QUARTERLY REVIEWS

THE MACROLIDE ANTIBIOTICS

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Introduction

NINETEEN HUNDRED AND SIXTY-THREE saw the coming of age of the term "antibiotic".[1] Such materials are now so prominent in clinical therapy that it seems surprising that streptomycin, the first actinomycetes-derived antibiotic to find clinical application, appeared only in 1944.[2] One of the most fascinating classes of antibiotics is the "macrolides", so named by Woodward.[3] These compounds, derived from *Streptomyces* species, are characterised by a many-membered, highly-substituted lactone ring, which often contains a conjugated polyene chromophore. Most of them possess a nitrogen-containing sugar residue attached to the ring; in some, the ring is linked to one or two additional sugar residues. Several members of the class are of considerable therapeutic importance.†

The molecular complexity of these antibiotics offers a considerable challenge to the structural organic chemist; this challenge has been met by classical chemical degradation methods, assisted of course by nuclear magnetic resonance spectroscopy, gas-liquid chromatography, etc., but not, in contrast to all comparable fields in recent years, by *X*-ray crystallography. The macrolides are hard to obtain as pure crystals, being usually solvated. Current interest centres around the biogenesis of the macrocyclic lactones and the sugars to which they are linked. Some progress has been made with the stereochemistry of the macrolide aglycones; these have been a fruitful breeding- and testing-ground of biogenetic theory, and further work on their stereochemistry might unravel not only the detailed mechanism of the build-up of the ring but also the relation that they bear to other natural products, such as the tetracyclines. The absolute stereochemistry of the tetracyclines has now been determined.[4]

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† In general the polyene macrolides are antifungal agents, and the nonpolyene macrolides antibacterial.

[1] Waksman and Woodruff, *J. Bact.*, 1942, **44**, 373.

[2] Schatz, Bugie, and Waksman, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 66.

[3] Woodward, *Angew. Chem.*, 1957, **69**, 50; Woodward, "Festschrift Arthur Stoll", Birkhauser, Basle, 1957, p. 524.

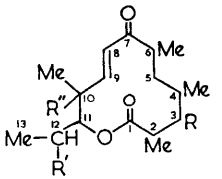
[4] Dobrynin, Gurevich, Karapetyan, Kolosov, and Shemyakin, *Tetrahedron Letters*, 1962, 901.

An interesting development has been the discovery of a class of compounds based on a macrocyclic tetralactone system—the macrotetrolides.[5]

This review will be concerned with the structure, stereochemistry, and biogenesis of the macrolides and the sugars they contain.

Structure Determination

Nonpolyene Macrolides.—*Methymycin*,[6] neo*Methymycin and Pikromycin*.[7] Methymycin, $C_{25}H_{43}O_7N$, is structurally one of the simplest of the macrolides, and its structure (I) was the first to be determined.[8] Glycosidic cleavage gave the aglycone methynolide (2) and the basic sugar desosamine (3), whose structure had been determined by oxidative degradation to crotonaldehyde and by other experiments.[9] Fusion of

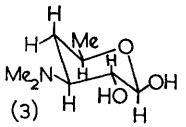


(1); R = desosamine residue, R′ = H, R″ = OH.

(2); R = R″ = OH, R′ = H.

(6); R = desosamine residue, R′ = OH, R″ = H.

(7); R = R′ = OH, R″ = H.



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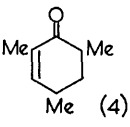

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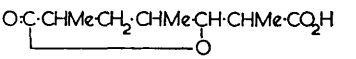


(5)

methymycin with potassium hydroxide yielded 2,4,6-trimethylcyclohex-2-en-1-one (4). Consideration of the possible reaction routes by which this ketone might be formed, together with the identification of the products from mild permanganate oxidation of methynolide, led to the final structure. One of the oxidation products was the lactone (5), which has also been obtained from *neo*methymycin, pikromycin, and narbomycin.

*neo*Methymycin, isolated from the mother liquors of methymycin, was shown to have structure (6).[10] It differs from methymycin only in that the hydroxyl group at C-10 and the hydrogen atom at C-12 in methymycin are interchanged. When treated with hydrochloric acid methymycin forms a spiroketal; spiroketals are not formed in the *neo*methymycin series, because of the different environment of the hydroxyl. Cleavage of *neo*-

[5] Beck, Gerlach, Prelog, and Voser, *Helv. Chim. Acta*, 1962, **45**, 620.

[6] Donin, Pagano, Dutcher, and McKee, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1953—4, p. 179.

[7] Brockmann and Henkel, *Naturwiss.*, 1950, **37**, 138; Brockmann and Henkel, *Chem. Ber.*, 1951, **84**, 284.

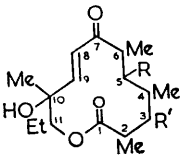
[8] Djerassi and Zderic, *J. Amer. Chem. Soc.*, 1956, **78**, 6390, and earlier papers.

[9] (*a*) Flynn, Sigal, Wiley, and Gerzon, *J. Amer. Chem. Soc.*, 1954, **76**, 3121; (*b*) Clark, *Antibiotics and Chemotherapy*, 1953, **3**, 663.

[10] (*a*) Djerassi and Halpern, *J. Amer. Chem. Soc.*, 1957, **79**, 2022; (*b*) Djerassi and Halpern, *Tetrahedron*, 1958, **3**, 255.

methymycin with dilute sulphuric acid gave two aglyconic products, *neo*methynolide (7) and *cycloneo*methynolide. In the latter an ether linkage is formed by addition of the C-12 hydroxyl group to the double bond of the $\alpha\beta$-unsaturated ketone at C-9.

Pikromycin was the first macrolide antibiotic to be discovered.[7] Degradative studies have established the structure as either (8a) or (8b).[11]



(8a); R = desosamine residue, R′ = H.

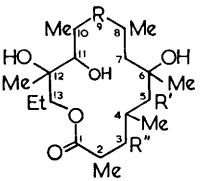
(8b); R = H, R′ = desosamine residue.

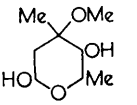
The anhydroaglycone, kromycin,[12] was shown to have a 5,6 double bond. C-5 would seem to be the more probable point of attachment of the sugar to the aglycone, both because the double bond is at 5,6 in kromycin and dihydrokromycin, and because the ease of removal of the sugar suggests a linkage β to the ketone group.

Erythromycin.[13,9b] This therapeutically useful and structurally complex broad-spectrum antibiotic, $C_{37}H_{67}O_{13}N$, has been assigned structure (9).[14]

(9); R = CO, R′ = desosamine, R″ = cladinose residue.

(10); R = CH_2, R′ = R″ = OH.





(11)

The active ketone group hindered the isolation of well-defined degradation products; the antibiotic was reduced to the biologically inactive but more tractable dihydroerythromycin (as 9; R=CH_2 instead of R=CO). When hydrolysed this gave the aglycone dihydroerythronolide (10) and the sugars desosamine (3) and cladinose (11). The structure of cladinose was indicated by degradation to acetaldehyde and β-formylcrotonic acid.[15] Erythromycin itself on mild acid hydrolysis yields the neutral sugar cladinose and the basic compound erythralosamine (magnamycin, oleandomycin, leucomycin A_1, and the spiramycins behave similarly).

