Communications to the editor

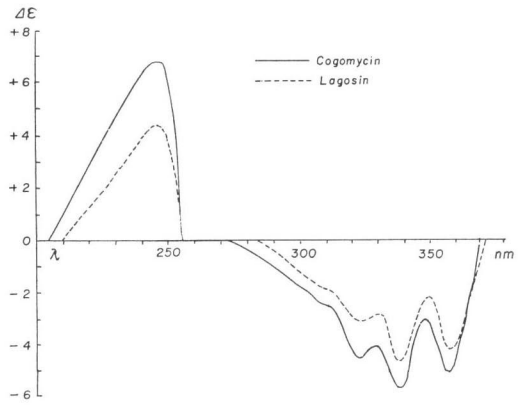
THE STRUCTURE OF COGOMYCIN*

Sir:

In our earlier paper[1] we reported on the structural studies of cogomycin (**1**) an antifungal antibiotic[2] which was shown to be 2-(1-hydroxyhexyl)-16, 27-dimethyl-3, 5, 7, 9, 11, 13, 14, 15, 26-nonahydroxyheptacosa-16, 18, 20, 22, 24-pentaene-27-olide. Cogomycin belongs to the 2231 subgroup of BÉRDY's classification of antibiotics[3]. It was concluded that the structure of cogomycin is identical with that of fungichromin[4] and lagosin[5], respectively, disregarding stereochemistry. The relatively small differences between the CD curves of cogomycin and lagosin (Fig. 1) may originate from differences in the absolute configuration at one or more chiral centers or from small amounts of closely related substances having different spectral properties.

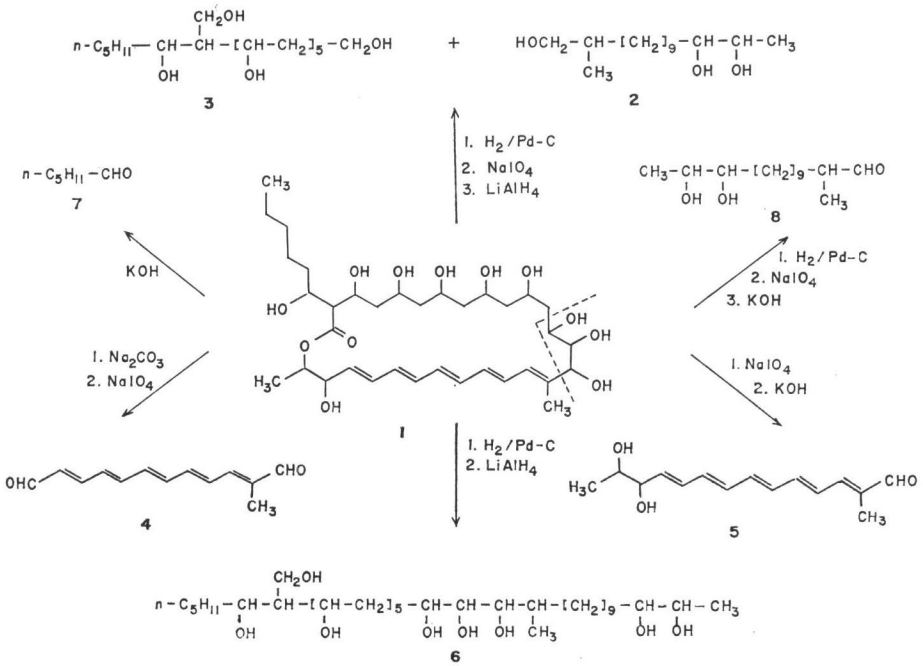
Now we present further evidence of the proposed structure, and it is proved by chemical methods that cogomycin contains the 1, 2, 3-triol partial structure indicated in formula **1** and postulated previously[1] on the basis of a detailed mass spectrometric study. Finally, the ^{13}C-NMR spectrum of cogomycin and that of 2-methyl-2, 4, 6, 8, 10-dodecapentaenedial (**4**) isolated from cogomycin are discussed.

Fig. 1. The CD spectra of cogomycin and lagosin



The degradation reactions of cogomycin

Fig. 2. Degradation reactions of cogomycin



* Part II. For Part I. see Ref. 1.

discussed in the previous[1] and present papers are summarized in Fig. 2.

Upon reaction with $NaIO_4$ and $LiAlH_4$ (according to COPE[4]) decahydrocogomycin[1] gave two compounds (**2** and **3**) which were separated on the basis of their different solubilities.

