

erhöht, wobei sich der gebildete Borsäureester zersetzte und 0,83 g Gemisch der Olefine **10** u. **4** überdestillierte. Durch präparative Gas-Chromatographie erhielt man daraus 0,36 g **10**:  $R_t = 3,3$  Min.;  $[\alpha]_D^{20} = +69^\circ$ ;  $n_D^{20} = 1,4520$ ;  $d_4^{20} = 0,7788$  (Literatur [1]:  $[\alpha]_D^{20} = +64^\circ$ ;  $n_D^{20} = 1,4526$ ;  $d_4^{20} = 0,7836$ ). – MS.:  $M^+$ : 136 (1);  $m/e$ : 121 (40), 107 (72), 93 (100), 81 (98), 67 (44), 53 (52), 41 (70), 27 (40). – Das daneben zu  $\sim 45\%$  entstandene *cis*- $\beta$ -Hymenethoren (**4**) zeigte  $[\alpha]_D^{20} = +161^\circ$ .

9. (R)-(-)-*trans*-2,6-Dimethyloctatrien-1,4,7 (**9**; *trans*-Achillene). 3,2 g *trans*-Alkohol **7** ( $[\alpha]_D^{20} = -5,9^\circ$ ) wurden wie vorstehend beschrieben mit 0,8 g  $B(OH)_3$  bei  $130^\circ/150$  Torr dehydratisiert. Aus dem nach Destillation erhaltenen Gemisch der Triene **9** und **3** (Bildungsverhältnis  $\sim 1:1$ ) isolierten wir 1,1 g reines **9** durch präparat. Gas-Chromatographie unter den eingangs erwähnten Bedingungen:  $R_t = 3,6$  Min.;  $[\alpha]_D^{20} = -3,8^\circ$ ;  $n_D^{20} = 1,4461$ ;  $d_4^{20} = 0,7820$ . – MS.:  $M^+$ : 136 (0,1);  $m/e$ : 121 (26), 107 (21), 93 (25), 81 (100), 79 (45), 67 (20), 53 (27), 41 (34), 27 (16).

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## 112. Crystal Structure of the Antibiotic Monensin Similarities and Differences between Free Acid and Metal Complex

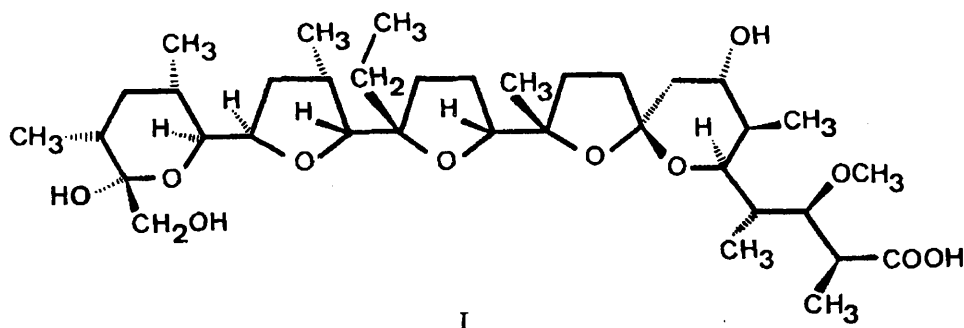
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(30. IV. 71)

*Summary.* The structure of monensin,  $C_{38}H_{62}O_{11}$ , has been determined by X-ray analysis of its crystalline monohydrate (orthorhombic,  $a = 15.15$ ,  $b = 23.61$ ,  $c = 10.65$  Å,  $Z = 4$ , space group  $P2_12_12_1$ ). Phases were assigned by direct methods, making use of the 'tangent formula'. Although the conformation of the free acid resembles that of the silver salt in being cyclic, there are differences in the hydrogen bonding pattern. These features are discussed in relation to the complexation of metal ions by monensin.

Monensin (monensic acid,  $C_{36}H_{62}O_{11}$ ) is an antibiotic, which reverses the translocation of alkali metal cations across mitochondrial membranes caused by valinomycin, nonactin, etc. [1]. Its molecular structure has been determined by X-ray



analysis of a crystalline silver salt as I [2] [3]. The analysis showed that the complex anion forms a macrocycle secured by a pair of hydrogen bonds between the negatively charged oxygen atoms of the carboxylate group and the two hydroxyl groups at the other end of the molecule; the  $Ag^+$  ion, enclosed in the resulting cavity, is coordinated to six oxygen atoms (4 ether, 2 hydroxyl) at distances of 2.4–2.7 Å in an irregular arrangement. Crystallographic data [3] for the potassium and sodium salts indicate that their structures must be very similar.

