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Review Article

Synthesis of Tetracycline Analogs

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NATURAL PRODUCTS possessing valuable physiological activity almost invariably have complicated structures; but simpler analogs representing part or parts of a natural product molecule may possess comparable activity, and the synthesis and testing of possible analogs has yielded useful new pharmaceuticals. This empirical approach to the synthesis of new drugs and antibiotics will eventually be replaced by more direct routes as soon as the mode of action of each family of compounds is fully understood. But while such knowledge is being slowly accumulated, useful advances have often accompanied the patterns of physiological activity shown by numerous analogs.

This article reviews the contributions of the study of analogs to the present understanding of the structural features essential for the characteristic activity of the tetracycline antibiotics. Large numbers of tetracycline analogs have been prepared by chemical modification of the natural products, and by modified fermentation techniques, and a comparative assessment of "tetracycline activity" in this series has revealed some of the basic structural requirements, variation of which may further yield simpler, highly active analogs. Physiologically active degradation products of the antibiotics are available by total synthesis, and other linearly fused tetracyclic, tricyclic, and bicyclic compounds have been prepared as potentially useful substitutes.

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The objective of the present review may thus be fulfilled by a sequence of subsections describing the properties of the known tetracyclines and of the closely related compounds obtained from them; a critical discussion of the theory of the mode of action of the tetracyclines, and experimental facts relating to this theory; and the results of the synthesis and testing of analogs. Other reviews of the tetracyclines have appeared, stressing either their chemistry (1–4) or their general pharmacological properties and use (5, 6). General reviews are available (7, 8); that by Professor Shemyakin and his colleagues is a particularly complete account—both of the chemical and pharmacological aspects of the subject—of work published to mid-1960. The Russian treatise is to be published in English translation (9); the present review, therefore, aims at a complete literature coverage of the chemistry and pharmacological activity of the antibiotics and their analogs for the period 1960 to mid-1962. All known tetracycline analogs and reported pharmacological properties are listed in this review (Tables I and II), but the primary literature references quoted in (8) are not repeated here. However, the section describing *Totally Synthetic Tetracycline Analogs* aims at a complete coverage of the literature.

NATURALLY OCCURRING TETRACYCLINES

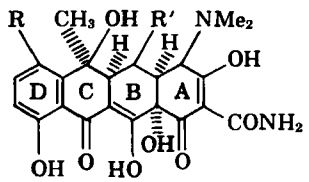
A strain of *Streptomyces*, uncataloged in 1948, was found to produce a remarkably effective antibiotic (10) which has since proved to be the first-discovered tetracycline. The pure active princi-

TABLE I.—TETRACYCLINES PRODUCED BY *Streptomycetes*

Name	Activity	References
Tetracycline	Highly active (8)	(8, 16, 17, 156)
7-Chlorotetracycline	Three to four times as active as tetracycline (8, 22, 60)	(8, 10, 11)
5-Hydroxytetracycline	Same activity as tetracycline (8, 22, 36, 60)	(8)
7-Bromotetracycline	Similar to chlortetracycline (8)	(19, 20, 21)
6-Demethyltetracycline	Same activity as tetracycline (8, 22, 60)	(22)
6-Demethyl-7-chlorotetracycline	Slightly less active than chlortetracycline (8, 22, 60)	(22)
5a,11a-(5,5a-?)[a] Dehydro-7-chlorotetracycline	Inactive (60). More than 50 times less active than tetracycline against *S. aureus* (8, 23)	(23)
2-Acetyl-2-decarboxamidotetracycline	Only 10% of the activity of tetracycline	(25)
2-Acetyl-2-decarboxamido-7-chlorotetracycline	Only 30% of the activity of tetracycline	(26)
2-Acetyl-2-decarboxamido-5-hydroxytetracycline	Only 10% of the activity of tetracycline	(26)

[a] Scott and Bedford (24) have suggested that the infrared spectrum of the dehydro-7-chlorotetracycline is more compatible with the 5,5a-location of the double bond.

ple was isolated as an orange-yellow hydrochloride (11); it was consequently named Aureomycin,[1] and its source was named *Streptomyces aureofaciens*. Degradative studies (12, 13) pointed to structural similarities with Terramycin,[2] a broad-spectrum antibiotic discovered in 1950 as a metabolite of *Streptomyces rimosus* (14). The brilliantly conducted study of the chemistry of Terramycin had progressed rapidly, and its structure and probable stereochemistry was published in 1953 (15); the name "tetracycline" was proposed (12) for a structure (I; R = R' = H) to which Aureomycin and Terramycin were simply related. Convenient to this nomen-

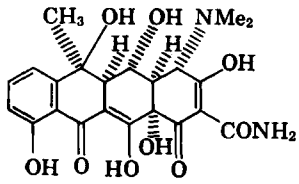


I

R = R' = H, tetracycline
R = Cl, R' = H, Aureomycin[1]
R = H, R' = OH, Terramycin[2]

clature was the later discovery that tetracycline itself is a highly active antibiotic which can be obtained by hydrogenolysis of chlortetracycline (16, 17), and is also produced by *S. aureofaciens* and by other *Streptomycetes* (18). Modifications to the environment in which the antibiotics are produced and the use of mutant *Streptomycetes* have since yielded a range of differently substituted tetracyclines. The members of this family available by biosynthesis are listed in Table I.

Results of the X-ray structural analysis (28) of oxytetracycline suggest that the molecule should be depicted as II.



II

Chemical evidence has been accumulated in support of both the α-orientation II (51, 157) and of the β-orientation I (15) of the dimethylamino-substituent at the 4-position in oxytetracycline; but the ease of epimerisation at this position must be responsible for these conflicting results (51), and it might be wisest now to picture naturally occurring 4- and 5-substituted tetracyclines as possessing the α-orientation at these positions, as shown in II. Recent papers (24, 29) are, indeed, adopting the relative stereochemistry indicated by the X-ray method. Independent X-ray studies (27, 163) have shown further that chlortetracycline and oxytetracycline possess the same configurations at all common asymmetric centers, and it is probable that all other naturally occurring tetracyclines may be assigned to this same configurational family.

CHEMICAL MODIFICATION OF NATURALLY OCCURRING TETRACYCLINES

Extension of the available totally synthetic routes to yield new tetracyclines cannot be an economic proposition, since the natural products are now relatively cheap and may be converted into a range of differently substituted tetracyclines by simple procedures. The variety of functional groupings, while conferring on the

[1] Subsequently the trade name of Lederle Laboratories for chlortetracycline hydrochloride.
[2] Subsequently the trade name of Chas. Pfizer and Co. for oxytetracycline hydrochloride.

molecule a bewildering complexity, makes it possible to envisage a host of small, feasible modifications; some modifications have been performed and, in general, the resulting compounds retain antibiotic activity if the natural configuration of the intact framework of the molecule is unaltered. Epimerisation at positions 4 and 5a results in almost complete loss of activity,[3] and the natural stereochemistry of the molecule is thus shown to be an essential prerequisite of physiological activity (105). Even though the inversion at C_6 which occurs (29) during the removal of the 6-hydroxy group by catalytic hydrogenolysis does not significantly reduce the antibiotic activity of the molecule, 6-deoxytetracyclines with the natural configuration of the 6-methyl group are appreciably more active than their C_6-epimers (29).

Methods are available for the selective removal and for the alteration of some existing substituents, and for the introduction of new functional groupings. New tetracyclines thus obtained from the natural products are listed in Table II, and their reported activities are quoted. A place is found in the Table for any particular modified tetracycline by checking its formula through the following sequence:

(*A*) 6-Deoxytetracyclines
  (*a*) 6-Deoxytetracyclines (excepting 5a,-6-anhydrotetracyclines)
  (*b*) 6-Demethyl-6-deoxytetracyclines
  (*c*) 6-Methylene-6-demethyl-6-deoxytetracyclines
  (*d*) 5a,6-Anhydrotetracyclines
  (*e*) Dedimethylamino-5a,6-anhydrotetracyclines
(*B*) 2-Carboxamide-modified tetracyclines
(*C*) Dimethylamino-modified tetracyclines
(*D*) Dedimethylamino-tetracyclines
(*E*) O-Acylated- and O-alkylated-tetracyclines
(*F*) Other modified tetracyclines

Comparative figures are available for many of the more active naturally occurring and chemically modified tetracyclines, and these figures are listed in Table III. The commonly used assay methods (57, 58) yield some inconsistent results, and activities are therefore quoted in Table II in qualitative terms, either in the words used in the reference cited or as implied by the figures in Table III.

Although a useful variety of transformations has been achieved in this series, it should be emphasized that the methods now available lead only to certain classes of analogs. Thus, D-ring substituents cannot be introduced by electrophilic substitution reactions into the parent tetracyclines, but may be introduced into more stable 6-deoxy- and 5a,6-anhydrotetracyclines.

Many analogs are thus potentially accessible only by total synthesis; but the development of methods which can augment the range of modified tetracyclines may now be expected. The new methods may involve ever more circuitous routes, and the general pattern is likely to involve the conversion of the natural products into their more stable anhydro-derivatives, followed by specific substitution and reconversion into the substituted tetracycline by oxygenation. The 6-hydroxy-group can be introduced into anhydroaureomycin by microbiological agents (59), or *via* the 6-hydroperoxy-compound (obtained by bubbling oxygen through an irradiated benzene solution of the anhydro-compound) (24), and these procedures, which yield the tetracycline with the natural C_6 configuration, are likely to be widely used. Oxygenation of certain 12a-deoxytetracyclines is also a simple matter by a microbiological method (*Circularia lunata*) (62, 63), by means of perbenzoic acid (64) [not applicable to 12a-deoxytetracycline (65, 51)], or with oxygen in the presence of sodium nitrite (61, 63) or in the presence of a noble metal (66). Other inorganic oxidizing agents can be used for 12a-hydroxylation (150).

The range of modified tetracyclines listed in Table II includes derivatives (for example, the halogen-substituted and diazonium modifications) suitable for further elaboration into antibiotics with novel substituents; particularly, the 6-methylenetetracyclines offer an entry into a new family of 6-substituted 6-deoxytetracyclines likely to possess high activity.

MODE OF ACTION OF THE TETRACYCLINES

The tetracycline molecule clearly depends more for useful activity upon the presence of the sequence of oxygen functions, from the phenolic hydroxyl at C_{10} and the groups at C_{11} and C_{12} through to the ring A 1,3-diketone grouping, than upon the presence of substituents at carbons 4–9. Other essential structural requirements also may be deduced from the relative activities of the various classes of modified tetracyclines; first, that the 2-carboxamide substituent also seems to have an essential role, since its replacement by a cyano- or acetyl-grouping greatly reduces antibiotic activity in this series. 2-Carboxamide-N-mono-substituted tetracyclines retain full activity, and this may indicate that the —CO—NH— grouping at the 2-position is a minimum requirement for activity. This conclusion suggests that the 2-substituent should be capable of forming the chelated structure III

[3] 4-Epi-tetracyclines are active *in vivo* but are almost devoid of activity against the standard assay organisms; conversion into the natural isomer might occur in the tissues of the laboratory animals, resulting in the observed *in vivo* activity.

