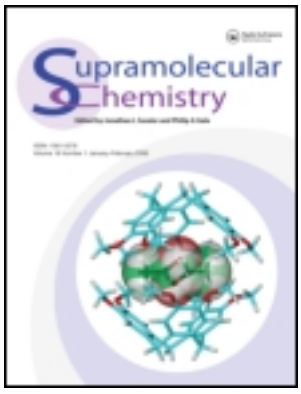

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Reaction of monensin silver salt with methyl iodide: smooth alkylation of a tightly hydrogen-bonded carboxylate

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Reaction of monensin silver salt with methyl iodide: smooth alkylation of a tightly hydrogen-bonded carboxylate

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Despite its structural similarity to the sparingly reactive sodium salt of monensin, the silver salt of monensin was smoothly alkylated with methyl iodide on the carboxyl group to give the methyl ester of monensin.

Keywords: monensin; ionophore; ion selective electrode; esterification; intramolecular hydrogen bond

Introduction

Monensin **1** (Figure 1) is a polyether ionophore that forms lipophilic complexes with metal cations and is capable of controlling the transport of cations across cell membranes (*1*). With these properties, monensin exhibits antibiotic activity and has been used as a coccidiostat for poultry. In the search for more efficient and selective cation-binding substances, the ionophoric properties of monensin derivatives, including esters and amides, have been investigated (*2–12*). The ionophoric properties of monensin esters have been studied in ion-selective electrodes (*13*, *14*), and the methyl ester **2** has been employed in a clinical system for the quantitative analysis of sodium cations in human blood (*15–17*). For this purpose, the methyl ester **2** must be free from contamination by sodium cations.

Monensin **1** is susceptible to direct esterification under acidic conditions. Under neutral to basic conditions, the carboxyl group on monensin must be activated. Unlike O(25)- or O(26)-protected monensins (*10*), however, the carboxyl group of monensin **1** or its sodium salt **4** is only sparingly reactive because its pseudocyclic structure is locked by two intramolecular hydrogen bonds between the carboxyl group and O(25) and O(26) atoms as demonstrated by X-ray crystallographic analyses (Figure 2) (*18–20*). The esterification of monensin has, therefore, been facilitated by disrupting the hydrogen-bond-enforced pseudocyclic complex by generating a naked carboxylate. This can be accomplished by either the combined use of the free acid form of monensin plus bulky organic bases or using the sodium salt of monensin plus stronger ionophores as crown ethers or cryptands to capture the sodium cation. For example, the reaction of monensin **1** with methyl iodide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 4 days at room temperature gave monensin methyl ester **2** in 75% yield (*21*), and the reaction of monensin **1** with methanol in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-pyrrolidinopyridine gave **2** in 88% yield (*22*). Monensin sodium salt **4** was esterified with 1-bromoacetylpyrene in the presence of dicyclohexyl-18-crown-6 in 30.6% yield (*23*), and with benzyl bromide in the presence of cryptand[2.2.2] for 1 day at room temperature in 98% yield (*24*).

In this paper, we report on our findings that the silver salt of monensin **3**, though it has a pseudocyclic structure very similar to that of the sodium salt of monensin **4**, was smoothly alkylated with methyl iodide on the carboxyl group to produce the methyl ester **2** (Scheme 1).

Results and discussion

The silver salt of monensin monohydrate **3** was prepared by the reaction of monensin sodium salt **4** with an aqueous solution of silver nitrate (*24*, *25*). We prepared the silver salt using the reaction of monensin (free acid, monohydrate) **1** and wet silver oxide in order to eliminate contamination by sodium cations. The analytical data were consistent with those previously reported for **3**.

A tetrahydrofuran solution of the monensin silver salt dihydrate **3** (*24*) and an excess amount of methyl iodide were mixed and heated under reflux for 3 h. Powdery crystals of silver iodide, AgI, precipitated out and were filtered off. The filtrate was chromatographed on silica gel to give monensin methyl ester **2** in 66% yield. The structure of the methyl ester, free from complex formation with AgI, was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopies, mass spectrometry and elemental analysis.

