SYNTHESIS OF MACROCYCLIC ANTIBIOTICS.

10.* SYNTHESIS OF THE C^9–C^{13} FRAGMENT OF NEOMETHINOLIDE

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In previous communications [1-3] we have described the synthesis of the C^9–C^{13} fragments of methimycin and the antibiotic US-17. We here report the preparation of the C^9–C^{13} fragment of the last representative of the group of 12-membered macrocycles, neomethimycin, the structure of which was conclusively established recently by its total synthesis from noncarbohydrate precursors [4].

Retrosynthetic examination of the structure of the C^9–C^{13} fragment of neomethimycin showed the α-oxide (I) [5] to be the most convenient starting material, into which it was required to introduce regioselectively the C-methyl group at C^2. It has moreover been shown recently that reaction of (I) with $LiCuMe_2$ followed by benzylation leads to the preferential formation of (IV) [6], which can be converted in two steps into the required fragment (VII).

We have found that the reaction of (I) with 2-lithio-1,3-dithiane gives exclusively the alcohol (II), benzylation of which gives (III), which on desulfurization affords the α-methylglucoside (IV). This route to (IV) is more convenient than that described in [6]. In addition, the intermediate mercaptal (II) can be used in other syntheses. The structures of (II)-(IV) were established by PMR and ^{13}C NMR spectroscopy, and by comparison of their spectral data with those of the analogous compounds described in [6].

The conversion of the methylglycoside (IV) into the mercaptal (V) takes place relatively slowly under the conditions found by us previously [7] for pyranosides of similar structure. This reaction is more conveniently carried out with propane-1,3-dithiol in the presence of $ZnCl_2$ as catalyst. In this case, no thioglycosides are formed and the removal of the O-benzyl group does not take place, in contrast to the conditions used in [6]. Subsequent benzoylation of (V) gives (VI). The structures of the latter compounds follow from their ^{13}C NMR spectra. In the spectra of both compounds, the signals for the dithanyl group are clearly apparent (53.1, 30.7, 30.5, and 26.2 for (V), 52.6, 30.8, 30.6, and 26.1 for (VI)), together with those for C^2 (39.9 and 40.1 ppm **respectively), and** the CH_2 groups (73.6 and 74.2 ppm). As compared with (V), the spectrum of (VI) shows a low-field shift of the signal with a chemical shift (CS) of 68.2 ppm, and this may therefore be assigned to C^4, and a high-field shift of the signals with CS 83.0 and 18.9 ppm, which may be assigned to C^3 and C^5 respectively.

Hydrolysis of the dithiaacetal group in (VI) gives the aldehyde (VII), a specifically protected C^9–C^{13} fragment of neomethindolide. In the ^{13}C NMR spectrum of this compound, unlike that of the preceding compound, there are no signals for the dithiaacetal group. A signal appears at low field (203.4 ppm) for the C^1 aldehyde function. The signal for C^2 is shifted to low field (Δδ 8.4 ppm), unambiguously indicating its position. A doublet is present at low field (9.75 ppm) in the PMR spectrum, corresponding to the aldehyde proton. The signal for H^2, which is also readily identifiable, is also markedly shifted to low field as a result of the influence of the neighboring aldehyde group. The positions and multiplicity of the signals for the remaining protons confirm the structure as (VII) (Scheme 1).

Hydrolysis of (III) with aqueous acetic acid followed by reduction with $NaBH_4$ gives the diol (VII). When the latter was chromatographed on silica in the system chloroform–acetone, it was seen that it had been completely converted into the O-isopropylidene derivative (IX) with the formation of a seven-membered ring. The reverse conversion of (IX) to (VIII) also

*For communication 9, see [1].

