SYNTHETIC STUDIES TOWARDS TERRARUBEIN

by

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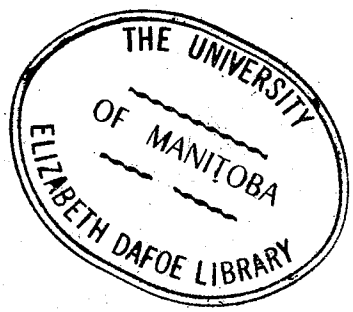

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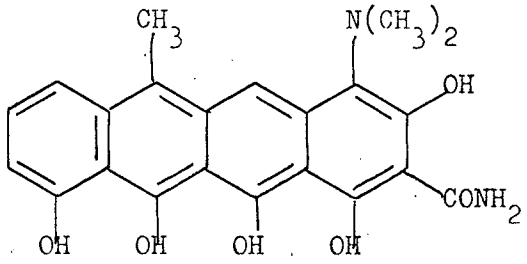
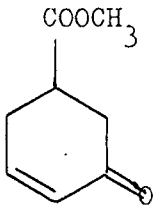
ABSTRACT

An intermediate to an important compound terrarubein (XIV) was prepared. Methyl cyclohex-2-ene-1-one-5-carboxylate (XLI) was synthesized from 3,5-dihydroxybenzoic acid through high pressure hydrogenation, methylation with diazomethane and sodium borohydride reduction. The ethylene acetal of 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI) was synthesized from 1,7-dihydroxynaphthalene (LVII) through the following sequence: methylation with dimethyl sulfate, followed by dissolving metal reduction, acid hydrolysis, acetylation, ozonolysis, methylation with diazomethane, acetal formation and lithium aluminum hydride reduction. Attempts to convert the corresponding alcohol (LXVI) to the olefin (LXVIII) by pyrolyzing the corresponding acetate, benzoate and tosylate were unsuccessful. However, the indene (LXXV) was prepared from the ester (LXIV) by Dieckmann condensation. The bicyclic compound (XLV), the aromatic ring of which is similar to that of terrarubein (XIV), a distant relative of tetracycline, was synthesized from the condensation of the isoxazole (XLII) and the cyclohexenone (XLI) with sodium hydride in anhydrous tetrahydrofuran followed by methylation with diazomethane. The conversion of the

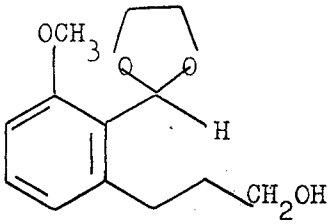
tetralone (XLV) to terrarubein (XIV) will be studied other students.



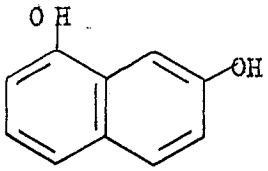
XIV



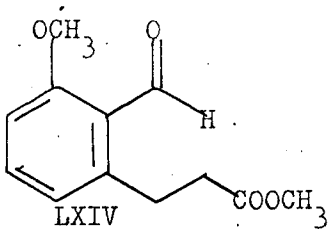
XLI



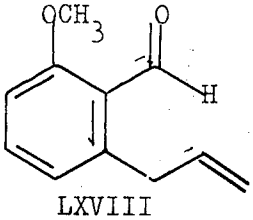
LXVI



LVII



LXIV



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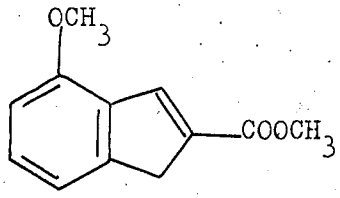
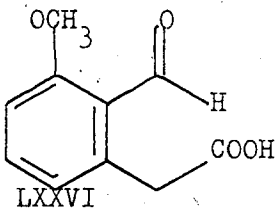
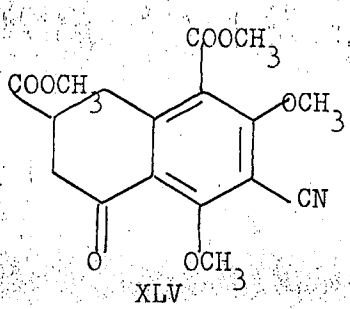


