo-Inosamine-2 and scyllo-Inosamine

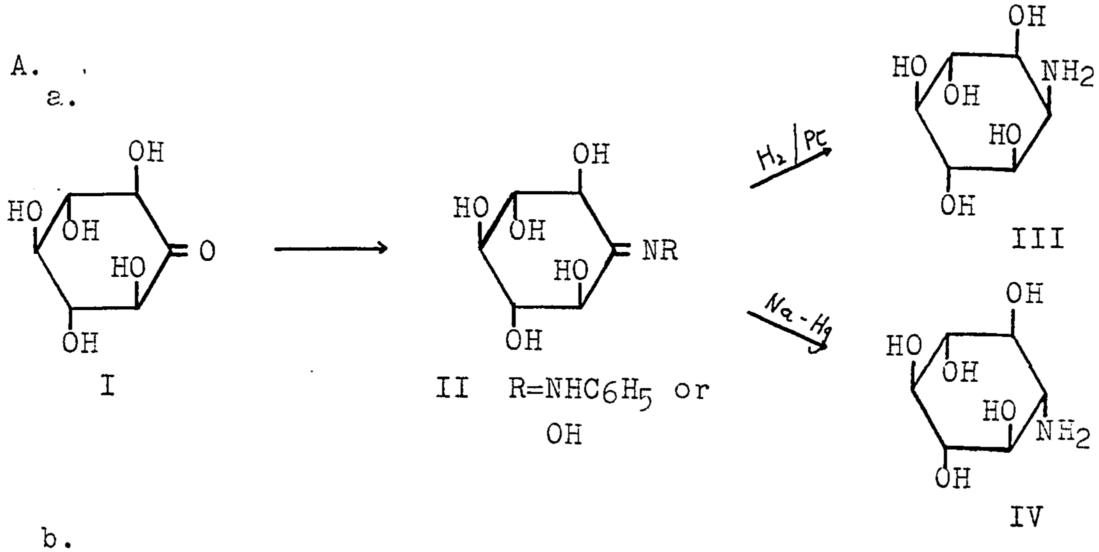
These products were prepared by the hydrogenation of the phenylhydrazone (or oxime) (II) of *myo*-inosose-2 (I). Catalytic hydrogenation over platinum oxide in acetic acid yielded exclusively *myo*-inosamine-2 (III) whereas, with sodium amalgam at pH 5.5-6.5, a mixture containing mainly *scyllo*-inosamine (IV) was obtained (61).

b. (±)-epi-Inosamine-2(4) and (±)-myo-Inosamine-4(6)

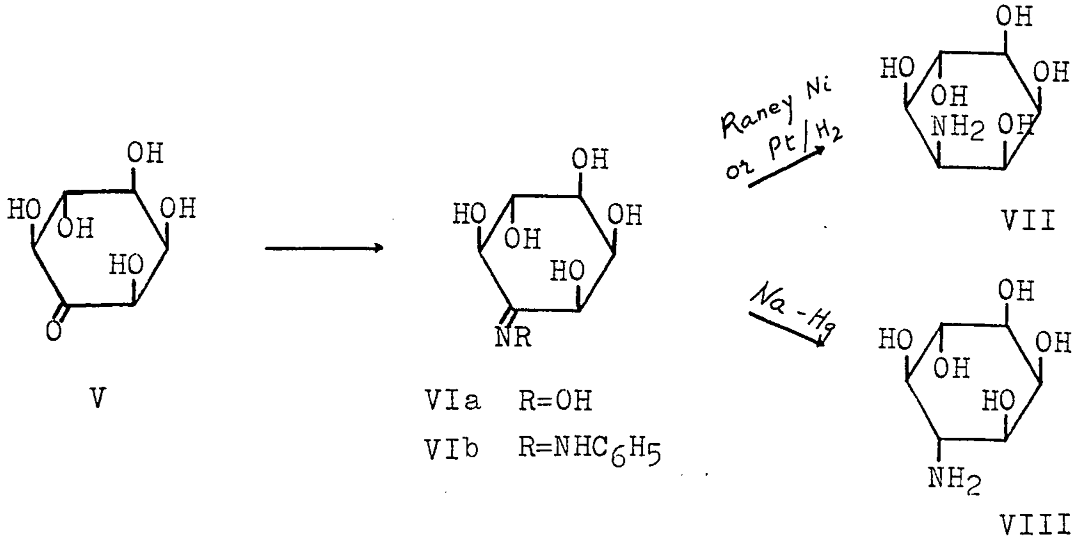
Hydrogenation over platinum oxide (62) of the oxime (VIa) of *epimyo*-inosose (V) gave a single epimer, *epi*-

A.

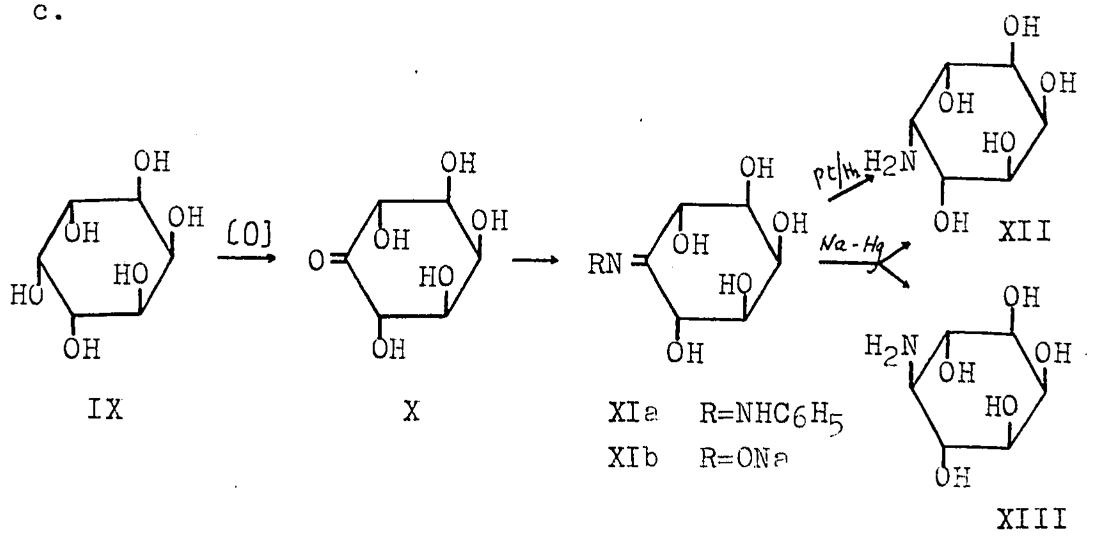
a.


H₂/Pt
Na-Hg
I
II R=NHC6H5 or OH
III
IV

b.


Raney Ni or Pt/H₂
Na-Hg
V
VIa R=OH
VIb R=NHC6H5
VII
VIII

c.


[O]
Pt/H₂
Na-Hg
IX
X
XIa R=NHC6H5
XIb R=ONa
XII
XIII

inosamine-2(4) (VII). The same compound was similarly obtained from the phenylhydrazone (VIb) (61,63). On the other hand, when the oxime was reduced with sodium amalgam, the epimeric amine, myo-inosamine-4(6) (VIII) was the main product (64).

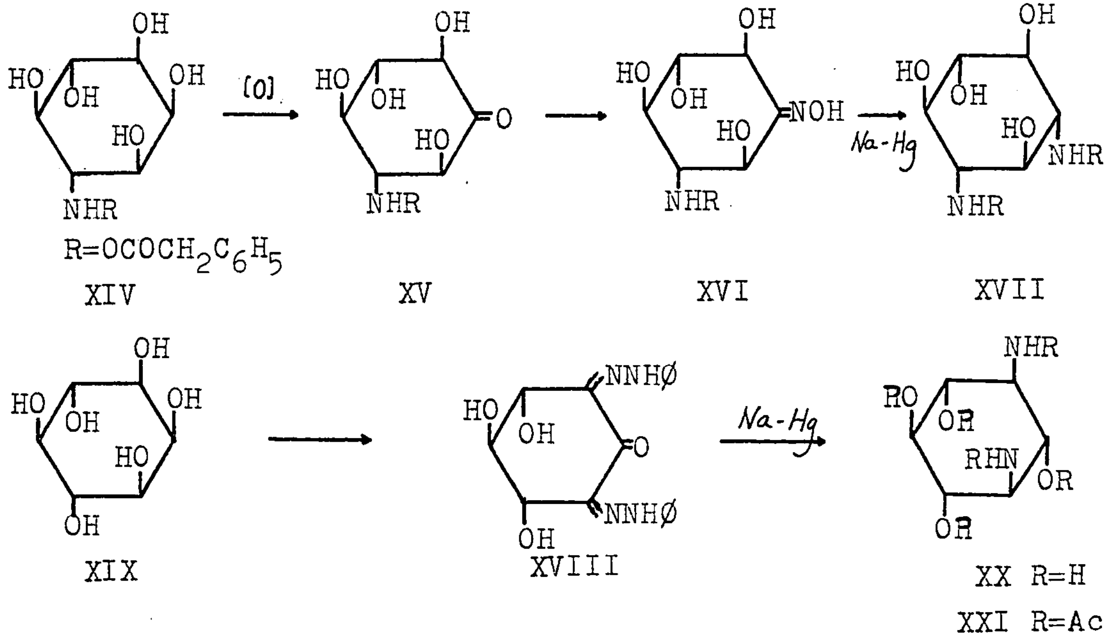
c. neo-Inosamine-2 and myo-Inosamine-5

Catalytic oxidation of neo-inositol (IX) in the presence of platinum oxide lead to the inosose X. Its phenylhydrazone (XIa) on catalytic hydrogenation in the presence of platinum gave neo-inosamine-2 (XII) (58), and the sodium oximate (XIb) was reduced by sodium amalgam to a mixture of XII and myo-inosamine-5 (XIII) (65).

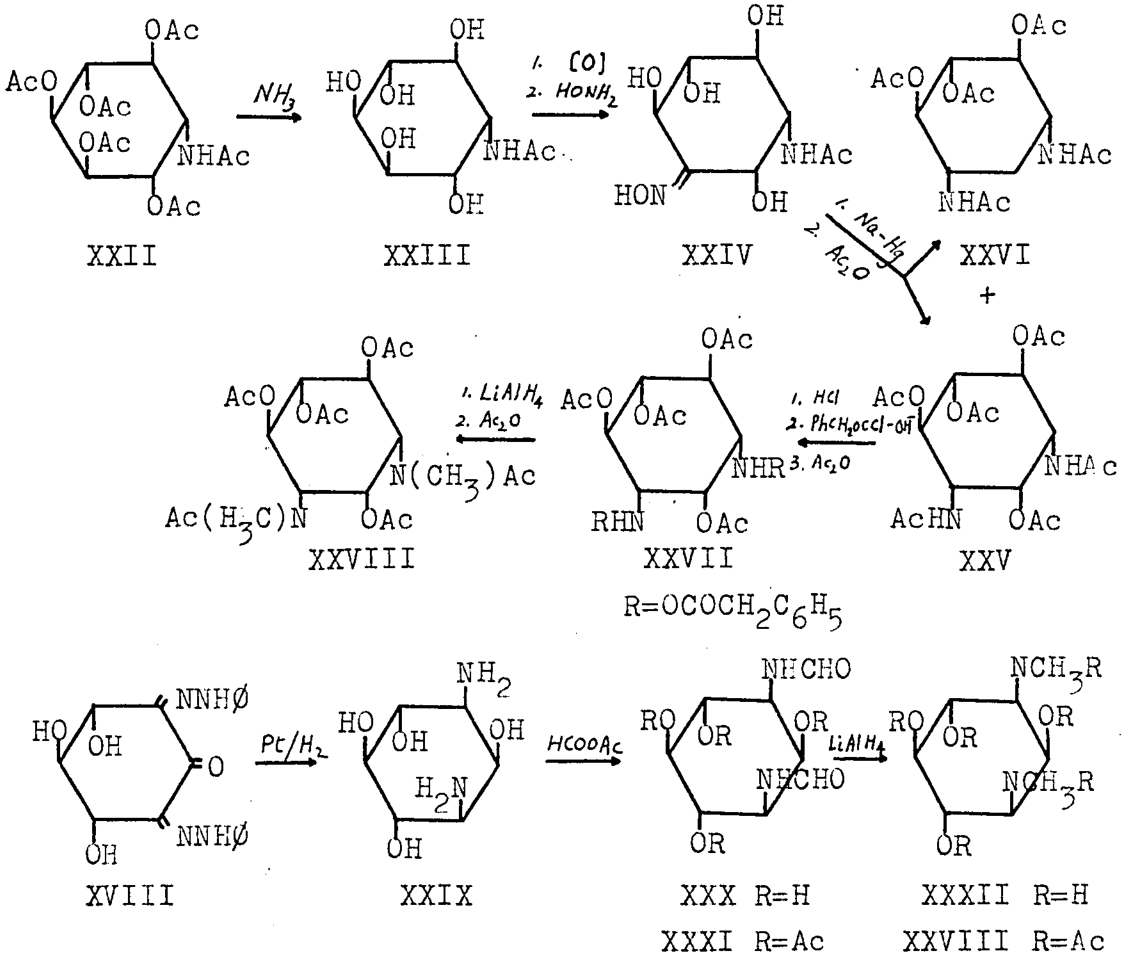
d. Streptamine

The method of catalytic oxidation of inositol derivatives, which has been studied in great detail by Heyns and his co-workers, was employed in a sequence of reactions leading to a synthesis of streptamine (66). The essential point in this method is that axial, secondary hydroxyl groups are converted with good yields into keto groups while equatorial hydroxyl groups remain unattacked.

The N-carbobenzoxy derivative (XIV) of (±)-myo-inosamine-4(6) was oxidized in the presence of platinum, whereby attack of the axial hydroxyl group only occurred. The resulting N-carbobenzoxy-2-oxo-myo-inosamine-4(6) (XV) d.


[O]
Na-Hg
Na-Hg
NHR
NHØ
R=OCOCH2C6H5
XIV
XV
XVI
XVII
XIX
XVIII
XX R=H
XXI R=Ac

e.


NH3
1. [O]
2. HONH2
1. Na-Hg
2. Ac2O
1. LiAlH4
2. Ac2O
1. HCl
2. PhCH2OCCl-OH
3. Ac2O
Pt/H2
HCOOAc
LiAlH4
N(CH3)Ac
Ac(H3C)N
R=OCOCH2C6H5
XXII
XXIII
XXIV
XXVI
+
XXV
XXVII
XXVIII
XVIII
XXIX
XXX R=H
XXXI R=Ac
XXXII R=H
XXVIII R=Ac

was converted into the oxime (XVI), which was reduced with sodium amalgam to give a trans-oriented amino group. Finally, the streptamine was isolated as its dicarbobenzoxy derivative (XVII) in a 18% yield based on XV.

In 1967, Lichtenthaler, Leinert and Suami (54) reported a synthesis starting from trans-3,4,5-trihydroxy-2,6-bis(phenylhydrazono)cyclohexanone (XVIII), which was prepared from myo-inositol (XIX) (67). Compound XVIII was reduced by sodium amalgam in glacial acetic acid to a single isomer, streptamine (XX). Its hexaacetate (XXI) was isolated in a 30% yield (based on XVIII).

e. Actinamine

Actinamine was first synthesized by Nakajima et al. in 1965 (53). In this synthesis, hexaacetyl-rac-inosamine-1 (XXII) (68) was deacetylated by saturated methanolic ammonia to N-acetyl-rac-inosamine-1 (XXIII) whose less hindered axial hydroxyl group was oxidized over platinum (68). The oxime (XXIV) of the resulting ketone was reduced by sodium amalgam, then acetylated to yield hexaacetyl-myo-inosadiamine-1,3 (XXV) and pentaacetyl-2-deoxystreptamine (XXVI) (26). Compound XXV was hydrolyzed by acid and subsequently carbobenzoxylated and acetylated to give N,N'-bis-carbobenzoxy-tetra-O-acetyl-myo-inosadiamine-1,3 (XXVII). Reductive cleavage of the carbobenzoxy groups with lithium aluminum hydride followed by acetylation gave hexaacetyl-actinamine (XXVIII). The production of 2-deoxystreptamine (XXVI) may be explained by an oxidation of the second axial hydroxy group in XXIII and subsequent reduction.

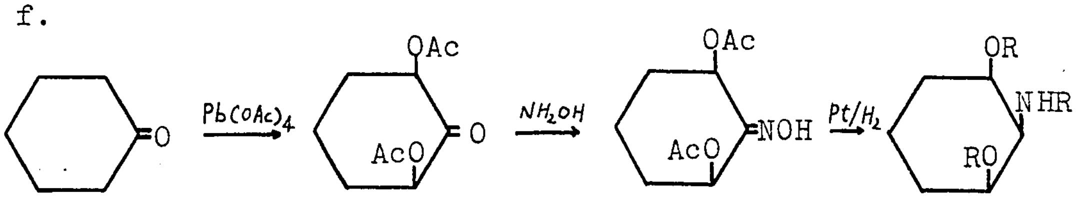
In 1967, Lichtenthaler et al. (54) synthesized actinamine from the bis-phenylhydrazone XVIII, whose catalytic hydrogenation furnished <u>myo</u>-inosadiamine-1,3 (XXIX). N-Formylation yielded the diformyl compound XXX which, upon O-acetylation to XXXI, was reduced with lithium aluminum hydride in tetrahydrofuran to give actinamine (XXXII). Hexaacetyl actinamine (XXVIII) could be isolated in a 23% yield based upon XXIX.

f. <u>cis,cis-2-Amino-1,3-cyclohexanediol</u> (70)

<u>cis</u>-2,6-Diacetoxycyclohexanone (XXXIV) was prepared by the oxidation of cyclohexanone (XXXIII) with lead tetraacetate in boiling benzene (71). The reduction of the oxime (XXXV) was carried out in glacial acetic acid over platinum (72). The crude reduction product was acetylated, and the triacetyl derivative (XXXVI) was hydrolyzed to <u>cis</u>, <u>cis</u>-2-amino-1,3-cyclohexanediol (XXXVII).

g. <u>Deoxyinosadiamines</u> (73)

From four stereoisomeric N-acetyl-tri-O-acetyl-conduramines (Table II) (74), N-acetyl-tri-O-acetyl-deoxyinosamines were prepared by the addition of hypobromous acid and catalytic debromination of the resulting bromohydrins (75). The deoxyinosamine derivatives on oxidation f.

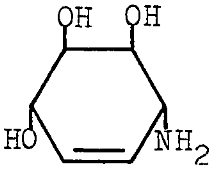
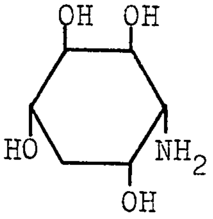
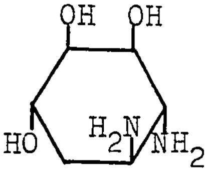
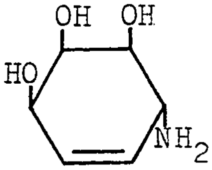
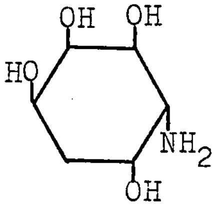
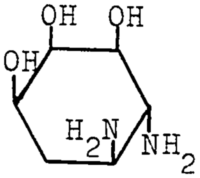
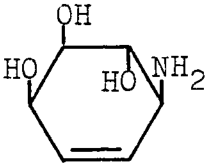
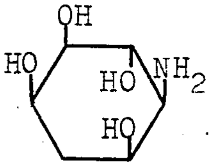
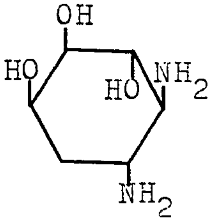
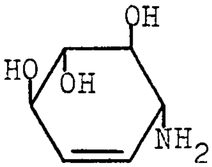
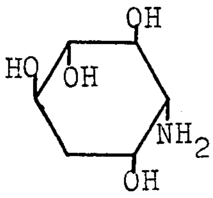


XXXIII XXXIV XXXV XXXVI R=Ac

XXXVII R=H

g.