TABLE II.—SUBSTITUENT-MODIFIED TETRACYCLINES

-tetracycline	Activity	Refs.
-6-Deoxytetracyclines		
6-Deoxytetracycline	Slightly less active than tetracycline	(29)
6-epi-methyl-	Half as active as tetracycline (29); similar activity to tetracycline (8).	(8, 30, 38)
5-Hydroxy-	More active than oxytetracycline	(29)
6-Epi-methyl-5-hydroxy-	Less than half the activity of oxytetracycline	(8, 30, 38)
4-Epi-	.....	(38)
4-Epi-5-hydroxy-	.....	(38)
6-Epi-methyl-dedimethylamino-	.....	(8, 30)
6-Epi-methyl-7-bromo-	More active than tetracycline	(31, 32)
6-Epi-methyl-7-iodo-	Less active than tetracycline	(31, 32)
6-Epi-methyl-7-^{131}iodo-	.....	(32, 33)
6-Epi-methyl-7-nitro-	Half of the activity of chlortetracycline	(31, 159)
6-Epi-methyl-9-nitro-	Inactive	(31, 159)
6-Epi-methyl-9-amino-	One-tenth of the activity of chlortetracycline	(31, 159)
6-Epi-methyl-9-amino-7-bromo-	Thirty-five per cent of the activity of chlortetracycline	(31)
6-Epi-methyl-9-amino-7-nitro-	Forty per cent of the activity of chlortetracycline	(31)
6-Epi-methyl-9-acetamido-	Half as active as the 9-amino-compound	(159)
6-Epi-methyl-9-diazonium-	Weakly active	(32)
6-Epi-methyl-9-azido-	Weakly active	(32)
6-Epi-methyl-9-nitro-5-hydroxy-	Inactive	(34)
6-Epi-methyl-9-ethoxythiocarbonylthio-	.....	(32)
11a-Fluoro-5-hydroxy-	.....	(37)
11a-Fluoro-6,12-oxido-	.....	(37)
11a-Fluoro-6,12-oxido-5-hydroxy-	.....	(37)
11a-Fluoro-6,12-oxido-dedimethylamino-	.....	(37)
11a-Fluoro-6,12-oxido-5-hydroxy-dedimethylamino-	.....	(37)
11a-Chloro-6,12-oxido-	.....	(36)
11a-Chloro-6,12-oxido-5-hydroxy-	.....	(36)
7-Chloro-6-hydroperoxy-5a,11a-(5,5a-?) dehydro-	.....	(24)
-6-Demethyl-6-deoxytetracyclines		
6-Demethyl-6-deoxytetracycline	One to two times as active as tetracycline (see Table III)	(8, 30, 39)
4-Epi-	.....	(39)
6-Benzylthiomethyl-	.....	(29)
7-^{3}H-	.....	(32)
7-Chloro-	Three times as active as tetracycline	(32)
7-Bromo-	Two times as active as tetracycline	(32, 34)
7-Iodo-	Same activity as tetracycline	(31, 32)
7-Nitro-	Five to ten times as active as tetracycline (see Table III)	(31, 159)
7-Amino-	Half to two times as active as tetracycline (see Table III)	(31, 159)
7-Formamido-	Same activity as the 7-amino-compound	(159)
7-Diazonium-	Twenty per cent of the activity of tetracycline	(32)
7-Azido-	1$^1/_2$ times as active as tetracycline	(32)
7-Ethoxythiocarbonylthio-	Fifty per cent of the activity of tetracycline	(32)
7-Bromo-9-nitro-	Only slight activity	(34)
7,11a-Dibromo-	.....	(34)
9-Nitro-	Inactive (31); nearly half as active as tetracycline (34)	(31, 159)
9-Amino-	1$^1/_2$ times as active as tetracycline (32)	(31, 32, 159)
9-Formamido-	More active than the 9-amino-compound	(159)
9-Azido-	Same activity as tetracycline	(32)
9-Diazonium-	Slight activity	(32)
9-Ethoxythiocarbonylthio-	Slight activity	(32)
11a-Fluoro-	.....	(37)
11a-Fluoro-dedimethylamino-	.....	(37)
11a-Fluoro-6,12-oxido-	.....	(37)
11a-Chloro-	.....	(36)
11a-Chloro-5-hydroxy-	.....	(36)
11a-Bromo-	.....	(32, 34)
O^{12a}-Formyl-	.....	(35)
12a-Deoxy-	.....	(35)

TABLE II.—*Continued*

-tetracycline	Activity	Refs.
12a-Deoxy-dedimethylamino-	.....	(35)
4a,12a-Anhydro-	.....	(35)
-6-Methylene-6-demethyl-6-deoxytetracyclines		
6-Methylene-6-demethyl-6-deoxytetracycline	Same activity as tetracycline	(36)
7-Chloro-	.....	(36)
5-Hydroxy-	Two times as active as oxytetracycline	(36)
7-Bromo-5-hydroxy-	.....	(36)
7-Iodo-5-hydroxy-	.....	(36)
7-Chloro-5-hydroxy-	Six times as active as oxytetracycline	(36)
11a-Fluoro-	.....	(36)
11a-Chloro-	.....	(36)
11a-Chloro-5-hydroxy-	.....	(36)
7,11a-Dichloro-5-hydroxy-	.....	(36)
-5a,6-Anhydrotetracyclines		
5a,6-Anhydrotetracycline	Active against a number of gram-positive and gram-negative, and acid-fast bacteria, also against *actinomycetes*. More active than tetracycline Against *T. vaginalis in vivo* (8). Slight activity (60)	(8, 40)
4-Epi-	.....	(8)
5-Hydroxy-	.....	(8)
7-Chloro-	Active against a number of gram-positive, and gram-negative, and acid-fast bacteria; active against a number of *Actinomycetes* in concentration $\leqslant 1\gamma$/ml. More active than tetracycline against *T. vaginalis in vivo* (8); 5% of the activity of chlortetracycline	(8, 41)
7-Chloro-6-demethyl-	.....	(8)
7-Bromo-	.....	(8)
7-Chloro-9-benzyl-	Active against *T. vaginalis* in concentration 50 γ/ml.	(8)
7-Chloro-6-demethyl-12a-deoxy-	.....	(42)
9-*tert*-Butyl-	Active against *T. vaginalis in vivo* (1.6 γ/ml.) and more active *in vivo* than tetracycline (8)	(8, 158)
9-*tert*-Butyl-7-chloro-	Active against *T. vaginalis in vitro* (0.8 γ/ml.), more active than tetracycline *in vivo* (8)	(8, 158)
9-*tert*-Amyl-5-hydroxy-	.....	(8, 158)
5-Acetoxy-O^{12a}-acetyl-	Active against a number of microorganisms, including several resistant to tetracycline	(8)
12a-Deoxy-	Active against certain tetracycline-resistant bacteria (42)	(35, 42, 51)
12a-Deoxy-6-demethyl-	.....	(42)
4a,12a-Anhydro-	.....	(8)
7,8-Dihydro-12α-hydroxy-12-deoxo-	Inactive	(60)
7,8-Dihydro-12β-hydroxy-12-deoxo-	Inactive	(60)
7,8-Dihydro-12-deoxo-	.....	(8, 30, 43)
Benzaldehyde derivative of 7,8-dihydro-12-deoxo-	Antibacterial	(43)
Salicylaldehyde derivative of 7,8-dihydro-12-deoxo-	Antibacterial	(43)
p-Nitrobenzaldehyde derivative of 7,8-dihydro-12-deoxo-	Antibacterial	(43)
5-Nitrofurfuraldehyde derivative of 7,8-dihydro-12-deoxo-	Antibacterial	(43)
2-Cyano-2-decarboxamido-5-hydroxy-O^{10}-benzenesulfonyl-	.....	(8)
N^2-*tert*-Butyl	Active against a number of gram-positive, gram-negative, and acid-fast bacteria	(8, 131)
N^2-*tert*-Butyl-7-chloro-	Active against a number of gram-positive, gram-negative, and acid-fast bacteria; also several other microorganisms	(8)
N^2-*tert*-Butyl-9-*tert*-butyl-	Active against a number of microorganisms	(8)
N^2-*tert*-Butyl-9-*tert*-butyl-7-chloro-	Active against *T. vaginalis in vitro* (0.8 γ/ml.)	(8)
N^2-*tert*-Amyl-5-hydroxy-	.....	(8)
N^2-Piperidinomethyl-	.....	(8)
N^2-(Dimethylbenzyl)methyl-7-chloro-	.....	(8)
N^2-Acetonyl-5-hydroxy-	.....	(8)

TABLE II.—*Continued*

-tetracycline	Activity	Refs.
N^2-Acetonyl-5-acetoxy-O^{12a}-acetyl-	.....	(8)
N^2-(9-Xanthyl)-	.....	(8, 44)
Dedimethylamino-5a,6-anhydrotetracyclines		
Dedimethylamino-5a,6-anhydrotetracycline	.....	(8)
5-Hydroxy-	Active against a number of micro-organisms, including several resistant to tetracycline	(8)
5-Hydroxy-12a-epi-	Active	(8)
5-Hydroxy-12a-deoxy-	Active	(8)
5-Hydroxy-12a-deoxy-12a-epi-methyl-	Active	(8)
7-Chloro-	Active against a number of microorganisms, including several resistant to tetracycline	(8)
12a-Deoxy-	.....	(8, 50, 51)
12a-Deoxy-7-chloro-	.....	(8)
12a-Deoxy-7-chloro-6-demethyl-	.....	(8)
4a,12a-Anhydro-	.....	(8)
4a,12a-Anhydro-7-chloro-	.....	(8)
O^{10}-Methyl-	Active	(8)
O^{10}-Methyl-9-bromo-	.....	(103)
O^{10}-Methyl-12a-epi-	.....	(8)
O^{10}-Methyl-12a-deoxy-	.....	(8)
$O^{10,11}$-Dimethyl-	.....	(8)
$O^{10,11}$-Dimethyl-7-chloro-12a-deoxy-	.....	(8)
N^2-Acetonyl-	.....	(8)
N^2-Acetonyl-5-hydroxy-	.....	(8)
N^2-Acetonyl-7-chloro-	.....	(8)
N^2-Acetonyl-5-hydroxy-12a-epi-	.....	(8)
N^2-Acetonyl-5-hydroxy-12a-deoxy-	.....	(8)
N^2-Acetonyl-5-hydroxy-12a-deoxy-12a-epi-methyl-	.....	(8)
9-Chloro-	.....	(50)
9-Bromo-	.....	(50)
9,12a-Dibromo-12a-deoxy-	.....	(50)
(x)-Bromo-7-chloro-	.....	(50)
2-Carboxamide-modified tetracyclines		
2-Cyano-2-decarboxamido-	Less than 5% of the activity of tetracycline (8) Slight activity (60)	(8)
2-Cyano-2-decarboxamido-7-chloro-	.....	(8)
2-Cyano-2-decarboxamido-5-hydroxy-	.....	(8)
2-Cyano-2-decarboxamido-7-bromo-	.....	(8)
2-Cyano-2-decarboxamido-4-epi-7-chloro-	.....	(8)
2-Cyano-2-decarboxamido-O^{10}-benzenesulfonyl	.....	(8)
2-Cyano-2-decarboxamido-4-epi-O^{10}-benzenesulfonyl-	.....	(8)
2-Cyano-2-decarboxamido-5-hydroxy-O^{10}-benzenesulfonyl-	.....	(8)
N^2-Aminomethyl-	.....	(8)
N^2-Diethylaminomethyl-	.....	(8)
N^2-Dibenzylaminomethyl-	.....	(8)
N^2-(β-Hydroxyethyl)aminomethyl-	.....	(8)
N^2-Di(β-hydroxyethyl)aminomethyl-	.....	(8)
N^2-Di(β-diethylaminoethyl)aminomethyl-	.....	(8)
N^2-Pyrrolidinomethyl- ("Reverin")	Same activity as tetracycline against a wide range of gram-positive and gram-negative organisms	(8)
N^2-Pyrrolidinomethyl-5-hydroxy-	.....	(8)
N^2-Piperidinomethyl-	.....	(8)
N^2-Piperidinomethyl-4-epi-	.....	(8)
N^2-Piperidinomethyl-5-hydroxy-	.....	(8)
N^2-Morpholinomethyl-	Highly active	(8)
N^2-Morpholinomethyl-7-chloro-	.....	(8)
N^2-Morpholinomethyl-5-hydroxy-	.....	(8)
N^2-Morpholinomethyl-methiodide	Highly active	(8)
N^2-{N'-(β-Hydroxyethyl)}-piperazinomethyl-	.....	(8)
N^2-(N'-Methyl)piperazinomethyl-7-chloro-	.....	(8, 45)
N^2-(9-Xanthyl)-	.....	(8, 44)
N^2-(9-Xanthyl)-7-chloro-	.....	(44)
N^2-(9-Xanthyl)-7-bromo-	.....	(44)
N^2-(9-Xanthyl)-5-hydroxy-	.....	(44)
Dimethylamino-modified tetracyclines		
4-Epi-	Seven to 50 times less active than tetra-	(8, 46, 47)