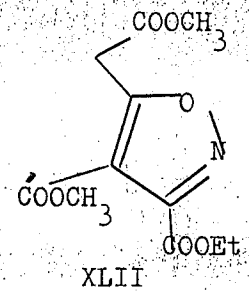
LXXV



LXXVI



XLV



XLII

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INTRODUCTION

Tetracyclines are pale yellow crystalline solid with antibiotic activity. They are produced from various strains of Streptomyces and have a tetracyclic skeleton of the general structure as shown in Scheme 1. Examples are:

Aureomycin	I	R=H	R_1=Cl
Terramycin	II	R=OH	R_1=H
Tetracycline	III'	R=R_1=H	
7-bromotetracycline	IV	R=H	R_1=Br

The first tetracycline, aureomycin (I) (chlorotetracycline), was isolated in 1948 by Duggar[1]. It was obtained from Streptomyces aureofaciens. Streptomyces is a common inhabitant of soil from which antibiotics, notably streptomycin, aureomycin, terramycin and neomycin, are obtined. In 1950, Finlay[2] prepared terramycin (II) from fermentation of Streptomyces rimosus. Tetracycline (III) was obtained from hydrogenolysis of chlorotetracycline in 1953[3]. In 1957, McCormick[4] found a family of tetracyclines which have no methyl group attached to the C-6 position, e.g. demethylchlorotetracycline (V).

Tetracyclines are widely used in clinical practice. Similar to Penicillin, tetracycline is effective against

both gram-positive and gram-negative bacteria[5]. It is also active against rickettsiae and viruses such as members of lymphogranuloma[5]. Tetracyclines act principally by interfering with the normal protein synthesis of the microorganism.

Due to the wide application of tetracycline in medicine, extensive research has been performed in the past twenty years. The main research in tetracycline chemistry is divided into three branches.

(a) Isolation and determination of structures of new tetracyclines.

(b) Degradative studies of naturally occurring tetracyclines and studies of their antibiotic activity.

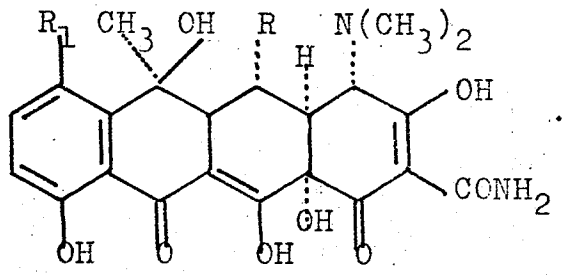
(c) Total synthesis of tetracycline or its biologically active derivatives.

The first tetracycline whose structure was completely elucidated was terramycin (II), reported by Woodward et al[7,8] in 1952 and 1953. This structural assignment was furthur substantiated by x-ray study[9]. The biological conversion of 1,3,10,11,12-pentahydroxynaphthacene-2-carboxamide (VII) to the antibiotic[10] illustrates the close relation of tetracycline to naphthacene[10].

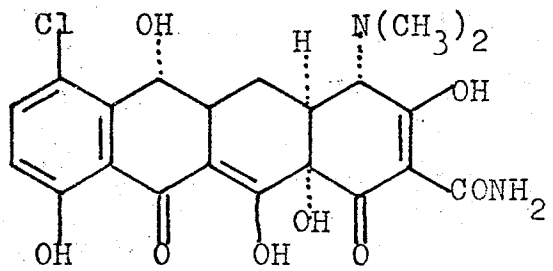
The antibiotic activity of tetracycline depends on the structure and stereochemical features of (VI). Variations other than in the stereochemistry of R_1, R_2, R_3, R_4, cause a decrease or complete elimination of the biological activity[11].

Epimerisation at positions 4 and 5a results in complete loss of activity while inversion at C-6 affects the biological activity slightly. It was also shown that the carboxamide substituent at the C-2 position is also essential. Replacement of the carboxamide by cyanide or acetoxy group reduces the activity greatly. Removal of 12a hydroxy group also removes the biological activity [12].