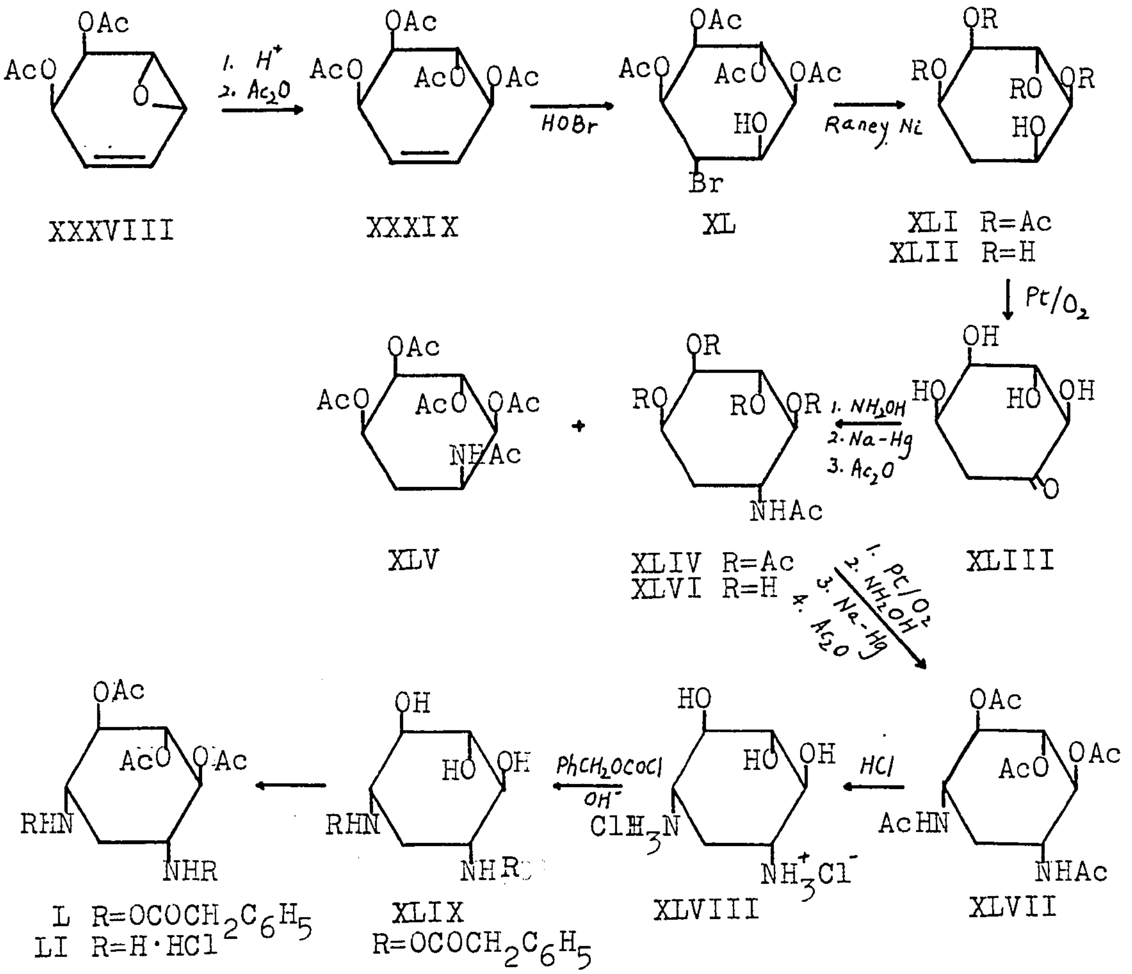
Table II The Deoxyinosadiamines Obtained from Conduramines

Conduramines	Deoxyinosamines	Deoxyinosadiamines
 A-1	 3-*allo*-1	 1-*muco*-2,3
 C-4	 1-*allo*-5	 2-*epi*-1,6
 F-4	 3-*epi*-1	 3-*myo*-4,5
 B-1	 3-*myo*-1	

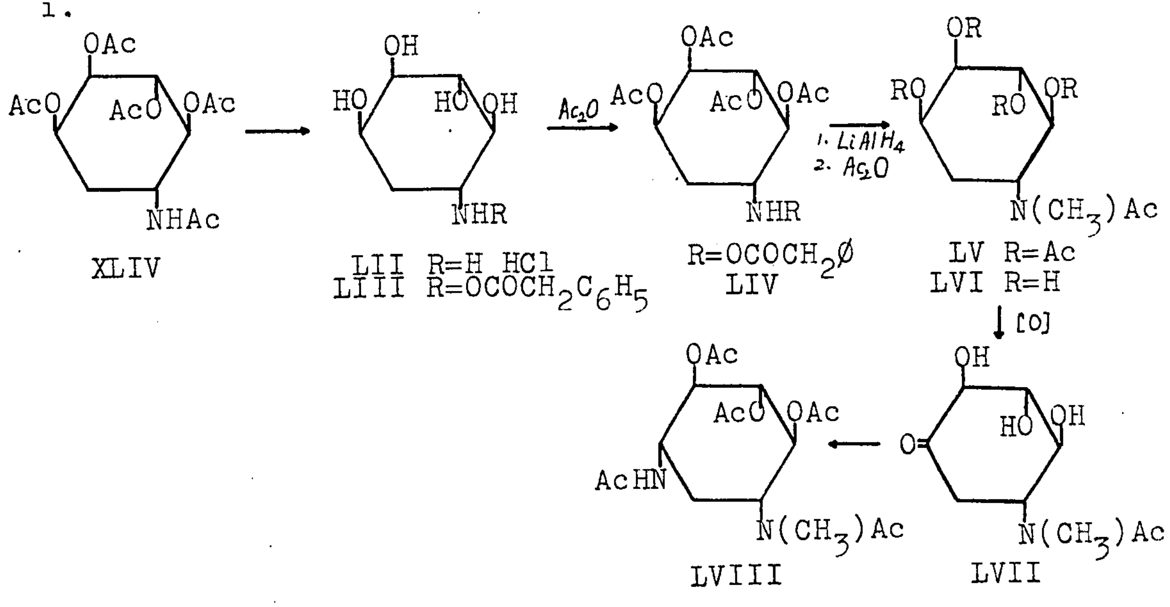
gave four stereoisomeric tetraacetyl-deoxyinosaminoses, three of which were converted into deoxyinosadiamines via their oximes. The configurations shown in Table II were determined on the basis of n.m.r. data.

h. 2-Deoxystreptamine (49)

The epoxide group of diacetyl-1,2-anhydro-conduritol-E (XXXVIII) (74) was opened by acid hydrolysis, and the product was acetylated to give mainly tetra-O-acetyl-conduritol-F (XXXIX) (76). Compound XXXIX added hypobromous acid diaxially (75), and the bromohydrin (XL) was debrominated by hydrogenation over Raney nickel to give a tetra-O-acetyl-3-deoxy-epi-inositol (XLI). After deacetylation to 3-deoxy-epi-inositol (XLII), which possesses two axial hydroxyl groups flanking the methylene group, one of these was converted into an amino group by successive catalytic oxidation, oximation, and sodium amalgam reduction. After acetylation, two stereoisomeric amines were isolated, namely pentaacetyl-3-deoxy-myo-inosamine-4 (XLIV) and pentaacetyl-3-deoxy-epi-inosamine-2 (XLV), the former in higher yield. The amine XLIV was de-O-acetylated to XLVI which, by a similar reaction sequence, was converted to pentaacetyl-2-deoxystreptamine (XLVII). Hydrochloric acid hydrolysis then gave 2-deoxystreptamine dihydrochloride (XLVIII). N-Carbobenzoxylation (to XLIX), acetylation (to L), and hydrogenolytic removal of the h.


XXXVIII
1. H+
2. Ac2O
XXXIX
HOBr
XL
Raney Ni
XLI R=Ac
XLII R=H
Pt/O2
XLIII
1. NH2OH
2. Na-Hg
3. Ac2O
XLIV R=Ac
XLVI R=H
+
XLV
1. Pt/O2
2. NH2OH
3. Na-Hg
4. Ac2O
XLVII
HCl
XLVIII
PhCH2OCOCl
OH-
XLIX
R=OCOCH2C6H5
L R=OCOCH2C6H5
LI R=H·HCl

i.


XLIV
LII R=H HCl
LIII R=OCOCH2C6H5
Ac2O
R=OCOCH2Ø
LIV
1. LiAlH4
2. Ac2O
LV R=Ac
LVI R=H
[O]
LVII
LVIII

carbobenzoxy groups afforded tri-O-acetyl-2-deoxystreptamine dihydrochloride (LI).

i. (±)-Hyosamine (49)

Pentaacetyl-3-deoxy-myo-inosamine-4 (XLIV) was heated with hydrochloric acid to give the deacetylated compound (LII) whose N-carbobenzoxy derivative (LIII) was acetylated (to LIV), reduced with lithium aluminum hydride in tetrahydrofuran (77) and reacetylated, to give N-acetyl-N-methyl-tetra-O-acetyl-3-deoxy-myo-inosamine-4 (LV). The deacetylated derivative (LVI) of LV was oxidized catalytically, then reacted with hydrazine and reduced by sodium amalgam. Final acetylation yielded pentaacetyl-(±)-hyosamine (LVIII).

B. Hydrogenation of nitrocyclitols

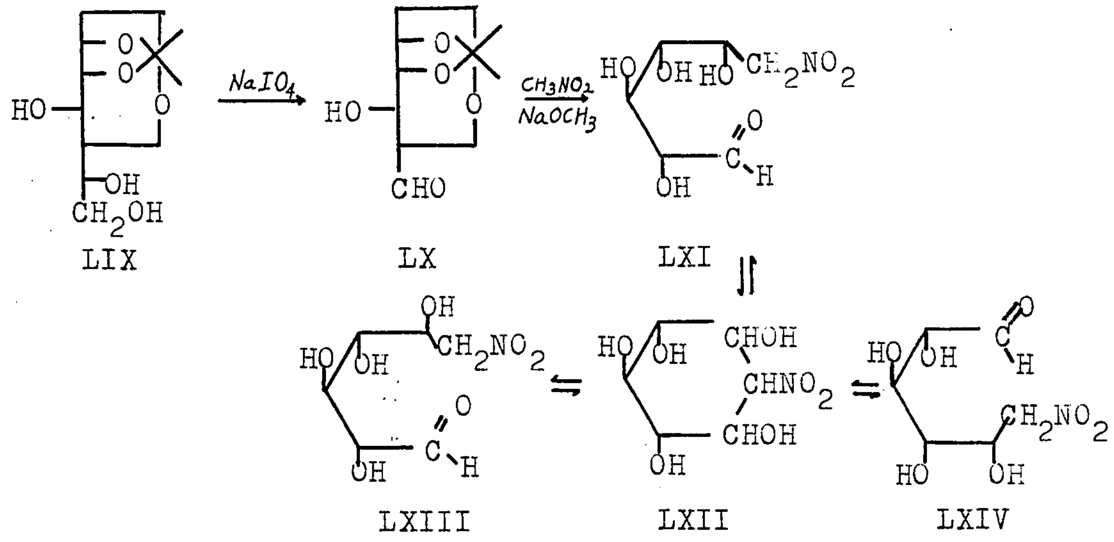
Nitrocyclitols, which have become available by the work of H. O. L. Fischer and his co-workers (78,79), can be converted by catalytic hydrogenation into the corresponding amines (80,81).

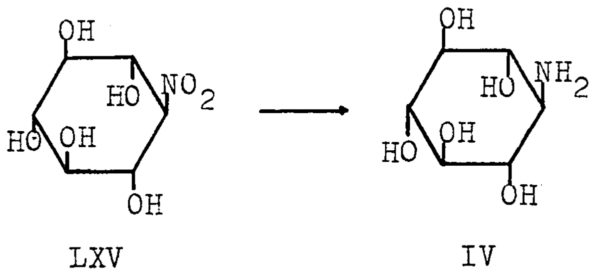
a. muco-Inosamine-3 and scyllo-Inosamine (79)

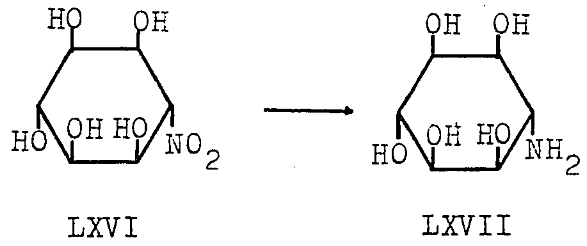
Starting from 1,2-O-isopropylidene-D-glucofuranose (LIX), which was subjected to glycol cleavage, 5-aldo-1,2-O-isopropylidene-D-xylo-pentafuranose (LX) was obtained. The latter, upon condensation with nitromethane in the

B.

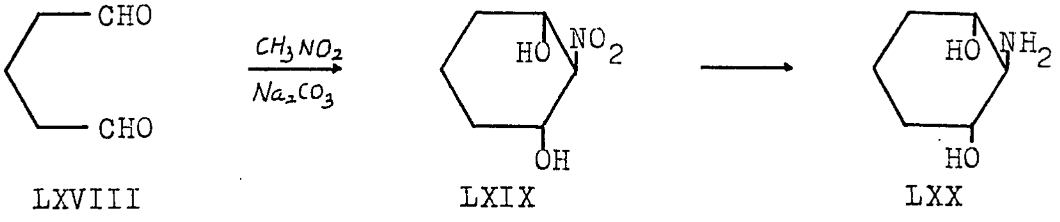
a.


NaIO₄
CH₃NO₂
NaOCH₃
LIX
LX
LXI
LXIII
LXII
LXIV


LXV
IV


LXVI
LXVII

b.


CH₃NO₂
Na₂CO₃
LXVIII
LXIX
LXX

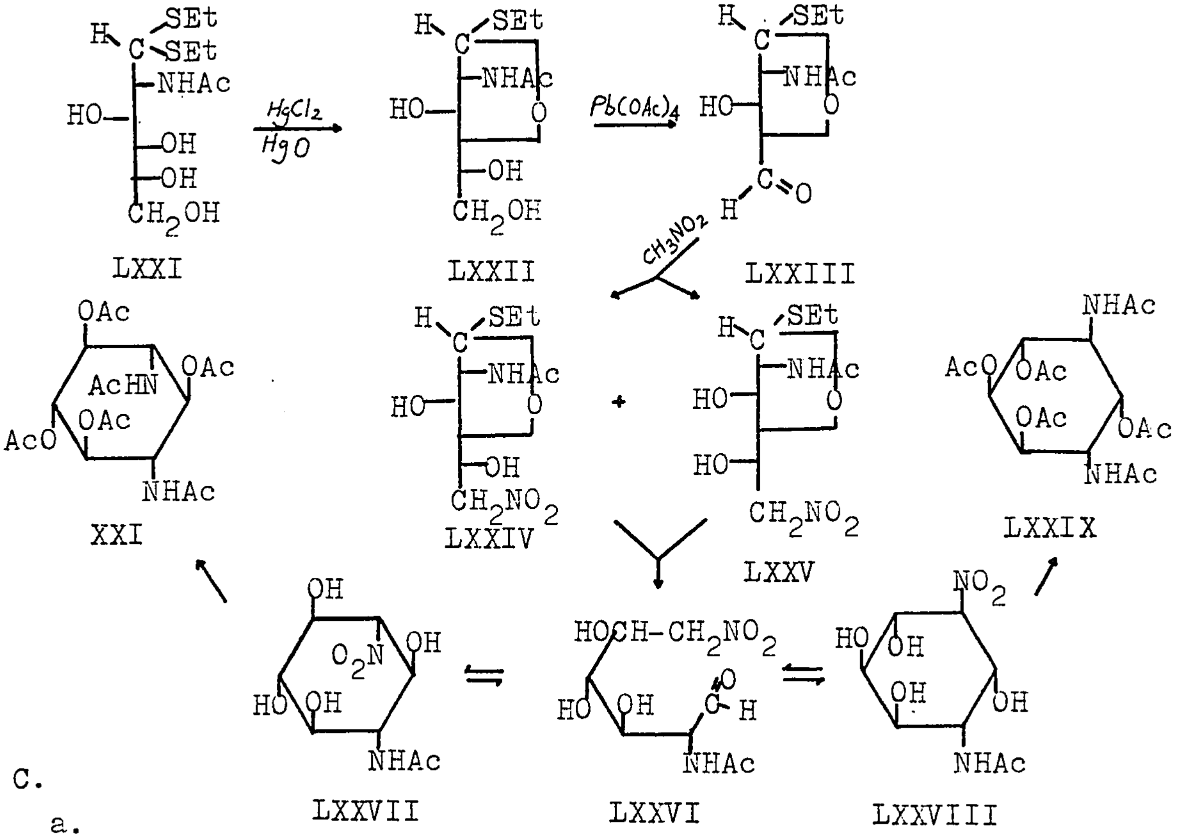
presence of sodium methoxide, yielded a mixture of the isopropylidene derivatives of 6-nitro-6-deoxy-D-glucose (LXI) and -L-idose (LXIII). Removal of the isopropylidene groups gave the free nitroaldoses which cyclized with remarkable facility under the influence of base, giving a mixture of nitrodeoxyinositols (LXII) (81). Catalytic hydrogenation furnished aminodeoxyinositols. One of these, isolated in pure state, was <u>scyllo</u>-inosamine (IV) (79,82) and the other was <u>muco</u>-inosamine-3 (LXVII) (83,84).

b. <u>trans,trans-2-Amino-cyclohexane-1,3-diol</u> (85)

Glutaric dialdehyde (LVIII) was condensed with nitromethane to give <u>trans</u>,<u>trans</u>-2-nitrocyclohexane-1,3-diol (LXIX) which, upon catalytic hydrogenation (86), afforded the corresponding aminodiol (LXX).

c. <u>Streptamine and 1,3-(-)-inosadiamine</u>

Using the nitromethane approach, Wolfrom and associates (87) were the first to synthesize streptamine as early as 1950. Starting from the diethylthioacetal (LXXI) of N-acetyl-D-glucosamine, they removed one of the mercaptan groups by hydrolysis in the presence of mercuric chloride and mercuric oxide to obtain ethyl 2-acetamido-2-deoxy-α-D-glucothiofuranoside (LXXII). The latter underwent glycol fission with lead tetraacetate. The product (LXXIII) was condensed with nitromethane under basic c.



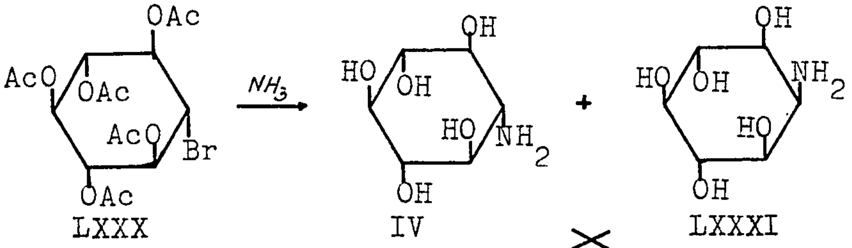
LXXI LXXII LXXIII

XXI LXXIV LXXV LXXIX

LXXVII LXXVI LXXVIII

C.

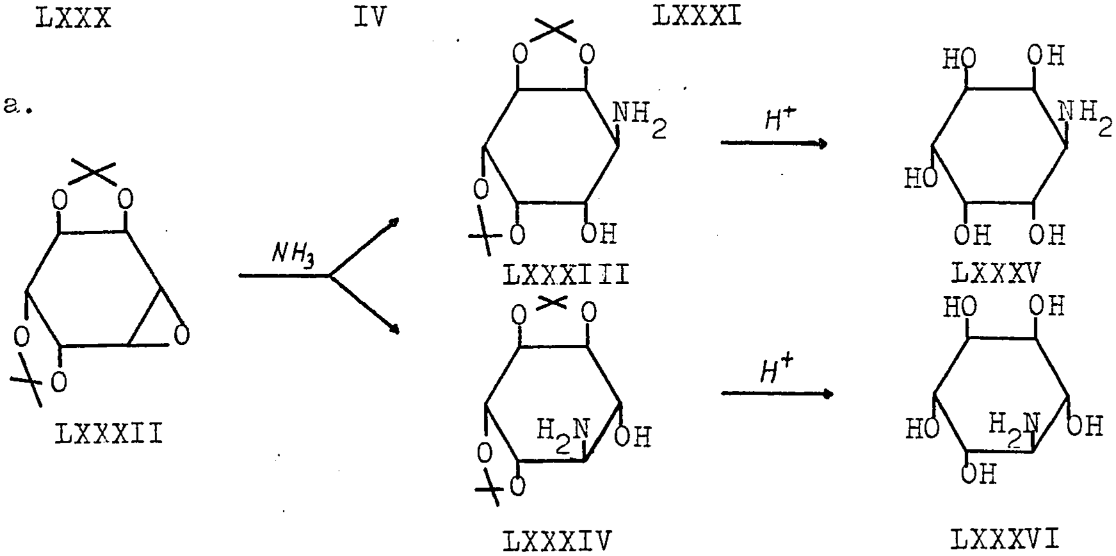
a.



LXXX IV LXXXI

D.

a.



LXXXII LXXXIII LXXXIV LXXXV LXXXVI

condition, giving a mixture of ethyl 2-acetamido-6-nitro-2,6-dideoxy-α-D-glucothiofuranoside (LXXIV) and the corresponding L-idose derivative (LXXV). A mixture of the free nitroaldoses (LXXVI) was obtained by hydrolysis of the ethylthio group, and these were the key intermediates of the synthesis. Base-catalyzed intramolecular cyclization provided a mixture of nitroacetylamino-dideoxyinositols (LXXVII) (LXXVIII). After catalytic hydrogenation of the nitro group and complete acetylation, the hexaacetyl-streptamine (XXI) could be isolated. Besides streptamine an isomer, 1,3-(-)-inosadiamine, was isolated as a hexa-acetate (LXXIX) in this synthesis.

C. Action of ammonia on bromocyclitols

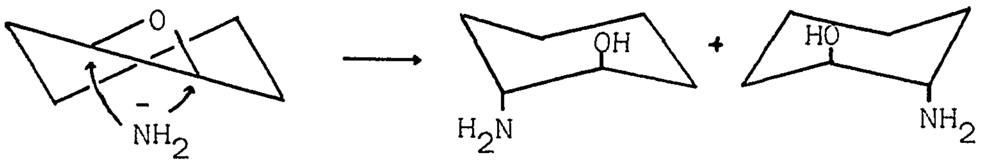
Ammonia can displace a bromine atom, either by an S_N2 mechanism with Walden inversion, or through neighbouring acetoxy group participation with retention of configuration.

a. scyllo-Inosamine

scyllo-Inosamine has been obtained (88) from a pentaacetoxy-bromocyclohexane prepared by the treatment of myo-inositol with acetyl bromide. Bromo-scyllo-inositol (LXXX) reacted with ammonia in dioxaneto give a small amount of scyllo-inosamine (IV), in addition to an isomer corresponding to the formula (LXXXI).

D. Action of ammonia on anhydrocyclitols

The oxirane ring of anhydrocyclitols can be opened by ammonia at two positions (89), with an initial formation of two trans-diaxial groups.



a. neo-Inosamine-3 and laevo-Inosamine-4 (90)

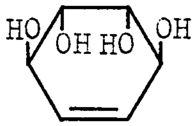
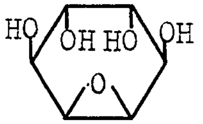
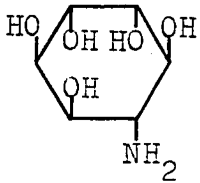
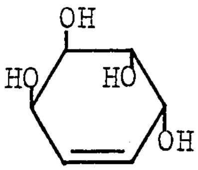
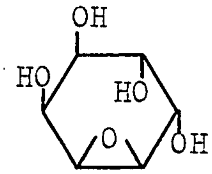
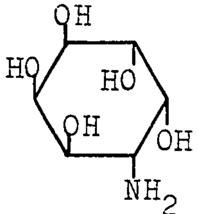
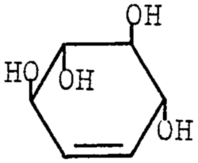
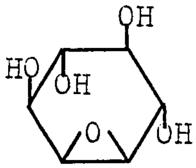
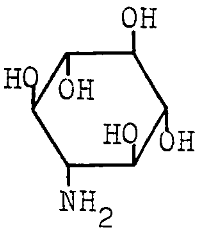
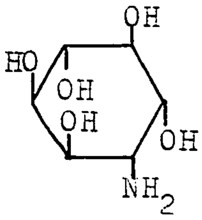
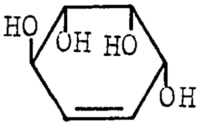
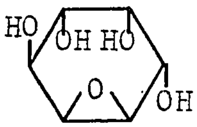
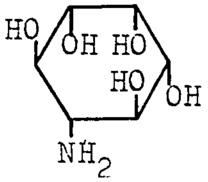
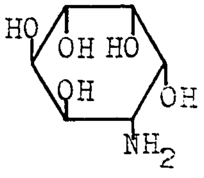
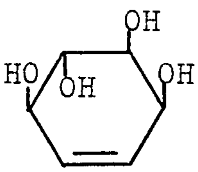
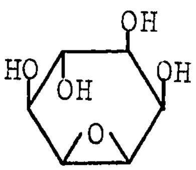
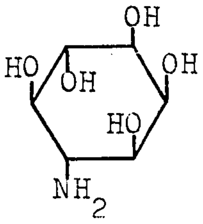
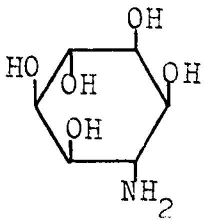
(-)-3,4-Anhydro-1,2:5,6-diisopropylidene-*allo*-inositol (LXXXII), when heated with methanolic ammonia, gave a mixture of LXXXIII and LXXXIV. After removal of the isopropylidene residues by acid hydrolysis, *neo*-inosamine-3 (LXXXV) and *laevo*-inosamine-4 (LXXXVI) could be separated.

b. Inosamines from conduritol epoxides

Nakajima et al. (89) converted the five stereoisomeric conduritol epoxides to eight isomeric inosamines by means of ammonia in methanol. The configurations attributed to these inosamines are based on those of the starting materials and on the principle of *trans* opening of the epoxide group (Table III).

b.