TABLE II.—*Continued*

-tetracycline	Activity	Refs.
	cycline; active *in vivo* (8); slight activity (60)	
4-Epi-5-hydroxy-	Twenty-five times less active than tetracycline against *S. aureus;* active *in vivo* (8, 22)	(8, 22)
4-Epi-7-chloro-	Six times less active than tetracycline against *S. aureus;* active *in vivo* (8, 22)	(8, 22)
4-Epi-7-bromo-	Twenty times less active than 7-bromotetracycline against *S. aureus;* active *in vivo*	(8)
4-Epi-6-demethyl-	Eight times less active than tetracycline against *S. aureus* (8, 22)	(8, 22)
4-Epi-6-demethyl-7-chloro-	Four times less active than tetracycline against *S. aureus* (8, 22)	(8, 22)
4-Epi-12a-deoxy-	.....	(51)
Methiodide	Slight activity (8, 60)	(8, 48, 155)
4-Epi-methiodide	.....	(8, 48)
7-Chloro- methiodide	Slight activity	(8, 155)
12a-Deoxy- methiodide	.....	(35)
Dedimethylamino-tetracyclines		
Dedimethylaminotetracycline	Highly active against a variety of microorganisms (8); 15% of the activity of tetracycline (60)	(8, 155)
7-Chloro-	Highly active against a large number of microorganisms	(8)
5-Hydroxy-	Highly active against a number of microorganisms	(8)
7-Bromo-	Active	(8)
12a-Deoxy-	.....	(8, 13, 50, 51)
12a-Deoxy-7-chloro-	.....	(8)
12a-Deoxy-7-chloro-6-demethyl-	.....	(8)
12a-Deoxy-12a-epi-methyl-5-hydroxy-	.....	(8)
4,12a-Anhydro-	.....	(35, 50, 51)
O^4-Acetyl- (or O^9-acetyl-)	.....	(53)
11a-Bromo-	.....	(50)
11a,12a-Dibromo-12a-deoxy-	.....	(50)
12a-Bromo-12a-deoxy-	.....	(50, 52)
12a-epi-5-hydroxy-	.....	(138)
O-Acylated- and O-alkylated-tetracyclines		
O^{12a}-Formyl-	.....	(35, 49)
O^{12a}-Acetyl-	Highly active	(8)
O^{12a}-Acetyl-7-chloro-	Highly active	(8)
O^{12a}-Acetyl-5-hydroxy-	Highly active against a large number of microorganisms	(8)
O^{12a}-Acetyl-5-acetoxy-	Active	(8)
O^{10}-Acetyl-5-hydroxy-(?)	.....	(35)
$O^{10,12a}$-Diacetyl-5-hydroxy-	.....	(35)
O^{10}-Propionyl-5-hydroxy-(?)	.....	(35)
O^{12a}-Propionyl-5-hydroxy-	Highly active	(8)
$O^{10,12a}$-Dipropionyl-5-hydroxy-	.....	(35)
O^{12a}-Palmityl-	.....	(8)
O^{12a}-Phenylcarbamyl-	Antibacterial	(35, 153)
O^{12a}-Phenylcarbamyl-5-hydroxy-	.....	(35, 153)
O^{12a}-(*p*-Methoxyphenyl)carbamyl)-	.....	(153)
$O^{3,12}$-Dimethyl-5-hydroxy-	.....	(8)
Other modified tetracyclines		
7-^{3}H-	.....	(145)
7-^{3}H-6-demethyl-	.....	(31)
7-Chloro- -^{14}C	.....	(88)
7-^{36}Chloro-	.....	(21, 146)
7-^{36}-Chloro-5a,11a-(5,5a-?)dehydro-	.....	(147)
5a-Epi-	Less than 2% of the activity of tetracycline against *S. aureus* (8, 23, 60)	(8, 23, 46, 55)
12a-Deoxy-	Inactive (60); 2% of the activity of tetracycline against *S. aureus* (51) Appreciably active (35, 56).	(8, 35, 51, 56, 153, 154)
12a-Deoxy-5-hydroxy-(?)	.....	(35)
4a,12a-Anhydro-	Slight activity (35)	(35, 50, 51, 153)
9-Pyrrolidinomethyl-	.....	(54)

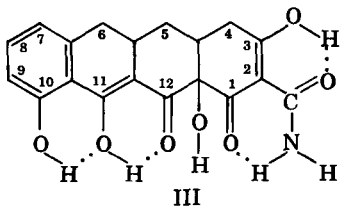
involving the oxygen functions at positions 1 and 3. Second, the removal of the 12a-hydroxyl group deprives tetracycline of its activity, but O^{12a}-esters are highly active (49); the presence of a substituent larger than hydrogen may be the simple requirement at this position. Thus, replacement of the 12a-hydroxyl group of dedimethylamino-5-hydroxy-5a,6-anhydrotetracycline by methyl with simultaneous inversion of configuration yields an active antibiotic, though the very different antibacterial spectrum of 5a,6-anhydrotetracyclines (suggesting that a different mode of antibacterial action applies to this class (130, 131)) reduces the validity of this comparison. The presence of a 9-nitro-substituent greatly reduces antibiotic activity, whereas 7-chloro-tetracyclines are invariably more active than their unsubstituted analogs. The phe-

TABLE III.—RELATIVE ACTIVITIES OF SUBSTITUENT-MODIFIED TETRACYCLINES

-tetracycline	Ref:	(31)	(26)	(60)	(60)	(36)	(32)	(22)	(29)	(34)
	Assay:	(58)	(57)	(58)[a]	(58)	(57)	(58)	[b]	(57)	(57)
Tetracycline			100	100	100	1000	100	25		
5-Hydroxy-				80	100	1000		24	1000	
7-Chloro-		100		350				100		
6-Demethyl-				100	95			24		
7-Chloro-6-demethyl-				300				75		
7-Chloro-5a,11a-(5,5a-?) dehydro-				1						
2-Acetyl-2-decarboxamido-			10							
2-Acetyl-2-decarboxamido-5-hydroxy-			10							
2-Acetyl-2-decarboxamido-7-chloro-			30							
6-Deoxy-									700	
6-Deoxy-6-epi-methyl-		18		70	70		70		500	
6-Deoxy-5-hydroxy-									1400	
6-Deoxy-6-epi-methyl-5-hydroxy-				50	36				400	
7-Bromo-6-deoxy-6-epi-methyl-		30					140			
7-Iodo-6-deoxy-6-epi-methyl-		14					60			
7-Nitro-6-deoxy-6-epi-methyl-		60								
9-Nitro-6-deoxy-6-epi-methyl-		<1								
9-Amino-6-deoxy-6-epi-methyl-		14					60			
9-Amino-7-bromo-6-deoxy-6-epi-methyl-		35								
9-Amino-7-nitro-6-deoxy-6-epi-methyl-		41								
9-Diazonium-6-deoxy-6-epi-methyl-							10			
9-Azido-6-deoxy-6-epi-methyl-							10			
9-Nitro-6-deoxy-6-epi-methyl-5-hydroxy-										<10
6-Demethyl-6-deoxy-		40		200	170		160		900	900
7-Chloro-6-demethyl-6-deoxy-							300			
7-Bromo-6-demethyl-6-deoxy-		60					200			1300
7-Iodo-6-demethyl-6-deoxy-		30					120			
7-Nitro-6-demethyl-6-deoxy-		160								4600
7-Amino-6-demethyl-6-deoxy-		21					40			975
7-Diazonium-6-demethyl-6-deoxy-							20			
7-Azido-6-demethyl-6-deoxy-							150			
7-Ethoxythiocarbonylthio-6-demethyl-6-deoxy-							50			
7-Bromo-9-nitro-6-demethyl-6-deoxy-										25
9-Nitro-6-demethyl-6-deoxy-		3								200
9-Amino-6-demethyl-6-deoxy-		40					160			760
9-Azido-6-demethyl-6-deoxy-							90			
9-Diazonium-6-demethyl-6-deoxy-							17			
9-Ethoxythiocarbonylthio-6-demethyl-6-deoxy-							10			
6-Methylene-6-demethyl-6-deoxy-						1200				
6-Methylene-6-demethyl-6-deoxy-5-hydroxy-						2300				
6-Methylene-6-demethyl-6-deoxy						6300				
6-Deoxy-7-chloro-5-hydroxy-5a,6-anhydro-					6					
2-Cyano-2-decarboxamido-					1					
4-Epi-					6			1.6		
4-Epi-7-chloro-								4.2		
4-Epi-5-hydroxy-								1.1		
4-Epi-6-demethyl-								3		
4-Epi-7-chloro-6-demethyl-								7		
Methiodide				1						
Dedimethylamino-				15						
5a-Epi-				1						
12a-Deoxy-				1						

[a] Pelcak and Dornbush's method (58) was modified for this set of results by the addition of 10% normal horse serum to the test medium. This modification yields results more closely paralleling those of *in vivo* tests. [b] *In vitro* against *S. aureus*.

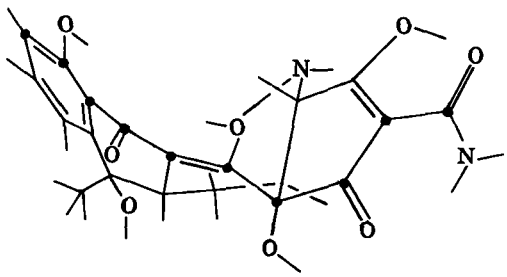
nolic hydroxyl group at position 10 is assumed to have an important role (*vide infra*), and its effective performance may be impaired by hydrogen-bonding with the nitro-group (34). The opposite effect of the 7-chloro-substituent is consistent with its capability (67) of electron-release to the para-position.



III

The deduction (138) that the 11 and 12 oxygen functions, augmented by the effect of the phenolic hydroxyl at C_{10}, are primarily responsible for holding metal ions with which tetracyclines form strong chelates (68–70) does not satisfactorily explain the function of the A-ring substituents, if the antibiotic activity of the tetracyclines is accepted to be due to the disturbance of certain enzyme systems by chelation of vital trace metals (68). Ferric ions are strongly held by the tetracyclines (68, 69); also by 8-hydroxyquinoline, which is a potent antibacterial (71–73). The tetracyclines may inhibit protein synthesis by chelation of essential metals, resulting in the production of unstable, small molecular weight RNA (74), but no experimental evidence is yet available in support of this theory. It is known, however, that chlortetracycline inhibits the action of an aromatic nitro-reductase by combining with manganese ions essential to the function of this enzyme (75); also that oxidative phosphorylation in liver mitochondria preparations, inhibited by the presence of chlortetracycline (76, 77), again proceeds normally when an excess of magnesium ions is added to the nutrient medium (77). Significantly, it has been found that the antibacterial action of chlortetracycline and of oxytetracycline is inhibited in the presence of magnesium ions (78). The conclusion, drawn from studies of *E. coli* extracts, that chlortetracycline exerts its antibiotic action by inhibiting electron-transport in sensitive organisms (79) takes account of the fact that the electron-transport enzymes and nitro-reductases of *Neurospora crassa* (80) and of *E. coli* (81, 82) are known to be metalloflavins. Chlortetracycline-sensitive nitro-reductase concentrates contain easily dissociable flavin, whereas the flavin is firmly bound in resistant species (83); the point of inhibition by the antibiotic is concluded to be the stage of reoxidation of conjugated flavoproteins (79).