Fermentation of a non-chlorinating mutant of Streptomyces aureofaciens produces 7-chloro-6-demethyltetracycline (IX) from a substituted pretetramid (VIII). Pretetramid (X) was also converted to 6-demethyltetracycline (XI) by using non-chlorinating mutants of Streptomyces aureofaciens[10]. Similarly, both 6-methyl-pretetramid (XII) and terrarubein (XIV) gave the corresponding tetracyclines. However, it seems pretetramid is a better precusor than terrarubein because the latter gave a lower yield of tetracycline than the former[10].



SCHEME 1. I, II, III, IV.



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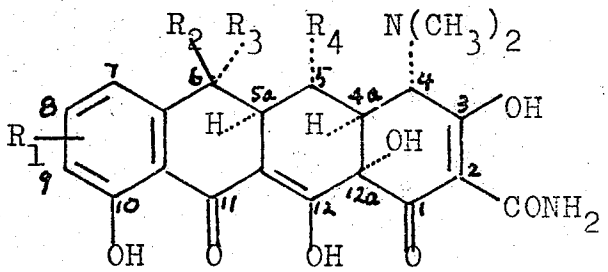
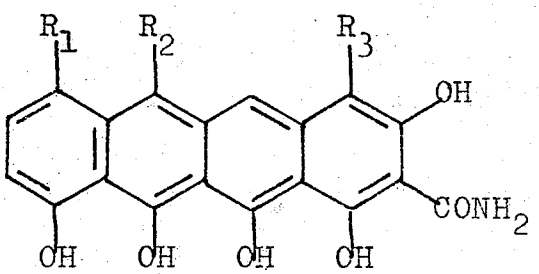
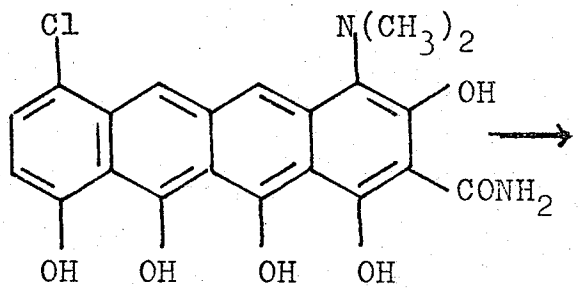


VI



VII $R_1=R_2=R_3=H$



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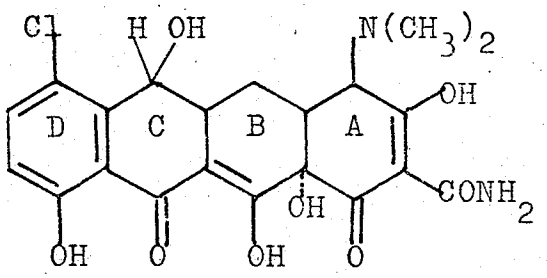

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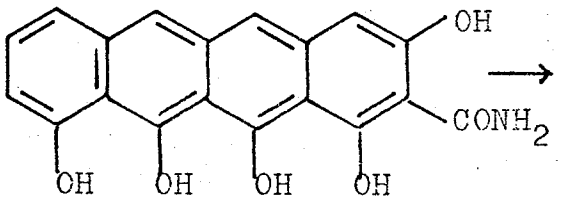
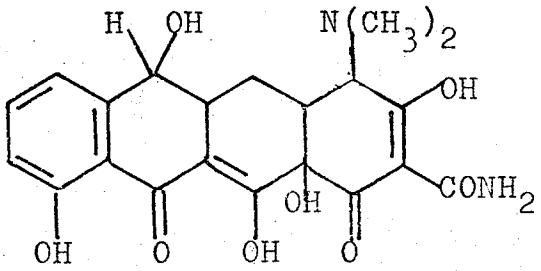
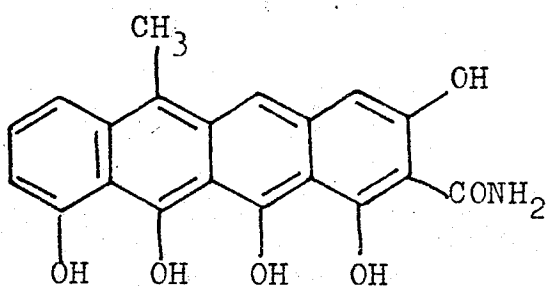