[11] (*a*) Anliker and Gubler, *Helv. Chim. Acta*, 1957, **40**, 119, 1768; (*b*) Brockmann and Oster, *Chem. Ber.*, 1957, **90**, 605.

[12] Brockmann and Strufe, *Chem. Ber.*, 1953, **86**, 876.

[13] McGuire, Bunch, Anderson, Boaz, Flynn, Powell, and Smith, *Antibiotics and Chemotherapy*, 1952, **2**, 281.

[14] Wiley, Gerzon, Flynn, Sigal, Weaver, Quarck, Chauvette, and Monahan, *J. Amer. Chem. Soc.*, 1957, **79**, 6062, and earlier papers.

[15] Wiley and Weaver, *J. Amer. Chem. Soc.*, 1956, **78**, 808.

Characterisation of the products of periodate oxidation of dihydroerythronolide in neutral and alkaline media, together with other evidence, indicated structure (10) for this molecule.

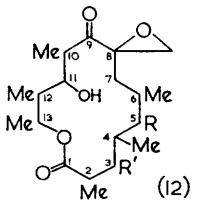
One of the degradation products of erythromycin was a 2,4-dimethylpentane-1,3,5-triol,[16] the enantiomorph of a compound isolated from chalcomycin (see later).

Erythromycin B[17] has greater acid stability than erythromycin;[18] it was shown to differ from erythromycin only in not having a hydroxyl group at C-12.[19] The lack of this hydroxyl precludes the irreversible acid-catalysed formation of a spiroketal which, in erythromycin, deactivates the molecule.

Erythromycin C was obtained from mother liquors after removal of erythromycin and erythromycin B. It differs from erythromycin only in the absence of the methoxyl group from the neutral sugar. The neutral sugar, $C_7H_{14}O_4$, from erythromycin C has now been shown[20b] to be mycarose, although at first[20a] it was believed to differ from that compound.

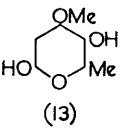
Oleandomycin.[21] In itself a useful member of the macrolide group of antibiotics, oleandomycin has attracted considerable attention because of its synergistic action against certain micro-organisms when used in combination with oxytetracycline and tetracycline. It gives analytical data corresponding to $C_{35}H_{61}O_{12}N$ and the structure, which is similar to those of erythromycin and narbomycin, has been established as (12).[22]

Under mild alkaline conditions the 11-hydroxyl group was lost, giving a 10,11 double bond. The resulting compound gave, when hydrolysed with methanol–sulphuric acid, the neutral sugar L-oleandrose (13), a substance also found in the oleander plant.[23] Further hydrolysis in benzene–aqueous hydrobromic acid gave desosamine and a compound converted by base into anhydrolide (as 12; no 11-OH, Δ^{10}, R=R′=OH).



(12)

(12); R = desosamine residue, R′ = L-oleandrose residue.

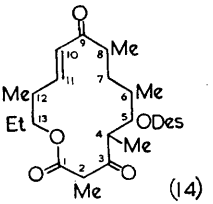


(13)

[16] Gerzon, Flynn, Sigal, Wiley, Monahan, and Quarck, *J. Amer. Chem. Soc.*, 1956, **78**, 6396.
[17] Pettinga, Stark, and Van Abeele, *J. Amer. Chem. Soc.*, 1954, **76**, 569.
[18] Gerzon, Monahan, Weaver, Sigal, and Wiley, *J. Amer. Chem. Soc.*, 1956, **78**, 6412.
[19] Wiley, Sigal, Weaver, Monahan, and Gerzon, *J. Amer. Chem. Soc.*, 1957, **79**, 6070.
[20] (*a*) Wiley, Gale, Pettinga, and Gerzon, *J. Amer. Chem. Soc.*, 1957, **79**, 6074; (*b*) Hofheinz and Grisebach, *Z. Naturforsch*, 1962, **17***b*, 852.
[21] Sobin, English, and Celmer, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1954—5, p. 827.
[22] Els, Celmer, and Murai, *J. Amer. Chem. Soc.*, 1958, **80**, 3777; Hochstein, Els, Celmer, Shapiro, and Woodward, *ibid.*, 1960, **82**, 3225.
[23] Blindenbacher and Reichstein, *Helv. Chim. Acta*, 1948, **31**, 2061.

Extensive nuclear magnetic resonance studies on anhydrolide derivatives together with oxidative degradation of damylanhydrolide (12; no 11-OH, Δ^{10}, R = desosamine, R′ = OH) and oleandomycin established the structure (12) for oleandomycin. An interesting feature, shared with magnamycin, pimaricin and nystatin, is an epoxide grouping. Unlike magnamycin and pimaricin, in oleandomycin the epoxide is external to the ring.

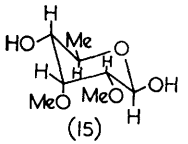
Narbomycin.[24] Narbomycin, $C_{28}H_{47}O_7N$, has been shown to have the structure (14).[25] Desosamine and the lactone (5) were obtained by hydrolytic and degradative experiments; this showed the antibiotic to be a macrolide.[26] Hydrogenation with palladium–calcium carbonate in ethanol gave dihydronarbomycin; with Adams' catalyst tetrahydronarbomycin was obtained. Permanganate–acetone oxidation gave the lactone (5).



(14)

In contrast to narbomycin, dihydronarbomycin gave, on mild acid hydrolysis, a group of crystalline isomeric aglyconic products of formula $C_{20}H_{32}O_4$, separable by chromatography on alumina. Most of the degradative work was done on these products and their derivatives. Extensive use was made of nuclear magnetic resonance techniques.

Chalcomycin.[27] Chalcomycin is probably a macrolide. Methanolysis of the antibiotic gave the methyl glycosides of two new sugars, mycinose and chalcose. Degradative experiments established their structures as (15)



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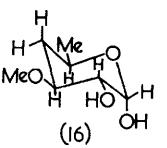

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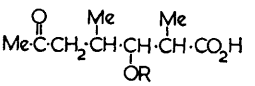
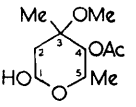


(17) R = chalcose

and (16) respectively.[28] Chalcose is identical with lankavose (q.v.). Lemieux oxidation of chalcomycin yielded 3-chalcosyloxy-2,4-dimethyl-6-oxoheptanoic acid (17),[29] which was further degraded to the enantiomorph of a compound isolated from erythromycin.

[24] Corbaz, Ettlinger, Gäumann, Keller-Schierlein, Kradolfer, Kyburz, Neipp, Prelog, Reusser, and Zähner, *Helv. Chim. Acta*, 1955, **38**, 935.
[25] Prelog, Gold, Talbot, and Zamojski, *Helv. Chim. Acta*, 1962, **45**, 4.
[26] Anliker, Dvornik, Gubler, Heusser, and Prelog, *Helv. Chim. Acta*, 1956, **39**, 1785.
[27] Parke, Davis and Co., Belg. P. 587,213/1960.
[28] Woo, Dion, and Bartz, *J. Amer. Chem. Soc.*, 1961, **83**, 3352; Dion, Woo, and Bartz, *ibid.*, 1962, **84**, 880.
[29] Woo, Dion, and Bartz, *J. Amer. Chem. Soc.*, 1962, **84**, 1512.