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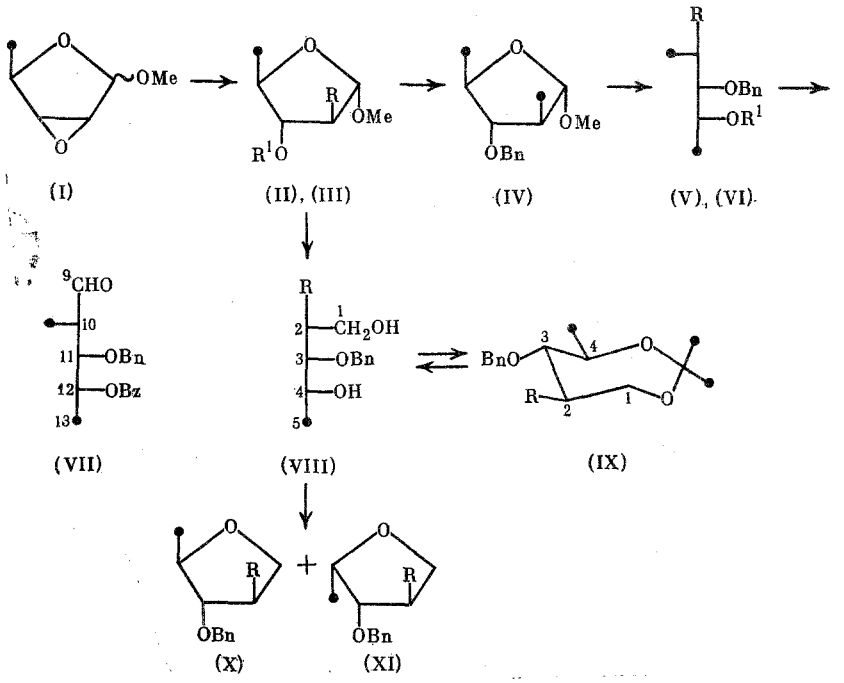
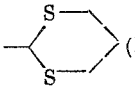
Scheme 1



$R^1 = H$ (II), (V); Bn (III); Bz (VI); R =  (II); (III); (V); (VI); (VIII)—(XI).

occurred readily on evaporating a solution of (IX) in aqueous acetic acid. The structures of (VIII) and (IX) were confirmed by their ^{13}C NMR spectra. As compared with the spectra of (VIII), that of (IX) contained three new signals at 100.7 ppm (singlet), 25.0 and 24.4 ppm (quartets under double heteronuclear resonance conditions), leading to the conclusion that the first signal corresponds to a carbon atom carrying no protons, and each of the two latter signals are bonded to three protons. Consequently, these signals can only be assigned to the Me_2C group, the position of the first signal indicating that the ring must contain more than five atoms [8]. This was also confirmed by the fact that the positions of the signals for C^1 and C^4 both in (IX) and in (VIII) were essentially unchanged. Since there is no alternative, it must be assumed that the seven-membered ring in (IX) is formed readily. In the PMR spectrum of (IX), it is easy to discern the signals for virtually all the protons. Their positions and multiplicity are in good agreement with the proposed structure. For example, the H^3 proton, as a result of the presence of the benzyl group, occurs at high field and is readily identified, and the coupling constants $J_{2,3} = J_{3,4} = 9.5$ Hz indicate the axial arrangement of protons H^2, H^3, and H^4, and the chair conformation of (IX).

Attempts to ditosylate (VIII) with a view to subsequent reduction of the primary alcoholic grouping to obtain the C^9–C^{13} fragment of 10-epineomethinlide were found to result in the formation, in addition to the required ditosylate, of anhydrides (X) and (XI) in a ratio of 83:17. Their formation is probably due to intramolecular substitution of the free hydroxyl group by the tosyloxy-group formed. The structures of (X) and (XI) were established from an examination of their PMR and ^{13}C NMR spectra. It will be seen from the ^{13}C NMR spectra that no tosyl groups are present in (X) or (XI), but all the functions present in (VIII) are retained. The greatest shifts are seen for C^1 ($\Delta\delta$ 8.8 ppm) and C^4 ($\Delta\delta$ 11.7 ppm for (X) and 8.9 ppm for (XI)). This low-field shift of the signals for these atoms is characteristic of O-alkyl derivatives of alcohols, and provides support for the anhydride-type structure of (X) and (XI). The ^{13}C NMR spectrum of (X), unlike that of (XI), is extremely similar to that of the methylglycoside (III). Its most characteristic feature is the low-field shift of the signal for C^3, which is analogous to that observed by us in furanoses of similar structure [9]. This is evidence in favor of the cis-disposition of the substituents at C^2 and C^4, and of a trans-substituent at C^3. There is a literature analogy to the shifts of the signals for C^2 in 1,3-dimethylcyclohexanes and cyclopentanes [10,11].