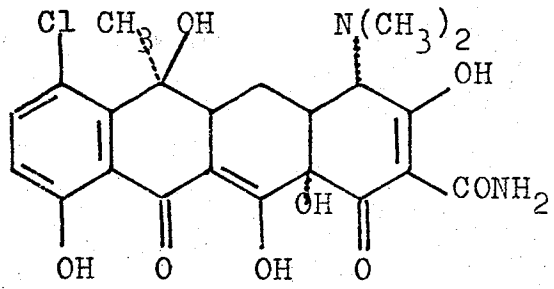
X



XI



XII



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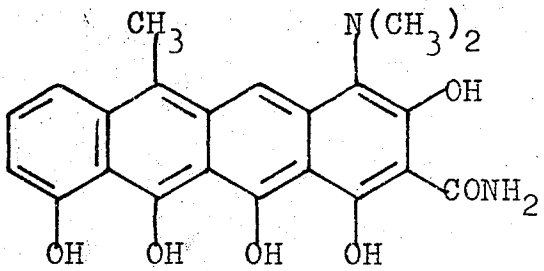
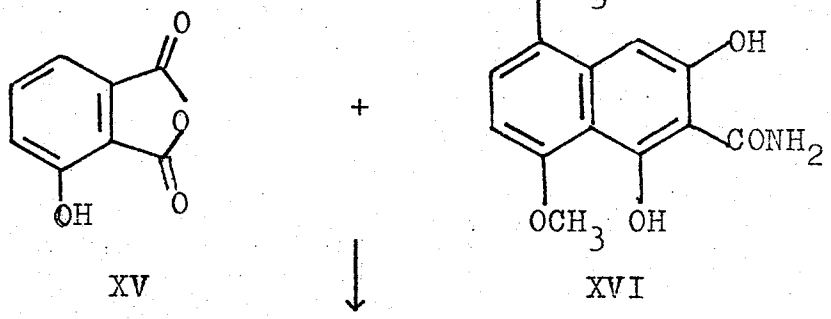
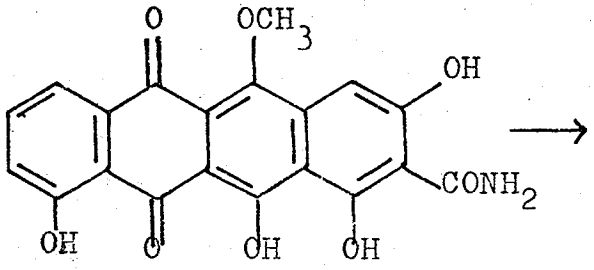


XIV



XV + XVI



Pretetramid (X)