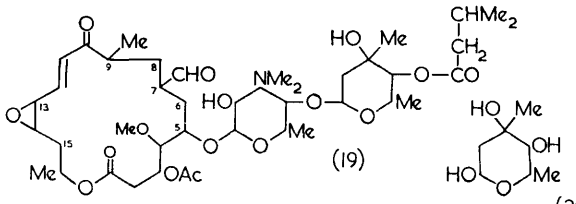
Lankamycin.[30] Like chalcomycin, lankamycin does not contain an amino-sugar. Its biological properties and colour tests enabled it to be classed as a macrolide. The molecular formula $C_{43}H_{74}O_{17}$ has been suggested.[31] Acid hydrolysis gave lankavose and acetylarcanose. Lankavose was shown by thin-film and paper chromatography and by its infrared spectrum to be identical with chalcose (16). The structure of acetylarcanose was shown to be (18); arcanose has the same structure as cladinose (11)



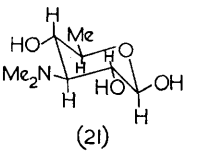
(18)

but its stereochemistry differs at C-4 or C-5 or both. A 4-*O*-acetyl sugar has also been isolated from the leucomycin complex (see later).

Magnamycin (*carbomycin*).[32] The determination of the unambiguous structure (19) for magnamycin was a major achievement.[3] It is perhaps indicative of the difficulty of the structural investigations that the empirical formula that had been tentatively assigned[33] was established as $C_{42}H_{67}NO_{16}$ only after the structure had been assigned. A short review of the work is given by Brink and Harman,[34] who conclude ". . . Time devoted by the reader to perusal of the original article[3] could hardly be better spent." It is sufficient for our purposes to note the following points: (i) Mild



(19) (20)



(21)

hydrolysis with methanol–hydrochloric acid gave carimbose, $C_{30}H_{47}NO_{12}$, and the methyl glycoside of the 4-isovaleryl derivative of the neutral sugar mycarose (20).[35] The structure of mycarose was shown by oxidation to the corresponding lactone and by periodate oxidation to acetaldehyde, aceto-acetaldehyde, and formic acid. (ii) Vigorous acid hydrolysis of carimbose destroyed the lactone nucleus and gave the amino-sugar mycaminose

[30] Gäumann, Hütter, Keller-Schierlein, Neipp, Prelog, and Zähner, *Helv. Chim. Acta*, 1960, **43**, 601.
[31] Keller-Schierlein and Roncari, *Helv. Chim. Acta*, 1962, **45**, 138.
[32] Tanner, English, Lees, and Routien, *Antibiotics and Chemotherapy*, 1952, **2**, 441; Pagano, Weinstein, and McKee, *ibid.*, 1953, **3**, 899.
[33] Wagner, Hochstein, Murai, Messina, and Regna, *J. Amer. Chem. Soc.*, 1953, **75**, 4684.
[34] Brink and Harman, *Quart. Rev.*, 1958, **12**, 93.
[35] Regna, Hochstein, Wagner, and Woodward, *J. Amer. Chem. Soc.*, 1953, **75**, 4625.

(21).[36] Mycaminose was oxidised by periodate (one mole) to formic acid and a new C_7 sugar; further periodate gave acetaldehyde. Also, rapid elimination of dimethylamine on treatment with alkali suggested that the basic substituent was β to the aldehyde group of the sugar. (iii) Treatment of magnamycin with potassium iodide–acetic acid converted the 13,14-epoxide grouping into a double bond; the resulting compound was identical with natural magnamycin B.[37]

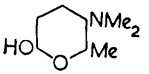
The Leucomycins.[38] The leucomycin complex has been separated into six biologically active components by column chromatography on a carboxylic resin, a mixture of citrate buffer and ethanol being used as eluant.[39] Other macrolides containing dimethylamino-sugars can be separated from minor components by this method, where previously separation had only been achieved by countercurrent distribution. The probable empirical formulae of the members of the complex are:

A_1 $C_{46}H_{81}O_{17}N$	B_1 $C_{35}H_{59}O_{13}N$	B_3 $C_{34}H_{53}O_{13}N$
A_2 $C_{65}H_{111}O_{22}N$	B_2 $C_{38}H_{65}O_{16}N$	B_4 $C_{38}H_{59}O_{16}N$

Mycaminose (21) was obtained from the leucomycins by drastic hydrolysis.[40] Mild hydrolysis of leucomycin A_1 gave the 4-isovaleryl derivative of mycarose (20) or a stereoisomer.[41] The mycarose 4-isovalerate may be linked to either the 2- or the 4-position of mycaminose (cf. in magnamycin). 4-*O*-Acetylmycarose has been obtained from minor components of the leucomycin complex.[42]

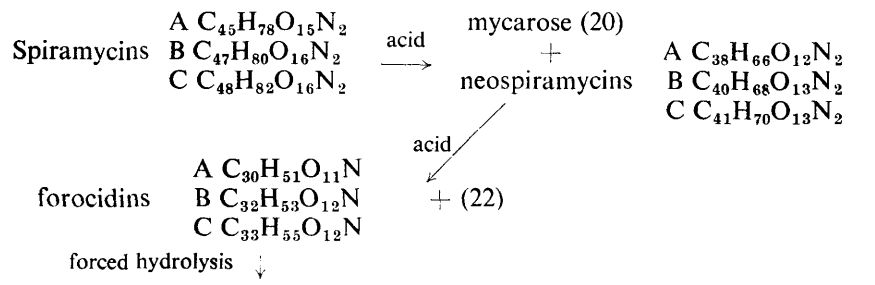
The Spiramycins.[43] The spiramycin complex has been separated into three components, A, B, and C,[44] identical with the foromacidins A, B, and C.[45] The reaction scheme shown has been worked out.[46]

As with magnamycin and leucomycin A_1, the spiramycins contain both mycarose and mycaminose; in addition they contain the dimethylamino-



(22)

[36] Hochstein and Regna, *J. Amer. Chem. Soc.*, 1955, **77**, 3353.
[37] Hochstein and Murai, *J. Amer. Chem. Soc.*, 1954, **76**, 5080.
[38] Hata, Sano, Ohki, Yokoyama, Matsumae, and Ito, *J. Antibiotics* (*Japan*), 1953, **6** A, No. 2, 87.
[39] Abe, Suzuki, Watanabe, and Satake, *J. Chem. Soc. Japan*, 1960, **81**, 969; Watanabe, *Bull. Chem. Soc. Japan*, 1960, **33**, 1100; Watanabe, Nishida, Abe, and Satake, *ibid.*, 1960, **33**, 1104.
[40] Watanabe, *Bull. Chem. Soc. Japan*, 1961, **34**, 15.
[41] Watanabe, Nishida, and Satake, *Bull. Chem. Soc. Japan*, 1961, **34**, 1285.
[42] Watanabe, Fujii, and Satake, *J. Biochem.* (*Japan*), 1961, **50**, 197.
[43] Pinnert-Sindico, Ninet, Preud'homme, and Cosar, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1954—5, p. 724.
[44] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1957, 443, 734, 1059.
[45] Corbaz, Ettlinger, Gäumann, Keller-Schierlein, Kradolfer, Kyburz, Neipp, Prelog, Wettstein, and Zähner, *Helv. Chim. Acta*, 1956, **39**, 304.
[46] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1960, 150.