The following spectral properties indicate that the chloroform-soluble **2** (mp: 56~58°C, lit. mp[4]: 57~59°C and 63~64.5°C) is 13-methyl-2, 3, 14-tetradecanetriol. Compound **2** does not absorb ultraviolet light above 220 nm. In its IR spectrum absorptions attributable to aliphatic methyl, methylene and hydroxyl groups are discernible. The 100 MHz PMR spectrum of **2** suggests the presence of two $C\underline{H}_3$-CH< groups (δ=0.88 (d) and 1.09 (d) ppm; $J^{(1)} \approx J^{(2)} \approx 7$ Hz) and three O$\underline{H}$ groups (δ=3.56 ppm, broad absorption) in addition to $C\underline{H}_2$ groups. The 14 eV mass spectrum of **2** exhibits a weak M+H peak at *m/e* 261. The observed ion of highest mass in the 70 eV mass spectrum (Fig. 3) corresponds to M^+ lost H_2O (*m/e* 242). The *m/e* 230 ion arises from the protonated molecular ion by loss of a CH_2OH group. The *m/e* 45 and 215 ions originate from the undetectable M^+ by rupture of the chain between the neighbouring OH groups. From the *m/e* 215 ion successive elimination of two water molecules has been observed (*m/e* 197 and 179). Further skeletal rupture of these ions leads to very abundant hydrocarbon peaks at the lower mass region.

The 70 eV mass spectrum of the pertrimethylsilyl derivative of **3** (Fig. 4) shows a very weak peak at *m/e* 972 which corresponds to the molecular ion with the expected chemical composition: $C_{19}H_{32}(OTMS)_8$. The other ions observed can be derived from the proposed structure by elimination of TMSOH molecules, by ruptures of the skeleton at positions β to the TMSO groups and by combination of these processes in a similar manner to compound **5** in Ref.[1]. Ions losing 1~5 TMSOH groups successively were observed in the spectrum (ion series *m/e* 882, 792, 702, 612, 522). The primary ruptures of the skeleton could lead either to *m/e* 869 and the complementary 103 ion or *m/e* 173 or 683 ions. This latter fragment was detectable only after having lost TMSOH units (series *m/e* 593, 503, 413, 323). From the *m/e* 869 ion successive elimination of TMSOH molecules gives rise to a series of ions *m/e* 779, 689, 599, 509. The chemical composition of the ions of these series were checked by measuring the exact mass of ions at *m/e* 612, 599 and 503 using high resolution.

The proton noise-decoupled ^{13}C-FT-NMR spectrum of cogomycin exhibits 31 resolved peaks. The multiplicity of the signals in the off-resonance CW decoupled spectrum and the assignments of some of these peaks are shown in Fig. 5.

The given assignments are based on the following arguments. The methyl carbons at 12.2 and 18.5 ppm appear as first-order quartets in the off-resonance decoupled spectrum while

Fig. 3. The monoisotopic, 70 eV mass spectrum of compound **2**

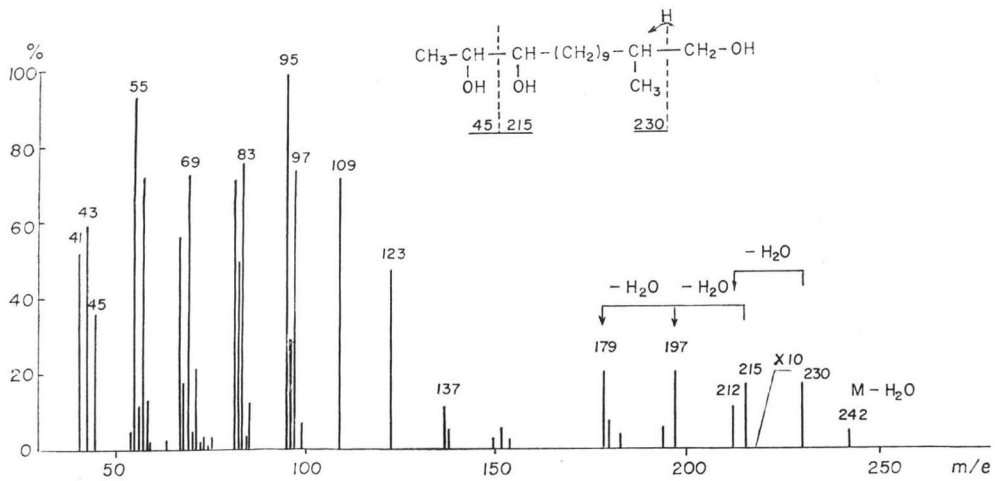


Fig. 4. The monoisotopic, 70 eV mass spectrum of the pertrimethylsilyl derivative of compound **3**