Unlike the ^{13}C NMR spectrum of (X), in that of the anhydride (XI) the signals for C^3, C^4, and C^5 are shifted to much higher field. This leads to the conclusion that (X) and (XI) differ only in the structure in the C^3–C^5 region. Since it is difficult to suggest any other changes on tosylation of (VIII) at C^3 and C^5, it is most likely that the configuration at C^4 is different: D for (X) and L for (XI). This is confirmed by the specific rotations of these compounds (−7.1° for (X) and +19.5° for (XI)), the greatest contribution towards which in the absence of an anomeric center being made by the configuration at C^4. The PMR spectra of (X) and (XI) are well-resolved, and the coupling constants are in full agreement with the spectra of the corresponding furanoses [12].

EXPERIMENTAL

PMR and ^{13}C NMR spectra were obtained on a Bruker WM-250 instrument (solutions in $CDCl_3$, internal standard TMS, δ, J in Hz). Specific rotations were measured on a Perkin-Elmer 141M polarimeter in chloroform. TLC was carried out on silica gel L (5-40 mμ), and column chromatography on Silpearl silica gel (20-40 mμ) in a benzene–ether gradient at an excess pressure of 1 atm.

Methyl-2,5-didesoxy-2-C-(1,3-dithian-2-yl)-α-D-arabinofuranoside (II). To a solution of 5 g (42 mmole) of 1,3-dithiane in 100 ml of THF was added at −30°C 18 ml of 2.38 N n-BuLi in hexane (43 mmole), and the mixture stirred for 4 h. The α-oxide (I) (1.45 g, 11.5 mmole) in 20 ml of THF was then added, and the mixture kept at −15°C for 20 h. It was then decomposed with 10 ml of methanol, evaporated, and the residue chromatographed to give 1.64 g (57%) of a syrup, $[\alpha]_D^{20}$ +18.0° (C 1.0). PMR spectrum: 4.80 d (1H, H^1, $J_{1,2}$ = 2.5), 2.43 m (1H, H^2, $J_{2,3}$ = 6, $J_{2,SCHS}$ = 9), 3.70 m (1H, H^3), 3.93 d.q (1H, H^4), $J_{2,4}$ = 7.5), 3.90 d (1H, SCHS), 2.80, 2.0, 1.78 m (7H, $SCH_2CH_2CH_2S$, OH), 3.30 s (3H, OMe), 1.25 d (3H, Me-4, $J_{4,Me-4}$ = 6). ^{13}C NMR spectrum: 105.8 (C^1), 47.3 (C^2), 78.1 (C^3), 79.7 (C^4), 17.5 (C^5), 58.1 (SCHS), 28.7, 28.7 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 25.3 ($SCH_2\underline{C}H_2CH_2S$), 54.8 (OMe).