mycaminose (21) + 1 mol. of acetic acid from forocidin B
1 mol. of propionic acid from forocidin C
+ residue, $C_{22}H_{36}O_8$, from each forocidin (as polymer).

substituted "sugar" (22). It was shown that in the forocidins the mycaminose residue is attached to a macrocyclic lactone ring. Permanganate oxidation of the forocidins gave β-hydroxybutric acid, fumaric acid, and an acid which is probably isomeric with the C_{13} acid isolated as one of the oxidation products of magnamycin.[3]

Tylosin.[47] Tylosin appears to be $C_{45}H_{77}NO_{17}$. Mild acid hydrolysis yields desmycosin and mycarose (20). Further degradation gave mycaminose (21). Unlike the products from mild hydrolysis of other antibiotics, desmycosin is also an antibiotic.

Acumycin.[48] Acumycin, $C_{38}H_{61}O_{12}N$, is well established as a macrolide. It yields mycaminose on hydrolysis, and appears to be similar to magnamycin.

The Oligomycins.[49] Separation of the oligomycin complex by column-chromatography has given three components:[50] A, $C_{24}H_{46}O_6$; B, $C_{22}H_{46}O_6$; C, $C_{28}H_{46}O_6$. A tentative structure for oligomycin A has been put forward,[51] but it has not as yet been substantiated. If, as is suggested, the molecule contains no sugar residue, it would be unique among known non-polyene macrolide structures.

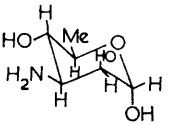
Other nonpolyene macrolides. Antibiotics which belong to this group but about whose structure little is known as yet are PA-133A, PA-133B, PA-108, and PA-148,[52] tertiomycin A and B,[53] angolamycin,[54] and

[47] McGuire, Boniece, Higgens, Hoehn, Stark, Westhead, and Wolfe, *Antibiotics and Chemotherapy*, 1961, **11**, 320.
[48] Bickel, Gäumann, Hütter, Sackmann, Vischer, Voser, Wettstein, and Zähner, *Helv. Chim. Acta*, 1962, **45**, 1396; Bickel, Vischer, Wettstein, and Zähner, *Gazzetta*, 1963, **93**, 130.
[49] Smith, Peterson, and McCoy, *Antibiotics and Chemotherapy*, 1954, **4**, 962.
[50] Masamune, Sehgal, van Tamelen, Strong, and Peterson, *J. Amer. Chem. Soc.*, 1958, **80**, 6092.
[51] Sehgal, Ph.D. Thesis, University of Wisconsin, 1960. (*Diss. Abs.*, 1960, **21**, 1382).
[52] Murai, Sobin, Celmer, and Tanner, *Antibiotics and Chemotherapy*, 1959, **9**, 485.
[53] Miyoke, Iwasaki, and Tawewaka, *J. Antibiotics (Japan)*, 1959, **12** A, 59.
[54] Corbaz, Ettlinger, Gäumann, Keller-Schierlein, Neipp, Prelog, Reusser, and Zähner, *Helv. Chim. Acta*, 1955, **38**, 1202.

miamycin.[55] Other possible members are nitrosporin,[56] amaromycin,[57] and griseomycin.[58]

Polyene Macrolides.—Many antifungal antibiotics possessing the characteristic ultraviolet absorption spectra of conjugated olefinic chromophores have been isolated. Some have been shown to have macrocyclic lactone rings; others contain the characteristic macrolide sugars. It is often difficult to assess from a report whether a given polyene antibiotic is a macrolide or not. This review will be limited to those compounds for which the assignment of a macrolide structure is fairly certain.

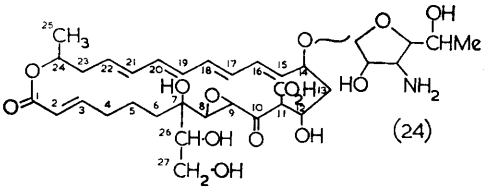
(i) *Glyconic Polyene Macrolides. Nystatin.*[59] Nystatin (tentative formula $C_{46}H_{77}O_{19}N$) possesses a conjugated tetraene chromophore, a primary amino-group, a lactone group, and four *C*-methyl groups.[60] The molecule includes the sugar mycosamine (23), the structure of which



(23)

was established by degradative methods,[61] and is possibly similar to the molecule of amphotericin B (see later). Nystatin liberates iodine from potassium iodide–acetic acid, indicating the presence of an epoxide grouping.[62] Antimycoin is similar to nystatin.[63]

Pimaricin.[64] This tetraene antibiotic, $C_{34}H_{49}O_{14}N$, has been assigned structure (24).[62] This was the first full structure of a polyene macrolide to



(24)

[55] Schmitz, Misiek, Heinemann, Lein, and Hooper, *Antibiotics and Chemotherapy*, 1957, **7**, 37.

[56] Umezawa and Takeuchi, *J. Antibiotics (Japan)*, 1952, **5**, 270.

[57] Hata, Sano, Tatsuta, Sugawara, Matsumae, and Kanamori, *J. Antibiotics (Japan)*, 1955, **8** A, 9.

[58] Van Dijck, Van de Voorde, and De Somer, *Antibiotics and Chemotherapy*, 1953, **3**, 1243.

[59] Hazen and Brown, *Proc. Soc. Exp. Biol. Med.*, 1951, **76**, 93.

[60] Dutcher, Boyack, and Fox, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1953—4, p. 191.

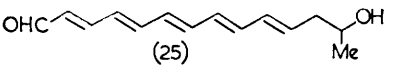
[61] Walters, Dutcher, and Wintersteiner, *J. Amer. Chem. Soc.*, 1957, **79**, 5076; Dutcher, Walters, and Wintersteiner, *J. Org. Chem.*, 1963, **28**, 995.

[62] Patrick, Williams, Wolf, and Webb, *J. Amer. Chem. Soc.*, 1958, **80**, 6689.

[63] Roubitscheck, Acker, and Waksman, *Antibiotics and Chemotherapy*, 1952, **2**, 179; Schaffner, Steinman, Safferman, and Lechevalier, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1957—8, p. 869.