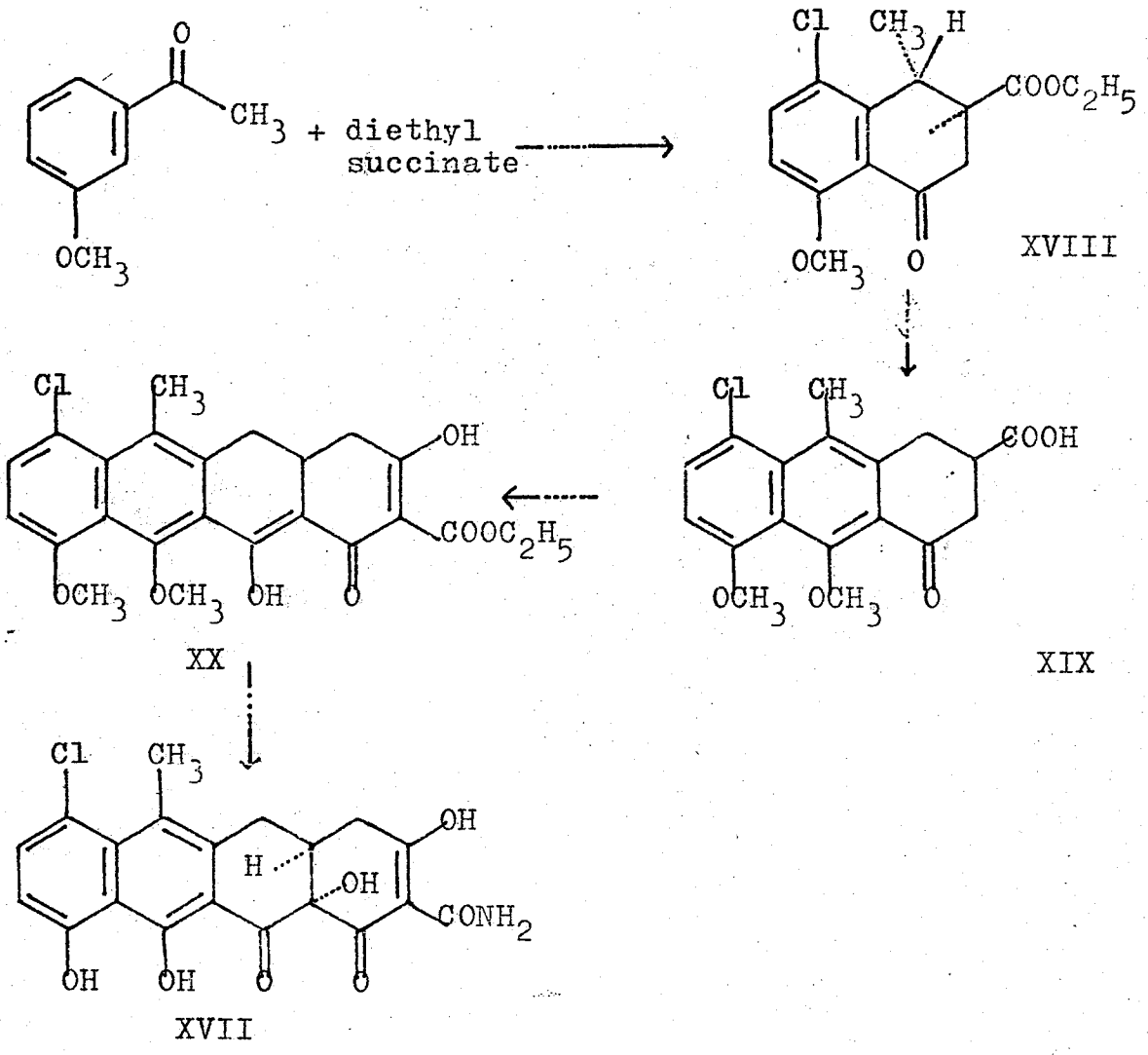
SCHEME 2. Synthesis of pretetramid (X).

It was reported[10] that pretetramid is obtained by fusing 3-hydroxyphthalic anhydride (XV) and 1,3-dihydroxy-5,8-dimethoxynaphthalene-2-carboxamide (XVI) in the presence of aluminum chloride and sodium chloride. The product was converted to pretetramid by refluxing with phenol in the presence of hydriodic acid and potassium hypophosphite. (Scheme 2).