Methyl-2,5-didesoxy-2-C-(1,3-dithian-2-yl)-3-O-benzyl-α-D-arabinofuranoside (III). To a solution of 1.5 g (6.9 mmole) of (II) in 5 ml of DMSO was added 6 ml of a 2N solution of $NaCH_2SOCH_3$ in DMSO, and the mixture stirred for 0.5 h, 1.5 ml of $PhCH_2Br$ added, and stirring continued for 1 h. The mixture was diluted with 50 ml of chloroform, washed with water, evaporated, and the residue chromatographed to give 1.34 g (67%) of product mp 62-63°C (light petroleum), $[\alpha]_D^{20}$ +53°C (C 2.0). PMR spectrum: 4.92 d (1H, H^1, $J_{1,2}$ = 1), 2.50 m (1H, H^2, $J_{2,SCHS}$ = 7; $J_{2,3}$ = 4.5), 3.70 d.d (1H, H^3, $J_{3,4}$ = 6.5), 4.05 d.q (1H, H^4, $J_{4,5}$ = 6.5, $J_{4,Me-4}$ = 6.5), 1.22 d (3H, Me-4), 3.30 s (3H, OMe), 3.92 d (1H, SCHS), 4.45 and 4.58 d (2H, $C\underline{H}_2Ph$, J_{gem} = 12), 2.78, 2.0, 1.80 m (6H, $SCH_2CH_2CH_2CH_2S$), 7.28 m (5H, C_6H_5). ^{13}C NMR spectrum: 105.1 (C^1), 48.5 (C^2), 86.5 (C^3), 7.7 (C^4), 18.4 (C^5), 57.5 (SCHS), 54.6 (OMe), 72.3 ($\underline{C}H_2Ph$), 29.9 and 30.1 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 25.5 ($SCH_2\underline{C}H_2CH_2S$), 138.2-127.5 ($C_6H_5$).

Methyl-2,5-didesoxy-2-C-methyl-3-O-benzoyl-α-D-arabinofuranoside (IV). To a suspension of skeletal nickel, obtained from 10 g of a 50% Ni–Al alloy, boiled in acetone for 2 h, was added a solution of 0.6 g (1.8 mmole) of (III) in 20 ml of acetone, and the mixture boiled with stirring for 13 h. It ws then filtered through a layer of silica, evaporated, and chromatographed to give 0.4 g (94%) of a syrup, $[\alpha]_D^{20}$ +51° (C 2.0). PMR spectrum: 4.55 d (1H, H^1, $J_{1,2}$ = 2), 2.28 m (1H, H^2, $J_{2,Me-2}$ = 7.5; $J_{2,3}$ - 4), 3.20 d.d (1H, H^3, $J_{3,4}$ = 6), 4.12 d.q (1H, H^4, $J_{4,Me-4}$ = 6.5), 1.08 d (3H, Me-4), 1.30 d (3H, Me-2), 4.60 and 4.52 d (2H, $C\underline{H}^2Ph$, J_{gem} = 11.5), 7.30 m (5H, C_6H_5). ^{13}C NMR spectrum: 110.3 (C^1), 46.4 (C^2), 90.9 (C^3), 78.7 (C^4), 19.4 (C^5), 17.4 (Me-2), 54.8 (OMe), 72.0 ($\underline{C}H_2Ph$), 138.2-127.6 (C_6H_5).

2,5-Didesoxy-2-C-methyl-3-O-benzyl-D-arabinose Trimethylenedithioacetal (V). To a solution of 0.15 g (0.63 mmole) of (IV) in 3 ml of propane-1,3-dithiol was added 0.2 g of $ZnCl_2$. The mixture was stirred at 0°C for 0.5 h, transferred to a silica column, and chromatographed in benzene to give 0.179 g (91%) of a syrup, $[\alpha]_D^{20}$ −6.5° (C 2.0). ^{13}C NMR spectrum: 53.1 (C^1), 39.9 (C^2), 83.0 (C^3), 68.2 (C^4), 18.9 (C^5), 12.9 (Me-2), 73.6 ($\underline{C}H_2Ph$), 30.7 and 30.5 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 26.2 ($SCH_2\underline{C}H_2CH_2S$), 138.8-127.6 ($C_2H_5$).