It has been pointed out that epimerisation at positions 4 and 5a results in almost complete loss of antibiotic activity, and that the 6-epimer is significantly less active. As can be visualized from the scale drawing IV, the spatial relationships between parts of the molecule must be affected by epimerisation, but it is not obvious that the consequent changes in the shape of the molecule would limit the chelating ability of the sequence of oxygen functions involved—though interaction between the 4-dimethylamino-group and the oxygen functions at carbons 10, 11, and 12 is a distinct possibility in 4-epi-tetracyclines. Unless the varying antibiotic activities shown by modified tetracyclines can be directly related to their ability to form more or less strong metal chelates, then other factors must also be essential to the activity of this group of antibiotics.



IV

BIOSYNTHESIS

An exact understanding of the stepwise synthesis of tetracyclines *in vivo* can suggest ways by which new tetracyclines may be obtained from normal and mutant *Streptomycetes*, utilizing nutrient media in which new substrates replace the "building blocks" essential to the normal biosynthetic route.

The production of 7-chlorotetracycline by *S. aureofaciens* is dependent upon the presence of ionic chlorine in the nutrient medium, but the total yield of tetracyclines produced under conditions of low halide concentration is unchanged since tetracycline itself then forms in increased amount (21). Thiocyanate, added to the usual *S. aureofaciens* nutrient medium, also inhibits 7-chlorotetracycline synthesis but the total yield of tetracyclines is again unchanged (146, 21). The same organism can be induced to synthesize 6-demethyl-7-chlorotetracycline in addition to 7-chlorotetracycline by contamination of the nutrient medium with sulfonamides (84); the proportion of the 6-demethyl compound formed under these conditions can be made smaller by the addition of methionine to the medium. Halogenation and methylation are thus shown to be

late steps in the biosynthetic sequence. Mutant strains of the tetracycline-producing organisms can produce only modifications of the normal product of their earlier generations in some cases because they cannot complete the biosynthetic route; thus, the 7-chloro-5a,11a-(5,5a-?)dehydrotetracycline produced by *S. aureofaciens* "S 1308" (23, 59) is converted into 7-chlorotetracycline by the normal strain of the organism (59), also by other mutants (146). The 6-demethyl- and the 2-acetyl-2-decarboxamido-tetracyclines listed in Table I are also produced by mutant *Streptomycetes*.

The "head-to-tail" linkage of acetate units (86), predicted by Robinson (85), has been demonstrated to be the route by which the skeleton is largely built up, the 6-methyl substituent and the dimethylamino methyl groups being derived from methionine (87). Glutamic acid is probably the basis of the larger part of ring A(87).

Incorporation of isotopically-labeled acetic acid (both carboxyl-^{14}C- and methyl-^{14}C- labeled forms) (87, 88), glycine-2-^{14}C (88), and methionine-$^{14}CH_3$ (87) has been separately demonstrated. The dimethylamino group in chloro-

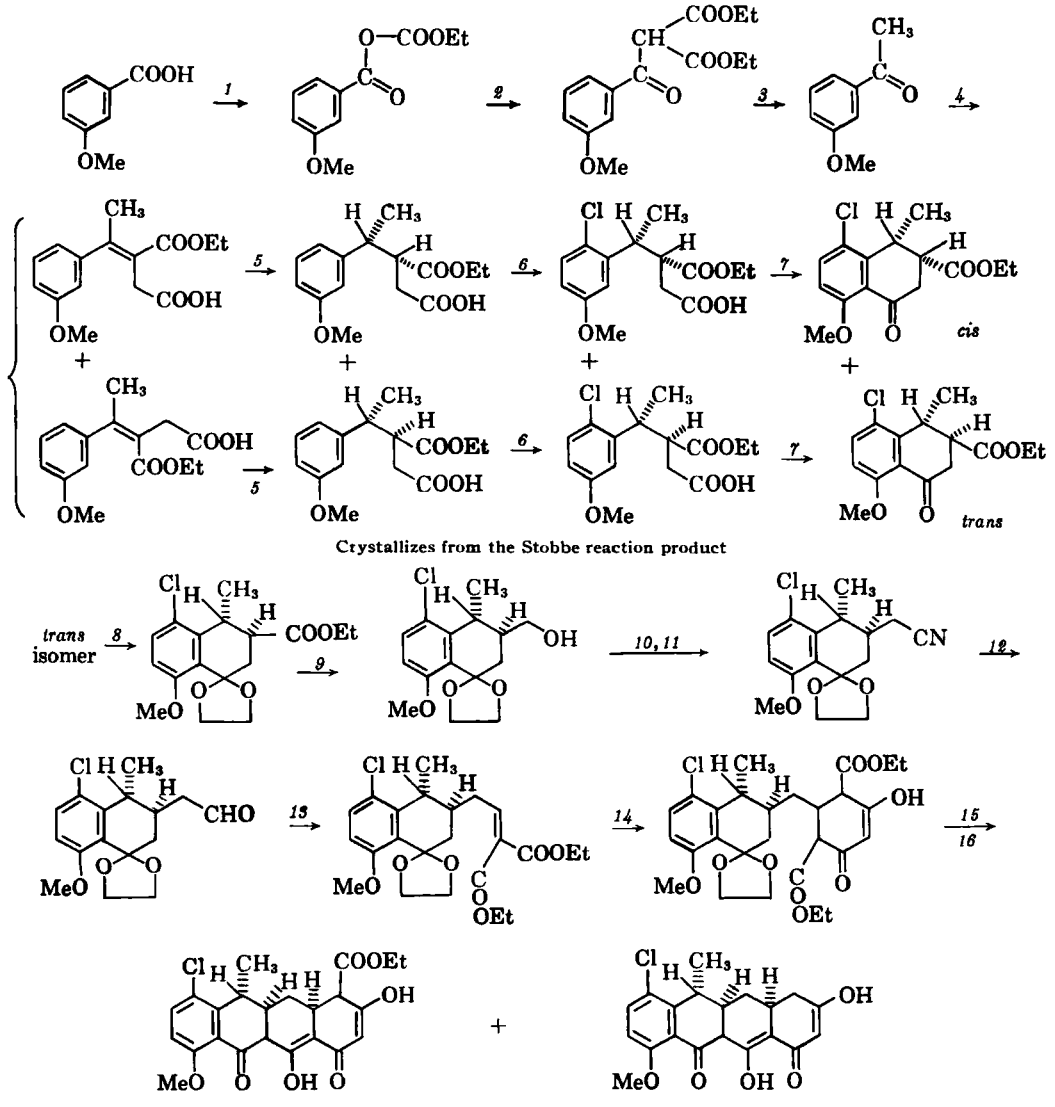
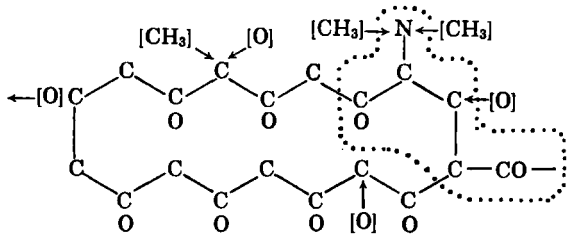


Fig. 1.—Synthesis of (±)-dedimethylamino-6,12a-dideoxy-decarboxamido-7-chlorotetracycline (101, 102, 162). Reagents: (*1*), ClCOOEt/N-methylmorpholine/benzene; (*2*), (EtOOC—$\bar{C}$H—COOEt) Mg^{++} ($\bar{O}$Et); (*3*), aq. H_2SO_4/AcOH/heat; (*4*), diethyl succinate/NaH; (*5*), H_2/Ni; (*6*), 1 equiv. Cl_2/CCl_4; (*7*), polyphosphoric acid; (*8*), ethylene glycol; (*9*), $LiAlH_4$; (*10*), methanesulfonyl chloride/pyridine; (*11*), KCN/dimethylformamide/water; (*12*), $LiAl(OEt)_3H$; (*13*), diethyl malonate/AcOH/piperidine; (*14*), Na^+(CH_3CO—CH—COOEt)/ether/reflux; (*15*), aq. HCl; (*16*), NaH/anisole.



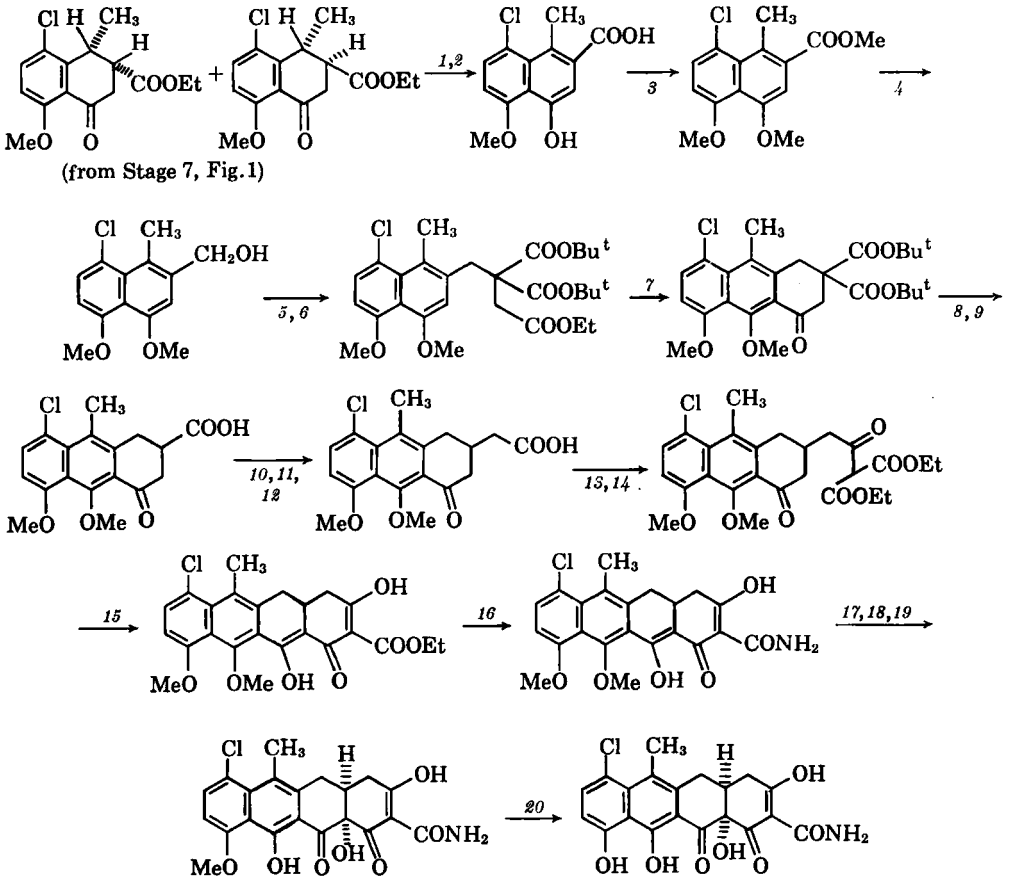
V

tetracycline contains 40% of the total radioactivity when glycine-2-^{14}C is used as substrate for *S. aureofaciens*, but carboxyl-^{14}C-glycine is not significantly utilized (88).