As pointed out by *Pinkerton & Steinrauf* [3], the numerous ring substituents severely restrict the conformational freedom of the monensin molecule. On the other hand, for complexation with metal ions to occur at a reasonable rate, the central cavity must be flexible enough to permit step-wise removal of the water molecules from the hydrated metal ion [4]. It has been suggested that the free acid and metal complex have 'radically different conformations' with the free acid in a possibly linear (non-cyclic) form [5]. However, IR. studies of the free acid show that there is hardly any change in the carbonyl stretching frequency over a wide concentration range [6], suggesting, at least, that the conformation is not sufficiently flexible to permit the usual intermolecular association of carboxylic acids into dimers.

Monensin crystallizes from absolute ethanol as a monohydrate ( $C_{36}H_{62}O_{11} \cdot H_2O$ ) with 4 formula units in a unit cell of dimensions  $a = 15.15$ ,  $b = 23.61$ ,  $c = 10.65$  Å, space group  $P2_12_12_1$ . The structure was solved by application of phase relationships, using the well-known tangent formula (1) [7]. At the present stage of refinement the conventional  $R$ -factor, based on approximately 2800 observed structure amplitudes, is 0.08.

$$\tan(\Phi_h) = \frac{\sum_{h'} |E_{h'} E_{h-h'}| \sin(\Phi_{h'} + \Phi_{h-h'})}{\sum_{h'} |E_{h'} E_{h-h'}| \cos(\Phi_{h'} + \Phi_{h-h'})} \quad (1)$$

Positional coordinates of all carbon and oxygen atoms are listed with the corresponding isotropic  $B$  values in the Table. Hydrogen positions are not included although in a final difference synthesis electron-density peaks corresponding to 58 out of the 64 hydrogen atoms present were found in stereochemically reasonable positions; these atoms were included in the structure-factor model of the final least-squares cycles. (The six 'missing' hydrogen atoms are all involved in hydrogen bonding.) Estimated

*Positional parameters and isotropic B-values*

The twelve starred atoms have been refined anisotropically; the B-values listed are taken from the last isotropic least-squares refinement cycle. The atom-numbering system corresponds to that of [3] and is indicated in Figure 1

Atom.	x	y	z	B[Å <sup>2</sup> ]	Atom	x	y	z	B[Å <sup>2</sup> ]
C(1)	-.0052	.7243	.4774	4.52	C(25)	-.1082	.5073	.4246	3.75
C(2)	.0426	.7666	.5625	4.76	C(26)	-.1693	.5579	.4252	4.72
C(3)	.1370	.7501	.5951	4.50	O(1)*	-.0242	.7346	.3705	5.97
C(4)	.2017	.7406	.4833	4.12	O(2)*	-.0232	.6760	.5315	5.21
C(5)	.1871	.6849	.4164	3.51	O(3)*	.1666	.7983	.6683	5.65
C(6)	.1899	.6313	.4984	4.28	O(4)	.0903	.5780	.3686	4.93
C(7)	.1793	.5795	.4150	4.79	O(5)	.2557	.6819	.3232	4.13
C(8)	.2438	.5804	.3047	4.74	O(6)	.1629	.6415	.1716	3.99
C(9)	.2446	.6359	.2351	4.09	O(7)	.0510	.6191	-.0235	4.00
C(10)	.3142	.6432	.1346	4.95	O(8)	.0335	.5082	.0849	4.02
C(11)	.2729	.6842	.0443	5.25	O(9)	-.0820	.5012	.2956	3.67
C(12)	.1725	.6732	.0546	4.21	O(10)	-.0343	.5171	.5019	4.43
C(13)	.1398	.6353	-.0506	4.29	O(11)*	-.1240	.6090	.3925	5.21
C(14)	.1852	.5786	-.0709	4.78	1CH3*	-.0110	.7739	.6837	6.72
C(15)	.1173	.5457	-.1417	4.87	2CH3*	.2417	.7875	.7445	6.50
C(16)	.0282	.5700	-.0974	3.99	3CH3*	.2017	.7910	.3941	5.43
C(17)	-.0236	.5308	-.0103	3.64	4CH3*	.2762	.6273	.5733	6.47
C(18)	-.0705	.4788	-.0657	3.92	5CH3*	.1198	.7278	.0625	5.09
C(19)	-.0875	.4463	.0541	4.32	6CH3*	-.1128	.6200	-.1775	6.23
C(20)	-.0042	.4558	.1300	3.97	7CH3*	-.0181	.4426	-.1584	5.55
C(21)	-.0178	.4572	.2726	3.62	8CH3*	.0243	.3564	.3168	5.81
C(22)	-.0503	.3996	.3221	4.11	9CH3*	-.1912	.4563	.5998	6.19
C(23)	-.0864	.4045	.4537	4.97	1CH <sub>2</sub>	-.0284	.5897	-.2079	5.51
C(24)	-.1541	.4522	.4670	4.37	H <sub>2</sub> O*	-.0608	.6497	.1802	7.43