Table III The Inosamines Obtained from Conduritol Epoxides

Conduritols	Anhydro-inositols	Inosamines	
 A	 2:3-*allo*-	 *rac*-4(5)	
 E	 (±)-1:2-*allo*-	*rac*-4(5)	 *neo*-1(3)
 B	 (+)-1:2-*myo*-	 *scyllo*-	 *rac*-2(6)
 C	 (+)-1:2-*neo*-	 *myo*-5	 *allo*-1(4)
 F	 (±)-2:3-*epi*-	 *myo*-4(6)	 *muco*-3

c. Conduramines (74)

Cis and *trans* "benzeneglycols" were converted into four diacetylbenzeneglycol monoepoxides (anhydroconduritols) by perbenzoic acid oxidation. These were further transformed into four conduramines by reaction with ammonia. The configuration of the conduramines were deduced from those of the starting materials and from the inosamines obtained by *cis* or *trans* hydroxylation. In the ammonolysis of a given epoxide, only one of the two possible stereoisomers was detected. Furthermore, the amino group was found to always enter at the carbon nearest to the double bond (Table IV).

d. Inosamine from conduramines (74)

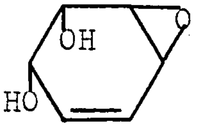
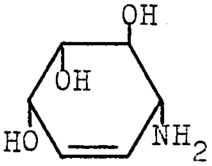
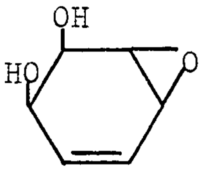
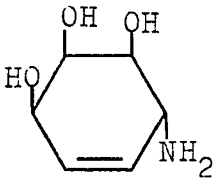
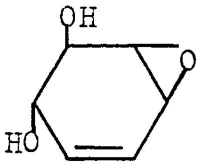
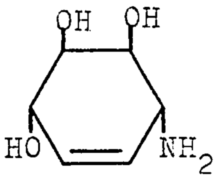
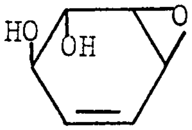
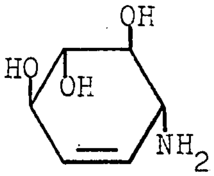
The double bond in conduramines could be oxidized by potassium permanganate to give *cis* glycol groups, or epoxidized by perbenzoic acid with subsequent oxirane ring opening by acid to give isomers with *trans* glycol groups. The isomeric inosamines have been synthesized in this manner (Table IV).

e. C-Aminomethyl-inositols (91)

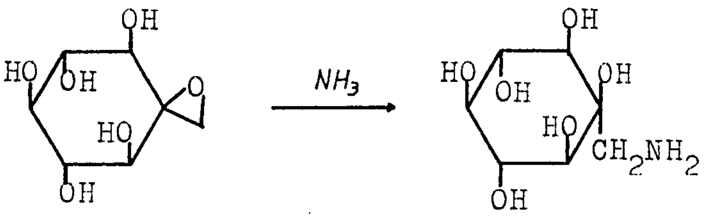
The spiran epoxide (LXXXVII, methyleneoxypentahydroxycyclohexane), obtained from *myo*-inosose-2 by treatment with diazomethane, was allowed to react with ammonia to give 2-aminomethyl-*myo*-inositol (LXXXVIII).

c.d.

Table IV *The Conduramines and Inosamines Obtained from Anhydroconduritols*

Anhydroconduritols	*Conduramines*	*Inosamines*
 (±) 1:2-E	 F-4	*rac*-5, *myo*-5, *muco*-1
 (±) 1:2-D	 C-4	*neo*-1, *myo*-4, *allo*-5
 (±) 1:2-C	 A-1	*muco*-3, *rac*-5, *rac*-2
 (±) 1:2-F	 B-1	*myo*-4, *scyllo*-, *rac*-1

e.



LXXXVII LXXXVIII

By treatment of the epoxide (LXXXVII) with primary amines, N-substituted aminomethyl-myo-inositols have also been obtained (92).

f. Inosadiamines (93)

By epoxidation of the N-acetyl derivatives of four stereoisomeric conduramines (aminocyclohexanetetrols) with perbenzoic acid and subsequent opening of the oxirane ring with saturated methanolic ammonia, seven stereoisomeric inosadiamines were prepared. These were isolated and characterized as their hexaacetates. The configurations of the compounds were deduced from the method of synthesis and from their n.m.r. spectra (Table V).

E. Hydrogenation of aromatic derivatives

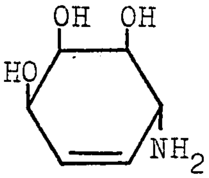
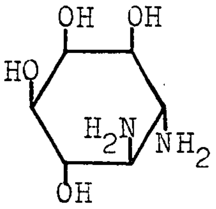
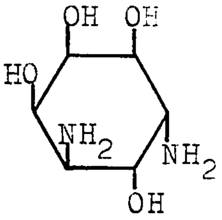
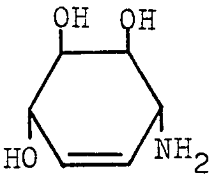
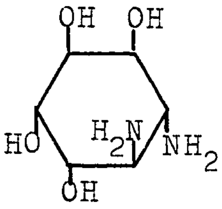
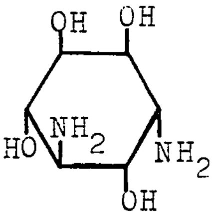
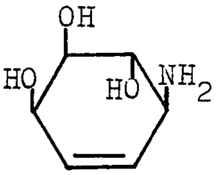
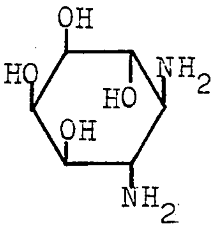
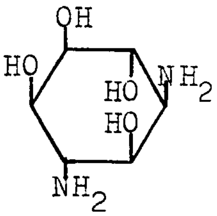
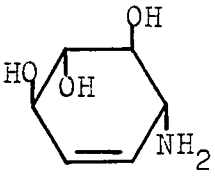
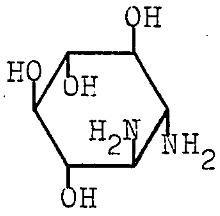
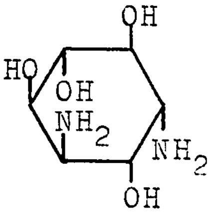
Certain nitrogen-substituted aromatic derivatives can be converted into aminocyclitols by catalytic hydrogenation.

a. 1,4-Diaminotetrahydroxycyclohexane (94)

The 1,4-diimide (LXXXIX) of rhodizonic acid, obtained by oxidation of 1,4-diaminotetrahydroxybenzene, was hydrogenated over palladium black, and one of the 1,4-diamino-cyclitols formed could be isolated as sulfate. The configuration of this 1,4-diaminotetrahydroxycyclohexane (XC) is unknown; the relatively high yield, 43%, is however noteworthy.

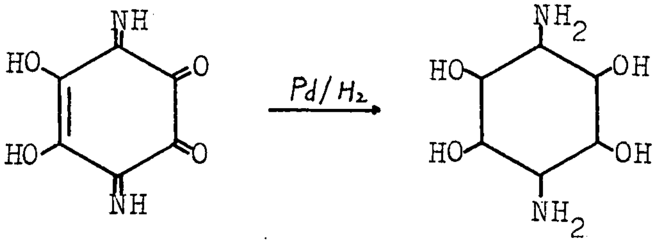
f.

Table V The Inosadiamines Obtained from Conduramines

Conduramines	Inosadiamines	
 C-4	 *myo*-4,5	 *allo*-1,5
 A-1	 *rac*-5,6	 *rac*-3,5
 F-4	 *myo*-4,5	 *muco*-1,3
 B-1	 *scyllo*-1,2	 *rac*-1,3

E.

a.



LXXXIX XC

b. 1,3,5-Triamino-2,4,6-trihydroxycyclohexane (94)

This inosatriamine (XCII) was prepared by catalytic hydrogenation of triaminophloroglucinol (XCI) in the presence of platinum and was isolated as its sulfate in 64% yield. The configuration is not known.

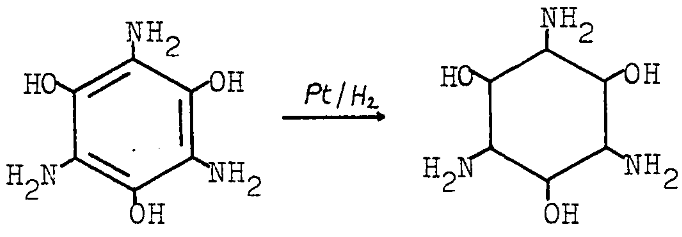
c. 1,3-Diamino-2-deoxy-inositols (95)

Catalytic hydrogenation of 4,6-dinitropyrogallol (XCIII) over platinum in aqueous acetic acid or sulfuric acid has furnished three stereoisomeric 1,3-diamino-4,5,6-trihydroxy-cyclohexanes (XCIV), to which the configurational formulae, 1,3-diamino-2-deoxy-*cis*-inositol (XCV), 1,3-diamino-2-deoxy-*epi*-inositol (XCVI), and 1,5-diamino-6-deoxy-*allo*-inositol (XCVII) were tentatively assigned.

d. 1,3-Diamino-4,6-dihydrocyclohexanes (1,3-diamino-2,5-dideoxy-inositols) (95)

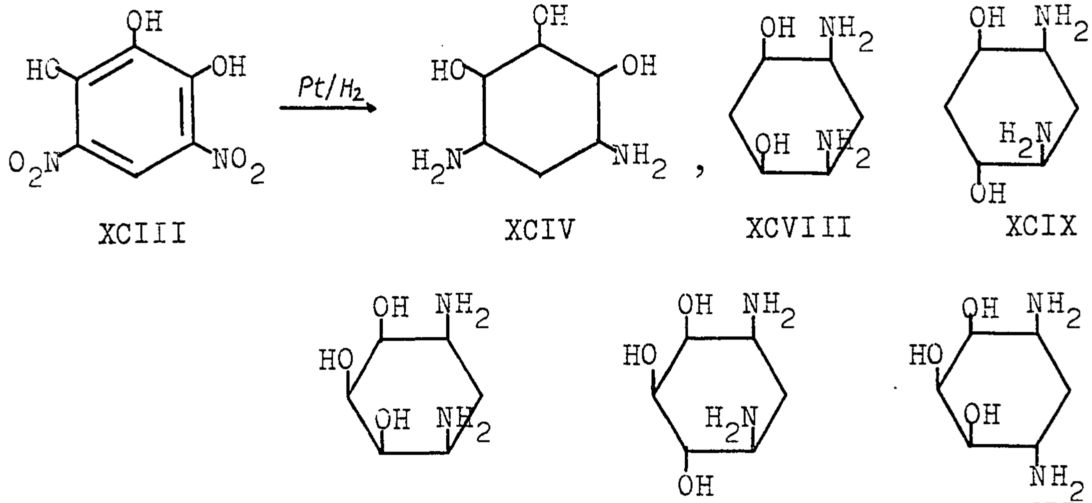
Catalytic hydrogenation of XCIII gave, in addition to XCIV, products of hydrogenolysis, two of which were found to be 1,3-diamino-4,6-dihydrocyclohexanes, probably 1,3-diamino-2,5-dideoxy-*cis*-inositol (XCVIII) and 1,3-diamino-2,5-dideoxy-*epi*-inositol (XCIX).

b.



XCI XCII

c.d.

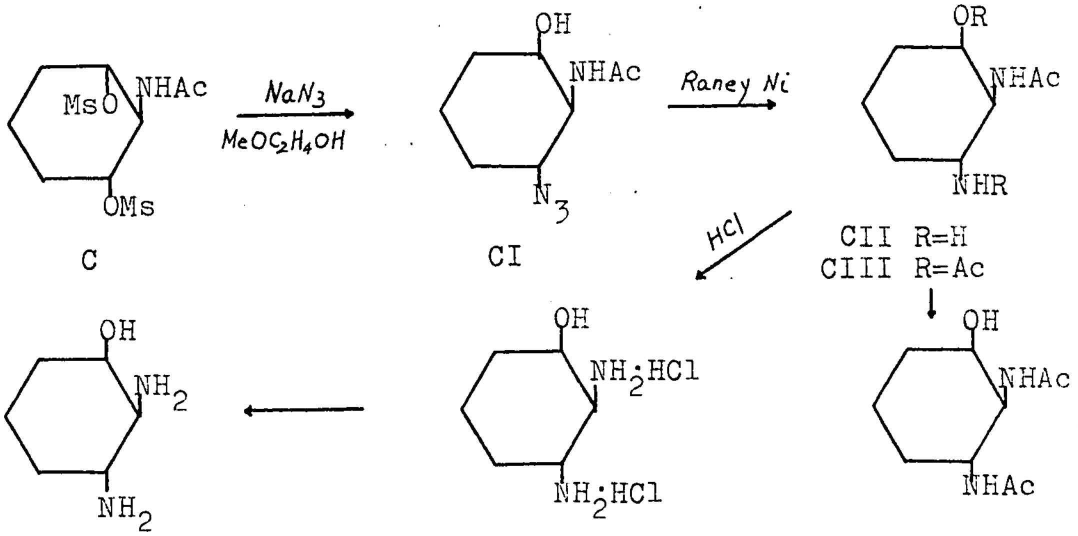


XCIII XCIV, XCVIII XCIX

XCV XCVI XCVII

F.

a.



C CI

CII R=H
CIII R=Ac

CVI CV CIV

F. Hydrogenation of azidocyclitols

Azidocyclitols can be reduced catalytically to the corresponding amino compounds. The azido group may be introduced through nucleophilic displacement of a sulfonyloxy group by azide ion. Depending upon the structure and configuration of the substrate as well as on the reaction conditions, such displacements may occur with or without neighboring group participation and may lead to isomeric products (96-101).

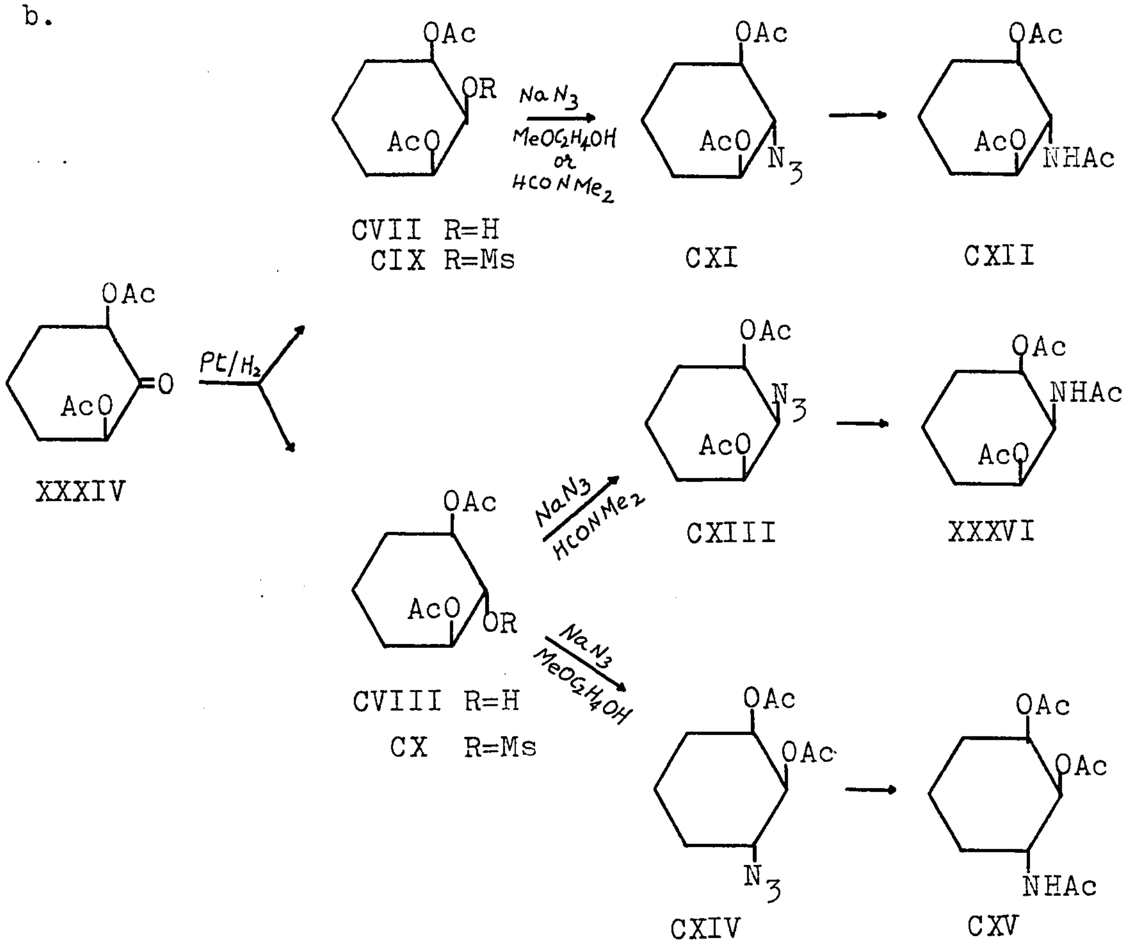
a. 2,3-Diaminocyclohexanol (101)

By treating di-O-mesyl-*trans*,*trans*-2-acetamido-1,3-cyclohexanediol (C) with sodium azide in boiling, aqueous 2-methoxyethanol, the DL-*cis*,*trans*-2-acetamido-3-azidocyclohexanol (CI) was obtained. This compound was hydrogenated over Raney nickel to give DL-2-acetamido-3-amino-cyclohexanol (CII). The latter was acetylated and the triacetyl derivative (CIII) was selectively de-O-acetylated by methanolic ammonia to give 2,3-diacetamidocyclohexanol (CIV). Hydrolysis of compound CII or CIII by 6N hydrochloric acid gave the 2,3-diaminocyclohexanol dihydrochloride(CV) from which by treatment with base the DL-*cis*,*trans*-2,3-diamino-cyclohexanol (CVI) was obtained.

b. 2-Amino-1,3-cyclohexanediol (97)

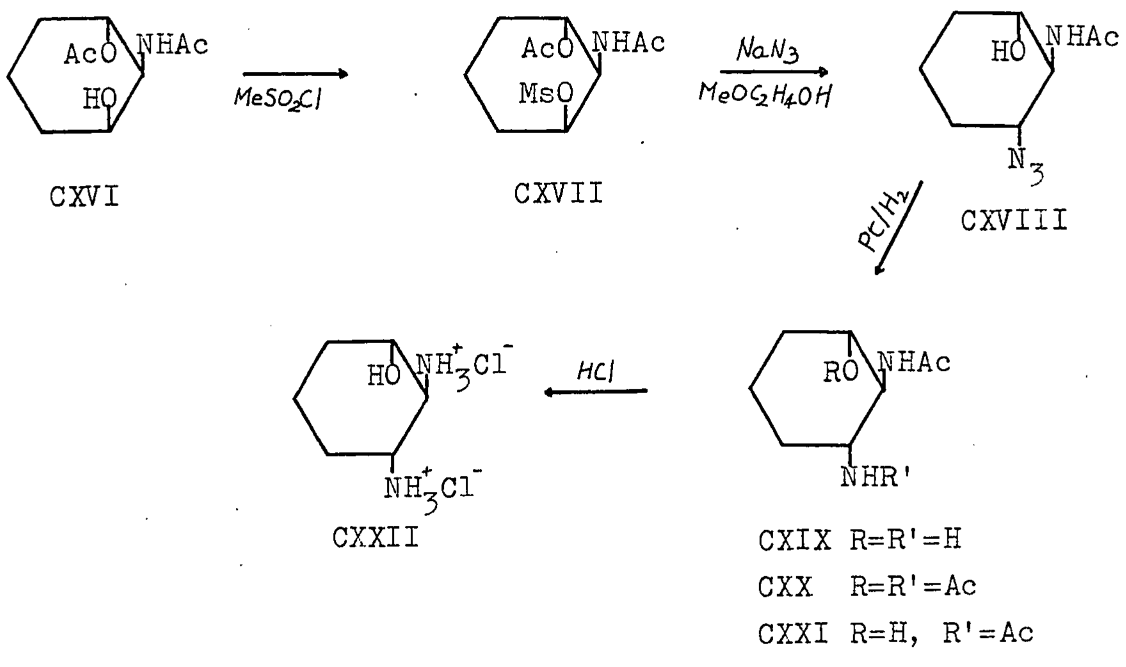
When cis-2,6-diacetoxycyclohexanone (XXXIV) was hydrogenated in ethanol over platinum oxide, a mixture of cis,cis-1,3-di-O-acetyl-cyclohexanetriol (CVII) and its trans,trans isomer was obtained. The mixture was separated, and each component afforded a 2-methanesulfonate. The cis, cis sulfonate (CIX) upon sodium azide displacement in either 2-methoxyethanol or dimethylformamide gave an oily azide (CXI) which by reduction and subsequent acetylation yielded trans,trans-2-acetamido-1,3-cyclohexanediol diacetate (CXII) (85,100). The trans,trans-2-methanesulfonate CX, when refluxed with sodium azide in dimethylformamide and upon subsequent hydrogenation and acetylation, gave cis,cis-2-acetamido-1,3-cyclohexanediol diacetate (XXXVI). However, when the solvent in the displacement reaction was changed to 2-methoxyethanol, DL-cis,trans-3-acetamido-1,2-cyclohexanediol diacetate (CXV) (102) was isolated. This can be rationalized by assuming neighboring group participation from the vicinal trans acetoxy group in the course of the reaction, to form an acetoxonium ion intermediate (96), which is attacked by the azide ion predominantly at the quasi-equatorial C-O bond (97,98), to form compound CXIV.

b.

