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# TRIS(3-METHOXYPROPYL)TIN AMINOBENZOATES AS POTENTIALLY TRYPANOCIDAL AGENT

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*A set of tris(3-methoxypropyl)tin aminobenzoates and N-(4,6-diamino-1,3,5-triazin-2-yl-)aminobenzoates as compounds with potential trypanocidal activity have been prepared and their solubility in water was determined. On the basis of their $^{13}C$ and $^{119}Sn$ NMR spectra and IR spectra, bonding relations in these esters are discussed and a model of the trigonal-bipyramidal coordination polyhedra around central tin atom is proposed.*

## Introduction

Organotin(IV) compounds show important biological activities [1], especially cancerostatic and fungicidal. These biological activities were thoroughly studied especially with butyltin(IV) compounds, with regard to their low toxicity for

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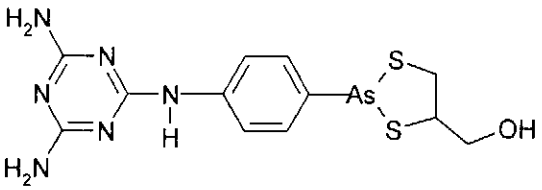
mammals [2]. Their application is often hampered by their hydrophobicity and thus low solubility in the hydrophilic biological media. Various researchers tried different ways to increase their hydrophilicity, especially by introducing polar centres into organic substituents bonded to tin atom. Thus, Susperregui *et al.* [3] prepared (3-(2-methoxy)ethoxypropyl) tin(IV) compounds with an increased solubility in water. Inspired by this, we have prepared in our laboratory similar 3-methoxypropyl-tin(IV) compounds [4]. These compounds were substantially more soluble than their butyl analogues, but their cancerostatic and fungicidal activity was surprisingly lower. Nevertheless, some of these compounds showed an interesting *in vitro* trypanocidal activity against the *Trypanosoma,* causing the human sleeping sickness, especially tris(3-methoxypropyl)tin(IV) chloride, similar to that of (3-(2-methoxy)ethoxy-propyl)tin chlorides [5–8]. The human sleeping sickness is widely common in sub-Saharan countries and for the medical treatment of second stage of this illness arsenic medicaments of the Arsobal type are mostly applied [3] (see structural formula).




These medicaments are relatively cheap, but highly toxic and thus death rate due to intoxication exceeds 5%. Therefore their replacement by less toxic medicaments is highly topical.

Although the mechanism of trypanocidal activity of organotin(IV) compounds is not known yet, we suppose that it will be similar to that of the arsenic-containing medicaments. Their activity consists in the blocking of cellular protective agent trypanothione (tripeptide with active -SH groups, bonded to the molecule of spermidine) by the formation of an inert compound with arsenic. With regard to the known thiophilicity of organotin(IV) compounds we assume that the formation of a similar inert compound of trypanothione with organotin compounds is highly probable.

The aim of this study was the preparation of 3-methoxypropyltin(IV) compounds having as far as possible similar structure as Arsobale, but without Sn–S bonds. A paper [6] examined the compounds based on (3-(2-methoxy)-ethoxypropyltin(IV) compounds having Sn–S bonds instead of As–S bonds, but their *in vivo* trypanocidal effect was mostly substantially weaker. Therefore, we proposed and realized the preparation of organotin(IV) esters of substituted benzoic acids of the type

$$X\text{-}C_6H_4COO\text{-}Sn(CH_2CH_2CH_2OCH_3)_3$$

where X = 2-$NH_2$ (*I*), 3-$NH_2$ (*II*), 4-$NH_2$ (*III*),
2-$(C_3N_3(NH_2)_2)NH$ (*IV*), 3-$(C_3N_3(NH_2)_2)NH$ (*V*),
4-$(C_3N_3(NH_2)_2)NH$ (*VI*)
where $C_3N_3(NH_2)_2$ = 4,6-diamino-1,3,5-triazin-2-yl-

The preparation of all these compounds has not been reported yet.

## Experimental

Preparation

Compounds *I–VI* were prepared either by converting sodium salt of the corresponding substituted benzoic acids with tris(3-methoxypropyl)stannic chloride in ethanol or better by the reaction of the substituted benzoic acids with tris(3-methoxypropyl)stannyl oxide in boiling toluene solution. The starting oxide was prepared by the reaction of tris(3-methoxypropyl)stannyl chloride with a surplus of the strong base

$$2X\text{-}C_6H_4COOH + (Mep_3Sn)_2O \rightarrow 2X\text{-}C_6H_4COO\text{-}Sn(Mep)_3 + H_2O$$