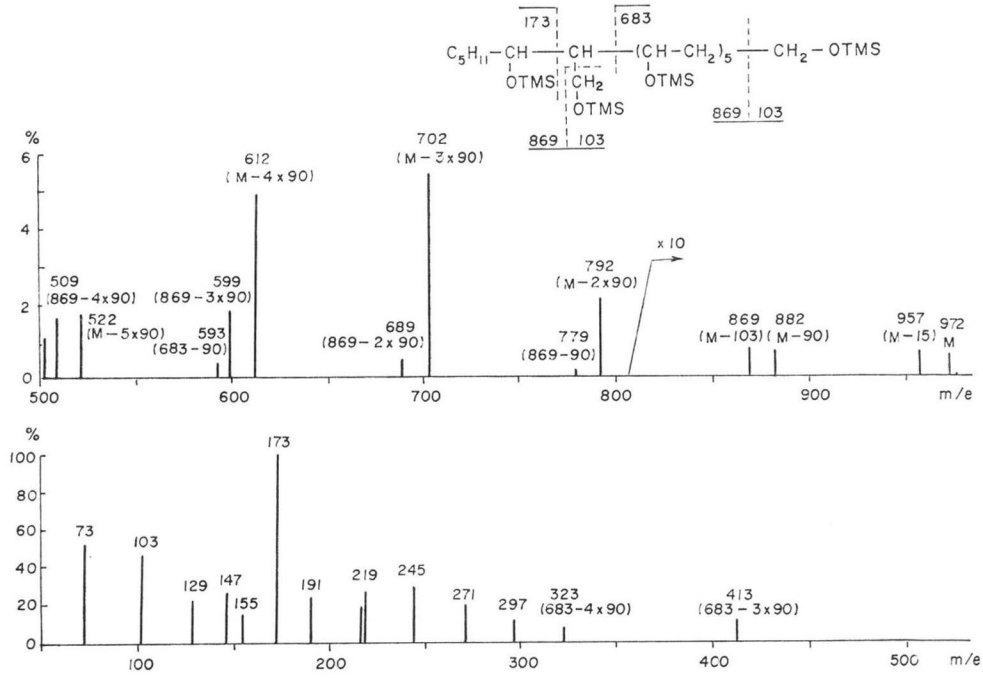
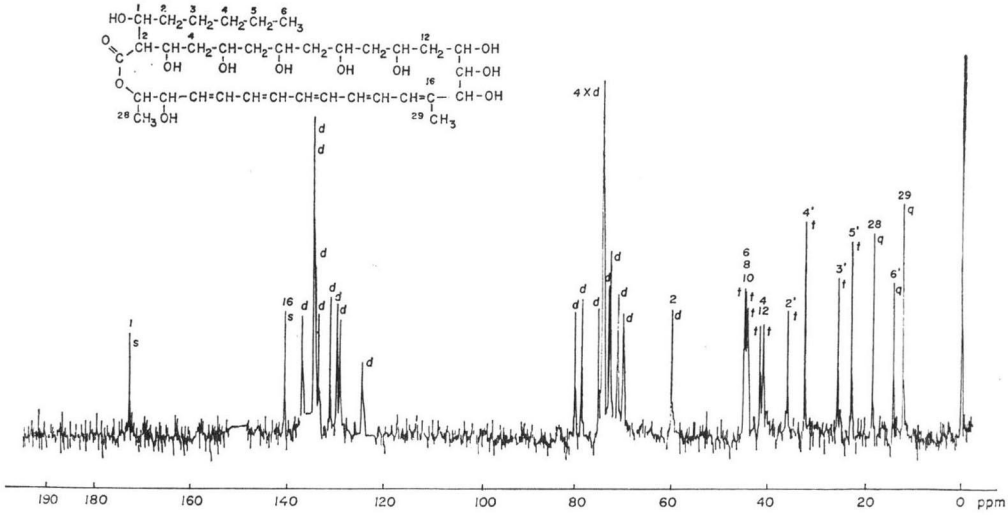
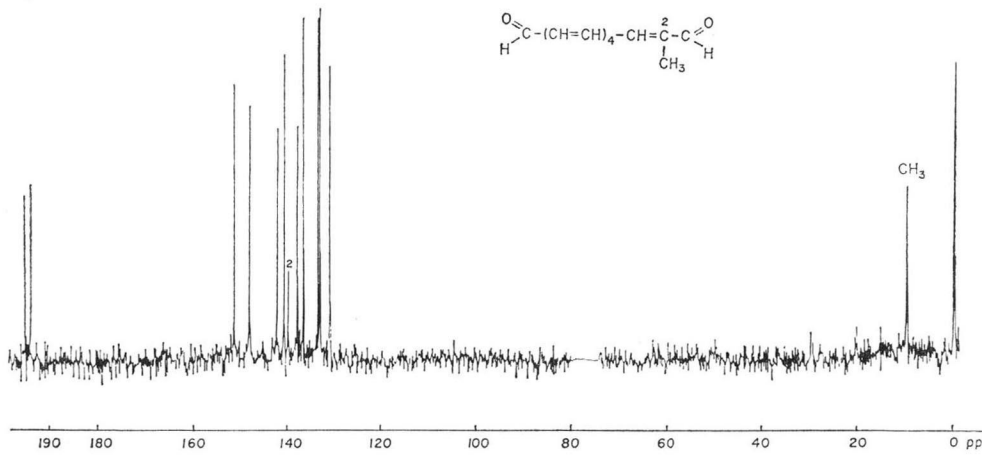