[64] Struyk, Hoette, Drost, Waisvisz, van Eek, and Hoogerheide, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1957—8, p. 878.

be published. Refluxing of the antibiotic with methanol–hydrochloric acid gave the methyl glycoside of mycosamine (23). Hydrogenation of *N*-acetylpimaricin gave *N*-acetyldodecahydropimaricin, which was oxidised by dichromate–sulphuric acid to sebacic acid, showing that the tetraene system did not carry alkyl groups. Alkali treatment gave ammonia and 13-hydroxytetradeca-2,4,6,8,10-pentaen-1-al (25), possibly by dealdolisation of a β-hydroxy-ketone system followed by elimination of the mycosamine part. The only points mentioned as doubtful are the position of the carboxyl group and the furanose configuration of the amino-sugar; but the possibility of **a** skeletal rearrangement during one of the transformations would seem



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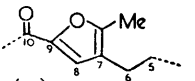


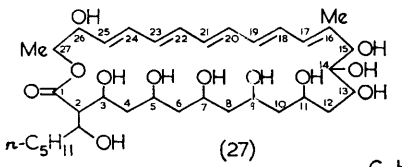
(26)

to have not yet been excluded. The triol grouping at positions 7, 26, and 27 is unique among macrolide structures. *N*-Acetylpimaricin consumes two molecules of periodic acid, one immediately and one after two hours; this would be expected for a tertiary hydroxyl as at C-7. Brief treatment of *N*-acetyldodecahydropimaricin with N-sulphuric acid gave a compound possessing the ultraviolet spectrum of an alkyl furyl ketone, and containing the grouping (26). It is suggested that the reduction of the epoxide makes the system 10,9,8,7,26,27 the equivalent of a deoxyhexose, the correct oxidation state for acid dehydration to a furyl ketone.

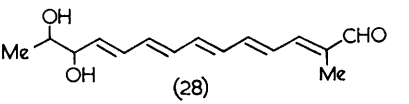
Tennecetin appears to be identical with pimaricin.[65]

Amphotericin B.[66] This amphoteric heptaene antibiotic has been assigned the tentative formula $C_{46}H_{73}O_{20}N$; it has been shown to possess a many-membered lactone ring and to contain mycosamine.

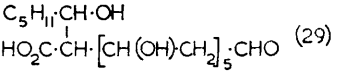
(ii) *Aglyconic Polyene Macrolides.—Lagosin.*[67] The structure of lagosin has been established as (27).[68] The first partial structure published[68a]



(27)



(28)



(29)

[65] Burns and Holtman, *Antibiotics and Chemotherapy*, 1959, **9**, 398; Divekar, Bloomer, Eastham, Holtman, and Shirley, *ibid.*, 1961, **11**, 377.

[66] Vandeputte, Wachtel, and Stiller, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1955—6, p. 587; Dutcher, Young, Sherman, Hibbits, and Walters, *op. cit.*, 1956—7, p. 866.

[67] Ball, Bessel, and Mortimer, *J. Gen. Microbiol.*, 1957, **17**, 96.

[68] (*a*) Dhar, Thaller, and Whiting, *Proc. Chem. Soc.*, 1958, 148; (*b*) Dhar, Thaller, Whiting, Ryhage, Ställberg-Stenhagen, and Stenhagen, *ibid.*, 1959, 154; (*c*) Dhar, Thaller, and Whiting, *ibid.*, 1960, 210; (*d*) Dhar, D.Phil. Thesis, Oxford, 1959.

indicated a large lactone ring, thus linking the polyene and macrolide antibiotics for the first time.

Lagosin reacted with periodate (2 mols.) in acidic solution, liberating formic acid. Alkaline hydrolysis of the glassy fission product gave the dihydroxy-aldehyde (28). This was converted by oxidation with silver oxide followed by hydrogenation and reduction with hydriodic acid and phosphorus into *iso*tridecanoic acid. Alkali treatment of lagosin gave *n*-hexaldehyde, presumably by retroaldol fission. Analytical results and crystallographic molecular-weight data agreed with the formula $C_{35}H_{58}O_{12}$, and all the carbon atoms of this molecule were isolated as known degradation products. The peracetate of lagosin could not be obtained completely pure; however, careful determinations of acetoxyl group on this and the fully acetylated derivatives of perhydrolagosin and the dioxo-ester from periodate fission indicated that all the oxygen atoms other than those of the lactone group were hydroxylic. The product other than (28) from hydrolysis of the periodate fission product was shown to be the C_{19} polyhydroxy-oxo-acid (29).

Fungichromin.[69] Early work[70] indicated that fungichromin was structurally very closely related to lagosin; it has now been shown, by methods very different from those used on lagosin, to possess the identical structure (27).[71] The infrared and ultraviolet spectra and chromatographic behaviour of lagosin and fungichromin are identical, but there are slight differences in optical rotations and *X*-ray powder patterns.

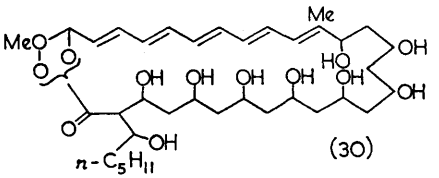
Decahydrofungichromin was reduced by lithium aluminium hydride to a polyol which was treated with phosphorus–hydriodic acid, then further reduced with lithium aluminium hydride and chromatographed on alumina. Hydrocarbon fragments were hydrogenated; the product was homogeneous and was shown to be 7,21-dimethyltritriacontane, which was synthesised. Decahydrofungichromin with neutral periodate, followed by reduction of the carbonyl compounds, gave two polyols $C_{15}H_{32}O_3$ and $C_{19}H_{40}O_8$, which were converted by phosphorus–hydriodic acid into 2-methyltetradecane and 7-methyloctadecane, respectively. In all cases the possibility of rearrangement was eliminated by preparation of hydrocarbons with identical mass spectra from the poly(toluenesulphonates) of the polyols as well as from the polyols.

Other experiments showed the position of closure of the ring and settled the other structural points.

Filipin.[72] Filipin is not attacked by sodium periodate, thus showing the absence of an $\alpha\beta$-glycol function, which contrasts with the behaviour of

[69] Tytell, McCarthy, Fisher, Bolhoffer, and Charney, "Antibiotics Annual," Medical Encyclopaedia Inc., New York, 1954—5, p. 716.
[70] Cope and Johnson, *J. Amer. Chem. Soc.*, 1958, **80**, 1504.
[71] Cope, Bly, Burrows, Ceder, Ciganek, Gillis, Porter, and Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 2170.
[72] Whitfield, Brock, Ammann, Gottlieb, and Carter, *J. Amer. Chem. Soc.*, 1955, **77**, 4799.

lagosin and fungichromin. A tentative structure based on a 24-carbon atom lactone ring was suggested in 1959.[73] The infrared spectra of filipin and lagosin are extremely similar, and it has been suggested[68c] that filipin possesses the structure (27) except that there is no hydroxyl at C-14. Djerassi[74] has employed nuclear magnetic resonance techniques on filipin peracetate to decide between the lagosin-type structure and another structure (30), $C_{37}H_{62}O_{12}$, containing an additional ·CH(OH)·CH_2· unit. The



(30)

nuclear magnetic resonance evidence favours the latter formulation, but measurements of ultraviolet absorption intensities favour $C_{35}H_{58}O_{11}$.[74a]

Pentamycin[75] (identical with moldicidin B[76]) resembles filipin.