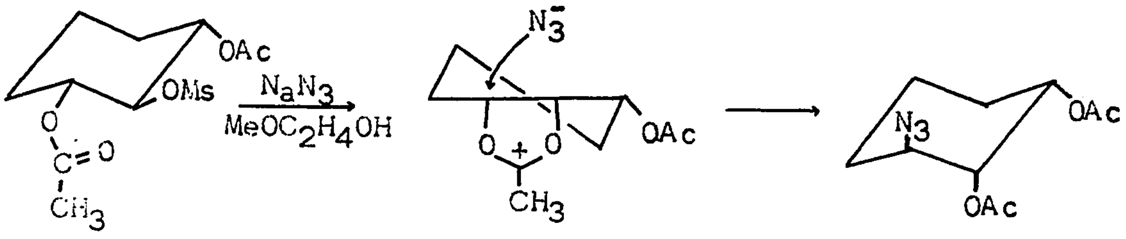


OAc
OR
AcO
NaN3
MeOC2H4OH
or
HCONMe2
CVII R=H
CIX R=Ms
OAc
AcO
N3
CXI
OAc
AcO
NHAc
CXII
OAc
AcO
=O
XXXIV
Pt/H2
OAc
N3
AcO
CXIII
OAc
NHAc
AcO
XXXVI
NaN3
HCONMe2
OAc
AcO
OR
CVIII R=H
CX R=Ms
NaN3
MeOC2H4OH
OAc
OAc
N3
CXIV
OAc
OAc
NHAc
CXV

c.



AcO
NHAc
HO
CXVI
MeSO2Cl
AcO
NHAc
MsO
CXVII
NaN3
MeOC2H4OH
HO
NHAc
N3
CXVIII
Pt/H2
HO
NH3+Cl-
NH3+Cl-
CXXII
HCl
RO
NHAc
NHR'
CXIX R=R'=H
CXX R=R'=Ac
CXXI R=H, R'=Ac



CX

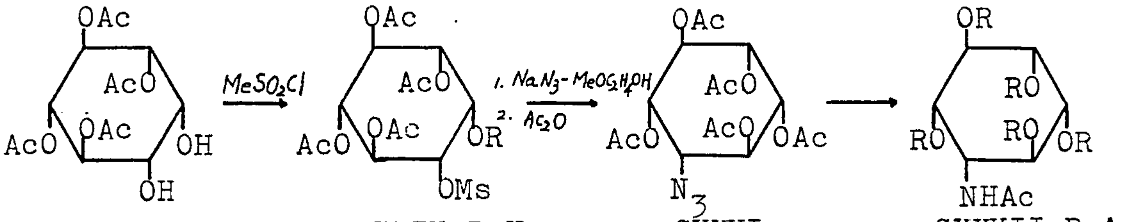
CXIV

c. *trans,trans-2,3-Diaminocyclohexanol* (103)

By treating 3-O-acetyl-DL-*cis*,*trans*-2-acetamido-1,3-cyclohexanediol (CXVI) (100) with methanesulfonyl chloride in pyridine, the 1-O-mesyl derivative (CXVII) was obtained. Displacement with sodium azide in refluxing 2-methoxyethanol gave DL-*trans*,*trans*-2-acetamido-3-azido-cyclohexanol (CXVIII) which was then hydrogenated to give DL-*trans*,*trans*-2-acetamido-3-amino-cyclohexanol (CXIX). From CXIX, the triacetyl derivative (CXX), the di-N-acetyl derivative (CXXI), and the dihydrochloride (CXXII) were prepared by standard procedures.

d. *muco-Inosamine-1* (104)

(±)-1,4,5,6-tetra-O-acetyl-*myo*-inositol (CXXIII) (105) was treated with methanesulfonyl chloride in pyridine to give selectively the 3-O-methylsulfonyl derivative (CXXIV) (106). On acetylation, CXXIV yielded a pentaacetate, (±)-3-O-methylsulfonyl-*myo*-inositol pentaacetate (CXXV). When compound CXXIV was heated with sodium azide in 2-methoxyethanol, an oily product was d.



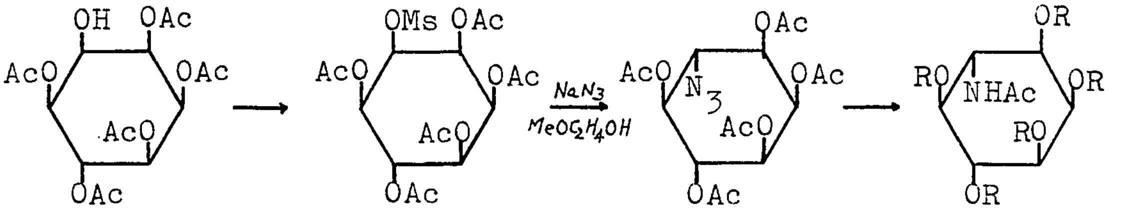
CXXIII

CXXIV R=H
CXXV R=Ac

CXXVI

CXXVII R=Ac
CXXVIII R=H

e.



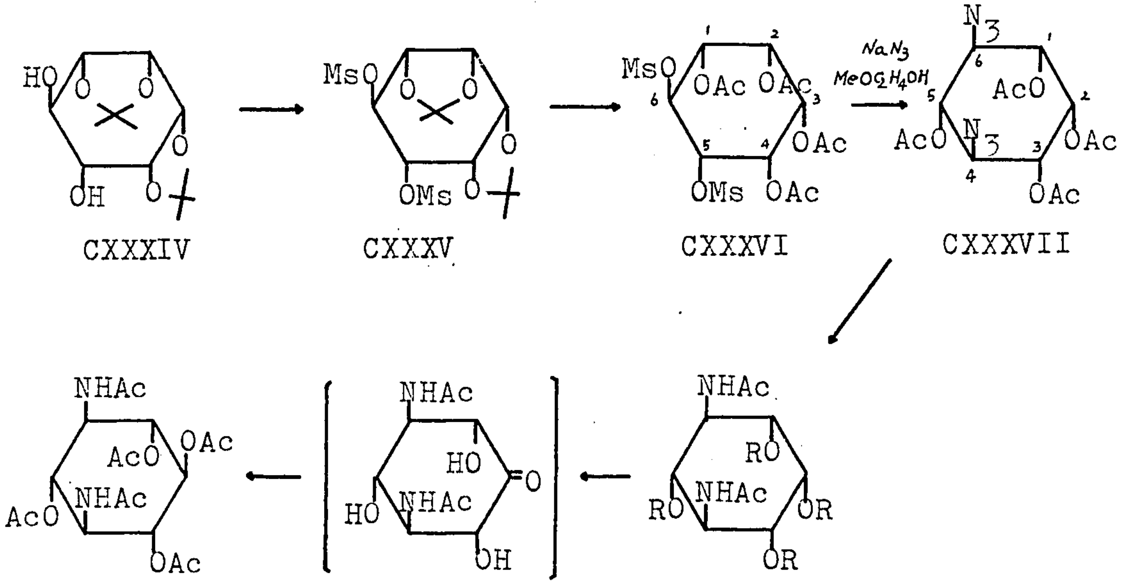
CXXIX

CXXX

CXXXI

CXXXII R=Ac
CXXXIII R=H

f.



CXXXIV

CXXXV

CXXXVI

CXXXVII

XXI

CXL

CXXXVIII R=Ac
CXXXIX R=H

obtained. This was acetylated, reduced with Raney nickel and reacetylated to give a hexaacetylinosamine (CXXVII). The selective deacetylation of CXXVII with ammonia in methanol gave N-acetyl-muco-inosamine-1 (CXXVIII).

e. myo-Inosamine-4 (107)

By a procedure similar to that described under (d), (±)-1,3,4,5,6-penta-O-acetyl-epi-inositol (CXXIX) (108) was converted via the mesylate CXXX and the azido derivative CXXXI into the hexaacetyl (CXXXII) and N-acetyl (CXXXIII) derivatives of myo-inosamine-4.

f. Streptamine (109)

(±)-1,2,3,4-Di-O-isopropylidene-epi-inositol (CXXXIV) (110) was converted to the dimesylate (CXXXV) which was then deacetonated with acetic acid and acetylated to give (±)-5,6-di-O-mesyl-epi-inositol tetraacetate (CXXXVI). When CXXXVI was treated with sodium azide in boiling, aqueous 2-methoxyethanol and the product was subsequently acetylated, 4,6-diazido-4,6-dideoxy-myo-inositol tetraacetate (CXXXVII) was obtained. Catalytic hydrogenation of CXXXVII and acetylation of the product gave hexaacetyl-4,6-myo-inosadiamine (CXXXVIII). Compound CXXXVIII was de-O-acetylated to CXXXIX, which was oxidized with platinum black in a stream of oxygen to give the ketone CXL (111). The ketone was then immediately reduced with sodium amalgam (65,112) in a slightly acidic medium and the reduction product was acetylated affording hexaacetylstreptamine (XXI).

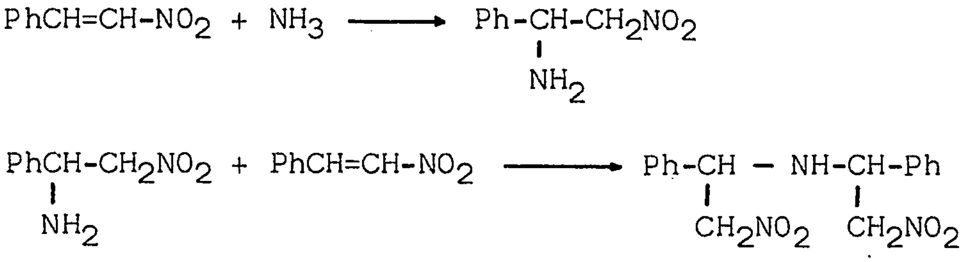
IV. The Reaction of Ammonia with Nitro Compounds as a Possible Route to Aminocyclitols

Among the various methods of introducing an amino group into a carbohydrate molecule there is one which has been applied to a few hexose derivatives and open-chain sugar alcohols but not yet to cyclitols. It is the action of ammonia upon suitable nitro derivatives. Since the aim of this thesis was to elaborate a new aminocyclitol synthesis on the basis of that reaction, as will be outlined more thoroughly in the next chapter, a review of the reaction will be given at first.

In α-nitroalkenes, the olefinic double bond is activated so that it readily adds ammonia, amines, and other nitrogenous bases, whereby the incoming nitrogen atom becomes attached in β-position to the nitro group.

$$-C(NO_2)=CH- \; + \; NH_3 \longrightarrow -CH(NO_2)-CH(NH_2)-$$

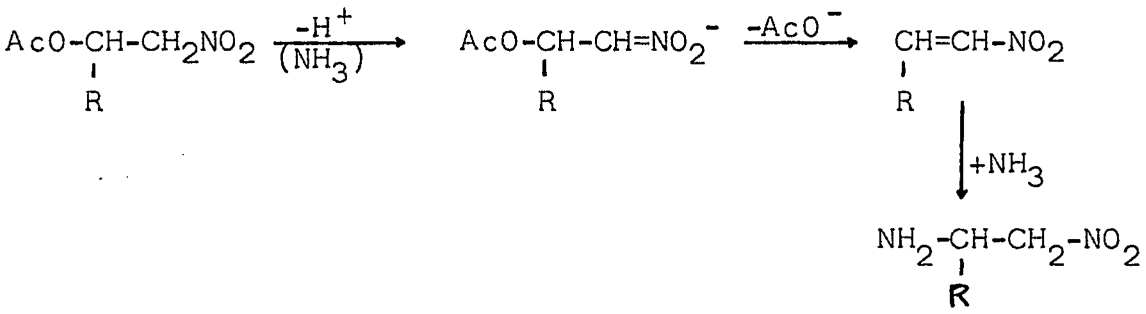
The first reaction of this kind was carried out by Posner (113) who added hydroxylamine to β-nitrostyrene. Later, aliphatic and aromatic amines and hydrazines as well as ammonia were added to β-nitrostyrene and to a variety of simple nitroalkenes (114-119). Although vic-aminonitro compounds can generally be obtained in this manner, complications may sometimes arise. Thus, the products occasionally are not very stable in the free amine state and then need to be stabilized as amine salts or as N-acetyl derivatives. Moreover, the adduct of ammonia to β-nitrostyrene, for instance, has been found to react with a second olefin molecule to give a dinitro sec-amine.



$$\mathrm{PhCH{=}CH{-}NO_2 + NH_3 \longrightarrow Ph{-}\underset{NH_2}{CH}{-}CH_2NO_2}$$

$$\mathrm{Ph\underset{NH_2}{CH}{-}CH_2NO_2 + PhCH{=}CH{-}NO_2 \longrightarrow Ph{-}\underset{CH_2NO_2}{CH} - NH{-}\underset{CH_2NO_2}{CH}{-}Ph}$$

In 1936, Chattaway (120) found that the action of ammonia (or p-toluidine, or phenylhydrazine) upon the acetates of certain β-nitro alcohols did not result in ammonolysis to acetamide (or N-substituted acetamides) as he had expected, but led to vic-nitroamines. This was later confirmed by Irving and Fuller (121,122) who explained that, under the influence of bases, nitro acetates suffer elimination of acetic acid to give intermediary nitroalkenes which rapidly add base forming the final product.

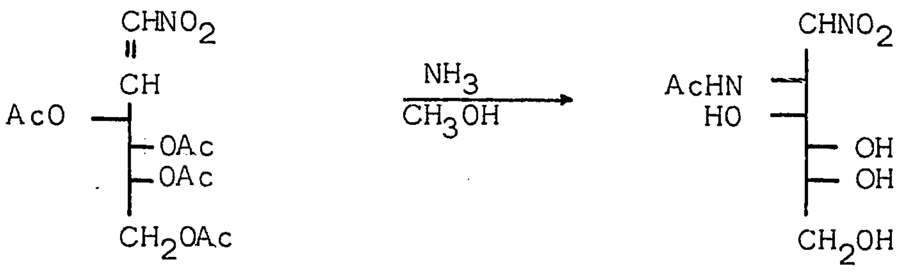


$$\underset{\displaystyle R}{AcO\text{-}\overset{}{CH}}\text{-}CH_2NO_2 \xrightarrow[(NH_3)]{-H^+} \underset{\displaystyle R}{AcO\text{-}CH}\text{-}CH{=}NO_2^- \xrightarrow{-AcO^-} \underset{\displaystyle R}{CH}{=}CH\text{-}NO_2 \xrightarrow{+NH_3} NH_2\text{-}\underset{\displaystyle R}{CH}\text{-}CH_2\text{-}NO_2$$

Therefore, if one wants to synthesize a vic-nitroamine from a nitro compound and ammonia, a β-nitroacetate is a convenient substitute for the less readily accessible and usually less stable α-nitroalkene. This has been shown on several examples (119,123).

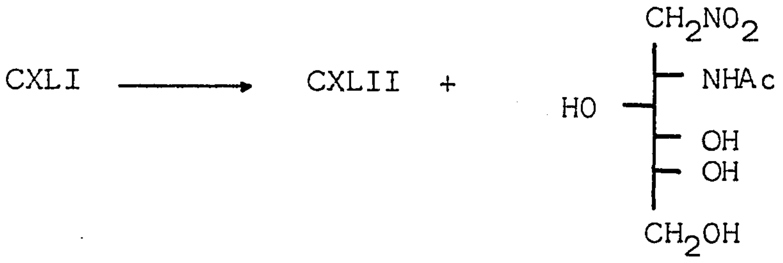
In carbohydrate chemistry both the addition of ammonia or amines to α-nitroalkenes and the elimination-addition with β-nitroacetates have found applications although to date these have been of a rather limited extent.

In 1959, O'Neill (124) allowed to react ammonia with D-arabino-tetraacetoxy-1-nitro-1-hexene (CXLI). By addition of the base to the C=C bond, with concurrent ammonolysis of the ester groupings and migration of one acetyl group to the amine function he obtained 1-nitro-1-deoxy-N-acetyl-D-mannosaminol (CXLII) in 82% yield. The same reaction was independently and almost simultaneously carried out by Sowden and Oftedahl (125) who, in addition



CXLI CXLII

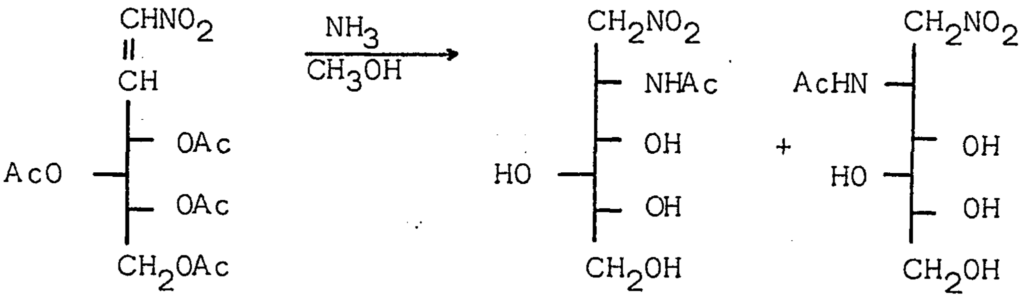
to CXLII, isolated in lesser amount the D-gluco isomer (CXLIII) of compound CXLII. The authors stated that the stereoisomers arose in a ratio of 6:1. More recently,



CXLIII

Gero and Defaye (126) obtained results similar to O'Neill's by working in the enantiomeric L-series; and Satoh and Kiyomoto (127) were able to simplify the procedure and improve the yields by adopting the elimination-addition method and using readily available pentaacetoxy-1-nitro-1-deoxy-D-mannitol as a starting material.

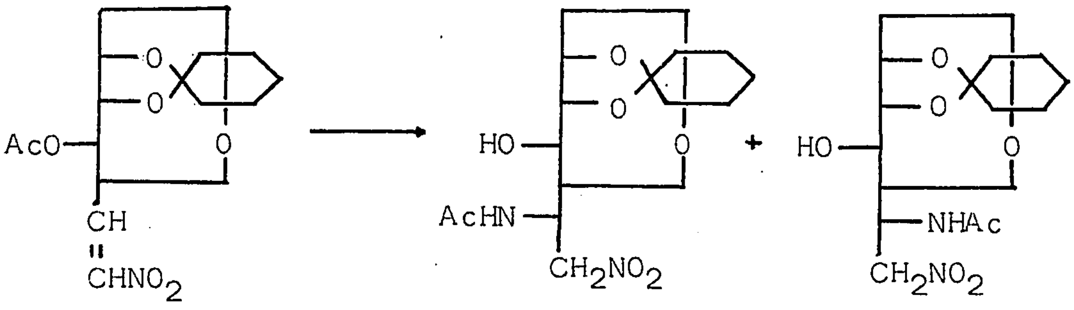
When Sowden and Oftedahl (128) treated with ammonia the D-xylo isomer (CXLIV) of compound CXLI, they observed a course of reaction fully analogous to that mentioned above. Again, two stereoisomeric N-acetyl derivatives were found, of which one, the D-*gulo* derivative (CXLV), predominated over the D-*ido* derivative (CXLVI).



CXLIV CXLV CXLVI

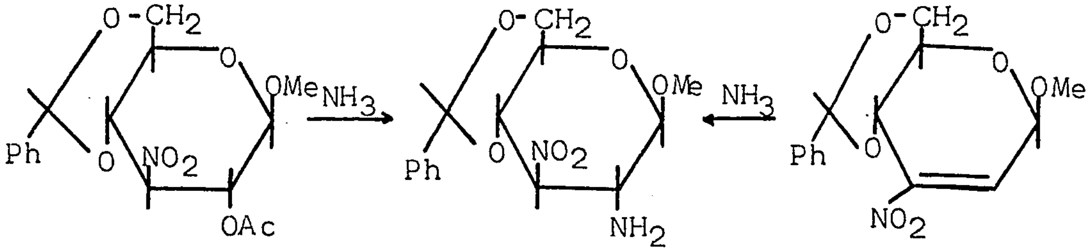
Sowden and associates (129) were able to add also various amines to unsaturated nitroalditols.

The addition of ammonia to 3-O-acetyl-1,2-O-cyclohexylidene-5,6-dideoxy-6-nitro-D-*xylo*-hexofuran-5-enose (CXLVII) which gave a 2:3 mixture of the 5-acetamido-hexose derivatives of D-*gluco* (CXLVIII) and L-*ido* (CXLIX) configurations, was reported by Paulsen (130).



CXLVII CXLIX CXLVIII

All the carbohydrate examples reviewed so far involved compounds containing a terminal nitro group. Recently, however, the principle was applied to sugars that contain a cyclic nitroolefin or β-nitro acetate moiety. Thus, Baer and Neilson (131) obtained methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (CLII) by the action of ammonia upon methyl **2**-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (CL) (132) or upon methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-hex-**2**-enopyranoside (CLI).



CL CLII CLI

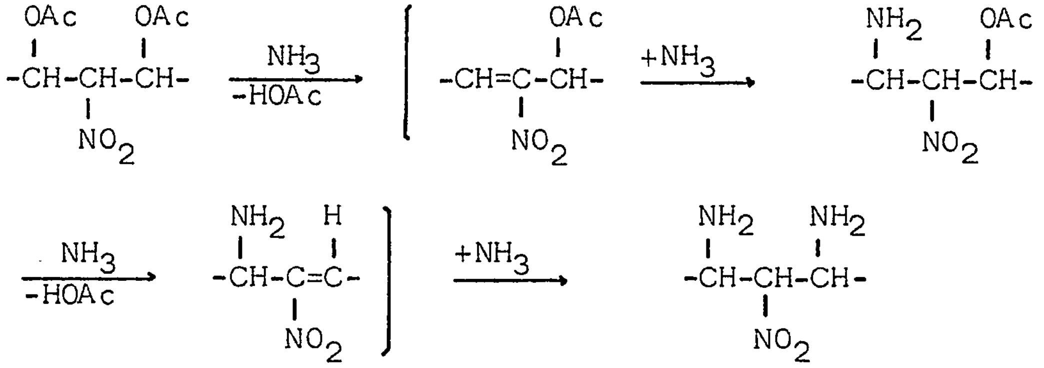
The reactions proceeded in excellent yields and furnished the <u>gluco</u> aminonitro derivative (CLII) as the predominant product along with about 10% of an isomer of undetermined configuration. The aminonitro derivative CLII was then converted in several steps into 2,3-amino-2,3-dideoxy-D-glucose.

Diethylamine, piperidine and ethyl glycine (133) as well as anthranilic acid (134) were among the nucleophiles that have been used successfully in analogous reactions with nitro glycosides.

In view of these results it appeared worthwhile to investigate whether the method can be employed also for syntheses of nitrogenous cyclitols.