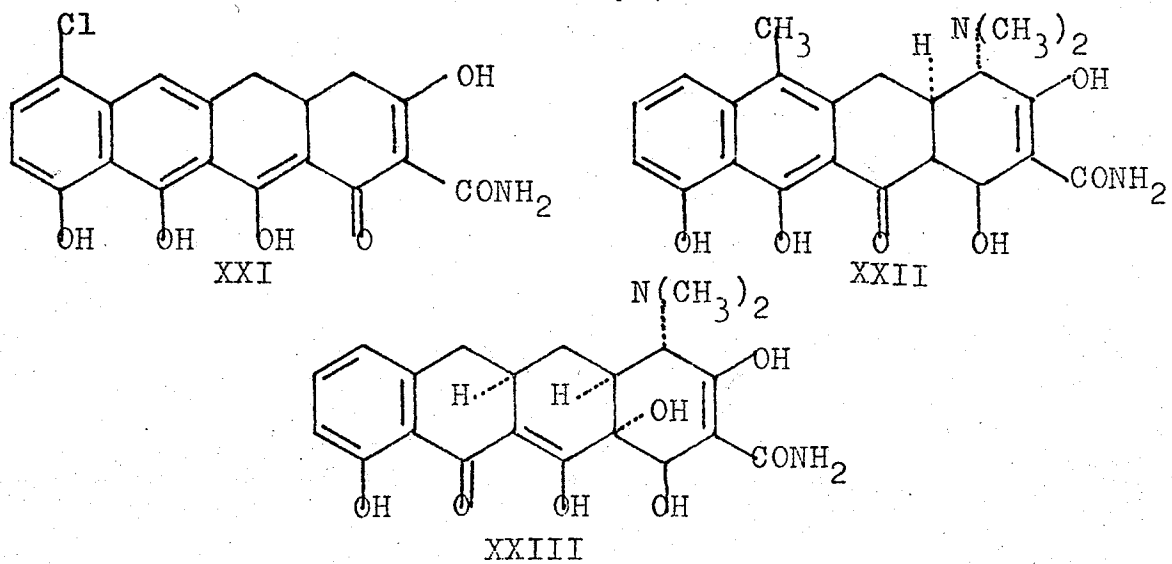
Muxfeldt et al[13] synthesized dedimethylamino-anhydro-aureomycin (XVII) by stepwise fusion of rings D, C, B and A.

The initial step involved a Stobbé condensation of 3-methoxy-acetophenone and diethylsuccinate. Catalytic hydrogenation followed by chlorination, dealkylation and cyclization gave trans-3-carboethoxy-4-methyl-5-chloro-8-methoxy-1-tetralone (XVIII) which was subsequently converted to (XIX). Fusion with malonic ester and cyclization in the presence of sodium hydride gave the tetracyclic skeleton (XX) which was later converted to the desired product (XVII). (Scheme 3) .

Other similar methods are shown in Boothe's[14] synthesis of (±)-dedimethylamino-12a-deoxy-6-demethylanhydrochlorotetracycline (XXI), Shemyakin's[15] synthesis of 12a-deoxy-5a,6-anhydrotetracycline (XXII) and Woodward's[16]



SCHEME 3. Synthesis of dedimethylamino-anhydroaureomycin (XVII)
(——→ - many steps)