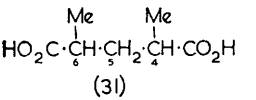
Other possible polyene macrolides known in December 1960 have been listed and some of their properties briefly summarised by Miller.[77]

Stereochemistry of the Macrolide Aglycones

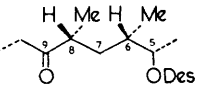
Each of the known macrolide structures contains several asymmetric centres within the aglycone. All possess an asymmetric centre α to the ring oxygen atom, and, with the exception of magnamycin and pimaricin, another in the β position. Determination of the configurations of these two centres in several of the molecules might be of considerable biogenetic interest.

Some of the relative stereochemical configurations in magnamycin (19) have been found.[3] Infrared spectral studies indicated a *trans*-configuration for the substituents on the double bond, and isolation of oxiran-*cis*-dicarboxylic acid showed the hydrogens of the ethylene oxide group to be *cis*. Oxidation of the molecule with nitric acid gave (—)-α-methylsuccinic acid, which not only gave the relative configuration of the groups about C-9, but also, since (—)-α-methylsuccinic acid is related to L-glyceraldehyde, established the absolute configuration at C-9 as (*S*), by the Cahn-Ingold-Prelog convention.[78] *neo*Methymycin (6) was degraded to the same methylsuccinic acid;[79] here the asymmetric centre of the product corresponds to that at C-4 in *neo*methymycin, and the absolute configuration at C-4 can therefore be given as (*S*). Ozonolysis of *neo*methynolide (7)

[73] Berkoz and Djerassi, *Proc. Chem. Soc.*, 1959, 316.
[74] Djerassi, Ishikawa, and Budzikiewicz, *Tetrahedron Letters*, 1961, 383.
[74a] Dhar, Thaller, and Whiting, forthcoming publication.
[75] Umezawa and Tanaka, *J. Antibiotics (Japan)*, 1958, **11** A, 26.
[76] Ogawa, Ito, Inone, and Nishio, *J. Antibiotics (Japan)*, 1960, **13** A, 353.
[77] Miller, "Pfizer Handbook of Microbial Metabolites", McGraw-Hill, New York, 1961.
[78] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[79] Djerassi, Halpern, Wilkinson, and Eisenbraun, *Tetrahedron*, 1958, **4**, 369.



(31)



(32)

gave the lactonic acid (5), which has been degraded[11a] to *meso*-$\alpha\alpha'$-dimethylglutaric acid (31). Hence the relative configuration of C-4 and C-6 is shown to be *cis* through (31), and an absolute configuration of (*R*) can be assigned to C-6. The acid (5) is a common degradation product of methymycin, *neo*methymycin, pikromycin, and narbomycin. Thus, there is available a standard of absolute stereochemistry for these molecules. For instance, the assignments (*S*) at C-6 and (*R*) at C-8 [see structure (32)] can be made for narbomycin (14).[25]

C-8 of erythromycin (9) has been isolated[79] by a multistage degradation of the antibiotic as the asymmetric centre of (+)-α-methylævulic acid, which is related *via* (+)-α-methylsuccinic acid to D-glyceraldehyde. C-8 therefore has the (*R*) configuration. C-8 and C-10 of erythromycin are contained in the degradation product (−)-2,4-dimethylpentane-1,3,5-triol, which is still optically active,[16] and C-10 has been assigned the (*R*) configuration. Tentative assignments have been suggested for C-2, C-3, C-4, C-9, and C-13.[79]

The absolute configurations at C-26 and C-27 in fungichromin (27) have been determined.[71] Fungichromin was ozonised in methanol; the ozonide was reduced catalytically. Oxidation with sodium periodate followed by lithium aluminium hydride reduction and acetylation gave propane-1,2-diol diacetate. (This, incidentally, was proof that ring closure in fungichromin was at C-27, not C-26; otherwise butane-1,2,3-triol triacetate would have been produced.) The propane-1,2-diol diacetate gave a positive rotation, and was synthesised from calcium (*R*)-(+)-lactate. Thus the absolute configuration at C-27 in fungichromin is (*R*). If C-26 had the (*R*) configuration, the relative configuration of the two centres would be *threo*; if C-26 were (*S*), the relative configuration would be *erythro*. Ozonolysis of fungichromin followed by catalytic hydrogenation, lithium aluminium hydride reduction, and acetylation gave 2*S*,3*R*(−)-*erythro*-butane-1,2,3-triol triacetate, the infrared spectrum of which was identical with the synthetic (±)-*erythro*-compound. No *threo*-isomer was present, showing that base-catalysed epimerisation of C-26 at the α-hydroxy-aldehyde stage did not take place.

The same centres in lagosin were isolated by ozonolysis of the cyclohexylidene derivative of the dihydroxy-aldehyde (28) followed by oxidative decomposition of the ozonide.[80] The infrared spectrum of the non-crystalline product was almost identical with that of the cyclohexylidene derivative of synthetic (±)-*erythro*-$\alpha\beta$-dihydroxybutyric acid, and very different from that of the (±)-*threo*-compound, indicating an *erythro*-relation for C-26 and C-27 in lagosin.

[80] Berry, B.Sc. Thesis, Oxford, 1962; Berry and Whiting, to be published.

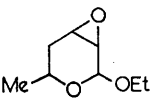
Sugar Components of The Macrolides

Some tentative but interesting correlations can be drawn for the sugars that occur most frequently in macrolide antibiotics. They are generally in the pyranose form, and all are 6-deoxy-sugars. If they contain nitrogen, the nitrogen atom is attached to C-3. Desosamine (3) is found only in combination with the smaller macrolide rings (containing 11 or 13 carbon atoms), always attached at C-3 or C-5 of the aglycone. Mycaminose (21) differs structurally from desosamine only in having a hydroxyl group at C-4; it occurs in conjunction with the neutral sugar mycarose (20), to which it is possibly connected by a C-4 oxygen linkage as in magnamycin (19). Mycarose and mycaminose seem to be associated with rather larger macrolide rings than desosamine. Mycosamine (23) differs from mycaminose in that the amino-group is not methylated. It is found in those polyenic macrolides that are probably of large ring size (notably pimaricin, nystatin, and amphotericin B). If this correlation between ring size and amino-sugar is valid, it may be that production of a sugar by the micro-organism influences the build-up of the aglycone ring. Of polyene macrolides, the known pentaenes do not contain sugars.

Desosamine (*Picrocin*) (3). The stereochemistry of desosamine is shown in (3). Alkaline degradation gave (*erythro* + *threo*)-2,5-dihydroxyhexanoic acid, which was further degraded to (−)-pentane-1,4-diol containing the asymmetric atom which was originally C-5 of desosamine. The absolute configuration of (−)-pentane-1,4-diol was correlated with that of (−)-lactic acid, and so with that of D-glyceraldehyde. This showed desosamine to be a D-hexose derivative.[81] The D-*xylo*-configuration has now been assigned to the molecule.[82,83,84] Woo *et al.*[84] used nuclear magnetic resonance techniques to show that in desosamine, desosamine hydrochloride, and diacetyldesosamine hydrochloride the hydrogens at C-1, C-2, C-3, and C-5 were all axial; with the configuration at C-5 established as D, the D-*xylo*-configuration follows. The data indicated that the β-anomer predominated.