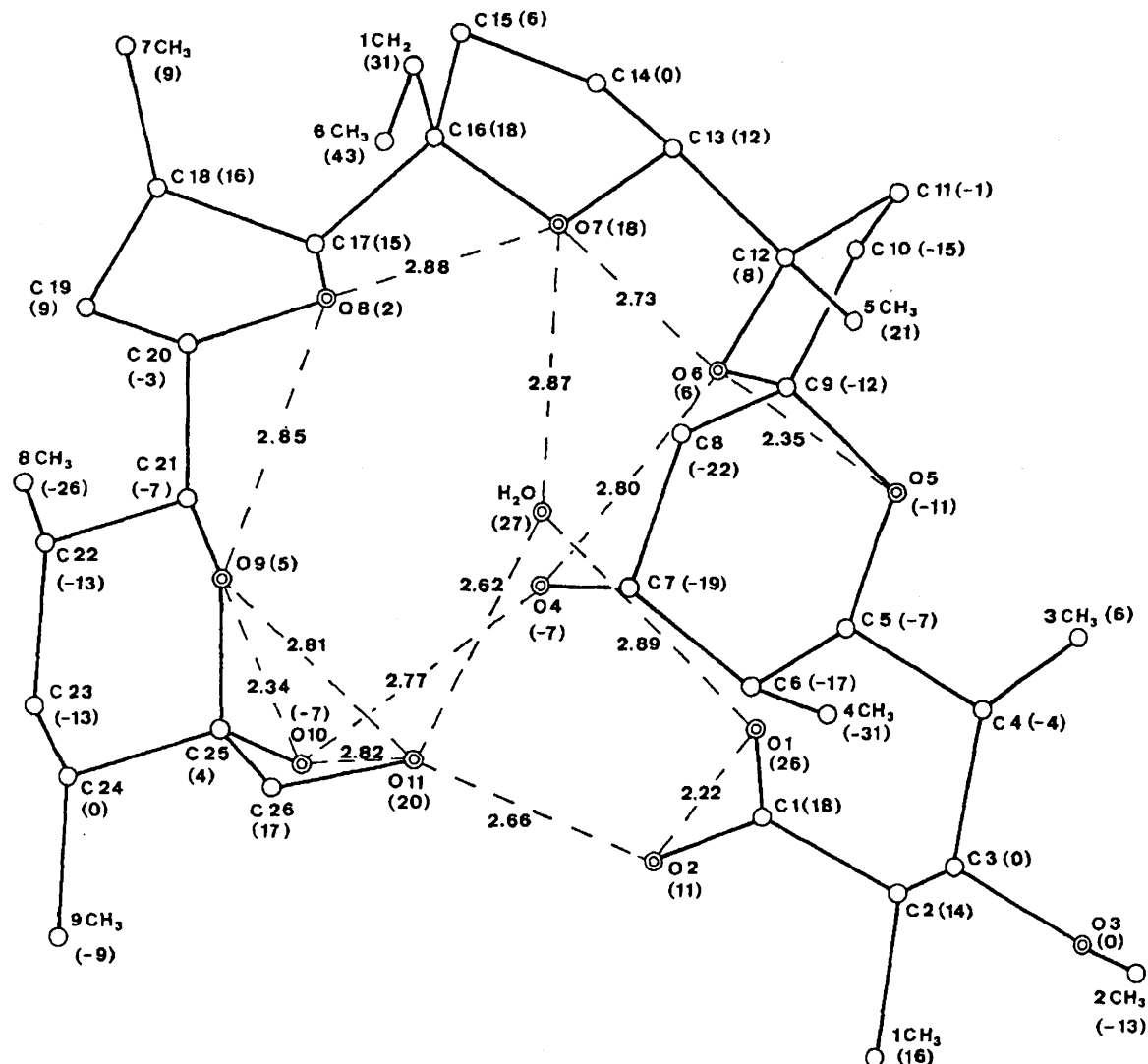


Fig. 1. The monensin molecule projected on the plane defined by C(3), C(14), C(24). Numbers in brackets give the distances of atoms from the reference plane in units of  $10^{-1}$  Å. O...O-distances (in Å) less than 3 Å are indicated. There are no intermolecular O...O-distances less than 3.91 Å (O(3)...O(11)).