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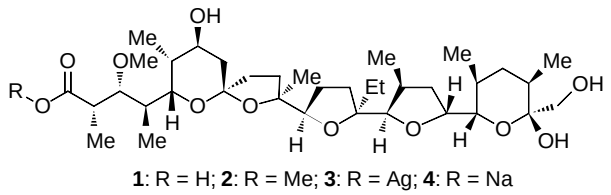


Figure 1. Structural formula of monensin and its derivatives.

The elevated reactivity of the silver salt is rather surprising in view of the following facts implying that monensin binds a silver cation more firmly than a sodium cation. According to an X-ray crystallographic analysis by Pinkerton and Steinrauf (*20*), monensin silver salt has a rigid structure in which a silver cation is confined in a pseudocyclic structure locked by two hydrogen bonds between the terminal carboxylate and O(25) and O(26) (Figure 2). This structure is very similar to that of the sparingly reactive sodium salt (*18*), and moreover, the formation constant for the silver salt **3** (log $K_f = 8.2 \pm 0.2$) (*26*) is larger by more than two orders of magnitude than that of the sodium salt **4** (log $K_f = 6.7 \pm 0.05$) (*26*). The low solubility of AgI most likely drove the esterification to completion by enhancing the irreversibility of the reaction.

The reaction of a silver salt of an acid with an alkyl halide is used infrequently for the preparation of simple aliphatic esters, but is sometimes valuable in making esters from acids that are unstable towards direct esterification (*27*). This is also the case for monensin, which is susceptible to esterification under acidic conditions (*1*). Silver iodide, a by-product, is recyclable and free from disposal problems owing to the established recycling system for silver halides in the photographic industry. In addition, this transformation has an advantage in preparing the methyl ester for sodium-cation selective electrodes because the use of the silver salt eliminates contamination by sodium cations.

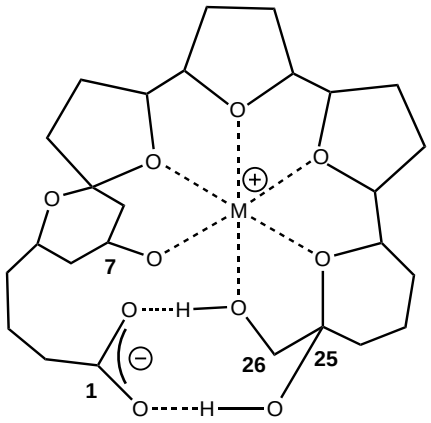


Figure 2. Schematic illustration of the pseudocyclic structure for a metal salt of monensin.

Conclusions

We have found that the silver salt of monensin, in contrast to the sparingly reactive sodium salt of monensin, was smoothly alkylated with methyl iodide on the carboxyl group to give the methyl ester of monensin. Although the yield (66%) was lower than those of previously reported reactions of monensin **1** with methyl iodide and DBU (75%) (*21*) or with methanol and DCC (88%) (*22*), this silver salt method nevertheless has practical advantages as follows: (1) short reaction time (3 h vs. 4 days); (2) simple work-up (AgI, the only non-volatile by-product, was easily removed by filtration); (3) the stable precursor, the silver salt of monensin **3**, was storable for a longer period than the free acid **1** and (4) recyclable by-product, AgI (as useful elements, silver and iodine). In view of the presumed reaction mechanism, this silver salt method is potentially applicable to other ionophoric carboxylic acids with monensin-like structures, including nigericin and salinomycin and alkyl iodides other than methyl iodide may be well employed.

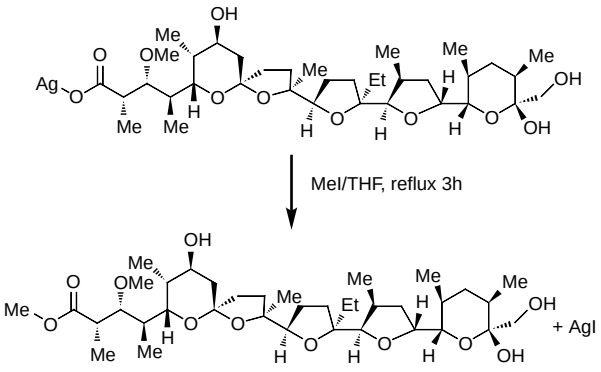
Experimental

General

Melting points were uncorrected. ^{13}C and ^{1}H NMR spectra were recorded on Bruker WH-90 and Varian EM-390 spectrometers, respectively. Mass spectra were measured with a JEOL JMS-01SG spectrometer, and IR spectra were obtained with a JASCO IR-S grating double-beam spectrophotometer.