Desosamine has been degraded to 3,4-epoxy-2-ethoxy-6-methyltetrahydropyran (33).[85] Formation of this compound by pyrolysis of desosamine methohydroxide establishes the *trans*-orientation of the C-2 hydroxyl and C-3 dimethylamine substituents, since it is known that of the *cis-trans* pair of β-amino-alcohols of cyclohexane, only the *trans*-isomer gives an epoxide when its methohydroxide is pyrolysed. This *trans*-relation at C-2 and C-3 limits the possible configurations of the molecule to D-*gluco* (or *xylo*) or D-*altro*. The racemic epoxide was synthesised and converted in low yield

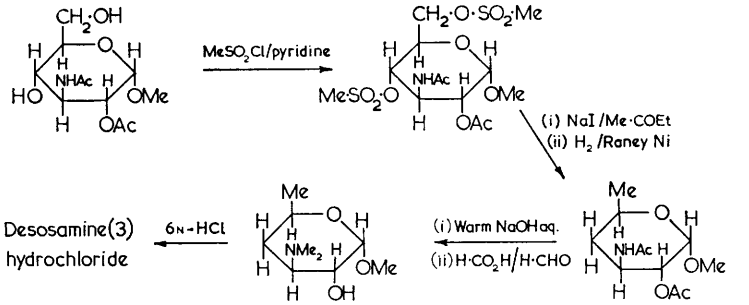
[81] Bolton, Foster, Stacey, and Webber, *J.*, 1961, 4831.
[82] Bolton, Foster, Stacey, and Webber, *Chem. and Ind.*, 1962, 1945.
[83] Hofheinz and Grisebach, *Tetrahedron Letters*, 1962, 377.
[84] Woo, Dion, Durham, and Mosher, *Tetrahedron Letters*, 1962, 735.
[85] Newman, *Chem. and Ind.*, 1963, 372.



(33)

into desosamine. Racemic desosamine has also been synthesised by Korte *et al.*[86]

A stereospecific synthesis of desosamine has very recently been worked out by Richardson;[86a] the reaction sequence is shown in scheme A. Reaction of the disulphonate derivative with sodium iodide in ethyl methyl



Scheme A

ketone gave the 4,6-di-iodo-derivative; this compound is presumably formed by elimination of the 4-methanesulphonyloxy-group with participation of the neighbouring *trans*-3-acetamido-group. The intermediate oxazolinium cation undergoes nucleophilic attack by iodide at C-4 of the pyranoside ring. This interesting example of neighbouring group participation enabled the di-iodo-derivative to be assigned the *gluco*-configuration.

It is of biogenetic interest that desosamine and the methyl glycoside of chalcose (16) are identical in configuration.[84]

Mycaminose (21). The stereochemistry of mycaminose is indicated in (21). Woodward originally suggested, on the basis of pK_a data for magnamycin and derivatives, that mycaminose possessed the *altro*-configuration.[3] However, alkaline degradation of the molecule indicated that the relative configuration at C-4 and C-5 is *erythro*; and synthetic 3,6-dideoxy-3-dimethylamino-L-altrose differed from mycaminose.[87] 3,6-Dideoxy-3-dimethylamino-β-D-glucose hydrochloride, identical with mycaminose hydrochloride, was synthesised from methyl 3-amino-3,6-dideoxy-α-D-glucoside.[88] It was suggested that Woodward's results would be explained if mycaminose exists in the boat form in magnamycin.[88] The β-D-glucose configuration of the molecule was also established by synthesis from methyl

[86] Korte, Bilow, and Heinz, *Tetrahedron*, 1962, **18**, 657.
[86a] Richardson, *Proc. Chem. Soc.*, 1963, 131.
[87] Foster, Lehmann, and Stacey, *J.*, 1962, 1396.
[88] Richardson, *J.*, 1962, 2758.

2,3-anhydro-α-D-*allo*pyranoside,[89] and by nuclear magnetic resonance studies on mycaminose triacetate.[90]

Mycosamine (23). Mycosamine was shown to be a 3-amino-3,6-dideoxy-D-aldohexose[61] and also to differ from synthetic 3-amino-3,6-dideoxy-D-aldohexoses with the D-*gluco*- and D-*talo*-configurations.[91] Degradative studies, as well as the preparation of various derivatives, indicated that the configuration was that of α-D-mannose.[92] *X*-Ray diffraction studies of crystalline mycosamine hydrochloride established this configuration,[93] which is shown in (23).

Neutral Sugars. The branched-chain sugars mycarose (20) and cladinose (11) are closely related. DL-Mycarose has been synthesised from 3-methyl-4-hex-3-enolactone,[94] and from the methyl ester of 3-hydroxy-3-methylhex-4-enoic acid.[94a] Nuclear magnetic resonance results indicated the L-configuration for mycarose, and also showed that mycarose and cladinose have the same conformation.[95] Cladinose can be converted into mycarose with boron trichloride. Isolation of L-lactic acid from carbon atoms 4, 5, and 6 of mycarose prove that mycarose and cladinose belong to the L-series. Synthetic racemic mycarose was resolved and the synthetic L-(−)-mycarose was found to be identical with the natural sugar.[96] Mycarose is thought to be 2,6-dideoxy-3-methyl-L-*ribo*-hexose, and cladinose its 3-methyl ether. Foster *et al.*, however, have suggested that the sugars have the L-*xylo*-configuration.[97]

Other neutral sugars are mentioned in the section on structure determination; of these, stereochemical assignments have been made for mycinose (15) and chalcose (16). The structure and stereochemistry of chalcose have very recently been confirmed by synthesis,[97a] and by conversion of desosamine (3) into chalcose.[97a]

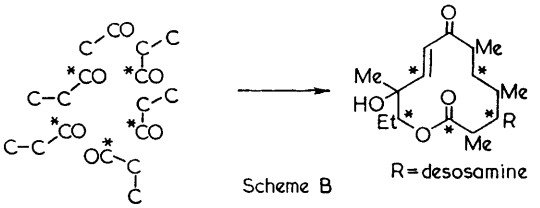
Biogenesis

Two alternative hypotheses have been advanced concerning the biosynthesis of macrolide antibiotics.[3] One[98,99] postulated methylation *via* methionine, choline, or an equivalent one-carbon donor system, of the methylene groups of a poly-β-ketomethylene skeleton derived from head-