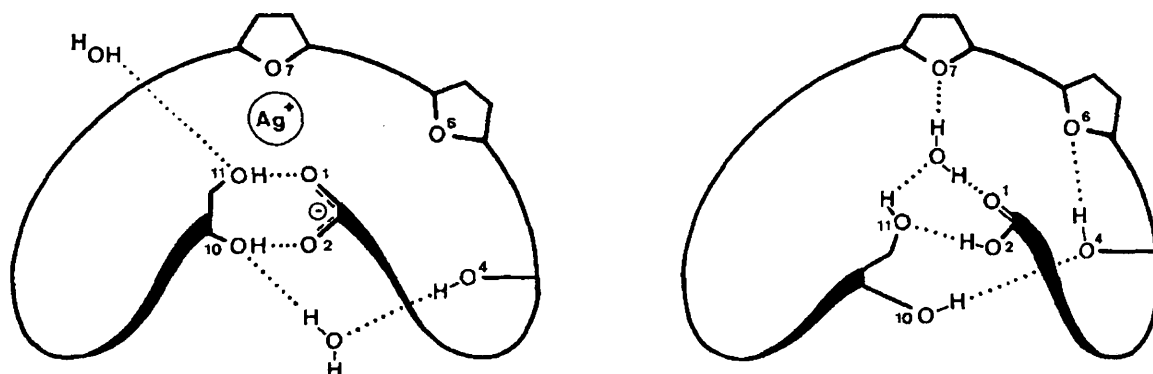


Fig. 2. Schematic representation of hydrogen-bonding patterns in monensin silver salt and free acid. Not all of the hydrogen positions indicated have been confirmed from difference syntheses, which tend to show electron-density accumulations close to both oxygen atoms in each hydrogen bond, possibly as the result of disorder in the hydrogen atom arrangement.

standard deviations of the positional coordinates of the listed atoms lie in the range 0.004–0.009 Å, except for the methyl groups where they are 0.009–0.012 Å.

Bond distances and angles derived from the coordinates are all close to expected values based on I so that the structure derived by analysis of the silver salt [2] [3] is confirmed in all details. The observed C–C distances lie in the range 1.494–1.558 Å (average 1.526 Å), the C–O distances in the range 1.410–1.461 Å (average 1.436 Å). The identification of the carbonyl and hydroxyl oxygen atoms of the carboxyl group follows from the observed distances: C(1)=O(1), 1.199 Å; C(1)–O(2)H, 1.306 Å.

Although the molecule can be described as existing in a cyclic conformation (Fig. 1) similar to that of the silver salt, there are important differences, mainly in the number and arrangement of hydrogen bonds (Fig. 2) and hence in the relative positions of the oxygen atoms surrounding the 'cavity'. In the free acid, one side of the cavity is drawn together by two intramolecular hydrogen bonds O(10)H...O(4)H...O(6), and the opposite side dilated by the presence of the water molecule hydrogen-bonded to O(1), O(7) and O(11). Some of the O...O distances change by more than 1 Å on passing from silver salt to free acid; however, the changes in corresponding torsion angles do not exceed 17° and are mostly much smaller. This shows how shape and function of a biologically important molecule can undergo significant alteration by the combined effect of a large number of small, co-operative structural changes associated with only minimal variation in conformational energy.

The structure of the hydrated monensin molecule suggests a model for a possible complexation mechanism. The hydrogen-bonded water molecule is oriented in such a way that it can also function as one of the water molecules in the hydration sphere of a metal ion during the initial complexation step. It is easy to imagine that the next step would be displacement of the bound water molecule, possibly as H<sub>3</sub>O<sup>+</sup>, by the partially hydrated metal ion, which would then be coordinated on one side by three oxygens of the monensin molecule and on the other side by water molecules. Inspection of a space-filling model shows that subsequent steps can take place with a minimum of atomic reorganization.