THE PURPOSE OF THIS RESEARCH

First, it was interesting to study the course of the reaction that might take place when ammonia is allowed to attack a secondary nitroalkane whose nitro group is flanked on both sides by acetoxy functions. It was considered that two amino groups might be introduced, thus:



$$-\overset{\mathrm{OAc}}{\mathrm{CH}}-\underset{\mathrm{NO_2}}{\mathrm{CH}}-\overset{\mathrm{OAc}}{\mathrm{CH}}- \xrightarrow[-\mathrm{HOAc}]{\mathrm{NH_3}} \left[-\mathrm{CH}=\underset{\mathrm{NO_2}}{\mathrm{C}}-\overset{\mathrm{OAc}}{\mathrm{CH}}- \xrightarrow{+\mathrm{NH_3}} -\overset{\mathrm{NH_2}}{\mathrm{CH}}-\underset{\mathrm{NO_2}}{\mathrm{CH}}-\overset{\mathrm{OAc}}{\mathrm{CH}}- \xrightarrow[-\mathrm{HOAc}]{\mathrm{NH_3}} -\overset{\mathrm{NH_2}}{\mathrm{CH}}-\underset{\mathrm{NO_2}}{\mathrm{C}}=\overset{\mathrm{H}}{\mathrm{C}}- \right] \xrightarrow{+\mathrm{NH_3}} -\overset{\mathrm{NH_2}}{\mathrm{CH}}-\underset{\mathrm{NO_2}}{\mathrm{CH}}-\overset{\mathrm{NH_2}}{\mathrm{CH}}-$$

Applied to suitably substituted nitrocyclitols such a reaction should lead to 1,3-diamino-2-nitrocyclitols which could serve as starting points for a variety of derivatives including 1,2,3-triamino, 1,3-diamino-2-hydroxy, 1,3-diamino-2-keto, and 1,3-diamino-2-deoxy compounds.

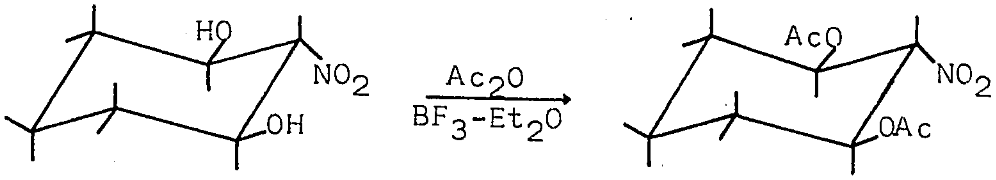
The synthesis of compounds of this kind would be of general interest, and it could conceivably open a new avenue to streptamine and related antibiotics components. The feasibility of the approach was to be studied, first on readily available trans,trans-1,3-diacetoxy-2-nitrocyclohexane, and later on pentaacetoxy nitrocyclohexanes (deoxynitroinositol pentaacetates).

RESULTS AND DISCUSSION*

I. The Action of Ammonia upon *trans,trans*-1,3-Diacetoxy-2-nitrocyclohexane

A. *trans,trans*-1,3-Diacetoxy-2-nitrocyclohexane

trans,trans-2-Nitro-1,3-cyclohexanediol (I) was prepared by the nitromethane cyclization of glutaric dialdehyde according to Lichtenthaler (85). Its acetylation to *trans,trans*-1,3-diacetoxy-2-nitrocyclohexane (II) was accomplished in a yield of 95% by the use of acetic anhydride and boron trifluoride, whereas the earlier author (85) had obtained II in a yield of 75% by catalysis with sulfuric acid. Boron trifluoride catalysis had not been tried in acetylations of nitro alcohols until recently when, in concurrent work in this Laboratory, it was found to be a very useful method (131,135). Samples of the diacetate II prepared by both procedures gave an undepressed mixed melting point and identical infrared spectra.



I

II

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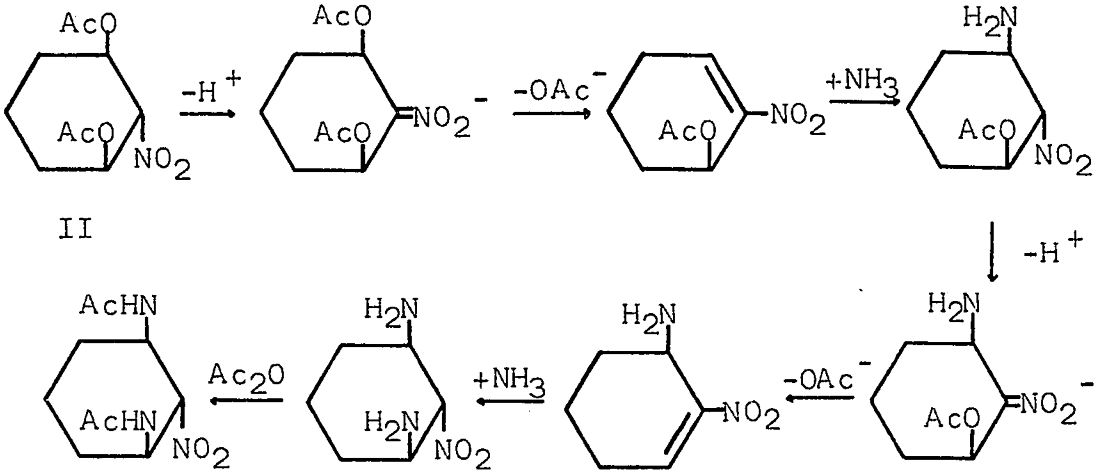
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

B. *trans,trans*-1,3-Diacetamido-2-nitrocyclohexane

trans,trans-1,3-Diacetoxy-2-nitrocyclohexane (II) in tetrahydrofuran solution was allowed to react with concentrated aqueous ammonia at 40° for eight hours. From the reaction mixture could be isolated an impure product that showed no sharp melting point and tended to decompose on standing in the air for one day. The material was sparingly soluble in methanol or ethanol. The infrared spectrum of a freshly prepared sample showed bands at 3350 and 1545 cm^{-1} and absence of absorption in the ester carbonyl region, in accordance with the structure of an aminonitro compound. Assuming that the material consisted largely of the diamine III, its yield was 38-44%. However, in view of the difficulty of obtaining a pure and stable product in satisfactory yields, isolation of III was abandoned in later experiments, and the crude reaction mixture was directly acetylated. In this way a stable, crystalline acetyl derivative, m.p. 285-286° with decomposition, was obtained. It proved to be 1,3-diacetamido-2-nitrocyclohexane (IV), and its yield based on II was 70.5%. Compound IV gave correct analytical data and its infrared spectrum exhibited bands at 3300 cm^{-1} (NH stretching vibration, bonded), 1660 cm^{-1} (amide-I band), and 1560 cm^{-1} (overlapping amide-II and asymmetrical nitro bands). Owing to poor solubility in suitable solvents, no n.m.r. spectrum of IV could be obtained, but the trans, trans configuration was deduced from spectra of derivatives (V,VI) to be described later.

No examples have been found in the literature for an introduction of two amino groups in β and β′ positions of aliphatic nitro compounds. The following mechanism is postulated.



II

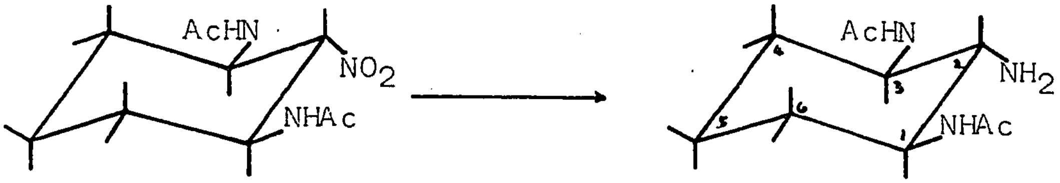
IV

III

C. Hydrogenation of trans,trans-1,3-diacetamido-2-nitrocyclohexane

a. trans,trans-2-Amino-1,3-diacetamidocyclohexane

1,3-Diacetamido-2-nitrocyclohexane (IV) was hydrogenated catalytically in acetic acid over prehydrogenated platinum dioxide. The uptake of hydrogen at room temperature and atmospheric pressure was fast initially, but the complete consumption of three moles of hydrogen, as required to convert the nitro into an amino group, took about 20 hours. A colorless crystalline product, m.p. 263-265° with decomposition, was obtained in a yield of 58-61%. Its elemental analysis agreed with 2-amino-1,3-diacetamidocyclohexane (V). Infrared absorptions were at 3370 cm^{-1} ($-NH_2$ stretching); 3300 cm^{-1}, (-NH stretching); 1640 cm^{-1} (amide-I band) and 1560 cm^{-1} (overlapping of $-NH_2$ bending and amide-II band). In the fingerprint region the spectrum was clearly different from that of the nitro precursor (IV).



IV

V

Conclusive evidence for the structure of V came from the n.m.r. spectrum (Fig. 9). The spectrum was taken in deuterium oxide, and the τ-values are given with reference to the DOH signal for which τ=5.20 ppm was assumed. The spectrum showed a broad peak at 6.38τ(2H); a triplet centered at 7.53τ(1H); a sharp singlet at 8.02τ and a multiplet centered at 8.42 τ which overlapped partially and together integrated to a total of 12 protons. The signals were assigned as follows.

The peak at lowest field is caused by the protons on the carbons that bear acetamido substituents (C-1 and C-3). Chemical shifts of similar magnitude (5.67-6.27τ) have been recorded for similar cases (100, 101,103,136,137). The triplet at 7.53τ, of one-proton intensity, must be due to H-2. Its symmetry and large splitting of 10.5 c.p.s. proves that H-2 must be axial and equally coupled with axial protons H-1 and H-3 (100, 138). It follows that all the three nitrogen functions must be equatorially arranged, i.e., possess the <u>trans</u>, <u>trans</u> configuration. As one example of analogous reasoning may be quoted the assignment of configurations to two diastereoisomeric 2-acetoxy-1,3-dimethoxycyclohexanes by Lemieux et al. (139). The sharp signal at 8.02 τ is attributed to the two N-acetyl groups. The fact that these two groups give only one signal supports the view that both groups have the same conformation, for it is well known that axial and equatorial acetamido signals have appreciable chemical shift differences (0.10-0.15 ppm) (85,97,100,101,103,135,137,140). In fact, such chemical shifts have frequently been used to make conformational assignments. However, most available data pertain to chloroform solution with an internal standard, and although similar regularities have been recorded for deuterium oxide solutions (140), in the absence of a reliable standard an assignment on this basis alone would be ambiguous. Finally, the multiplet at highest field is attributable to the three methylene groups (C-4,C-5,C-6) in the ring, in accordance with the literature giving a range of 7.37-9.28τ (100,136).

b. trans,trans-1,2,3-Triacetamidocyclohexane

The substance contained in the mother liquor of V was acetylated in methanol solution with acetic anhydride. 1,2,3-Triacetamidocyclohexane (VI) was obtained as colorless crystals that sublimed at 300°. From the

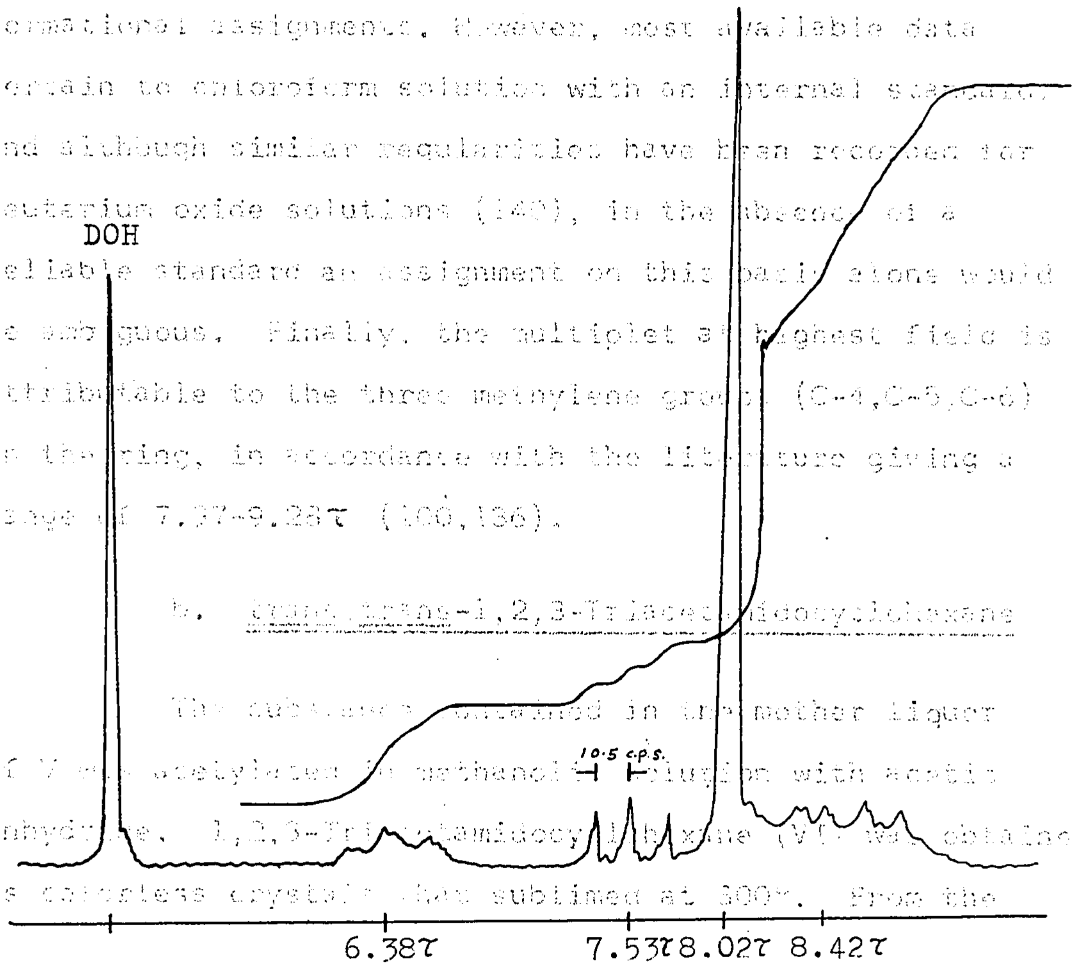
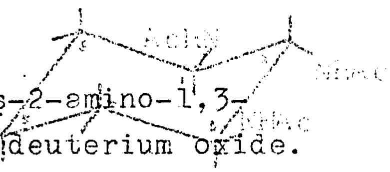


Fig.9. N.M.R. spectrum of trans,trans-2-amino-1,3-diacetamidocyclohexane (V) in deuterium oxide.

V

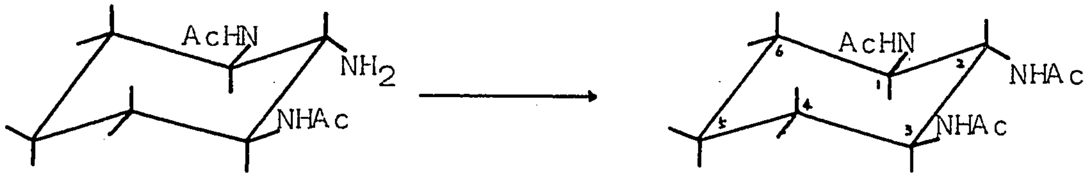


VI

for it is well known that axial and equatorial acetamido signals have appreciable chemical shift differences (0.10-0.15 ppm) (85,97,100,101,103,136,137,140). In fact, such chemical shifts have frequently been used to make conformational assignments. However, most available data pertain to chloroform solution with an internal standard, and although similar regularities have been recorded for deuterium oxide solutions (140), in the absence of a reliable standard an assignment on this basis alone would be ambiguous. Finally, the multiplet at highest field is attributable to the three methylene groups (C-4,C-5,C-6) in the ring, in accordance with the literature giving a range of 7.97-9.28τ (100,136).

b. <u>trans,trans</u>-1,2,3-Triacetamidocyclohexane

The substance contained in the mother liquor of V was acetylated in methanolic solution with acetic anhydride. 1,2,3-Triacetamidocyclohexane (VI) was obtained as colorless crystals that sublimed at 300°. From the



V

VI

amount of VI isolated it was calculated that at least 32-39% of V must have been present in the mother liquor. Therefore, the total yield in amine from the nitro compound IV was 93-97%.

The elemental analysis of the triacetyl derivative (VI) fitted the formula $C_{12}H_{21}N_3O_3$, and the infrared spectrum showed absorptions at 3300 cm^{-1} (-NH-stretching); 1645 cm^{-1} (amide-I band) and 1550 cm^{-1} (amide-II band). The absorption at 3370 cm^{-1} ($-NH_2$ stretching) present in V had disappeared, and the fingerprint regions of V and VI differed considerably.

Additional proof for the structure of VI came from n.m.r. studies. Due to the poor solubility of the compound in chloroform, a spectrum in that solvent failed to give information about the ring protons, but it did suggest that the acetamido groups were all of the same orientation, as only one signal (at 8.05 τ) was seen. The τ-value was in agreement with their equatorial disposition (85,97,100,101,103,136,137,140). A spectrum taken in deuterium oxide is depicted in Fig. 10. Again, the τ-values refer to the DOH peak taken to be at 5.20 τ. The group of signals consisting of a sharp singlet at 8.05 τ and a multiplet centered at 8.54 τ, with a total intensity corresponding to 15 protons, can be assigned to the nine protons of the three acetamido groups and the six protons at C-4, C-5 and C-6 (100,136). The broad peak at

6.24 τ (3H) is caused by the ring protons at C-1, C-2 and C-3 (100,101,103,136,137). Like in the chloroform spectrum, the single resonance given by the acetamido groups indicates that they are in identical conformations and, therefore, in trans,trans relationship.

Since the catalytic hydrogenation of the diacetamidonitro compound (IV) was carried out in acidic medium, which is known to favor retention of configuration (141), the establishment of the trans,trans configuration for V and VI is proof also for the stereochemistry of IV.

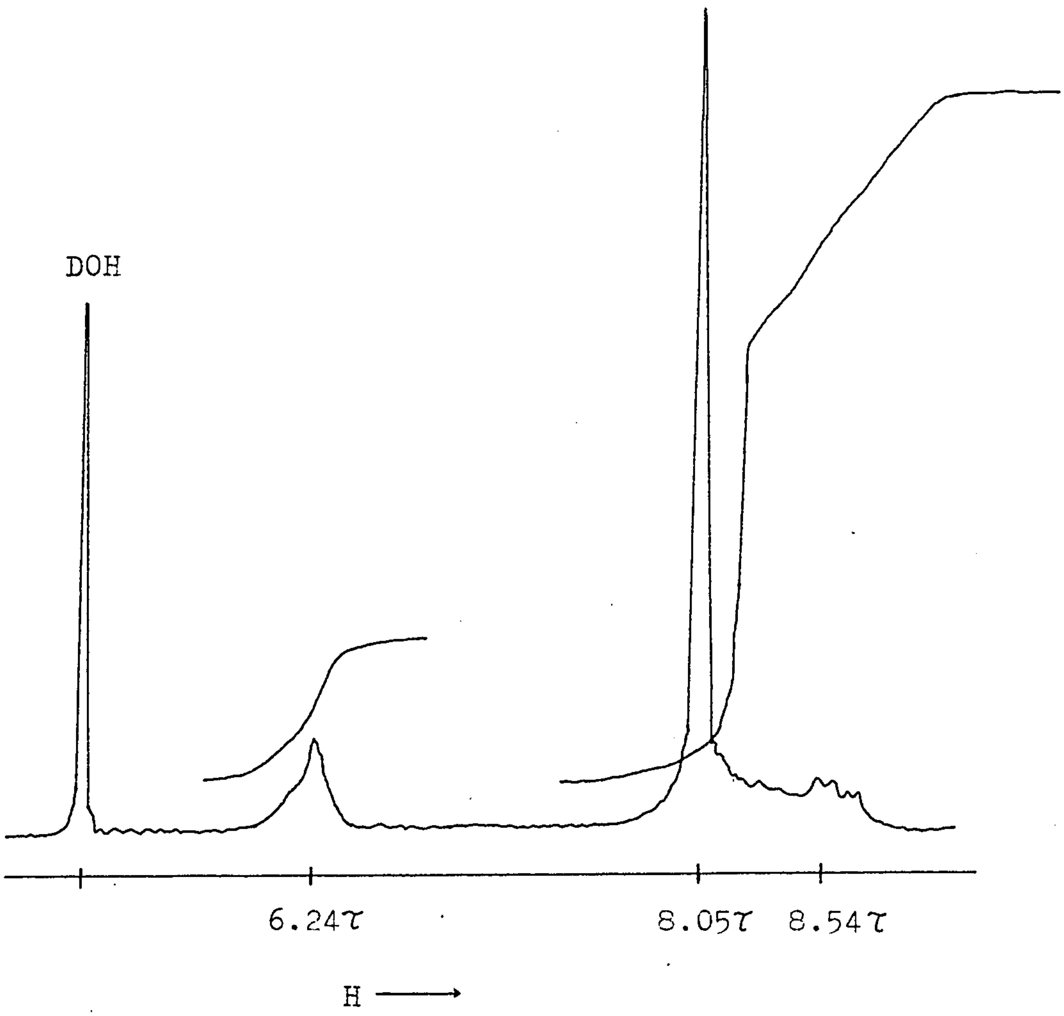


Fig.10. N.M.R. spectrum of trans,trans-1,2,3-triacetamidocyclohexane (VI) in deuterium oxide.

II. Oxidation of 1,3-Diacetamido-2-nitrocyclohexane to 2,6-Diacetamidocyclohexanone

The usual method for conversion of primary or secondary nitroalkanes into aldehydes or ketones, respectively, is the Nef reaction which consists in the action of strong mineral acid upon the sodium nitronate (142).

$$2R_2C{=}NO_2Na + H_2SO_4 \longrightarrow 2R_2C{=}O + N_2O + Na_2SO_4 + H_2O$$

Unfortunately, the reaction gives poor yields or fails with cyclic, sterically hindered nitro compounds such as nitroinositols (143). However, in 1962 Shechter et al. (144) were successful in converting certain sterically hindered nitro compounds into carbonyl compounds by permanganate oxidation, and their procedure was adopted in the present case.

$$3R_2C{=}NO_2K + 2KMnO_4 + H_2O \longrightarrow 3R_2C{=}O + 2MnO_2 + 3KNO_2 + 2KOH$$

1,3-Diacetamido-2-nitrocyclohexane (IV) was dissolved in aqueous, 0.1<u>N</u> potassium hydroxide, and magnesium sulfate was added to buffer the mixture which was then oxidized with a slight excess (3-7%) of potassium permanganate at 0-5°.

Since Shechter did not state the reaction times employed in his examples, and since all his reaction products could be isolated by steam-distillation (which was not expected to be feasible in our case), the most suitable ways of operation had to be worked out by trial. An initial difficulty existed in the poor solubility of IV in aqueous alkali, which made necessary a prolonged trituration for obtaining the nitronate solution. The required amount of permanganate was added in small portions, over a period of about 1.5-2 hours in 0.5 mmole runs or 3.5-4 hours in 1-mmole runs. Too rapid an addition was found to decrease substantially the yield of ketone.

After the addition was complete, the filtered solution was acidified slightly and evaporated to dryness. The residue was exhaustively extracted with chloroform. From the extract crystallized a small amount (3-6%) of starting material, and upon concentration the ketone VII could be isolated as colourless needles in 62-70% yield. Use of a 30% excess of permanganate did not improve the yield.