2,5-Didesoxy-2-C-methyl-3-O-benzyl-4-O-benzoyl-D-arabinose Trimethylenedithioacetal (VI). A mixture of 0.179 g (0.573 mmole) of (V) in 2 ml of pyridine and 1 ml of benzoyl chloride was kept at 0°C for 12 h. Water (10 ml) was then added, and the mixture extracted with chloroform. The extract was washed with water, 2 N H_2SO_4, and saturated $NaHCO_3$ solution,

and evaporated. The residue was chromatographed to give 0.169 g (70.5%) of a syrup, $[\alpha]_D^{20}$ −13.0° (C 1.0). ^{13}C NMR spectrum: 52.6 (C^1), 40.1 (C^2), 81.3 (C^3), 72.1 (C^4), 16.0 (C^5), 12.6 (Me-2), 30.8 and 30.6 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 26.1 ($SCH_2\underline{C}H_2CH_2S$), 138.8-127.5 ($C_6H_5$).

2,5-Didesoxy-2-C-methyl-3-O-benzyl-4-O-benzoylal-D-arabinose (VII). A mixture of 0.169 g (0.405 mmole) of (VI), 0.81 g (3 mmole) of $HgCl_2$, and 0.69 g (4 mmole) of $CdCO_3$ was boiled for 15 min in an acetone–water mixture (10:1) for 4 h. The mixture was then evaporated, and the residue chromatographed to give 0.137 g (80%) of a syrup, $[\alpha]_D^{20}$ −25.3° (C 3.0). PMR spectrum: 9.77 d (1H, HCa, $J_{1,2}$ = 1.5), 2.7 m (1H, H^2, $J_{2,3}$ = 4; $J_{2,Me-2}$ = 7.5), 4.15 d.d (1H, H^3, $J_{3,4}$ = 5.5), 5.35 m (1H, H^4, $J_{4,Me-4}$ = 6.5), 1.48 d (3H, H^5), 1.30 d (3H, Me-2), 4.72 and 4.60 d (2H, $C\underline{H}_2Ph$, J_{gem} = 11), 8.05-7.3 m (10H, C_6H_5). ^{13}C NMR spectrum: 203.4 (C^1), 4816 (C^2), 79.6 (C^3), 71.3 (C^4), 16.2 (C^5), 8.8 (Me-2), 73.8 ($\underline{C}H_2P$), 15.7 ($\underline{C}OP$), 137.8-127.8 (C_6H_5).

2,5-Didesoxy-2-C-(1,3-dithian-2-yl)-3-O-benzyl-D-arabinthol (VIII) and 2,5-Didesxoy-2-c-(1,3-dithian-2-yl)-3-O-benzyl-1,4-O-isopropylidene-D-arabinthol (IX). a) Compound (III) (0.67 g, 2 mmole) in 13 ml of a mixture of acetic acid and water (10:3) was boiled for 1.5 h, evaporated repeatedly with toluene, dissolved in 15 ml of methanol, 3 ml of water added followed by 1 g of $NaBH_4$, the mixture kept for 12 h, treated with KU-2 (H^+), evaporated repeatedly with methanol, and chromatographed on silica in the system chloroform–acetone (9:1). Yield of (VIII) 0.109 g (16.8%), mp 118-119°C (benzene–pentane), $[\alpha]_D^{20}$ −1° (C 4.15). ^{13}C NMR spectrum: 60.1 (C^1), 48.1 (C^2), 81.7 (C^3), 69.0 (C^4), 19.2 (C^5), 48.3 (SCHS), 30.9 and 30.6 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 73.7 ($\underline{C}H_2Ph$), 138.4-127.7 ($C_6H_5$). Yield of (IX) 0.58 g (83.2%), mp 88-89° (hexane), $[\alpha]_D$ −26.5° (C 2.0). PMR spectrum: 3.8 m (2H, H^1, $J_{1e,2}$ = 5, $J_{1a,2}$ = 7.5, $J_{1,1'}$ = 12.5), 2.1 m (1H, H^2, $J_{2,SCHS}$ = 2.5, $J_{2,3}$ = 9.5), 3.42 t (1H, H^3, $J_{3,4}$ = 3.5), 3.92 m (1H, H^4, $J_{4,Me-4}$ = 6.5), 1.33 m (9H, Me, Me_2Cl), 4.45 d (1H, SCHS), 4.80 and 4.68 d (2H, $C\underline{H}_2Ph$, J_{gem} = 11.5), 2.83, 2.58, s.05, 1.08 m (6H, $SCH_2CH_2CH_2S$), 7.35 m (5H, C_6H_5). ^{13}C NMR spectrum: 59.7 ($C\underline{M}e_2$), 51.7 (SCHS), 31.9 and 31.3 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 26.3 ($SCH_2\underline{C}H_2CH_2S$), 138.7-127.8 ($C_6H_5$).