The use of mutant strains (59) to oxygenate anhydrotetracyclines has been mentioned, and current investigation of precursor activity possessed by other tetracycline degradation products might be extended to make available new biosynthetic tetracyclines from modified precursors, and from new mutant *Streptomycetes*.

TOTALLY SYNTHETIC TETRACYCLINE ANALOGS

Confirmatory syntheses of degradation products obtained during the structural elucidation



(from Stage 7, Fig. 1)

(and 12a-epimer)

Fig. 2.—Synthesis of (±)-dedimethylamino-12a-deoxy-5a,6-anhydro-7-chlorotetracycline (101) and its conversion into (±)-dedimethylamino-5a,6-anhydro-7-chlorotetracycline (103, 162). Reagents: (*1*), Br_2/ether/500-watt lamp; (*2*), NaOH/MeOH; (*3*), CH_2N_2; (*4*), $LiAlH_4$; (*5*), PBr_3; (6), Na^+(EtOOC—CH_2—$\bar{C}$(COOBu^t)$_2$); (*7*), polyphosphoric acid; (*8*), dil. aq. NaOH; (*9*), diethyl phthalate/170°; (*10*), PCl_5 or oxalyl chloride; (*11*), CH_2N_2; (*12*), benzyl alcohol/180°; (*13*), PCl_5; (*14*) Mg^{++}(EtOOC—$\bar{C}$H—COOEt)$_2$; (*15*), NaH/anisole; (*16*) NH_3/NaOMe—MeOH; (*17*), HCl/AcOH; (*18*), CH_2N_2; (*19*), $PhCO_3H/CHCl_3$; (*20*), HCl/AcOH.

of oxytetracycline and chlortetracycline were announced between 1951 and 1959 (89–96, 148, 152), and papers describing syntheses of simple model compounds date from 1956. Initial stages in projected total syntheses of tetracyclines were announced in 1957 by several research groups, and their continued efforts during later years were augmented by work in other laboratories; the objective has recently been realized by the total synthesis of (±)-6-demethyl-6-deoxytetracycline (97).

The complex stereochemistry and substitution of the tetracycline molecule has inspired many different conceptions of its total synthesis, each route representing a particular approach to the solution of problems of stereochemistry and synthesis. The most successful approach follows, in broad outline, the probable biogenetic route; various forms of the Claisen condensation are employed in the stepwise fusion of rings C, B, and A to a benzene derivative carrying the ring D substituents and a basis for the construction of ring C. The approach is exemplified by each of the syntheses outlined in Figs. 1–6; the products obtained by the routes in Figs. 2, 3, 4, and 5 were proved to be identical to the appropriate tetracycline degradation products. Although an adaptation of Woodward's synthesis (Fig. 5) has not yet been announced which leads to a naturally occurring 6-substituted tetracycline, and Muxfeldt's and Boothe's earlier routes (Figs. 2 and 3, respectively) yield dedimethylamino-anhydrotetracyclines, the major problems in this approach to the total synthesis have been overcome. Other research groups have reported initial stages in related syntheses, *e.g.*, synthesis of VI (92) (see also (95)), VII (98), and stereoisomers of VIII (99) (see also (161)), and model reactions have supplied useful guidance to crucial steps—the introduction of the N,N-dimethylglycine residue in Woodward's synthesis was earlier worked out, in principle, by Shemyakin's

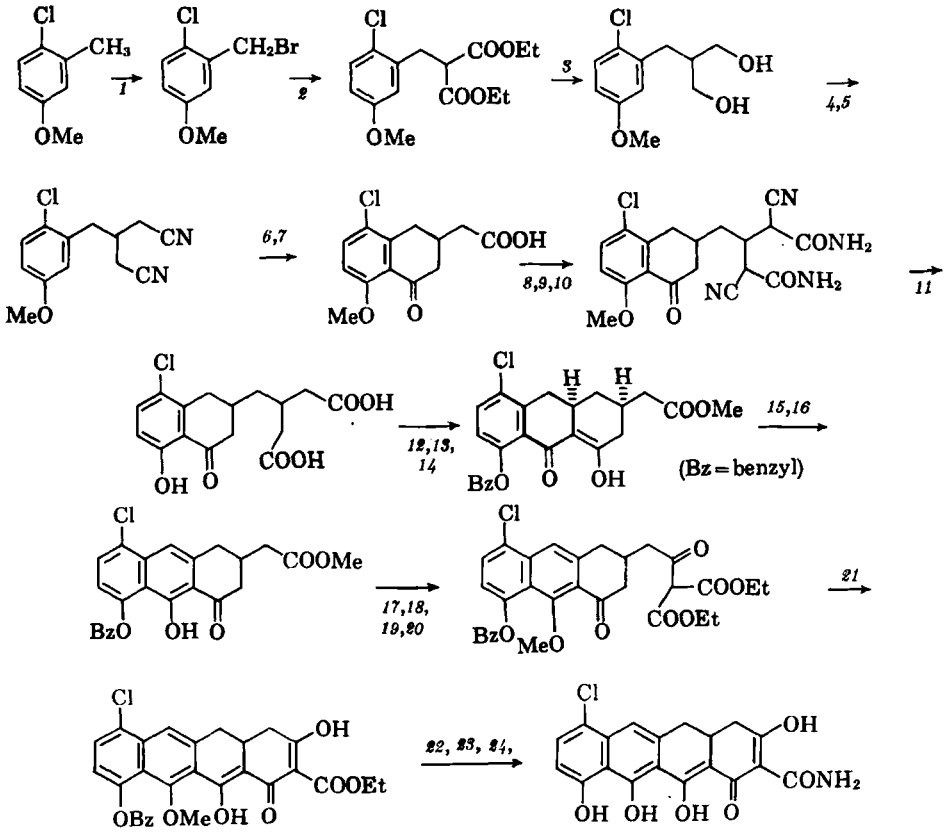
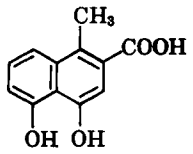
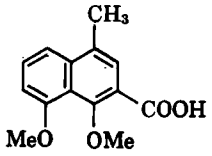


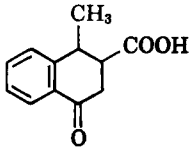
Fig. 3.—Synthesis of (±)-dedimethylamino-6-demethyl-12a-deoxy-5a,6-anhydro-tetracycline (104, 105, 135, 151). Reagents: (*1*), N-bromosuccinimide/peroxide; (*2*), Na^+(EtOOC—$\bar{C}$H—COOEt); (*3*), $LiAlH_4$; (*4*), methane sulfonyl chloride; (*5*), CN^-; (*6*), OH^-; (*7*), polyphosphoric acid; (*8*), oxalyl chloride; (*9*), Rosenmund reduction (5% Pd–$BaSO_4$); (*10*), cyanoacetamide/piperidine; (*11*), concd. HCl/AcOH; (*12*), benzyl chloride/boiling alkali; (*13*), $MeOH/H_2SO_4$; (*14*), NaH/toluene; (*15*), Br_2/NaOAc; (*16*), collidine (dehydrobromination); (*17*), Me_2SO_4/K_2CO_3; (*18*), mild alkaline hydrolysis; (*19*), ethyl chloroformate/NEt_3; (*20*), Mg^{++} ($\bar{O}$Et) (EtOOC—$\bar{C}$H—COOEt); (*21*), NaH/toluene; (*22*), H_2/10% Pd–C; (*23*), $HCOO^-NH_4^+$/140°; (*24*), boiling concd. HCl/AcOH.



VI



VII

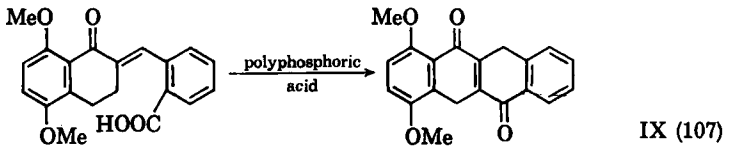


VIII

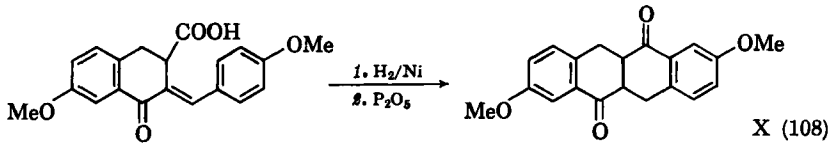
group (100), starting from cyclohexanone as a model.

Modification of each of the syntheses outlined above is easily visualized to yield many differently substituted tetracyclines, possibly with improved medical properties; and the outcome of other approaches to the total synthesis may provide alternative routes to modified tetracyclines.

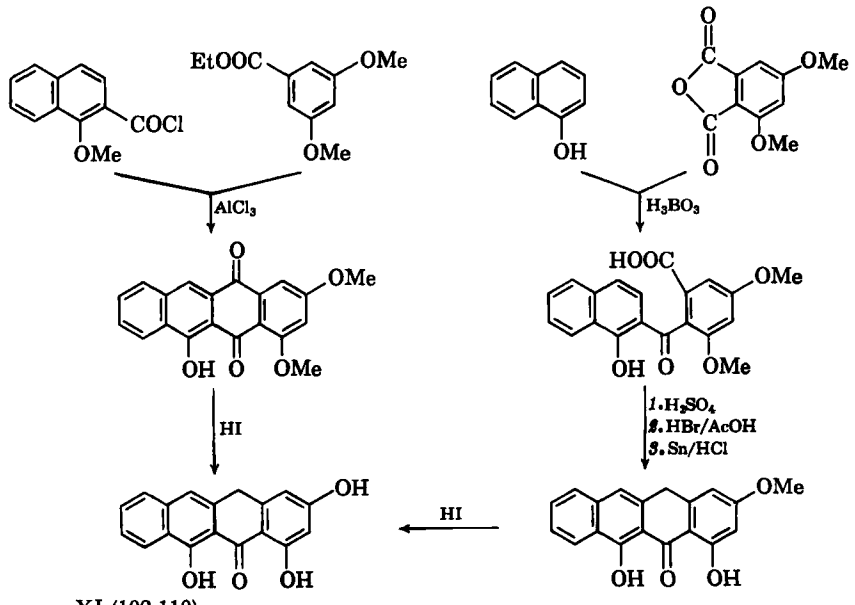
Naphthacene derivatives IX, X, and XI have been synthesized as more or less distant relatives of the antibiotics; compounds XI and XII of this group are closely similar to dedimethylamino-terrarubein, a degradation product of oxytetracycline (15). The naphthacene derivative XIII was found to possess less than 0.1% of the antimicrobial activity of chlortetracycline



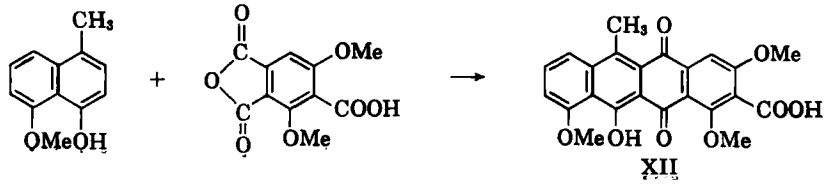
IX (107)



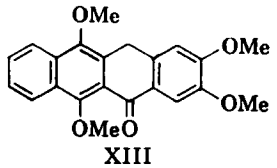
X (108)



XI (109,110)



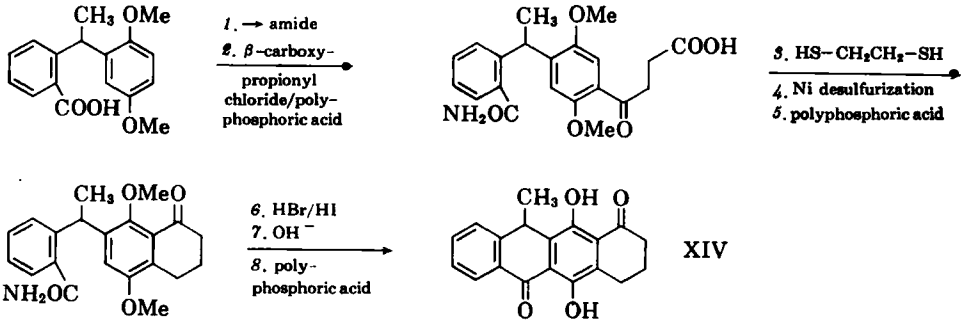
XII



XIII

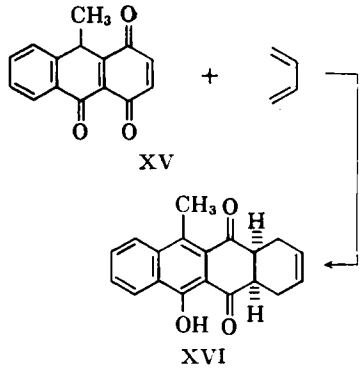
(111, 161); it is the only compound of this class whose antibiotic activity has been reported. The dark orange tetracycline analog XIV was built up as shown (112).