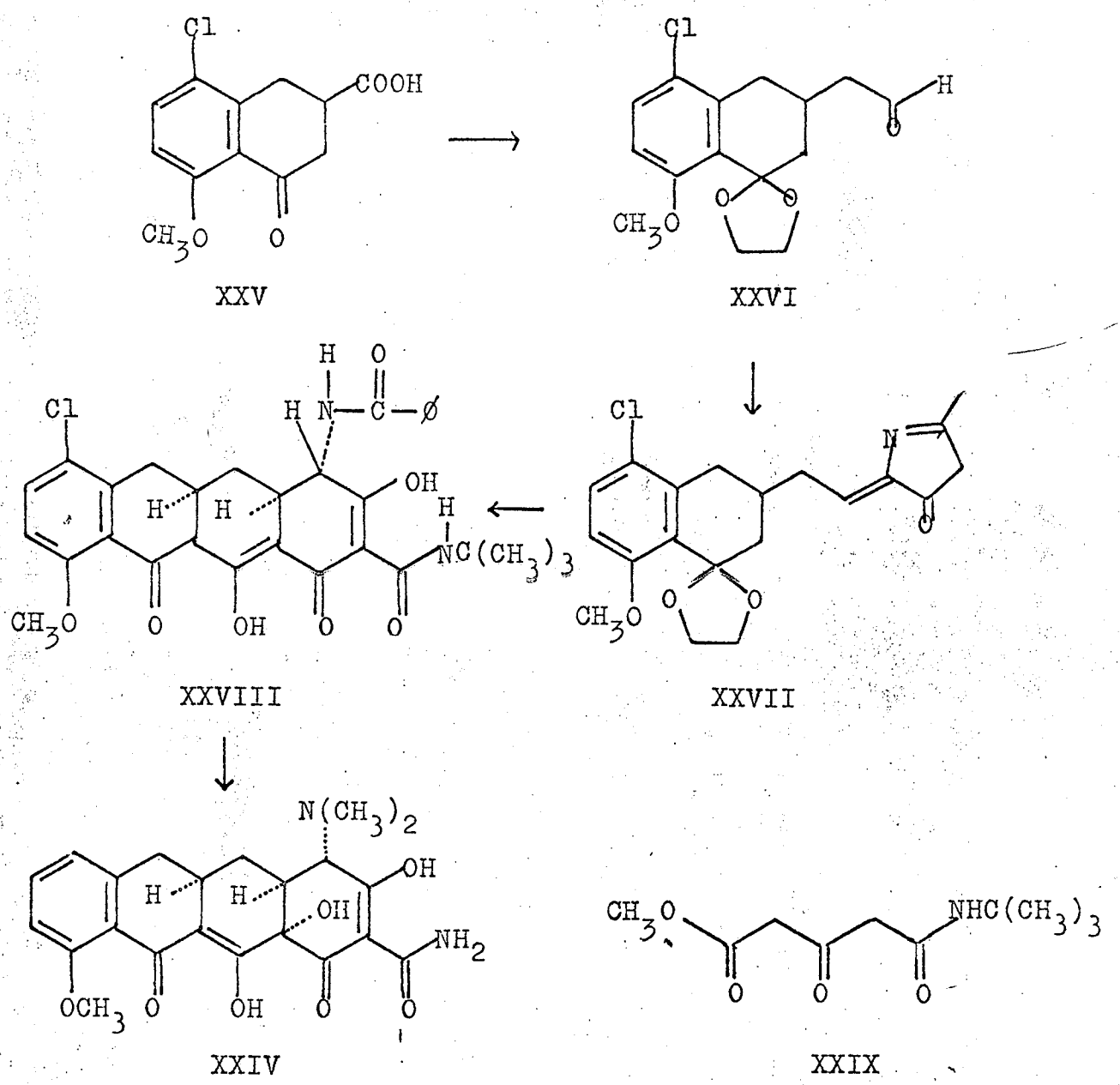


synthesis of dl-6-demethyl-6-deoxytetracycline (XXIII), all of which consisted of a stepwise fusion of rings C to D and then B and A .

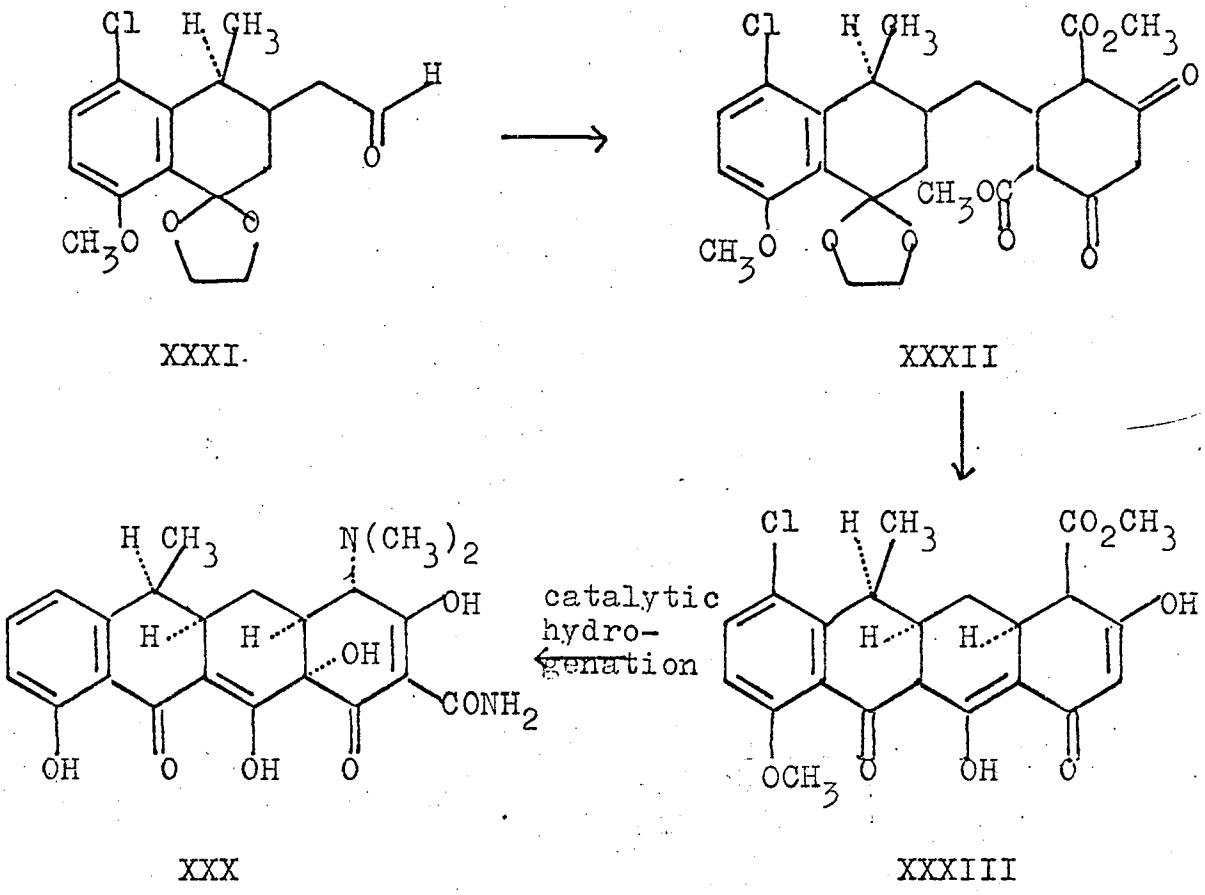
In Muxfeldt's[17] synthesis of dl-6-deoxy-6-demethyl-tetracycline (XXIV), the tetralone (XXV) was also used. Instead of a stepwise fusion of the tetralone (XXV) to the B ring, (XXV) was converted to the aldehyde-ketal (XXVI), which was condensed with hippuric acid in acetic anhydride and lead tetraacetate to give (XXVII). A tetracyclic compound (XXVIII) was obtained in one step by condensing (XXVII) with methyl-N-t-butyl-3-oxoglutaramate (XXIX) in the presence of sodium hydride. (Scheme 4).