2,6-Diacetamidocyclohexanone (VII) in alkaline solution has no ultraviolet absorption in the region of 250 $m\mu$, which indicates that the nitro group is no longer present. (Alkanenitronates absorb strongly in that region.) The infrared spectrum showed strong ketone carbonyl absorption at 1730 cm^{-1}. Other bands were at 3280 cm^{-1} (-NH - stretching); 1645 cm^{-1} (amide-I band); 1565 cm^{-1} (amide-II band). Upon heating, the compound decomposed over a range of 206-225° without melting. Elemental analysis confirmed the composition $C_{10}H_{16}N_2O_3$.

The n.m.r. spectrum of VII, taken in deuterated chloroform, gave a sharp peak at 7.95 τ, in the region where axial acetamido groups normally resonate (85,97,100, 101,103,136,137,140). The acetamido groups might nevertheless be equatorial, however, and the signal might be shifted downfield from its normal position near 8.05 τ by a deshielding effect exerted by the adjacent, magnetically anisotropic carbonyl group. A similar case has been found by Hasegawa and Sable (145) in pentaacetyl-scyllo-(myo)-inosose which, although it contains no axial acetoxyl groups, gives a signal corresponding to two acetoxyls at 7.84 τ, i.e., in the middle of the "axial" acetoxy region, about 0.1 ppm downfield from the "equatorial" acetoxy region. This signal probably represented the acetoxyl groups adjacent to the ring carbonyl group.

In order to characterize the ketone VII further, its 2,4-dinitrophenylhydrazone (VIII) was made. It was isolated in 69% yield as fine yellow crystals with a sharp melting point, 269-270°, and its analysis was correct for $C_{16}H_{20}N_6O_6$. The infrared spectrum showed absence of the keto carbonyl group; the amide-I and amide-II bands were present at 1675 and 1540 cm^{-1}, respectively, and strong aromatic nitro frequencies occurred at 1515 and 1500 cm^{-1}.

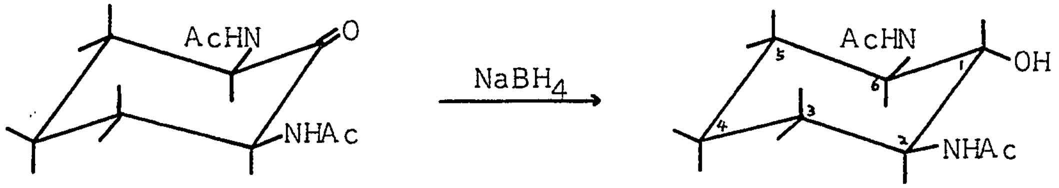
Due to the poor solubility in chloroform and methanol, no n.m.r. studies could be made on VIII.

III. The Reduction of 2,6-Diacetamidocyclohexanone

The keto group of compound VII was expected to be reduced to a hydroxyl group by sodium borohydride and to a methylene group by Clemmensen reduction.

A. Sodium Borohydride Reduction

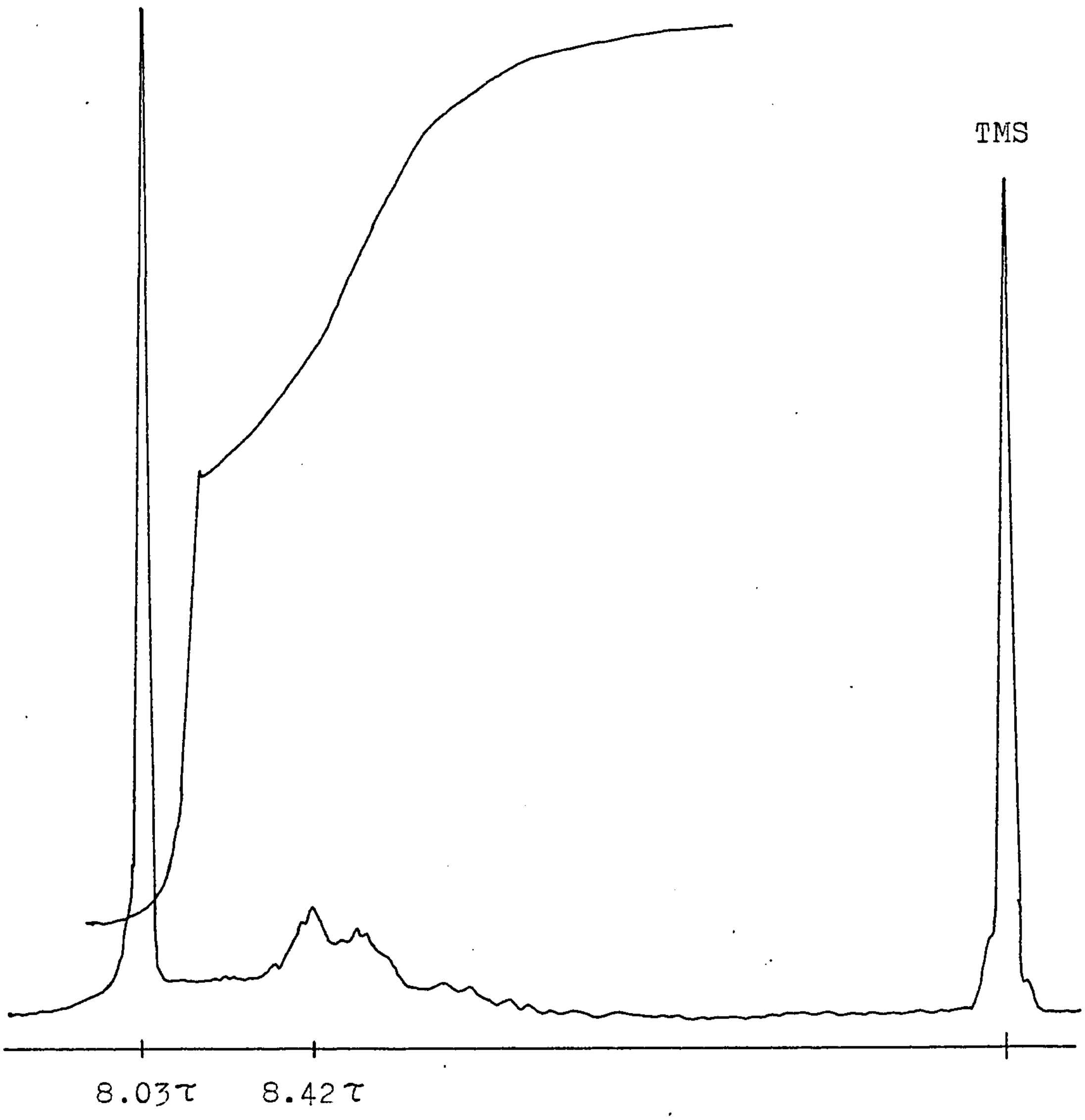
a. trans,trans-2,6-Diacetamidocyclohexanol



VII IX

2,6-Diacetamidocyclohexanone (VII) was reduced with sodium borohydride to give 2,6-diacetamidocyclohexanol (IX), in 65% yield. This compound sublimed around 210° and decomposed at 286.5-288°. The elemental analysis agreed with the composition $C_{10}H_{18}N_2O_3$. The infrared spectrum indicated that the keto carbonyl group present in VII had disappeared. Absorptions were at 3380 cm^{-1}, 3140 cm^{-1}, 3090 cm^{-1} (OH and NH stretching); 1630 cm^{-1} (amide-I band); 1550 cm^{-1} (amide-II band).

Since the alcohol was insufficiently soluble in chloroform, its n.m.r. spectrum was measured in methanol (Fig. 11). Hasegawa and Sable (145) compared the chemical

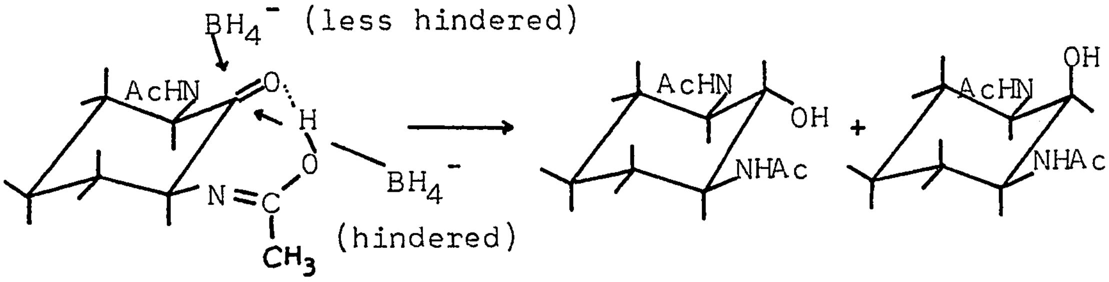


H ⟶

Fig.11. N.M.R. spectrum of trans,trans-2,6-diacetamido-cyclohexanol (IX) in methanol.

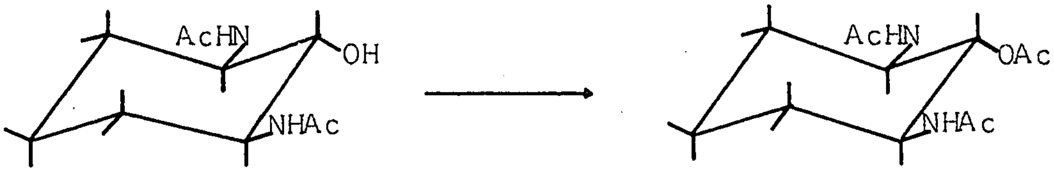
shift values of acetoxy and acetamido groups in chloroform with those obtained in mixtures of chloroform and methanol. They noticed only small solvent effects which did not cause ambiguities in conformational assignments. We have measured the acetoxy signal given by trans,trans-1,3-diacetoxy-2-nitrocyclohexane (II) in pure methanol and found a value of 7.98τ which was practically the same as that reported (85) for chloroform solution (7.99 τ). It therefore appears that the polarity difference of methanol and chloroform does not make comparisons of chemical shift data invalid. Hence, the sharp singlet at 8.03τ of compound IX is assigned to two equatorial acetamido groups (85,97,100,101,103,136,137,140). The intensity of the singlet is the same as that of the broad peak which is centered at 8.42τ and corresponds to the six ring protons at C-3, C-4, C-5 (100,136). All the other peaks are overlapped with the bands or side bands of methanol. The conformation of the hydroxyl group could not be determined from the spectrum, but a study of the O-acetyl derivative (XI) described in the next section revealed that compound IX has the trans,trans configuration. This fact was somewhat surprising since the literature (146) on borohydride reductions of inososes states that formation of axial hydroxyl groups takes place predominantly. It is possible that the cis,cis isomer (X) was also formed, to a maximum extent of 35%, but no attempt has been made to verify this.

In order to explain the preferential formation of the trans,trans compound IX, one might propose as a hypothesis hydrogen bonding of the keto group with a neighboring, enolized acetamido group. This could hinder equatorial approach of the borohydride anion so that axial approach, which places the oxygen atom into the equatorial position, becomes the predominant pathway. Alternatively, the two acetamido groups might be strongly solvated with water molecules and thereby exert a directing effect on the reaction. Further work will be required to provide a definite explanation for the observed reaction course.



VII IX X

b. trans,trans-2,6-Diacetamidocyclohexanol acetate



IX XI

The O-acetylation of compound IX was accomplished by two methods. In the first method, acetic anhydride and boron trifluoride were used. However, difficulties arose in the crystallization of the product and a low yield resulted. In the second method, the hydroxy compound was dissolved in glacial acetic acid and reacted with acetyl chloride. This gave the crystalline acetate in 86% yield. Its elemental analysis was in accord with the formula $C_{12}H_{20}N_2O_4$. The acetoxyl group gave infrared bands at 1730 cm^{-1} (C=O stretching) and 1245 cm^{-1}, 1050 cm^{-1} (C-O-C stretching). The amide peaks appeared as usual at 3300 cm^{-1} (NH stretching), 1650 cm^{-1} (amide-I), 1565 cm^{-1} (amide-II).

Because of poor solubility in chloroform, the n.m.r. spectrum of XI was taken in methanol (Fig. 12). Two sharp singlets at 8.03τ and 8.11τ were attributed to an equatorial acetoxyl group and two equatorial acetamido groups (85,97,100,101,103,136,137,140,145). A multiplet due to the six ring protons attached to C-3, C-4 and C-5 was centered at 8.5τ (100,136) and extended beneath the acetamido signal. The combined integral of the acetamido methyl and ring methylene signals was four times that of the acetoxy signal. The ring hydrogens at C-1, C-2, C-6 gave poorly resolved signals at lower field. However, from the equatorial arrangements of the substituents as determined by their chemical shifts followed the trans,trans-

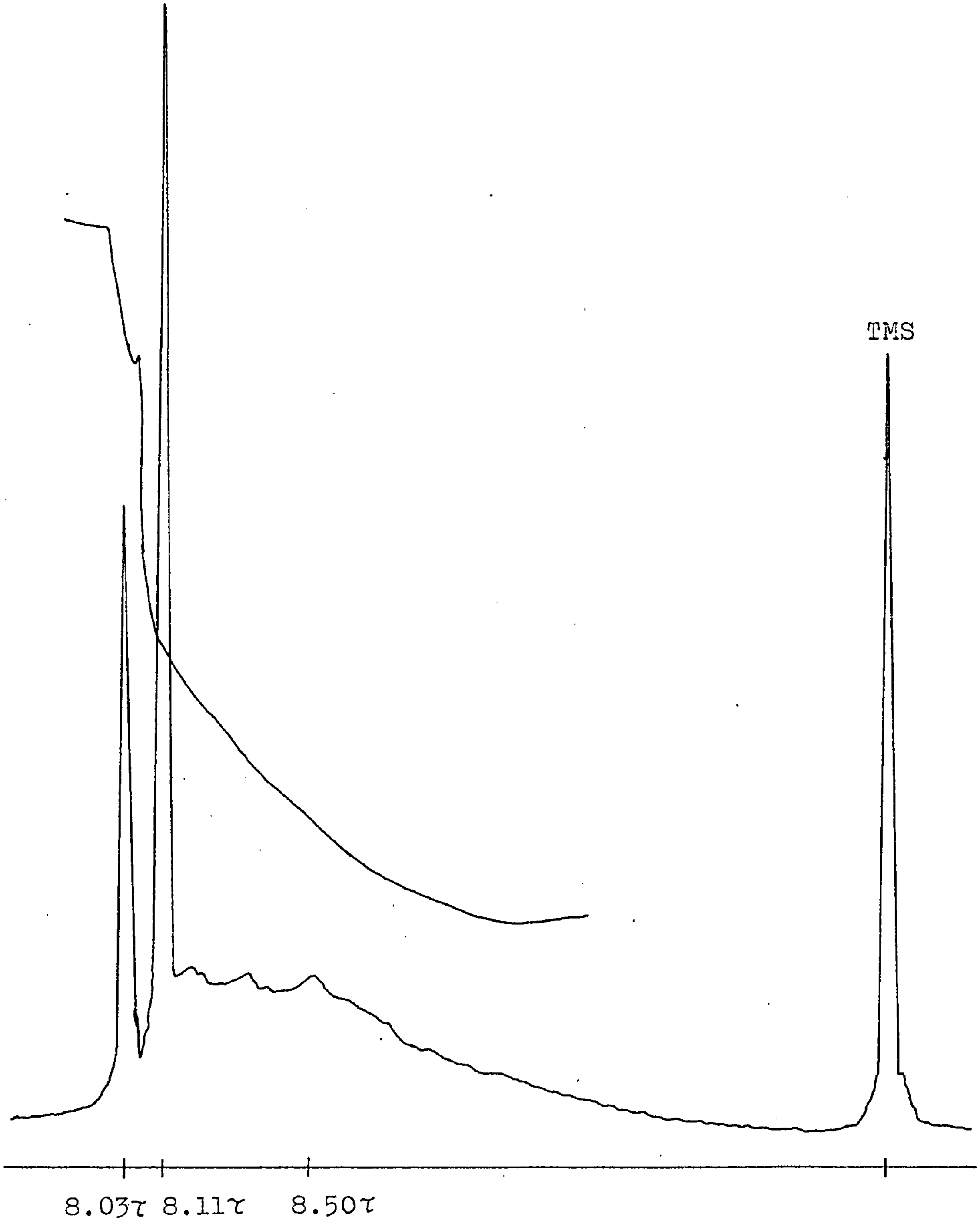
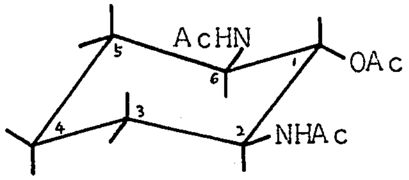


Fig.12. N.M.R. spectrum of trans,trans-2,6-diacetamido-cyclohexanol acetate (XI) in methanol.

configuration of XI.



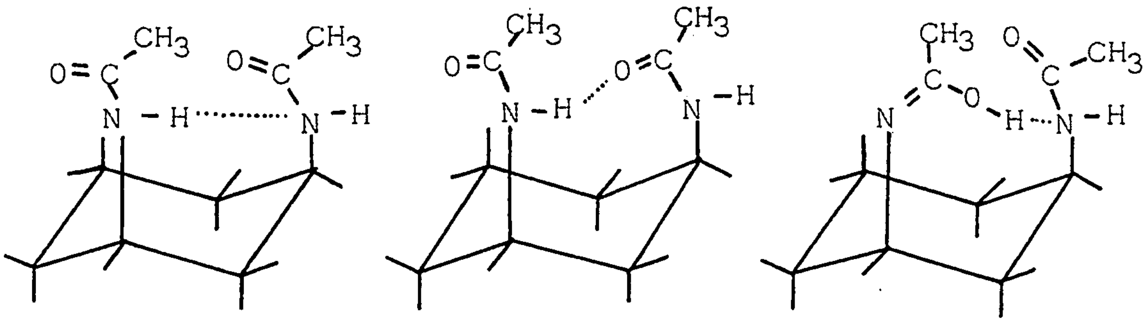
XI

B. Clemmensen Reduction

The keto carbonyl group in compound VII was expected to be reduced to a methylene group by zinc amalgam and hydrochloric acid. Reductions of cycloses to deoxycyclitols have been done only by catalytic hydrogenation over platinum dioxide in acid solution, but cyclitols were the main products in such cases (112, 147,148).

The Clemmensen reduction was therefore attempted, despite the possibility of complications that might arise from a partial loss of N-acetyl groups in the strongly acidic medium. A crystalline compound was isolated in a yield of 36%. The product sublimed near 200° and decomposed at 265-267°. Its infrared spectrum showed absorptions attributable to free and bonded NH stretching frequencies (3460 cm^{-1}, 3320 cm^{-1}, 3300 cm^{-1}, 3100 cm^{-1}) and also amide-I and amide-II bands (1640 cm^{-1}, 1565 cm^{-1}). It lacked the typical absorptions of amine hydrochlorides (2800-2400 cm^{-1} and 1500 cm^{-1}). In view of these data and a correct nitrogen analysis it is considered possible that the compound was 1,3-diacetamidocyclohexane (XII), but further confirmation is required*.

The presence of infrared bands which suggested (at least partial) hydrogen bonding of the amide groups could be due to intermolecular association,but perhaps also to intramolecular bonding as depicted:



XII

Unfortunately, insufficient material was available to settle unambiguously the nature of this product, although various modifications of the reduction and work-up procedure were tried in order to improve the yield.

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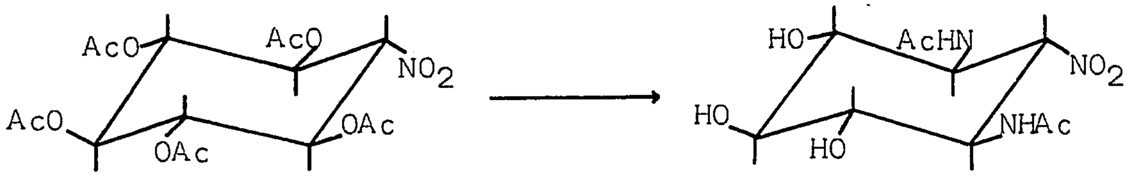
* In the literature (149) a 1,3-diacetamidocyclohexane of m.p. 256° has been described. It was obtained by acetylation of the diamine that arose from reduction, with sodium and alcohol, of 1,3-cyclohexanedione dioxime. No comment on the stereochemistry of the compound was made.

IV. The Action of Ammonia upon Pentaacetyl-deoxynitro-*scyllo*-inositol

Deoxynitro-*scyllo*-inositol was prepared from 1,2-O-isopropylidene-α-D-glucofuranose according to the literature (84). The nitro inositol was then acetylated with acetic anhydride, using either concentrated sulfuric acid (84) or boron trifluoride as a catalyst.

Pentaacetyl-deoxynitro-*scyllo*-inositol (XIII), m.p. 256-257° (lit. 255-256°) (84), reacted with ammonia in dioxane and tetrahydrofuran much more easily than compound II. The reaction mixture, after only one hour's standing at room temperature, was evaporated and the product was immediately N-acetylated with acetic anhydride in methanol. 1,3-Diacetamido-2-deoxy-2-nitro-*scyllo*-inositol (XIV) was obtained in a yield of 76%. The product sintered at 290° and decomposed at 295-299°. Elemental analysis agreed with the formula $C_{10}H_{17}N_3O_7$. The product showed several infrared bands in the 3400-



XIII XIV

3100 cm^{-1} region (OH, NH stretching). There were also bands at 1640 cm^{-1} (amide-I band) and 1560 cm^{-1} (overlapping amide-II and asym. nitro bands), but no bands attributable to acetoxy groups (in the 1740 and 1265 cm^{-1} region). As expected, the O-acetyl groups at C-4, C-5 and C-6 were ammonolyzed during the reaction.

N.M.R. spectra were taken both in deuterium oxide and in methanol. In both cases one sharp singlet was observed for the two acetamido groups, which were thereby proved to possess identical conformations. In the methanol spectrum the τ-value of the signal was 8.05, indicating equatorial arrangement of the acetamido groups (cf. the discussion on p.67, 25,49,54,73,75,93,107,150). It was not possible to analyze the signals given by the ring protons.

It is hoped that, in analogy to the reactions described in sections II and III, oxidative removal of the nitro group followed by reduction will provide a route from the 1,3-diacetamido- 2 -deoxy- 2 -nitroinositol (XIV) to streptamine and 2-deoxystreptamine.