The more successful analogs are likely to be those which incorporate features of the stereo-



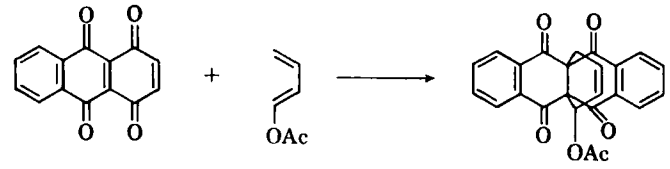
XIV

chemistry of the natural tetracyclines, and the Diels-Alder reaction has been used for the synthesis of a variety of compounds containing *cis*-fused rings corresponding to rings A and B. The tricyclic quinone XV has been reported (109, 113) to yield with butadiene the expected adduct XVI, although the same quinone was earlier (112) found to be unstable to Diels-Alder reaction conditions with butadiene.

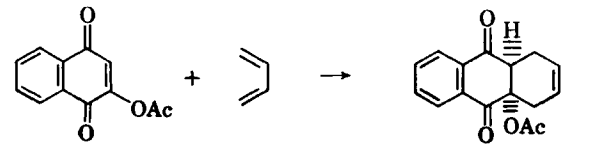


XV XVI

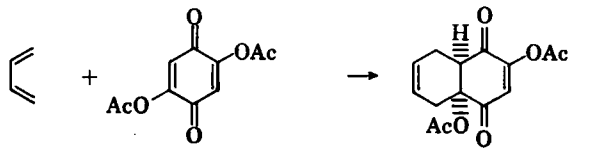
Quinazarinquinone XVII failed to yield the expected tetracycline analog with 1-acetoxybutadiene, but *cis-trans*-1,4-diacetoxybutadiene added



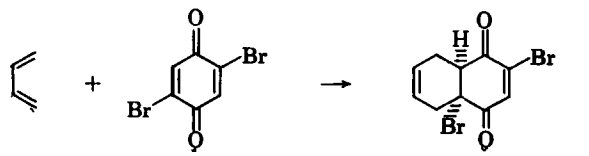
XVII



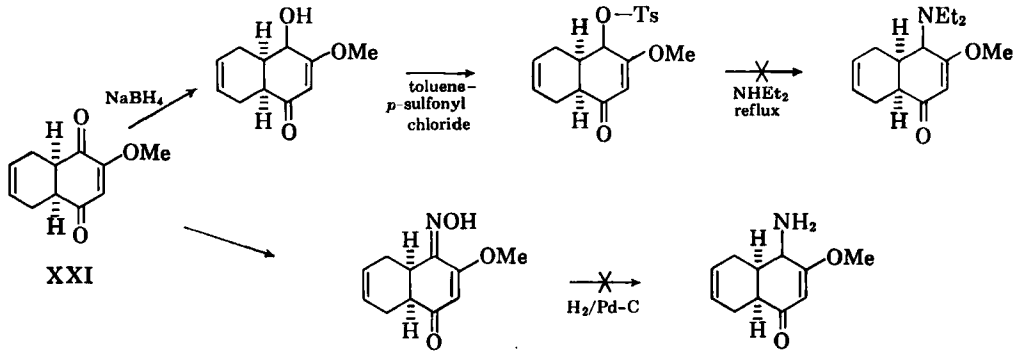
XVIII (115)



XIX (115)



XX (96)



normally (114). Related two- and three-ring model compounds have been prepared, some (XVIII, XIX) carrying an oxygen function at the ring junction. The unstable adduct XX could not be converted into XIX by treatment with silver acetate (96). One carbonyl group in the adduct XXI from butadiene and 2-methoxybenzoquinone can be selectively reduced, and the adduct can be converted into its mono-oxime; but efforts to introduce a nitrogen function corresponding to the ring A dimethylamino-substituent were not successful (116).

Nakamichi (117) has prepared adducts from *p*-toluquinol and a series of symmetrical and unsymmetrical dienes, and has reported that the adducts with isoprene and with cyclohexadiene showed marked *in vitro* activity.

The model compound XXII carries five oxygen functions, disposed in almost the same spatial arrangement as those of rings A and B of oxytetracycline, and may possess useful activity, in confirmation of the role played by the A- and B-ring substituents in conferring activity on the tetracycline molecule, when converted into its 2-carboxamide (118).

The Diels-Alder reaction has been applied also to the incorporation of the B-C ring-junction into intermediates potentially suitable for total synthesis of tetracyclines. Derivatives of juglone XXIII yield adducts XXIV with 1-acetoxybutadiene (119), with *cis-trans*-1,4-diacetoxybutadiene (120), and with 2- and 3-substituted butadienes (121), and one of the carbonyl groups in some of the various products is selectively

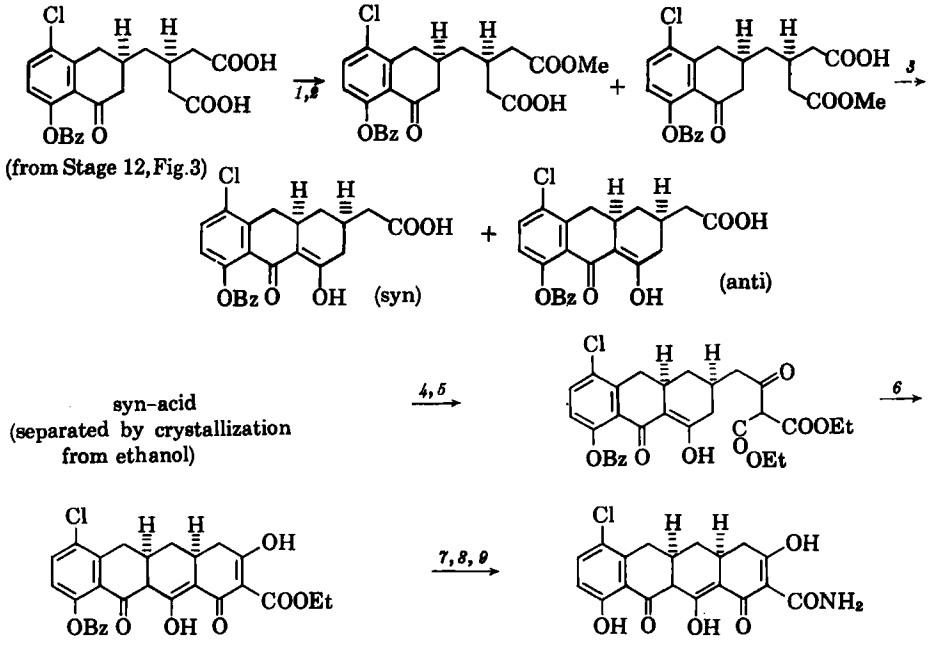
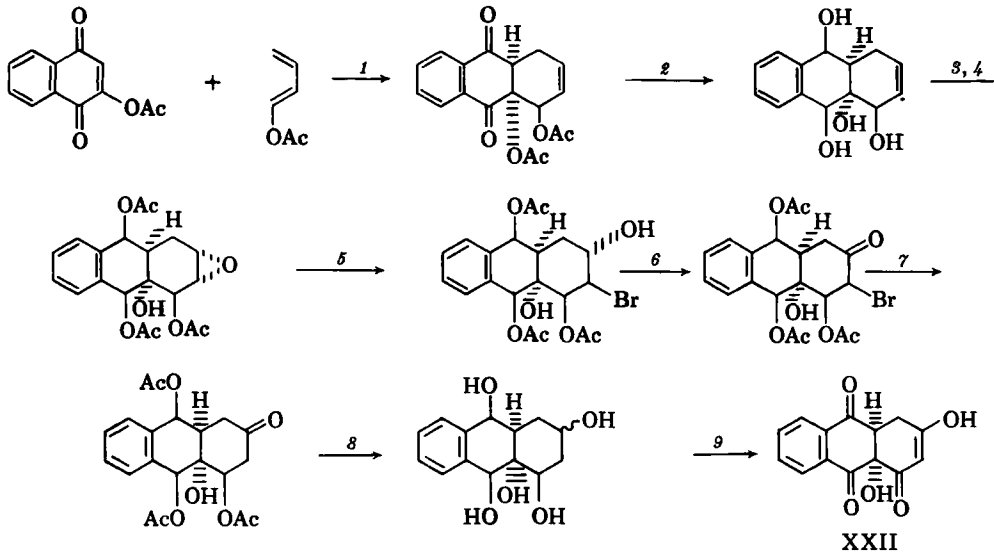
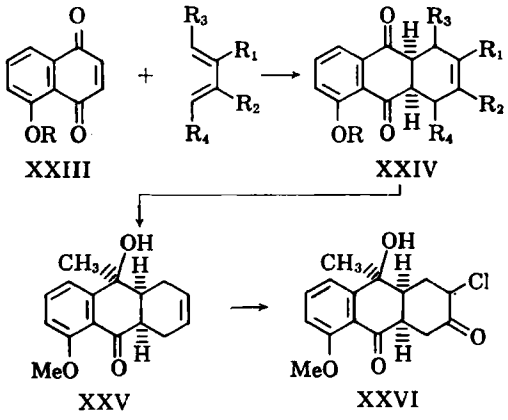


Fig. 4.—Synthesis of (±)-dedimethylamino-6-demethyl-6,12a-dideoxy-7-chlorotetracycline (106, 135). Reagents: (*1*), Ac_2O/reflux/1 hr.; (*2*), NaOMe/MeOH; (*3*), NaH/toluene; (*4*), ClCOOEt/NEt_3; (*5*) Mg^{++} ($EtOOC—\overset{|}{C}H—\overset{|}{C}OOEt_2$); (*6*), NaH/toluene; (*7*), H_2/10% Pd-C; (*8*), $HCOO^-NH_4^+$/140°; (*9*), Aq.HCl.



XXII

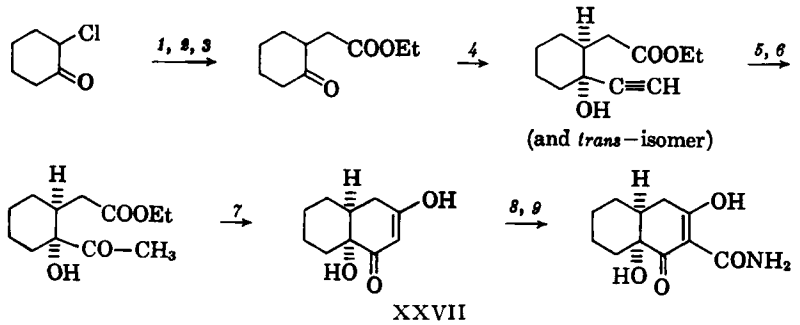
Reagents: (*1*), benzene, reflux; (*2*), $LiAlH_4$; (*3*), Ac_2O/pyridine; (*4*), monoperphthalic acid/dioxane; (*5*), 48% aq. HBr/$CHCl_3$; (*6*), CrO_3/AcOH; (*7*), Zn/AcOH; (*8*), $LiAlH_4$; (*9*), CrO_3, acetone.