In the synthesis of 6-deoxy-6-epitetracycline (XXX)[18], a tetralone derivative (XXXI) was also used. Reaction with malonic acid-dimethylester lengthened the side chain at the centre corresponding to C-4a in tetracycline, which was cyclised to form the A ring in (XXXII). The latter compound was cyclised in anisole in the presence of sodium hydride to give the C ring and therefore the tetracyclic product (XXXIII). (Scheme 5).

A Diels-Alder condensation was used by Muxfeldt[19] as the initial reaction in the synthesis of terramycin (II).



SCHEME 4. Synthesis of dl-6-deoxy-6-demethyltetracycline (XXIV).



XXXI XXXII

XXX XXXIII

SCHEME 5. Synthesis of 6-deoxy-6-<u>epi</u>tetracycline (XXX).

Juglone acetate and 1-acetoxybutadiene were condensed to form (XXXIV) which was converted to the aldehyde (XXXV) and subsequently to (XXXVI) by ozonolysis, hydrolysis and cleavage with aqueous sodium carbonate. (XXXVI) was reacted with thiazolone (XXXVII) and then methyl-3-oxoglutaramate (XXXVIII) to give (XXXIX). Acid hydrolysis of (XXXIX) followed by hydroxylation in basic medium with molecular oxygen gave the tetracyclic skeleton (XL). (Scheme 6).

Although some natural tetracyclines and a few compounds with naphthacenic skeleton have been synthesized, terrarubein (XIV) has not been synthesized. It is our aim to synthesize this compound. From a synthetic viewpoint, the high concentration of functional groups on ring A of terrarubein has made it the most difficult part of the whole molecule to prepare. Since ring A in terrarubein is aromatic, the difficulty in synthesizing the ring A of tetracycline is less. Therefore, instead of constructing the B, C and D ring first, as in the syntheses of terramycin or 6-deoxy-6-demethyltetracycline, it may be preferable in this case to build up the ring A first and then link it to B, C, D rings of terrarubein. Thus our first stage is the construction of the A ring of terrarubein, with suitable functional groups that with furthur development might lead to the synthesis of terrarubein.