EXPERIMENTAL

The melting points were taken in capillaries in an electrically heated aluminium block apparatus. All evaporations were done in vacuo at 30-35° (bath temperature) unless otherwise indicated. Infrared spectra were obtained from nujol mulls on a Perkin-Elmer Infracord or a Beckman IR-8 instrument. Ultraviolet absorptions were measured using a Perkin-Elmer Ultraviolet-Visible spectrophotometer, Model 202. The n.m.r. data were obtained with a Varian HA-60 instrument.

trans,trans-2-Nitro-1,3-cyclohexanediol (I)

The condensation of glutaraldehyde with nitromethane in the presence of sodium carbonate was performed according to the method of Lichtenthaler (85). trans,trans-2-Nitro-1,3-cyclohexanediol (I) was obtained in yields of about 47%. The product melted at 162-164° (Lit. (85), m.p. 159-161°) and showed infrared absorptions at 3320 cm^{-1} (s, OH stretching) and 1550 cm^{-1}, 1370 cm^{-1} (s, NO_2 stretching).

trans,trans-1,3-Diacetoxy-2-nitrocyclohexane (II)

To a suspension of 5g of the diol (I) in 12.5 ml of acetic anhydride, boron trifluoride-etherate was added drop by drop with swirling until all the crystals were dissolved. Heat was evolved. The light brown solution was then allowed to stand at room temperature for 15 minutes. The reaction mixture was evaporated, twice with the addition of cold methanol and finally to dryness. The crystalline residue was dissolved in hot ethanol, and water was then added until the solution became turbid. After standing at 4° for a few hours, the diacetate II (6.671g. m.p. 91-93°) crystallized as colourless needles. From the mother liquor a second crop of II (0.586g, m.p. 89-91°) was obtained, which brought the total yield to 7.26g (95.4%). Recrystallization from ethanol-water gave colourless needles melting at 90-91.5°. Literature (85), m.p. 89-90°. Infrared bands were at 1750 cm^{-1} (s, C=O stretching) and 1575 cm^{-1}, 1385 cm^{-1} (s, NO_2 stretching), and 1240 cm^{-1}, 1040 cm^{-1} (m, C-O-C stretching).

trans,trans-1,3-Diacetamido-2-nitrocyclohexane (IV)

trans,trans-1,3-Diacetoxy-2-nitrocyclohexane (II) (5g) was dissolved in 50 ml of tetrahydrofuran, and 50 ml of aqueous, concentrated ammonium hydroxide was then added at room temperature. The reaction mixture was stirred at 40° for 8 hours. At the end of this time, the two layers were separated, and the aqueous layer was extracted four times with tetrahydrofuran in 50 ml portions. The combined tetrahydrofuran layer and extracts were evaporated at a low temperature ($< 30°$) to give a pale yellow syrup which was then taken up in 25 ml of methanol. After cooling in an ice bath, acetic anhydride (10 ml) was added. The reaction mixture was stirred at room temperature for 16 hours during the course of which a solid gradually appeared in the solution. The first crop was then collected by filtration; 3.22g, decomposition at 283-284°. The mother liquor was evaporated repeatedly with methanol at low temperature ($< 30^\circ$) until the smell of acetic anhydride could no longer be detected. The residue was taken up in a small amount of water and a second crop of crystals (0.278g, decomposition 279-280°) could be filtered off. The total yield was 3.498g (70.5%). Recrystallization from ethanol-water gave fine needles of IV, m.p. 285-286° with decomposition (darkening around 267°). Infrared data are given in Table VI.

Anal. Calcd. for $C_{10}H_{17}N_3O_4$ (243.3): C,49.37; H,7.04; N,17.27

Found: C,49.61; H,7.22; N,17.03

In early experiments it was tried to purify the residue of the reaction mixture prior to acetylation. The syrupy residue was poured into cold water. A solid was obtained which was presumed to be the diamine III (38-44%). Infrared bands were at 3350 cm^{-1} (w, NH_2 stretching) and 1545 cm^{-1} (s, asym. nitro vibration), and no carbonyl band was present. The product darkened on standing in the course of a day.

trans,trans-2-Amino-1,3-diacetamidocyclohexane (V)

A sample of 1.22g (5 mmole) of 1,3-diacetamido-2-nitrocyclohexane (IV) in 65 ml glacial acetic acid and 30 ml of water was hydrogenated at ordinary temperature and pressure with platinum catalyst (0.7g of platinum dioxide, prehydrogenated in 10 ml of glacial acetic acid). The hydrogen uptake (410 ml) was complete after 20 hours. The catalyst was filtered off and the acetic acid was removed by repeated evaporations with ethanol. Finally, the crystalline residue was taken up in warm ethanol and ethyl acetate. Crystallization occurred after standing at room temperature for some time. A crop of white needles (653 mg, 61.2%) was collected. Recrystallization from ethanol-water gave V as fine needles, m.p. 263-265° with decomposition (darkening at 230°). Infrared spectrum see Table VI, n.m.r. spectrum see Fig. 9.

Anal.Calcd. for $C_{10}H_{19}N_3O_2$ (213.3): C,56.30; H,8.98; N,19.67
Found: C,56.14; H,9.03; N,19.88

trans,trans-1,2,3-Triacetamidocyclohexane (VI)

The mother liquor of V was evaporated and the residue dissolved in 10 ml of methanol. Acetic anhydride (2.5 ml) was added and the reaction mixture was stirred at room temperature for 12 hours. Solids separated during this time. The mixture was evaporated several times with ethanol until no smell of acetic anhydride could be detected. The residue was taken up in a small amount of ethanol. White crystals (412 mg) separated and were recrystallized from ethanol-water. The pure product sublimed at 300° with gradual decomposition. Infrared spectrum see Table VI, n.m.r. spectrum see Fig. 10.

Anal.Calcd. for $C_{12}H_{21}N_3O_3$ (255.3): C,56.45; H,8.29; N,16.46

Found: C,56.36; H,8.15; N,16.27

From the 412 mg of 1,2,3-triacetamidocyclohexane (VI) obtained here, it was calculated that the mother liquor had contained at least 344.3 mg of 2-amino-1,3-diacetamidocyclohexane (V). Thus, compound V had formed to the extent of at least 93.5%.

2,6-Diacetamidocyclohexanone (VII)

1,3-Diacetamido-2-nitrocyclohexane (IV) (243.3 mg) was dissolved in 170 ml of 0.1<u>N</u> potassium hydroxide by stirring for 12 hours, and 2<u>M</u> magnesium sulfate (24 ml) was added. The solution, which was milky due to precipitated magnesium hydroxide, was made up to a final volume of 500 ml with water. The mixture was then cooled to 0-5°. With constant stirring a solution of potassium permanganate (136 mg) in water (9 ml) was added, drop by drop, in a period of 3¼ hours. After the addition was complete, the mixture was stirred for 30 minutes at 0-5° and 60 minutes at room temperature. The manganese dioxide and magnesium hydroxide were filtered off by suction through celite. The violet filtrate was neutralized with 1N hydrochloric acid to give a colourless solution of pH 3. The solution was evaporated to dryness with successive additions of ethanol. The dried residue was then extracted ten times with 50 ml portions of boiling chloroform. After cooling, 8 mg of starting material was filtered off, and the chloroform solution was concentrated to dryness. Recrystallization of the crystalline residue from ethanol-petroleum ether (30-60°) afforded 143.8 mg (69.8%) of VII as colourless needles which sintered near 206°. The infrared spectrum is shown in Table VI.

Anal.Calcd. for $C_{10}H_{16}N_2O_3$(212.3): C,56.59; H,7.60; N,13.20

Found: C,56.49; H,7.49; N,13.34

2,6-Diacetamidocyclohexanone 2,4-dinitrophenylhydrazone (VIII)

A solution of 2,4-dinitrophenylhydrazine was prepared by dissolving 125 mg of the hydrazine in 5 ml of hot ethanol and 0.25 ml of concentrated hydrochloric acid. Part of this solution (1.5 ml) was added to a solution of 2,6-diacetamidocyclohexanone (VII) (28.1 mg) in 1.5 ml of ethanol. The reaction mixture was warmed on a steam bath for two minutes and then cooled with ice-water. Yellow crystals separated and were filtered off and washed with ice-cold ethanol. The dry product (24.15 mg) melted at 268-269°. To the filtrate, another portion of the 2,4-dinitrophenylhydrazine solution (0.5 ml) was added and the mixture was warmed again on a steam bath for two minutes. It was then kept in the refrigerator overnight and another crop of hydrazone (11.7 mg, m.p. 267°) was collected. The total yield of VIII was 35.9 mg (69%). Recrystallization from hot ethanol raised the melting point to 269-270°. Infrared spectrum see Table VI.

Anal.Calcd. for $C_{16}H_{20}N_6O_6$(392.4): C,48.98; H,5.14; N,21.43
Found: C,48.88; H,5.14; N,21.31

trans,trans-2,6-Diacetamidocyclohexanol (IX)

2,6-Diacetamidocyclohexanone (VII) (118.6 mg) was dissolved in 2.5 ml of hot water. Upon cooling, an ice-cooled solution of sodium borohydride (15 mg in 0.8 ml of water) was added. The pH value of the solution was ca. 9. The mixture was stirred at room temperature for 90 minutes. The excess sodium borohydride was then decomposed by treating the solution with Rexyn 101 (H^+) (wet, 2ml) for 15 minutes. The filtrate from the resin was evaporated several times with methanol until complete removal of boric acid was achieved (flame test). The residue, upon crystallization from ethanol-ethyl acetate, gave 77.6 mg (65.25%) of IX which decomposed around 260°. Recrystallization from ethanol gave fine needles that partially sublimed at ca. 210° and melted with decomposition at 286.5-288°. Infrared spectrum see Table VI, n.m.r. spectrum see Fig. 11.

Anal.Calcd. for $C_{10}H_{18}N_2O_3$(214.3): C,56.04; H,8.47
Found: C,55.97; H,8.37

trans,trans-2,6-Diacetamidocyclohexanol acetate (XI)

Method A

2,6-Diacetamidocyclohexanol (IX) (50 mg) was dissolved in 0.5 ml of hot glacial acetic acid, and acetyl chloride (0.3 ml) was added dropwise after cooling to room temperature. Heat was evolved and the reaction mixture became cloudy, separating eventually in two layers. The heterogeneous mixture was then warmed in a water bath at about 45° for 20 minutes with stirring, whereby a clear solution resulted. After cooling, the reaction mixture was evaporated repeatedly with excess methanol and finally with ethanol. Recrystallization of the crystalline residue from ethanol-petroleum ether (30-60°) gave 44.5 mg of XI as colourless needles. They showed decomposition starting at 265°. A second crop of 7.2 mg was obtained from the mother liquor; it began to sinter at 250°. The total yield of XI was 51.7 mg (86.1%). Recrystallization from hot ethanol gave 30.2 mg of needles which sublimed at 250° and sintered from 280°. Infrared spectrum see Table VI, n.m.r. spectrum see Fig. 12.

Anal.Calcd. for $C_{12}H_{20}N_2O_4$(256.3): C,56.24; H,7.87; N,10.93

Found: C,56.03; H,8.04; N,11.08

Method B

To a mixture of 50 mg of 2,6-diacetamidocyclohexanol (IX) and 0.2 ml of acetic anhydride, 20 drops of boron trifluoride-etherate solution was added. The crystals dissolved in about two minutes with evolution of heat. After standing at room temperature for 10 minutes, the reaction mixture was poured into cold methanol and evaporated several times with methanol to give a syrup. Crystallization from ethanol-petroleum ether (30-60°) gave 60.5 mg of crude product, which began to decompose at 205°. Recrystallization from ethanol gave 21.5 mg of needles which sublimed at 250° and sintered from 280°. The infrared spectrum is identical to that of the crystals obtained by method A.

1,3-Diacetamidocyclohexane (XII)

Zinc (500 mg) was converted into zinc amalgam in a small three-neck round bottom flask, and 0.5 ml of concentrated hydrochloric acid together with 1 ml of water were then added. To this, a solution of 2,6-diacetamidocyclohexanone (VII) (106 mg) in 1 ml water and 1 ml alcohol were added. While stirring, hydrogen chloride gas was slowly passed into the mixture. During this operation the temperature was kept around 40°. The supply of gas was stopped when all the zinc amalgam had dissolved. The mixture was stirred at room temperature overnight and was then evaporated with several additions of water to remove the excess hydrogen chloride. Finally, an aqueous solution of the product was deionized with Rexyn 101 (H^+) (26 ml, wet) and Dowex 1-X8(OH^-) (24 ml, dry). Evaporation to dryness with alcohol gave a crystalline residue. The crystals were triturated with a small amount of alcohol. This treatment caused separation of 36 mg (36.3%) of crystals that decomposed at 250-258°. Recrystallization from alcohol and ethyl acetate raised the decomposition point to 265-267°. Partial sublimation of the compound occurred around 200°. Infrared data are given in Table VI.

Anal.Calcd. for $C_{10}H_{18}N_2O_2$ (198.3): N,14.13
Found: N,13.86

Deoxynitro-scyllo-inositol pentaacetate (XIII)

The deoxynitro-*scyllo*-inositol pentaacetate (XIII) required for the next experiment was prepared according to literature directions. First, 1,2-O-isopropylidene-α-D-glucofuranose was made from glucose and acetone via 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose as described by Schmidt (151). Periodate oxidation of the monoisopropylidene compound followed by nitromethane condensation of the resulting aldehyde and acid hydrolysis of the isopropylidene group gave a mixture of 6-deoxy-6-

nitro-D-glucose and L-idose which was cyclized in alkaline medium to a mixture of deoxynitroinositol stereoisomers. The scyllo isomer was isolated by crystallization from dioxane. This synthesis was first reported by Grosheintz and Fischer (81). For the present work minor modifications described by Lichtenthaler (84) were employed. The pentaacetate of deoxynitro-scyllo-inositol was obtained by acetylation with acetic anhydride and sulfuric acid (84). Alternatively, a mixture (200 mg) of deoxynitro-scyllo- and myo-inositol was suspended in acetic anhydride (2.06 ml), and boron trifluoride etherate (20 drops) was added until all the crystals dissolved. Heat was evolved. Crystals separated out from the light brown solution shortly thereafter. After standing at room temperature for 5 minutes, the reaction mixture was cooled in an ice-water bath, and then filtered. The crystals were washed with dioxane. The crude product (93 mg, m.p. 270.5-272°) was recrystallized from hot dioxane. The pentaacetate XIII (76.9 mg) so prepared melted at 256-257° (Lit. (84), m.p. 255-256°).

1,3-Diacetamido-2-deoxy-2-nitro-scyllo-inositol (XIV)

Deoxynitro-scyllo-inositol pentaacetate (XIII) (200 mg) was dissolved in 3 ml of dioxane and 10 ml of tetrahydrofuran. The mixture was cooled in an ice-water bath for five minutes. Concentrated, aqueous ammonium hydroxide (4 ml) was added and the resulting, lightly yellow solution was stirred at room temperature for one hour. Cold ethanol was then added and the solution was evaporated to near dryness. The partially crystalline residue was immediately taken up in 10 ml of methanol. After cooling in an ice-water bath, acetic anhydride (0.6 ml) was added and the reaction mixture was stirred at room temperature for two hours. The yellow solution was then evaporated several times with ethanol, to give a crystalline residue which was taken up in hot ethanol. After standing for several hours, the solution deposited 88.4 mg (76.3%) of colourless crystals of XIV, m.p. 285° with darkening beginning at 250°. Recrystallization from ethanol-water gave 45 mg of XIV with m.p. 295-299° (decomposition; darkening at 290°). Infrared spectrum see Table VI.

Anal.Calcd. for $C_{10}H_{17}N_3O_7$(291.3): C,41.24; H,5.88; N,14.42

Found: C,41.26; H,6.10; N,14.32

Table VI The Most Characteristic Infrare

Infrared Frequencies (ν_{max}

Compounds	NH_2	NO_2	NH	NHAc (amide bands)	C-
trans,trans-1,3-Diacetamido-2-nitrocyclohexane (IV)		1560(s) 1370(s)	3300(s)	1660(s,I) 1560(s,II) 1315(ms,III)	
trans,trans-2-Amino-1,3-diacetamidocyclohexane (V)	3370(w)		3300(s)	1640(s,I) 1560(s,II) 1315(ms,III)	1140
trans,trans-1,2,3-Triacetamidocyclohexane (VI)			3300(s)	1645(s,I) 1550(s,II) 1315(ms,III)	
2,6-Diacetamidocyclohexanone (VII)			3280(s)	1645(s,I) 1565(s,II) 1320(ms,III)	
2,6-Diacetamidocyclohexanone 2,4-dinitrophenylhydrazone (VIII)		1500(s) 1515(s) 1315(ms)	3320(ms) 3250(w)	1675(s,I) 1540(s,II) 1310(ms,III)	
trans,trans-2,6-Diacetamidocyclohexanol (IX)			*	1630(s,I) 1550(s,II) 1320(ms,III)	
trans,trans-2,6-Diacetamidocyclohexanol acetate (XI)			3300(s)	1650(s,I) 1560(s,II) 1315(ms,III)	
1,3-Diacetamidocyclohexane (XII)			3460(ms) 3320(s) 3300(s) 3100(w)	1640(s,I) 1565(s,II) 1315(ms,III)	
Deoxynitro-scyllo-inositol pentaacetate (XIII)		1560(s) 1375(s)	**	1640(s,I) 1560(s,II) 1311(ms,III)	

*NH and OH in the region of 3380(s), 3140(w), 3090(ms).

**NH and OH in the region of 3420(ms), 3300(s), 3280(ms), 3120(ms).

Relative peak intensities are designated as follows:
weak (w); strong (s); medium strong (ms).

rared Frequencies

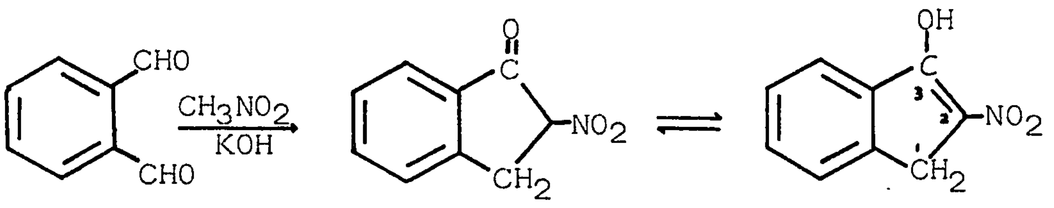
$_{max}$ in cm^{-1})

C-N	C=0 (keto)	C=C (phenyl)	OH	C=0 (acetate)	C-0-C (acetate)	CH_3 (acetoxy methyl)	Others
							3100(w)
1140(ms)							3100(ms)
							3100(ms)
	1730(s)						3100(ms) 1674 1600 > shoulder
		1630(s) 1615(s) 1500(s)					
			*				
				1730(s)	1245(s) 1050(ms)	1370(s)	3100(ms)
			**				

PART II*

INTRODUCTION

In 1910, Thiele and Weitz (152) condensed o-phthalaldehyde (I) with nitromethane in alcoholic solution in the presence of potassium hydroxide and obtained, upon acidification, a product which they believed to be 2-nitroindanone (II). The compound gave an acetate and a methyl ether thought to be derived from the tautomeric form, 3-hydroxy-2-nitroindene (III).



I II III

However, more than 50 years later the reaction was reinvestigated and was revealed to proceed according to the following sequence, 1-hydroxy-2-nitroindene (VI) rather than the isomer II or III being the final product (153):

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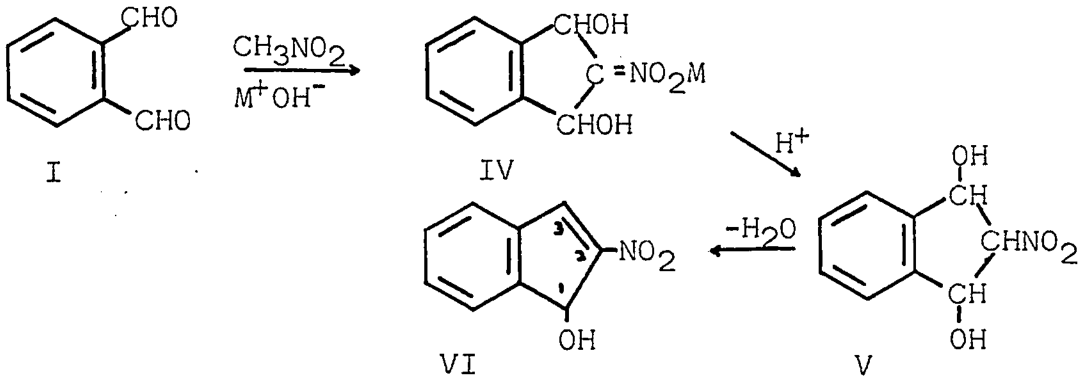
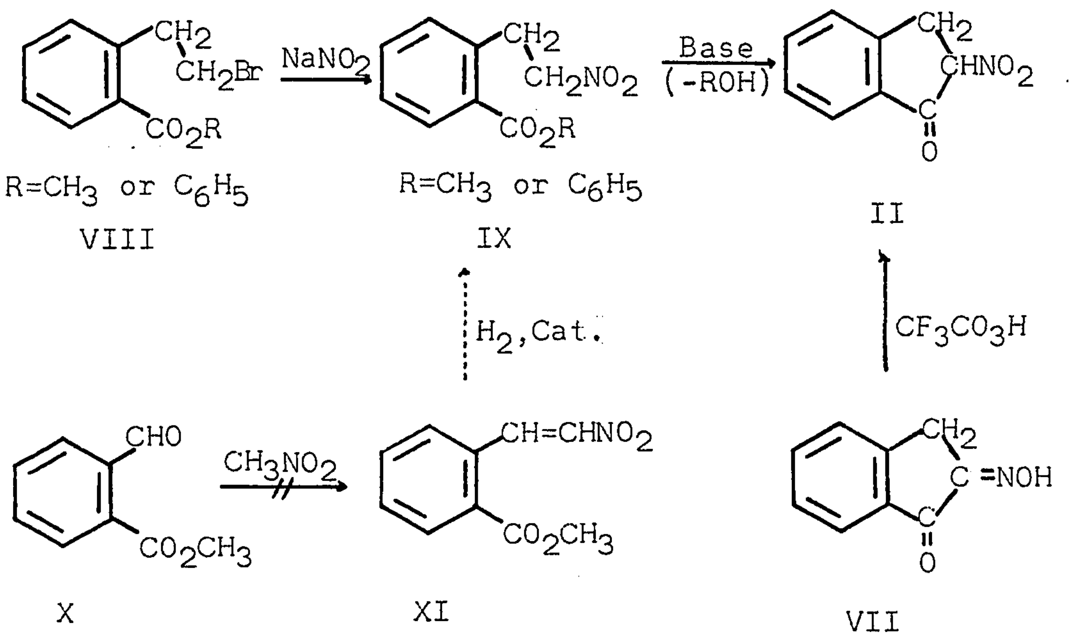
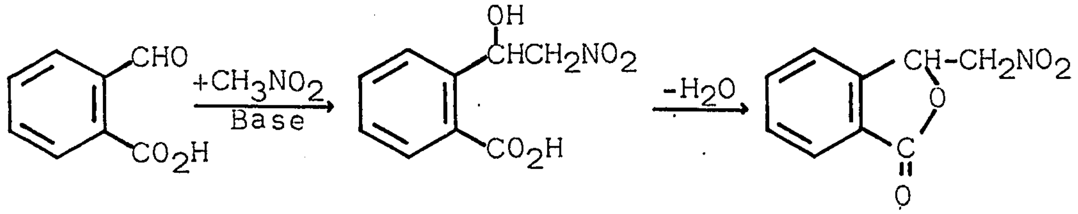
[*] For convenience, compounds in Part II are numbered using a new set of Roman numerals.