XXIII XXIV XXV XXVI

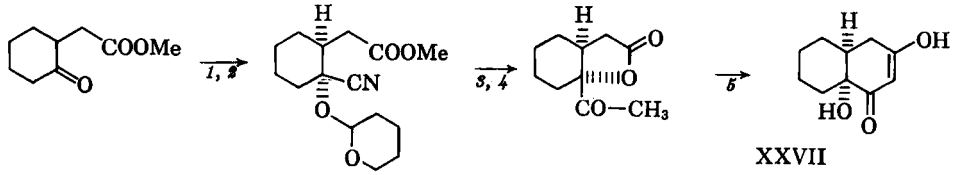
attacked during their reaction with one equivalent of methyl magnesium iodide (121, 122), yielding the useful intermediate XXV from the adduct XXIV (R = OMe, R_1, R_2, R_3, R_4 = H). Further elaboration (123) of XXV has yielded the chloroketone XXVI (for the synthesis of a tetracycline from an analog of XXV see Fig. 6), which appears suitable for use in the route developed for the synthesis, from 2-chlorocyclohexanone, of a model compound carrying the ring A substituents with the exception of the dimethylamino group (124, 125, 164).

The overall route should thus yield (±)-dedimethylamino-12-deoxy-tetracyclines with the natural stereochemistry. New routes to XXVII have been reported recently (126) by the Moscow workers, who have also achieved the synthesis



XXVII

Reagents: (*1*), $Na^+(EtOOC—\bar{C}H—COOEt)$; (*2*), hydrolysis; (*3*) decarboxylation; (*4*), $Na^+\ \bar{C}{\equiv}CH$; (*5*), $Hg(OAc)_2$; (*6*), H_2S; (*7*), NaOEt/EtOH/room temp.; (*8*), AcNCO; (*9*), NH_3/MeOH.



XXVII

Reagents: (*1*), $Me_2C(OH)CN/MeOH/K_2CO_3/20°$; (*2*), 2,3-dihydropyran/$POCl_3$; (*3*), MeMgI; (*4*), aq. HCl; (*5*), NaOEt.

of its 4-dimethylamino-analog XXVIII. The synthesis of a tetracycline, outlined in Fig 6, also involves the cyanohydrin-lactone sequence exemplified in the syntheses of the model compounds XXVII and XXVIII.

The possibility that the naphthoquinone-butadiene adducts XXIV might be selectively reduced, to yield tricyclic intermediates suitable for the synthesis of 6-demethyltetracyclines, has also been investigated (126). 1,4,4a,9a-Tetrahydroanthraquinone (XXIX) yields the ketol XXX with one equivalent of $LiAlH_4$, and further elaboration has yielded the epoxide XXXI suitable for the route outlined in Fig. 6.

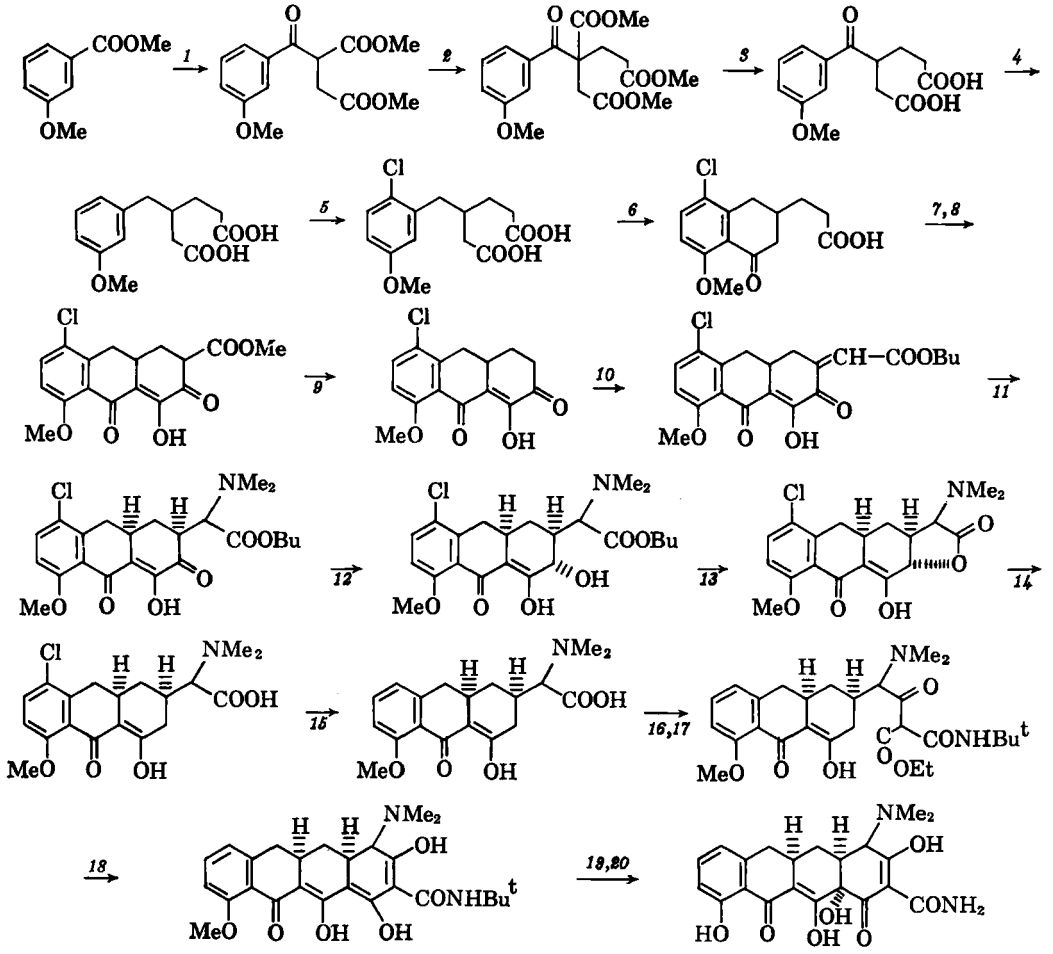
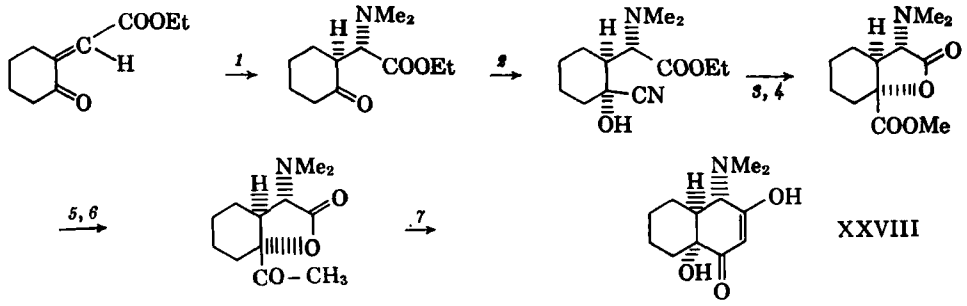
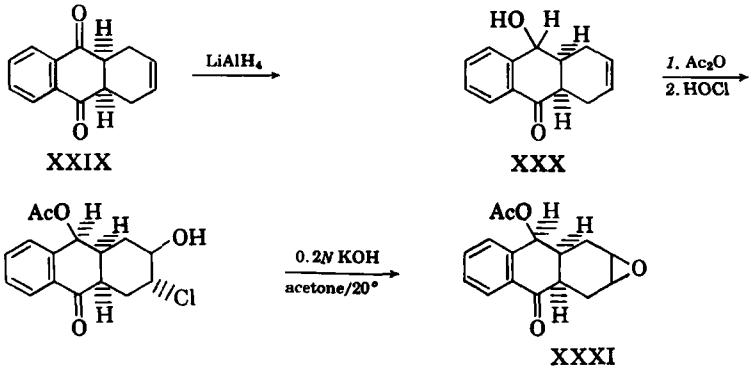


Fig. 5.—Synthesis of (±)-6-demethyl-6-deoxytetracycline (97). Reagents: (*1*), dimethyl succinate/NaH/dimethylformamide; (*2*), methyl acrylate/Triton B; (*3*), hot aq. H_2SO_4/AcOH; (*4*), H_2/Pd–C/AcOH/200 p.s.i.; (*5*), Cl_2/AcOH/15°; (*6*), HF/15°; (*7*), esterify; (*8*), dimethyl oxalate/1 equiv. MeOH/NaH/dimethylformamide; (*9*), hot aq. HCl/AcOH; (*10*), Mg^{++} $(\bar{O}Me)_2$/*n*-butyl glyoxalate/toluene; (*11*), Me_2NH/−10°; (*12*), $NaBH_4$/diglyme/low temp.; (*13*), toluene sulfonic acid/toluene; (*14*), Zn/HCOOH; (*15*), H_2/Pd–C/EtOH/NEt_3; (*16*), $ClCOOPr^i$; (*17*), Mg^{++} $(EtOOC—\bar{C}H—CONHBu^t)_2$; (*18*), NaH/dimethylformamide/120°; (*19*), hot 48% aq. HBr; (*20*), $CeCl_2/O_2$/dimethylformamide/MeOH/pH 5.



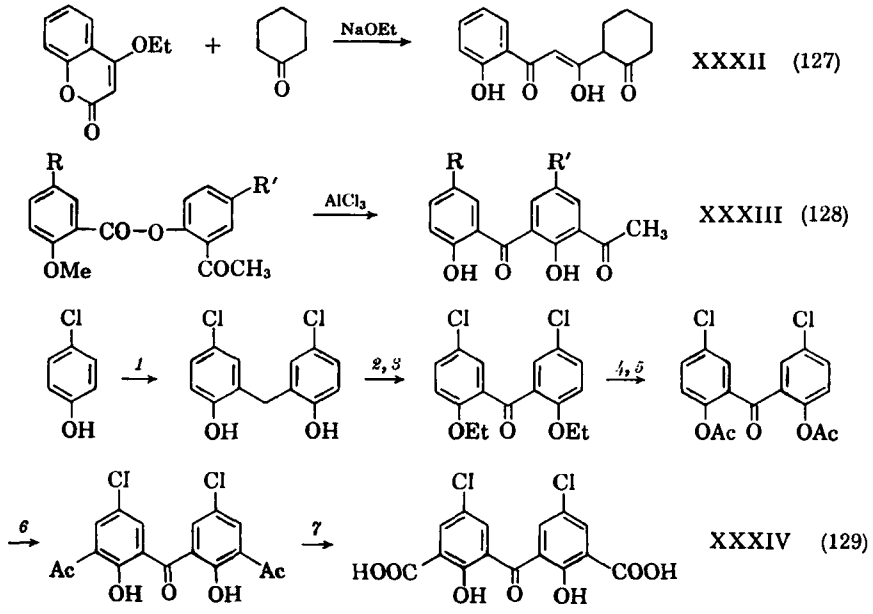
XXVIII

Reagents: (*1*), Me_2NH/hexane/0°; (*2*), $Me_2C(OH)CN/MeOH/K_2CO_3$/20°; (*3*), concd. HCl; (*4*), esterify; (*5*), Bu^tOAc/Bu^tOK; (*6*), aq. HCl; (*7*), NaOEt/EtOH/20°.