Materials

Monensin sodium salt (Carbiochem, **4**) was purchased and used without further purification. Methyl iodide (Wako Pure Chemical Industries, Osaka, Japan) was



Scheme 1. Reaction of monensin silver salt with methyl iodide.

passed through a short column of Al_2O_3 before use. Silver oxide was prepared according to a reported procedure (*28*). Monensin monohydrate **1** was prepared from the corresponding sodium salt as described previously (*29*): Milky white crystals, mp 113–116°C [117–122°C (*29*)]; IR (Nujol): 3540, 3330 and 1705 cm^{-1}.

Preparation of monensin silver salt dihydrate 3

To a solution of monensin monohydrate (**1**, 7 g, 10.2 mmol) in 30 ml of tetrahydrofuran were added 3 ml of water and 5 g (21.6 mmol) of Ag_2O. The mixture was stirred for 2 h at room temperature. The insoluble portion was filtered off and the solvent was removed below 40°C under reduced pressure. The residue was dissolved in 270 ml of acetone. After the insoluble portion was removed by elution through a short column packed with cellulose powder, water (120 ml) was added dropwise with vigorous stirring. The resulting crystals were collected on a suction funnel, rinsed with 50 ml of acetone–water (1:1 by volume) and dried under reduced pressure to give monensin silver salt dihydrate **3** as milky white crystals in 88.9% yield (13.3 g). Mp 183°C (dec.); IR (Nujol): 1550 cm^{-1}; *m/z* (FD) 779; ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 8.31, 10.59, 11.18, 14.62, 16.11, 16.76, 16.89, 27.36, 27.88, 30.00, 30.86, 32.22, 33.07 (2C), 33.66, 34.70, 34.96, 36.06, 36.71, 37.43, 39.51, 44.96, 57.96, 64,91, 68.42, 71.48, 76.28, 83.04, 85.38, 86.55, 87.59, 97.66, 108.19, 181.81; Anal. calcd for $C_{36}H_{61}AgO_{11}$ $2H_2O$: C 53.13, H 8.05; Found: C 52.95, H 8.04%.

Preparation of monensin methyl ester 2

Monensin silver salt dihydrate (**3**, 4.5 g, 5.5 mmol), tetrahydrofuran (2 ml) and methyl iodide (15 ml) were mixed and heated under reflux for 3 h. The reaction mixture was cooled to room temperature, the resulting precipitates of AgI were filtered off and at below 40°C the solvent was removed under reduced pressure to give almost pure methyl ester of monensin, which was chromatographed (silica gel, benzene–ethyl acetate 1:1 by volume) and the solvent removed below 40°C under reduced pressure. The residue was dried under reduced pressure for 20 h to give 2.5 g (66%) of monensin methyl ester **2** as a colourless foamy solid. Mp *ca.* 35°C [Huczyński et al. reported that **2** was an oil. (*21*)]; *m/z* (FD) 684; IR (Nujol): 1740 cm^{-1}; IR ($CHCl_3$): 3425, 3279, 1721 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 3.71 (CO_2CH_3) (*20*); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 8.06, 11.11, 12.22(2C), 15.72, 16.18, 17.41, 25.80, 27.94, 29.70, 31.19, 32.49, 32.94, 33.66, 34.50, 34.89, 35.21, 36.06, 36.91, 37.17, 39.12, 40.94, 58.29, 67.45, 68.10, 71.41, 76.28, 76.74, 81.74, 83.69, 85.77, 86.36, 87.27, 97.14, 107.80, 176.16; $[\alpha]_D = 51°$ (AcOEt); Anal. calcd. for $C_{37}H_{64}O_{11}$: C 64.89, H 9.42; Found: C 65.16, H 9.51%.

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