No synthesis of true 2-nitroindanone has been reported in the intervening time. The goal was therefore pursued in this laboratory, and Naik (154) recently succeeded in synthesizing the compound in two independent ways. One way was to oxidize 2-oximinoindanone (VII) with trifluoroperacetic acid. The other synthesis consisted of a Dieckmann-type cyclization of the methyl or phenyl ester of 2-(2-nitroethyl)benzoic acid (IX). The major problem in the latter approach was the preparation of such esters. They were finally obtained from the corresponding 2-bromoethyl esters (VIII) by displacement with sodium nitrite, but many experiments had at first been undertaken to produce IX ($R=CH_3$) in a different manner, namely, via methyl 2-(2-nitrovinyl) benzoate (XI). This nitrovinyl compound could reasonably be expected to give the saturated ester on selective hydrogenation. Unfortunately, numerous attempts to prepare XI by condensation of methyl phthalaldehydate (X) with nitromethane did not yield the desired product. Naik's syntheses of 2-nitroindanone are summarized in the following scheme:



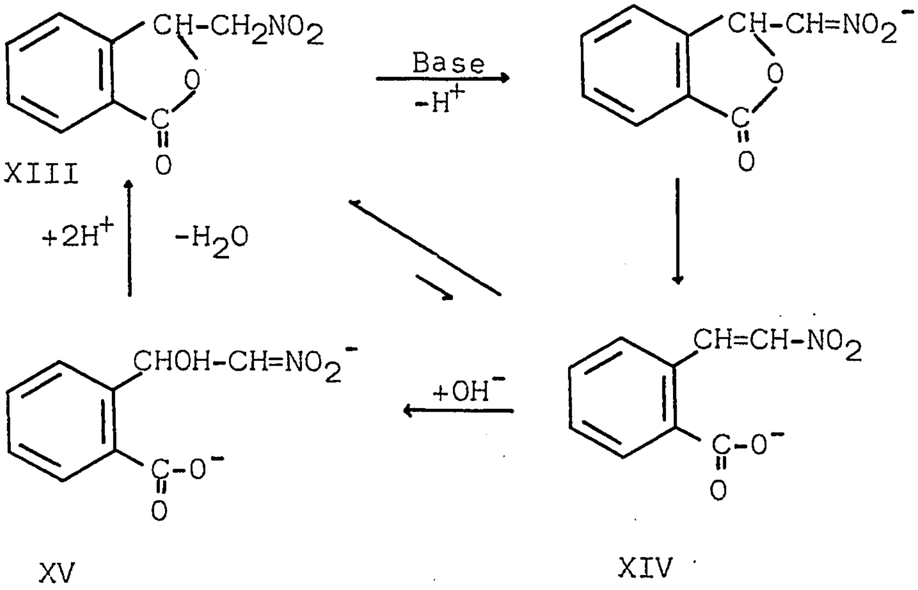
For the present thesis it was to be investigated whether methyl 2-(2-nitrovinyl) benzoate (XI) can be obtained from 3-phthalidylnitromethane (XIII), a compound that is prepared in good yield from commercially available phthalaldehydic acid (XII) and nitromethane (155).



XII XIII

It had been shown by Baer and Kienzle (156) that XIII, a β-acyloxynitro compound, undergoes eliminative lactone ring opening by the action of aqueous alkali and gives short-lived 2-(2-nitrovinyl)-benzoate anion (XIV).

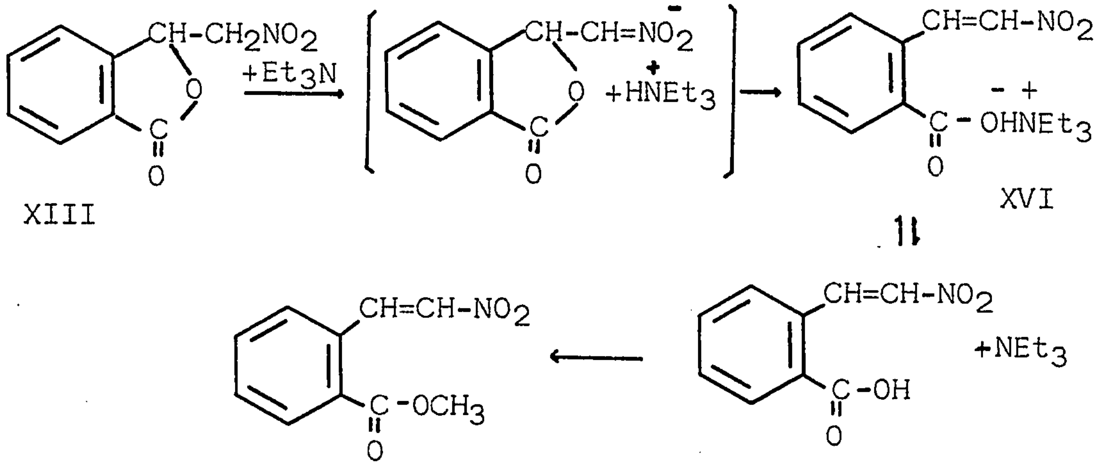
In the alkaline reaction medium, the anion rapidly added hydroxyl ion to give the dianion of 2-(1-hydroxy-2-nitroethyl) benzoic acid (XV). Acidification to below pH 5 led to complete regeneration of 3-phthalidylnitromethane, whether it was done at the stage of XV or during an early phase of the reaction when most of the substance existed as XIV.



However, spectroscopic evidence was obtained for a small proportion (ca. 10%) of 2-(2-nitrovinyl) benzoic acid to remain in equilibrium with 3-phthalidylnitromethane when the alkaline solution containing intermediate (XIV) was quickly buffered to pH 6. Isolation of the nitrovinyl compound was not possible.

In view of this behavior of 3-phthalidylnitromethane the following plan was conceived. It was considered that triethylamine in a nonhydroxylic solvent, while probably being capable of generating the anion XIV, would not subsequently be added across the double bond, so that stable triethylammonium 2-(2-nitrovinyl) benzoate should arise.

The salt would be in equilibrium with free acid and amine, and it was hoped that treatment with diazomethane would produce the ester XI.



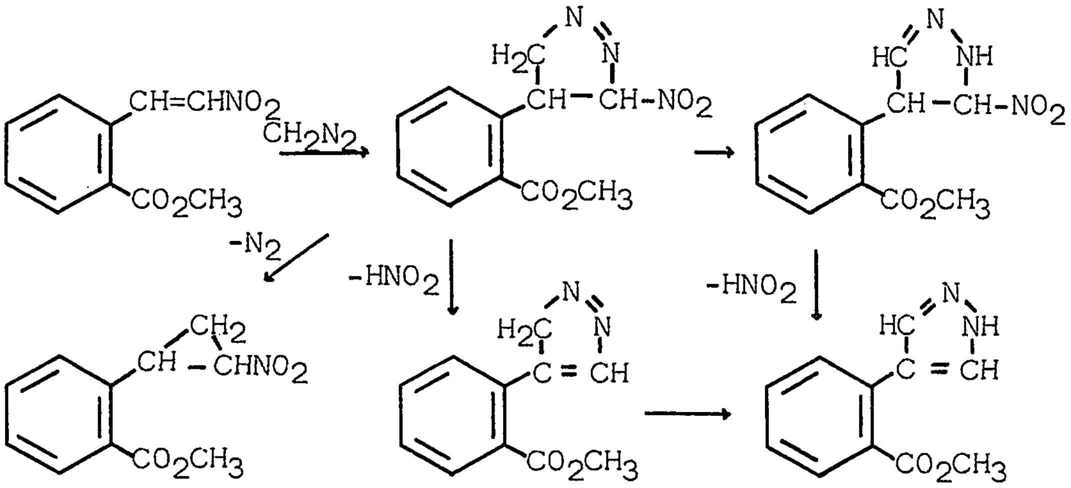
XIII

XVI

XI

XVII

However, it had to be borne in mind that a nitrostyrene derivative produced in such a manner might undergo, with excess diazomethane, one or more further reactions which might preclude its isolation. It is known that diazomethane can add to activated double bonds and form pyrazolines (157-161), pyrazoles (157-159), or cyclopropanes (162-164). Hence, one had to reckon with the possibility of various products being formed according to the following scheme:



Moreover, polymerization of the nitrostyrene was another side reaction that could occur. Nevertheless, in the hope that such complications could be minimized by proper choice of the reaction conditions, several attempts were made to obtain the ester XI in the way outlined above.

RESULTS AND DISCUSSION

3-Phthalidylnitromethane (XIII) was dissolved in dry methylene chloride, and triethylamine was added at room temperature. The characteristic ultraviolet spectrum of XIII, with its peaks at 273 and 281 $m\mu$, disappeared and a new peak was observed at 315 $m\mu$, which can be interpreted in terms of the formation of 2-(2-nitrovinyl)-benzoate ion (XIV) (156). A solution of diazomethane in ether was then added at 0^{o}, and after 20 minutes the excess diazomethane was destroyed, and the triethylamine and solvent were removed by extraction and evaporation, respectively. A brownish, crude reaction product was obtained which was purified by precipitation from trichloroethylene and n-butyl ether. This treatment gave a yellow solid which showed ultraviolet absorptions at 280 and 365 $m\mu$, but no longer the nitrostyrene peak at 315 $m\mu$. The infrared spectrum indicated the presence of ester carbonyl (1750 cm^{-1}), but there was no band in the region of the nitro group absorption. These spectral characteristics clearly indicated that the product was not the desired ester (XI). In another experiment the diazomethane treatment was performed at -14^{o} and the product, purified by precipitation from methanol and water, showed very similar absorptions in the ultraviolet as well as in the infrared.

Elemental analysis, methoxyl determination, and mass spectrometry confirmed that the product was not the ester XI, whose molecular formula would be $C_{10}H_9NO_4$ (mol. wt. 207; OCH_3, 14.9%). The empirical formula calculated from the values of carbon, hydrogen, and nitrogen analysis could best be expressed as C_4H_4NO, although the carbon value was somewhat too high. The peak of highest m/e ratio in the mass spectrum was at 248. If the empirical formula is multiplied by three and one hydrogen is added*, one arrives at $C_{12}H_{13}N_3O_3$, which corresponds to a molecular weight of 247. Possibly the molecule, which may be presumed to have basic character, captures a proton in the spectrometer - so that a molecular ion peak at 248 m/e is generated. A methoxyl content of 11.7% was found, while a molecular weight of 247 requires 12.55% for one OCH_3-group. Further work is needed to establish reliably the exact composition of this product. Should the above formula be confirmed, then it is evident that the product cannot be a nitropyrazoline, nitrocyclopropane, or pyrazole of the kind outlined in the Introduction. The data available at present do however suggest that nitrogen has been introduced by the diazomethane and that the nitro groups has suffered a change involving loss of oxygen.

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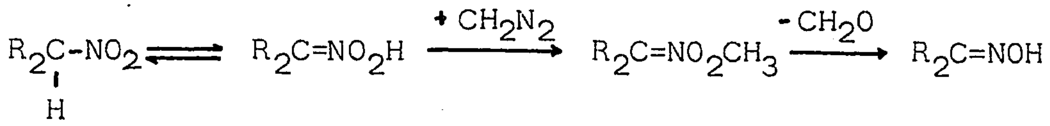
* In a molecular formula of a stable (non-radical) compound an odd number of N requires an odd number of H.

It is known that aliphatic nitro compounds can give nitronic esters which may spontaneously decompose to oximes, and such a possibility should be considered here.



$$R_2\underset{H}{\underset{|}{C}}-NO_2 \rightleftharpoons R_2C{=}NO_2H \xrightarrow{+CH_2N_2} R_2C{=}NO_2CH_3 \xrightarrow{-CH_2O} R_2C{=}NOH$$

An additional product was obtained in the reaction of phthalidylnitromethane and diazomethane. When the crude reaction product described above was kept in methylene chloride solution at 4° for two weeks, a small amount of a colourless material crystallized. The same substance was obtained as a sublimate when the crude reaction product was subjected to vacuum distillation up to a bath temperature of 200-210° (0.1-0.2 mm). Elemental analysis indicated the empirical formula $C_{11}H_9N_3O$ which in all likelihood is also the molecular formula (mol. wt. 199), since the mass spectrum of the compound showed a parent peak at 199 m/e. A methoxyl determination was negative, and no ester carbonyl band was seen in the infrared spectrum. Likewise, the spectrum lacked nitro absorption, and this was in agreement with the molecular formula. There was a strong band at 1675 cm^{-1}, possibly attributable to an amide function. The compound exhibited ultraviolet bands at 270 and 335 mμ.

In conclusion it may be said that under the experimental conditions studied in this work, methyl 2-

(2-nitrovinyl) benzoate (XI, $C_{10}H_9NO_4$) cannot be prepared from phthalidylnitromethane (XIII) and diazomethane. One obtains a methoxyl-free product of the composition $C_{11}H_9N_3O$ and a methoxyl-containing product tentatively described as $C_{12}H_{13}N_3O_3$. Neither compound has retained the nitro group.

EXPERIMENTAL

Unless otherwise indicated, ultraviolet spectra were measured using solutions of the compounds in methylene chloride, and infrared spectra were obtained from films produced by the evaporation of methylene chloride solution. The 3-phthalidylnitromethane (XIII) (165) used in the experiments was made (155) from phthalaldehydic acid (166) by nitromethane condensation.

Attempted preparation of methyl 2-(2-nitrovinyl) benzoate (XI)

(A.) 3-Phthalidylnitromethane (XIII) (579 mg, 3 mmole) was dissolved in 15 ml of methylene chloride (dried over aluminum oxide), and triethylamine (0.56 ml, 4 mmole) was added at room temperature. The colour of the mixture turned slightly yellow. An aliquot was withdrawn, diluted with methylene chloride, and an ultraviolet spectrum was taken. It was seen that the original peaks at 273 and 281 mμ had disappeared and a new peak had appeared at 315 mμ. The reaction mixture was then cooled in an ice-bath and ethereal diazomethane was added slowly until a sample withdrawn from the reaction mixture evolved nitrogen bubbles on acidification with acetic acid, indicating the presence of an excess of diazomethane. The ultraviolet spectrum now showed new peaks at 285 and 375mμ.

After 20 minutes the excess diazomethane was decomposed, and triethylamine extracted, by shaking the solution with 1N acetic acid. The methylene chloride-ether layer was separated from the aqueous layer in a separatory funnel and was washed several times with water until neutral; it was then dried overnight over magnesium sulfate. Evaporation to dryness finally gave a brown solid residue. The ultraviolet spectrum of this crude solid showed absorption maxima at 280 and 365mμ. The product was soluble in methanol, methylene chloride, chloroform, ethyl acetate, benzene, carbon tetrachloride and acetone, but insoluble in water, petroleum ether, and cyclohexane. Many unsuccessful attempts were made to recrystallize the crude substance with several solvents or mixtures of solvents. The crude solid was finally dissolved in trichloroethylene, and n-butyl ether was added to beginning turbidity. This caused the precipitation of a light orange powder which was collected and dried (163 mg). This substance showed the following infrared absorptions: 3500-3000 cm^{-1} (broad), 3000 cm^{-1} (w), 1725 cm^{-1} (s), 1640 cm^{-1} (w), 1600 cm^{-1} (w), 1575 cm^{-1} (w). There was no absorption attributable to a nitro group, thus the substance could not be the expected product.

The filtrate from the above material was then evaporated to dryness, and the residue was triturated with benzene whereby it dissolved partially. The benzene solution was concentrated to a yellow liquid which was distilled in vacuo at 0.05 mm Hg. A yellow distillate came over at 200° (oil-bath temperature). It showed ultraviolet maxima at 285 and 325mμ and infrared bands at 3000 cm^{-1} (m), 1730 cm^{-1} (s), 1600 cm^{-1} (w), 1534 cm^{-1} (m), 1260 cm^{-1} (s), 1137 cm^{-1} (m), 763 cm^{-1} (w), 745 cm^{-1} (broad). No crystalline substance resulted from attempts of crystallization.

The yellow liquid was finally taken up in methylene chloride, and the methylene chloride-soluble portion was kept in the refrigerator. After a few days, a small amount of a solid was deposited which had ultraviolet peaks at 280 and 335mμ, with intensities reversed in comparison to the peaks of the original distillate. More of this deposit appeared in the course of a month. For further data on it see the subsequent section.

(B.) 3-Phthalidylnitromethane (XIII) (1.158 g, 6 mmole) was dissolved in 30 ml of methylene chloride (dried over drierite) and triethylamine (1.26 ml, 9 mmole) was added at room temperature. The reaction mixture was then cooled in an ice-bath for five minutes and treated with diazomethane as described under (A.). The ultraviolet spectrum of a diluted aliquot showed absorptions at 280 and 370mμ. After five minutes, the reaction mixture was worked up as described before. The brown reaction product was divided into two equal portions which were dealt with as follows.

The first portion was distilled in a high vacuum (5×10^{-5} mm Hg). A yellow liquid distilled over in the range of 160-180° (oil-bath temperature). It had the following infrared bands: 3000 cm^{-1} (broad), 1725 cm^{-1} (s), 1641 cm^{-1} (v.w), 1611 cm^{-1} (w), 1525 cm^{-1}(m), 1345 cm^{-1} (m), 1280-1260 cm^{-1} (broad), 1140 cm^{-1} (m), 760 cm^{-1} (broad), 735 cm^{-1} (w). It showed ultraviolet absorptions at 280 and 318mμ. The distillate was rinsed from the distillation bulb with methylene chloride, and distillation of the residue was continued with increasing temperature.

A second fraction, a yellow liquid, was obtained at 200-210° (0.1-0.2 mm Hg) along with some white solid which sublimed. The yellow liquid was washed out with a small amount of methylene chloride (in which the crystalline sublimate did not dissolve), and its infrared spectrum in the region 1725-1575 cm^{-1} differed distinctly from that of the first fraction of the distillation. Both fractions had a similar spectrum in the region 1440-735 cm^{-1}, however. The infrared absorptions which were present in the second fraction but absent in the first fraction were: 1670 cm^{-1} (m), 1635 cm^{-1} (m), 1600 cm^{-1} (w). The second fraction had ultraviolet maximum at 278 and 323mμ.

The white sublimate was dissolved in hot methanol, and after cooling and some standing of the

solution, fine needles crystallized out. An infrared spectrum of this crystalline substance was taken in nujol mull. Absorptions were at 1675 cm^{-1} (s), 1600 cm^{-1} (s), 1485 cm^{-1} (w), 1185 cm^{-1} (m), 852 cm^{-1} (m), 840 cm^{-1} (w), but no nitro or ester absorptions were present. Ultraviolet absorptions were at 270 (ε, 8100) and 335 (ε, 5250) mμ. Elemental analysis of the recrystallized material (sublimed ca. 200°) gave the following values:
Found: C,66.06; H,4.71; N,21.23, 20.81
Calculated for $C_{11}H_9N_3O$ (199.22): C,66.31; H,4.55; N,21.09
The mass spectrum showed a parent peak at m/e 199. It was not possible to run an n.m.r. spectrum of this compound owing to its low solubility in suitable solvents, including DMF and DMSO. No methoxyl was found in a Zeisel determination.

The other half portion of the crude brown solid was not subjected to vacuum distillation but was dissolved in methylene chloride and left in the refrigerator. In the course of fifteen days a small amount of a solid separated. Its ultraviolet spectrum was identical with that of the white crystals obtained by vacuum distillation.

(C.) 3-Phthalidylnitromethane (XIII) (289 mg, 1.5 mmole) was dissolved in 20 ml of redistilled methylene chloride, and then cooled in an ice-salt bath to -14°. Chilled triethylamine (0.35 ml, 2.3 mmole) was added. After standing for five minutes, a slight excess of distilled diazomethane-ether solution, cooled also to -14°, was added. After 10 minutes, the dark solution was evaporated to dryness in vacuo while cooling with the ice-salt bath was maintained. The bath was then removed and the vacuum was disconnected after the flask had attained room temperature. In the air, the colour of the crude solid turned gradually from yellow to brown and finally to dark green. The material showed ultraviolet peaks at 280-285mμ and 370-375mμ in methylene chloride or methanol. Addition of hydrochloric acid had little or no influence on the absorptions, but addition of sodium hydroxide shifted the 370-375mμ absorption to 350mμ.

The crude reaction product was dissolved in methanol and poured into ice-water. A yellow solid precipitated which, after some stirring at 0°, was isolated, washed very thoroughly with cold water, and finally dried overnight in a desiccator under vacuum.

The dirty yellow solid started to decompose near 90° and foamed at 120°. Infrared spectra were measured in nujol mull and in a film from methylene chloride and revealed that the product probably was identical with that obtained under (A.) from trichloroethylene-butyl ether. They both showed a broad peak at 3450-3200 cm^{-1} and a weak and sharp one at 3000 cm^{-1}; there was carbonyl absorption at 1730 cm^{-1}(s), and some weak bands were in the region of 1640-1570 cm^{-1}. Ultraviolet absorptions were at 285 and 365mμ. Elemental analysis gave the following results:

Found: C,59.12; H,4.76;N,16.36; OCH_3,11.72

Calculated for C_4H_4NO: C,58.53; H,4.91; N,17.07

for $C_{12}H_{13}N_3O_3$ (247.3): C,58.28; H,5.30; N,16.99; OCH_3,12.55.

CLAIMS TO ORIGINAL RESEARCH

Part I

1. The reaction of ammonia with β, β'-diacetoxy sec-nitro compounds to introduce two amino groups was studied for the first time and applied to the cyclitol field.

2. The use of boron trifluoride as a catalyst for acetylation led to an improvement in the preparation of _trans_,_trans_-1,3-diacetoxy- 2 -nitrocyclohexane (III) and deoxynitro-_scyllo_-inositol pentaacetate (XIII).

3. The following new compounds were synthesized:
   (a) _trans_,_trans_-1,3-Diacetamido-2-nitrocyclohexane (IV)
   (b) _trans_,_trans_-2-Amino-1,3-diacetamidocyclohexane (V)
   (c) _trans_,_trans_-1,2,3-triacetamidocyclohexane (VI)
   (d) 2,6-Diacetamidocyclohexanone (VII)
   (e) 2,6-Diacetamidocyclohexanone 2,4-dinitrophenyl hydrazone (VIII)
   (f) _trans_,_trans_-2,6-Diacetamidocyclohexanol (IX)
   (g) _trans_,_trans_-2,6-Diacetamidocyclohexanol acetate (XI)
   (h) 1,3-Diacetamido-2-deoxy-2-nitro-_scyllo_-inositol (XIV)

Part II

In the course of attempting the synthesis of methyl 2-(2-nitrovinyl) benzoate (XI), a new compound with the molecular formula $C_{11}H_9N_3O$ has been obtained.

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