XXIX XXX XXXI

Several model compounds, XXXII–XXXIV, containing the chelating carbonyl and enolic oxygen functions of the tetracycline molecule have been synthesized; no activities have been reported. The tetrahydroanthracene XXXV possesses appreciable activity (30 oxytetracycline units per milligram) (130, 131, 132); its mono-, di-, and tri-chloro- and bromo-derivatives



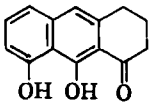
XXXII (127)

XXXIII (128)

XXXIV (129)

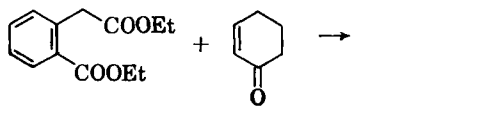
Reagents: (*1*), $CH_2O/MeOH/H_2SO_4$; (*2*), Et_2SO_4; (*3*), CrO_3/AcOH; (*4*), $AlCl_3/CS_2$; (*5*), Ac_2O/H_2SO_4 (*6*), $AlCl_3$/170°; (*7*), NaOI.

(substituents introduced into the 5, 7, and 10 positions by direct halogenation) are more stable to oxidation, and also possess antimicrobial activity (133).

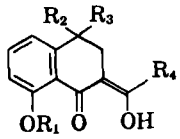


XXXV

Other related di- and tri-cyclic analogs of this part of the molecule have been prepared, in some cases particularly for pKa studies, and similarly-constructed intermediates in the synthetic routes outlined in Figs. 1–6 may possess activity comparable with that of XXXV. Trioxo-octahydroanthracenes and related naphthacenes (Fig. 4) are claimed to be generally useful as chelating, complexing, and sequestering agents for poly-



XXXVI (138)



XXXVII

(136,15) $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
(8) R_1 = Et; $R_2 = R_3 = H$; R_4 = cyclohexyl
(8) R_1 = benzyl; $R_2 = R_3 = H$; R_4 = Me
(137) $R_1 = R_2$ = Me; R_3 = OH; R_4 = Et

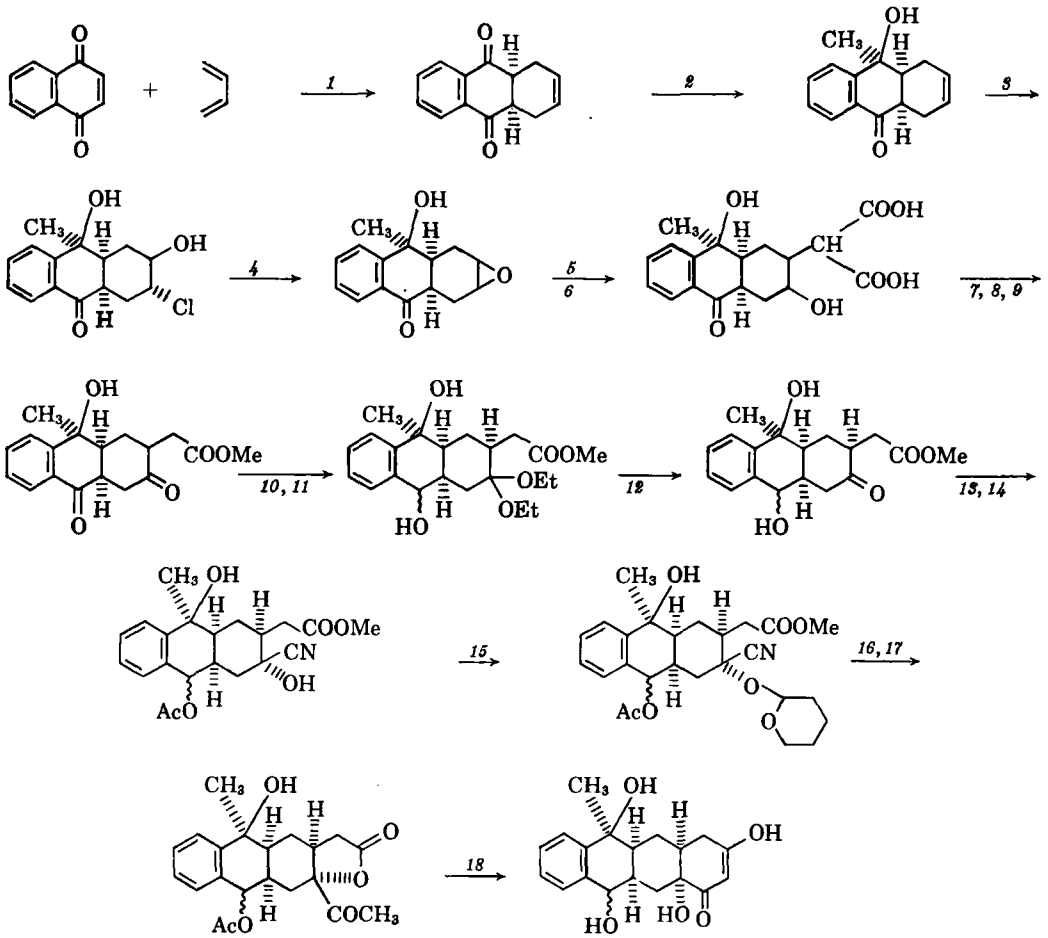
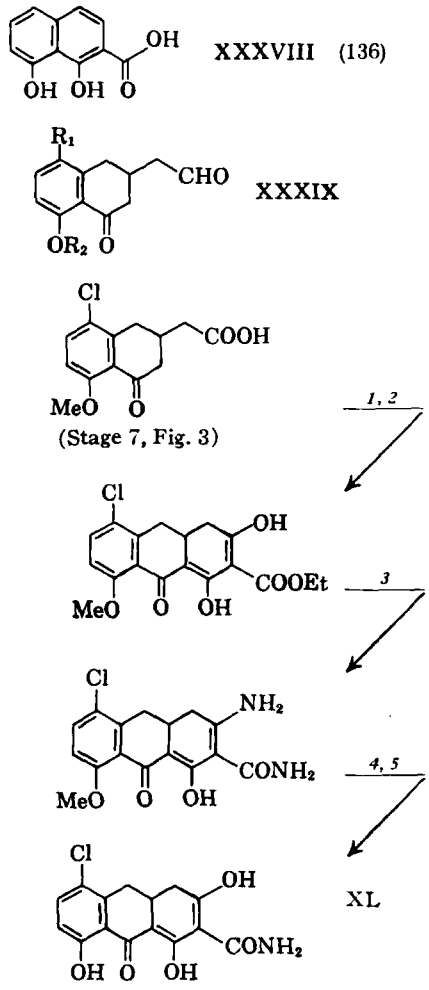
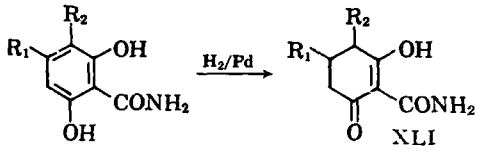


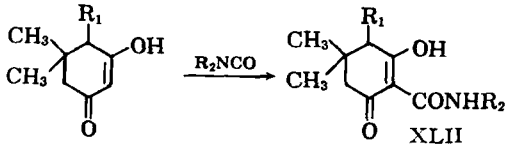
Fig. 6.—Synthesis of (±)-dedimethylamino-decarboxamido-10,12-dideoxytetracycline (121, 123, 126). Reagents: (*1*), 100°; (*2*), 1 equiv. MeMgI; (*3*), Bu^{t}OCl; (*4*), aq. KOH/dioxan; (*5*), Na^+ (EtOOC—CH—COOEt); (*6*), OH^-; (*7*), pyridine and piperidine/120°; (*8*), CrO_3/AcOH/35°/1 hr.; (*9*), CH_2N_2; (*10*), $HC(OEt)_3$; (*11*), $NaBH_4$; (*12*), hydrolysis; (*13*), Ac_2O; (*14*), acetone cyanhydrin/catalytic quantity of NH_3; (*15*), dihydropyran/$POCl_3$; (*16*), MeMgI; (*17*), warm AcOH; (*18*), NaOEt/EtOH.



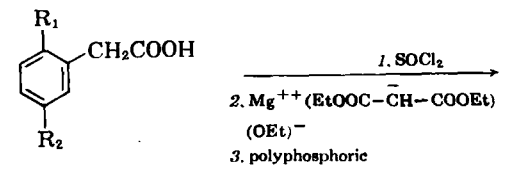
Reagents: (*1*), oxalyl chloride; (*2*), $Na^+(EtOOC—CH—COOEt)$; (*3*), NH_3/MeOH/80°/pressure/5 hr.; (*4*), 4 *N* aq. HCl; (*5*), HBr—AcOH.



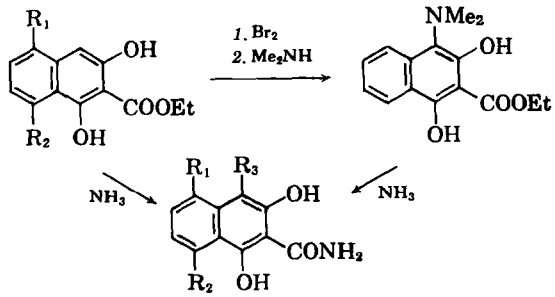
$R_1 = R_2 = H$	(8)
$R_1 = H$; $R_2 = NH_2$	(140)
$R_1 = H$; $R_2 = NMe_2$	(141)
$R_1 = Me$; $R_2 = H$	(138)



(a) $R_1 = R_2 = H$	(125)
(b) $R_1 = H$; $R_2 = Ph$	(125)
(c) $R_1 = Br$; $R_2 = Ph$	(140, 141)
(d) $R_1 = H$; $R_2 = Ac$	(125)
(e) R_1 = piperidino-; $R_2 = Ph$	(140, 141)



$R_1 = R_2 = H$
$R_1 = OMe$; $R_2 = H$
$R_1 = R_2 = OMe$



$R_1 = R_2 = R_3 = H$
$R_1 = OMe$; $R_2 = R_3 = H$
$R_1 = R_2 = OMe$; $R_3 = H$
$R_1 = R_2 = H$; $R_3 = NMe_2$
(8, 142, 144)

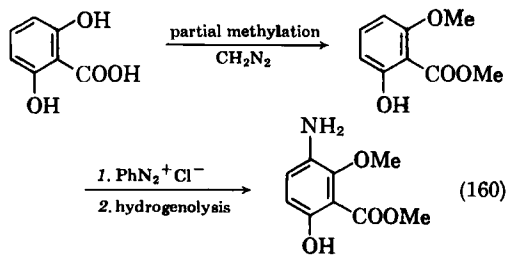
valent metal ions (134); dioxo-octahydroanthracene acetic acid derivatives are similarly effective (135), and tetraloneacetaldehyde derivatives (*e.g.*, XXXIX) possess fungicidal properties (149).

The model compound XL incorporates the main features of rings A, C, and D of 7-chloro-6-demethyl-6-deoxy-tetracycline, and of rings A, B, and D of chlortetracycline, but it is quite inactive (139). It is structurally related to the active tetrahydroanthracene XXXV, and the reason for the differing activities of these two compounds possibly lies in the differing potential chelation sites presented by them to metal ions.

Several ring A analogs are available, compounds XLII (b, c, and e) possessing weak tetracycline activity.

Appropriately substituted benzene and naphthalene models for ring A have been synthesized.

The minimum requirements for activity (discussed in the section of this review devoted to *The Mode of Action of the Tetracyclines*) revealed by antibiotic assays of tetracyclines derived from the natural products are a useful guide to future syntheses of simpler analogs. However, few of the available totally synthetic tetracycline analogs appear to have been tested; those bearing structural similarities with the



(160)

A-ring analogs, XLII, the BCD-rings analog, XXXV, and the *p*-toluquinol-isoprene and *p*-toluquinol-cyclohexadiene adducts (117) may possess similar activity.

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