[89] Foster, Inch, Lehmann, Stacey, and Webber, *J.*, 1962, 2116.
[90] Hofheinz and Grisebach, *Z. Naturforsch.*, 1962, **17***b*, 355.
[91] Richardson, *Proc. Chem. Soc.*, 1961, 255.
[92] von Saltza, Reid, Dutcher, and Wintersteiner, *J. Amer. Chem. Soc.*, 1961, **83**, 2785; von Saltza, Dutcher, Reid, and Wintersteiner, *J. Org. Chem.*, 1963, **28**, 999.
[93] Locke, Ph.D. Thesis, Rutgers Univ. (*Diss. Abs.*, 1962, **23**, 88).
[94] Korte, Claussen, and Göhring, *Tetrahedron*, 1962, **18**, 1257.
[94a] Grisebach, Hofheinz, and Doerr, *Chem. Ber.*, 1963, **96**, 1823.
[95] Hofheinz, Grisebach, and Friebolin, *Tetrahedron*, 1962, **18**, 1265.
[96] Lemal, Pacht, and Woodward, *Tetrahedron*, 1962, **18**, 1275.
[97] Foster, Inch, Lehmann, Thomas, Webber, and Wyer, *Proc. Chem. Soc.*, 1962, 254; Foster, Inch, Lehmann, and Webber, *Chem. and Ind.*, 1962, 1619.
[97a] Kochetkov and Usov, *Tetrahedron Letters*, 1963, 519; Foster, Stacey, Webber, and Westwood, *Proc. Chem. Soc.*, 1963, 279.
[98] Birch, English, Massy-Westropp, Slaytor, and Smith, *J.*, 1958, 365.
[99] Birch, *Fortschr. Chem. Org. Naturstoffe*, 1957, **14**, 186.

to-tail linkage of acetic acid units,[99,100] and is an extension of the known route leading to a variety of natural products. The second hypothesis[16,101] involves the incorporation of propionic acid units during the formation of the carbon skeleton. So far as the final products are concerned, these alternatives are structurally equivalent.

The validity of the propionate hypothesis was demonstrated by tracer studies of methymycin (1) biosynthesis in *Streptomyces venezuelae*.[102] Fermentation in the presence of [*methyl*-^{14}C]methionine gave methymycin labelled almost exclusively in the desosamine residue. Sodium [*carboxy*-^{14}C]-propionate was utilised as a unit with negligible redistribution of isotope. Assay results on the degradation products indicated that the methymycin aglycone is built up from five propionic acid units and one acetic acid unit as shown in scheme B. A naturally-occurring acetate–propionate condensation had been observed previously,[103] and by conversion of desosamine (3) into chalcose.[97a]



Scheme B

It was observed that [*carboxy*-^{14}C]propionate caused labelling of erythronolide, the aglycone of erythromycin (9), but not desosamine and cladinose. The reverse was true when the precursor was [*methyl*-^{14}C]-methionine.[104] Studies similar to those on methymycin indicated that erythronolide is derived entirely from seven propionate units.[105]

Of the other macrolide aglycones so far determined, narbomycin (14) contains one propionate unit more than methymycin; oleandomycin (12) contains six propionate units and one acetate; and lagosin (27) one propionate and sixteen acetate units.

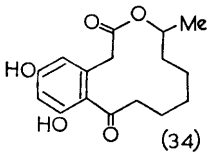
It has been suggested[16] that erythromycin appears to have a "*meso*" character, with the asymmetric centres between C-1 and C-8 possessing the opposite configuration from those between C-10 and C-13. It may be speculated that the macrolide rings are constructed from two fragments joined together at a late stage rather than by successive fusions of two-carbon or three-carbon units followed by cyclisation of the chain.[79]

[100] Collie, *J.*, 1907, 1806.
[101] Woodward, *Angew. Chem.*, 1956, **68**, 13.
[102] Birch, Pride, Rickards, Thomson, Dutcher, Perlman, and Djerassi, *Chem. and Ind.*, 1960, 1245.
[103] Saz and Weil, *J. Biol. Chem.*, 1960, **235**, 914.
[104] Vaněk, Majer, Liebster, Vereš, and Doležilová, Symposium on Antibiotics, Prague, 1959 (quoted in ref. 77).
[105] Corcoran, Kaneda, and Butte, *J. Biol. Chem.*, 1960, **235**, PC29; Grisebach, Achenbach, and Grisebach, *Naturwiss.*, 1960, **47**, 206.

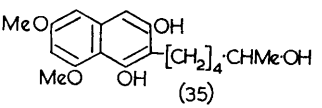
Magnamycin (19) poses the most interesting problem in macrolide biosynthesis. It is the only nonpolyenic macrolide known with an even number of carbon atoms in the ring. Woodward[3] postulated that the aldehyde group on C-7 arose through rearrangement of an unbranched precursor, built up from eight acetate units and one propionate. According to the direction of the rearrangement the aldehyde group arises from either the carboxyl or the methyl of an acetate residue. Miller[77] suggested that magnamycin is biosynthesised from two fatty acid chains, and that the aldehyde is derived from a methyl group. Grisebach and Achenbach investigated the distribution of radioactivity in magnamycin after its biosynthesis by *Streptomyces halstedii* grown in a medium containing [*carboxy*-^{14}C]-acetate and [α-^{14}C]-acetate.[106] They found that the acetate was not incorporated into the aldehyde group or into carbon atoms 5—7. Carbon atoms 8 and 9 and the methyl group on C-9 are derived from propionic acid or methylmalonic acid.[107] D-Glucose uniformly labelled with carbon-14 was largely incorporated into carbon atoms 5—7 and the aldehyde group. Further experiments showed that activity in the aldehyde group was greatest with labelled glucose as precursor. This was the first observation of the incorporation of a sugar derivative into a macrolide ring, and further work in this field will be of great interest.

Other developments in biosynthetic work are the observation that biosynthesis of antimycoin is accelerated by mevalonic acid,[63,108] and the suggestion that ethyl transfer (from ethionine) may be a generalised process in the biosynthesis of antibiotics.[109]

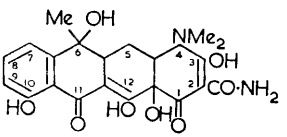
Curvularin (34),[110] which is composed of eight acetate units, may be a structural and biosynthetic link between the macrolides and the naturally-occurring acetate-derived phenols. An easy transannular cyclisation of di-*O*-methylcurvularin leads to the naphthalene derivative (35). Perhaps macrocyclic lactones are intermediates in the production of polycyclic



(34)



(35)



(36)

[106] Grisebach and Achenbach, *Tetrahedron Letters*, 1962, 569.
[107] Grisebach and Achenbach, *Z. Naturforsch.*, 1962, **17***b*, 6.
[108] Safferman, Ph.D. Thesis, Rutgers Univ. (*Diss. Abs.*, 1960, **20**, 4264).
[109] Dulaney, Putter, Drescher, Chaiet, Miller, Wolf, and Hendlin, *Biochim. et Biophys. Acta*, 1962, **60**, 447.
[110] Birch, Musgrave, Rickards, and Herchel Smith, *J.*, 1959, 3146.

aromatic acetate-derived compounds; it would be interesting to know more about the co-occurrence in Nature of macrolides and aromatic compounds. It is possibly significant that tetracycline antibiotics [derivatives of the structure (36)] are also produced by *Streptomyces* species; the basic molecule is derived from acetate.[111,112]

I thank Drs. T. G. Halsall and V. Thaller for suggesting that I write this Review, and Dr. M. C. Whiting for helpful guidance and criticism at all stages in its preparation.

[111] Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 58.
[112] Snell, Birch, and Thomson, *J. Amer. Chem. Soc.*, 1960, **82**, 2402.