b) Compound (IX) (0.58 g, 1.58 mmole) was heated at 100°C in 10 ml of 80% acetic acid for 1 h. The mixture was then evaporated with toluene and chromatographed on silica in the system benzene–ether (3:2) to give 0.48 g (90%) of (VIII).

1,4-Anhydro-2,5-didesoxy-2-C-(1,3-dithian-2-yl)-3-O-benzyl-D-arabinose (X) and 1,4-Anhydro-2,5-didesoxy-2-C-(1,3-dithian-2-yl)-3-O-benzyl-L-xylose (XI). A mixture of 0.48 g (1.43 mmole) of (VIII), 0.82 g (4.3 mmole) of TsCl, and 4 ml of pyridine was kept for 20 h at 20°C, then diluted with 50 ml of chloroform, washed with water, 2 N H_2SO_4, water, and saturated $NaHCO_3$ solution. It was then evaporated, and the residue chromatographed to give 0.207 g (45.5%) of (X) as a syrup, $[\alpha]_D^{20}$ −7.1° (C 1.0). PMR spectrum: 4.15 d.d (1H, H^1, $J_{1,1'}$ = 9.5, $J_{1,2}$ = 3.5), 3.90 m (2H, H^3, H^4, $J_{3,4}$ = 5, $J_{4,Me-4}$ = 6), 1.38 d (3H, Me-4), 4.08 d (1H, SCHS), 4.70 and 4.60 d (2H, $C\underline{H}_2Ph$, J_{gem} = 11.5), 2.85 m (4H, $S\underline{C}H_2CH_2\underline{C}H_2S$), 2.12 and 1.95 m (2H, $SCH_2\underline{C}H_2CH_2S$), 7.35 m (5H, C_6H_5). ^{13}C NMR spectrum: 69.0 (C^1), 49.6 (C^2), 87.7 (C^3), 80.7 (C^4), 18.8 (C^5), 72.2 ($\underline{C}H_2Ph$), 51.4 (SCHS), 30.2 and 30.0 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 25.7 ($SCH_2\underline{C}H_2CH_2S$), 138.2-127.5 ($C_6H_5$).

Yield of (XI) 0.043 g (9.5%), syrup, $[\alpha]_D^{20}$ +19.5° (C 1.0). PMR spectrum: 4.17 d.d (1H, H^1, $J_{1,1'}$ = 9, $J_{1,2}$ = 7.5), 3.75 d.d (1H, $H^{1'}$, $J_{1',2}$ = 6.5), 2.72 m (1H, H^2, $J_{2,SCHS}$ = 8.5, $J_{2,3}$ = 2.5), 4.08 d.d (1H, H^3, $J_{3,4}$ = 4.5), 3.93 m (1H, H^4, $J_{4,Me-4}$ = 6), 1.32 d (Me-4), 4.0 (1H, SCHS), 4.70 and 4.52 d (2H, $C\underline{H}_2Ph$, J_{gem} = 11.5), 2.88 m (4H, $S\underline{C}H_2CH_2\underline{C}H_2S$), 7.35 m (5H, C_6H_5). ^{13}C NMR spectrum: 68.9 (C^1), 48.9 (C^2), 82.8 (C^3), 77.9 (C^4), 14.2 (C^4), 71.6 ($\underline{C}H_2Ph$), 51.0 (SCHS), 30.2 and 30.0 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 25.7 ($SCH_2\underline{C}H_2CH_2S$), 138.2-127.5 ($C_6H_5$).

CONCLUSIONS

The C^9–C^{13} fragment of neomethinolide has been synthesized from D-xylose.

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