Fig. 5. The proton noise-decoupled ^{13}C-FT-NMR spectrum of cogomycin



the quartet at 14.2 ppm exhibits second-order effects. The condition for second-order splitting to occur ($J_{AB} \approx J^{red}_{AX} \approx \Delta\nu^{eff}_{AB}$) for an A_3B_nX system where X is the observed carbon atom[6,7] is fulfilled only for carbon 6' which can therefore be assigned to the signal at 14.2 ppm. The assignments for $\underline{C}H_3$-28 (18.5 ppm) and $\underline{C}H_3$-29 (12.2 ppm) are based on chemical shift arguments. The assignments of these methyl carbons are corroborated by the finding that the residual coupling constant $^1J^{red}_{CH}$ is 37 Hz for the signal at 12.2 ppm and 34 Hz for the signal at 18.5 ppm. Since the decoupler has been centered at high field the proton resonance corresponding to the signal at 12.2 ppm must occur at lower field. The ^{1}H

Fig. 6. The proton noise-decoupled ^{13}C-FT-NMR spectrum of 2-methyl-2, 4, 6, 8, 10-dodecapentaenedial



resonances for $C\underline{H}_3$-28 and -29 are found at 1.65 (d) and 2.1 ppm (s), respectively. The side chain carbons 2', 3', 4' and 5' appear as triplets at 35.8, 25.6, 32.2 and 23.0 ppm, respectively. Their assignments are based on chemical shift additivity rules[8,9] on the assumption that the side-chain behaves as a sterically unperturbed aliphatic alcohol. The five methylene carbons appear in two groups at *ca.* 41 and 44 ppm. The two peaks at 40.7 and 41.1 ppm are tentatively assigned to carbons 4 and 12, being shifted to higher field relative to carbons 6, 8 and 10 due to heavier substitution at the β carbons. Carbon 2 appears at 60.0 ppm while the eleven oxygen-bearing methine carbons are found between 70 and 80 ppm. The signals in the range of 120~140 ppm originate from the olefinic carbons. The peak at 140.1 is assigned to the C-16 carbon because it appears as a singlet in the off-resonance decoupled spectrum. The carbonyl carbon appears at 174.2 ppm as expected for an ester carbonyl carbon.

The ^{13}C-NMR spectrum thus allows to establish the exact number of methyl, methylene, carbonyl and quaternary carbons and even the majority of the methine carbons can be resolved. This spectrum clearly demonstrates the power of ^{13}C-NMR as a tool for the identification and structural elucidation of new polyene macrolide antibiotics.

For a comparison, the ^{13}C-NMR spectrum of compound **4**, obtained from cogomycin[1], was also recorded. It exhibits 13 signals (Fig. 6). The methyl carbon is found at 9.7 ppm while the olefinic signals appear between 130 and 150 ppm. The quaternary carbon at 139.5 ppm is identifiable due to its characteristically low intensity (lack of NOE). The aldehyde carbons 1 and 12 appear at 193.5 and 194.7 ppm, respectively.

The CD spectra were run on a Model 185 Roussel-Jouan dicrograph in EtOH at concentrations of about 0.5~1.5 mg/ml in 0.5 mm cells at 20°C. The mass spectra were taken on an A.E.I. MS 902 mass spectrometer. The ^{13}C-FT-NMR spectra were recorded at 25.16 MHz on a VARIAN XL-100-15. Cogomycin was measured in pyridine-d_5 (0.1 M) and compound **4** in $CDCl_3$ (0.1 M). Chemical shifts are given in ppm relative to internal TMS, being accurate to $\pm$0.04 ppm. Digital resolution is 1.25 Hz/point.

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