**Experimental.** – The observed density, 1.20 g · cm<sup>-3</sup>, indicated the presence of 1 molecule of H<sub>2</sub>O per formula unit C<sub>36</sub>H<sub>62</sub>O<sub>11</sub>. The m.p. 117–122° was 15° higher than reported [2]. The intensities of about 3300 independent reflexions were measured from a roughly cube-shaped crystal (0.45 mm in edge) with a 4-circle diffractometer (*Hilger & Watts* Model Y290, under control of a PDP-8 computer) using MoK $\alpha$  radiation monochromatized by reflection from graphite.

*Structure analysis by direct methods* [7]. From an extended list containing 500 reflexions ( $E > 1.35$ ) in the range  $\sin \Theta / \lambda < 0.55$  a short list of 150 reflexions ( $E > 1.9$ ) was prepared. The origin was defined by assigning the phase +90° to the three reflexions ( $E$ -values in brackets): 1,19,0(4.8); 1,18,0(3.5); 0,9,3(2.7) and four symbols  $a, b, c, d$  were associated with 7,11,6(3.7); 5,9,7(3.2); 10,11,4(3.4); 6,11,6(2.8). The symbolic addition procedure applied to the short list led to the probable assignments,  $a \sim \pm 90^\circ$ ,  $c \sim \pm 90^\circ$ ,  $d \sim 0$  or  $180^\circ$ . The value of  $a$  was arbitrarily chosen as positive, thus defining the enantiomorph (in the opposite sense to the correct one, as it turned out). With  $b$  taken as 45°, 135°, 225°, 315° each of the 16 resulting phase combinations yielded initial phases for 22 strong reflexions ( $E > 2.25$ ). Tangent refinement with the extended list was then carried out for each of the 16 starting sets (each 5 cycles), two of which showed a higher degree of internal consistency than the others, judging by standard criteria. The two corresponding  $E$ -maps were examined. One of them revealed two six-membered rings with substituents, a total of 14 atoms in reasonable stereochemical relationship! From this point, initial phases for further tangent refinements (extended list) were always taken from calculated  $E$ -values

(short list) based on partial structural information (reflexions were included in the starting set only if  $|E(\text{calc})| > 0.5 E(\text{obs})$ ). The 14-atom model then led to an  $E$ -map showing 28 reasonably related atoms, and repetition of the process to recognition of the entire monensin molecule plus its attached water molecule. The resulting  $R$  value of 0.31 was reduced to 0.08 in a series of least-squares refinements (5 cycles full matrix with isotropic  $B$  values, 1 cycle in 2 blocks with 12 atoms anisotropic, 36 isotropic). In the final cycle 58 H atoms (located from difference synthesis) were included in the structure model.

The above account is incomplete insofar as it passes over several initial approaches based on different  $E$ -lists and starting sets.

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### 113. Vernetzung von Phenolcarbonsäureestern von Polysacchariden durch oxydative phenolische Kupplung

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(2. IV. 71)

*Summary.* Guaran, a watersoluble polysaccharide, was esterified with various phenolic acids. Solutions of these esters formed gels upon oxidation. In these gels the phenolic ester groups were crosslinked by oxidative phenolic coupling, the corresponding dimeric phenolic acids being liberated by saponification.

Wässrige Lösungen von Pentosanen aus Weizenmehl haben die ungewöhnliche Eigenschaft bei Zugabe von Spuren von Oxydationsmitteln ( $\text{H}_2\text{O}_2$ ,  $\text{NaClO}_2$  usw.) zu gelieren [1]. Für diese sog. oxydative Gelierung wurde ihr Gehalt an Ferulasäure [2] verantwortlich gemacht [3]. Eine ähnliche Gelierung ist auch bei der Oxydation gewisser Proteine beobachtet worden [4]. Dabei tritt wahrscheinlich eine oxydative Kupplung der Tyrosinreste benachbarter Peptidketten zu Dimeren (Dityrosin) ein, wodurch eine kovalente Vernetzung der Proteinmolekeln stattfindet [5].

Bereits früher ist versucht worden, die Gelierung der Pentosane in Modellsystemen nachzuahmen, um den Geliermechanismus abklären zu können. Veresterung von Guaran, einem wasserlöslichen Polysaccharid ähnlich den Mehlpentosanen, mit Kaffeesäure führte zu gelierfähigen Produkten [6]. Als Geliermechanismus wurde die