Where Mep = $CH_3OCH_2CH_2CH_2$-

*Example of the synthesis: Preparation of tris(3-methoxypropyl)tin 2-((4,6-diamino-1,3,5-triazin-2-yl)amino)benzoate (IV).*
Into a reaction flask with a reflux condenser connected with an azeotropic adapter, 0.30 g 2-((4,6-diamino-1,3,5-triazin-2-yl)amino)benzoic acid (1.22 mmol), 0.43 g tris(3-methoxypropyl)stannyl oxide (0.62 mmole) and 30 ml toluene were introduced. The reaction mixture was refluxed for 6 hr and then stirred for another 2 hr. The raw product obtained by the evaporation of toluene was recrystallized from a mixture of chloroform/pentane. This procedure gave 0.35 g of the white microcrystalline product (yield of 48 %) with the m.p. 102 – 103 °C.

Results of elemental analysis of compounds *I – VI* are given in Table I.

Table I Basic physical data and solubility in water of compounds *I* – *VI*

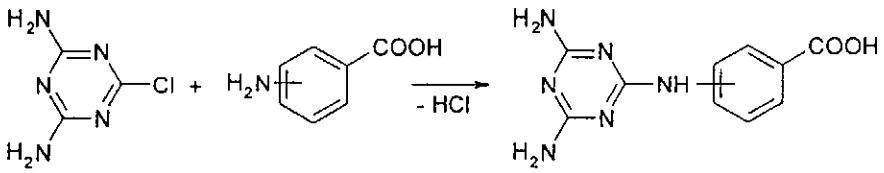
| Compound[a] No. | Elemental analysis[b] (found), % | | | | m.p., °C | solubility[c], g $l^{-1}$ |
|---|---|---|---|---|---|---|
| | C | H | N | ash | | |
| *I* | 48.33 | 6.79 | 2.49 | 26.48 | 26 – 29 | 0.26 |
| *II* | 48.40 | 7.29 | 2.73 | 27.12 | 31 – 33 | 0.25 |
| *III* | 48.36 | 6.81 | 2.55 | 28.16 | 35 – 37 | 0.31 |
| *IV* | 45.48 | 6.45 | 13.58 | 23.94 | 102 – 103 | 0.09 |
| *V* | 45.16 | 6.38 | 13.88 | 24.18 | 150 – 152 | 0.06 |
| *VI* | 45.13 | 6.37 | 13.73 | 24.65 | 146 – 148 | 0.22 |

[a]empirical formulas: comp. *I* – *III* $C_{19}H_{33}NO_5Sn$; comp. *IV* – *VI* $C_{22}H_{36}N_6O_5Sn$
[b]elemental analysis (calculated): comp *I* – *III* C: 48.13; H: 7.01; N: 2.95
comp. IV – VI C: 45.30; H: 6.22; N: 14.41
[c]recalculated from Sn-content in the saturated aqueous solution, determined by ICP/OES [7]

## Preparation of Starting Compounds

Tris(3-methoxypropyl)tin chloride was prepared according to the procedure described in paper [5] by the Kotchetchkov synproportional reaction from tetrakis(3-methoxypropyl) stannane and tin(IV) chloride at 220 °C.

The *N*-substituted aminobenzoic acids were prepared by the reaction of 2-chloro-4,6-diamino-1,3,5-triazine with the corresponding aminobenzoic acid according to paper [9]




The necessary 2-chloro-4,6-diamino-1,3,5-triazine was prepared from cyanuric chloride and ammonia according to [10].

## NMR Spectra

$^1H$, $^{13}C$ and $^{119}Sn$ NMR spectra of the studied compounds were measured at 360.13, 90.56 and 134.28 MHz, respectively, on a Bruker AMX 360 spectrometer,

using a 5 mm tuneable broad band probe in solutions of $CDCl_3$ and $(CD_3)_2SO$ at 300 K. The chemical shifts are given with respect to [TMS $\delta(^1H)$(HMDS) = 0.05 ppm; $\delta(^{13}C)(CDCl_3)$ = 77.00 ppm, $\delta(^{13}C)((CD_3)_2SO$ = 39.60 ppm] and $(CH_3)_4Sn$ [$\delta(^{119}Sn)$ = 0.00 ppm for $\nu(^{119}Sn)$ = 37.2906174 MHz] [11].

$^{13}C$ resonances were assigned on the basis of the value of $^nJ(^{119}Sn, ^{13}C)$ coupling constants and the standard $^{13}C$-APT techniques used in agreement with [12]. The $^1H$ resonances were assigned by means of expected spectral patterns, integral intensities and chemical shifts of non-bonded substituents [13].

The basic parameters of $^{13}C$ and $^{119}Sn$ NMR spectra of compounds *I–VI* are collected in Table II and $^1H$ NMR spectra in Table III. Numbering of carbon/hydrogen atoms is shown in scheme

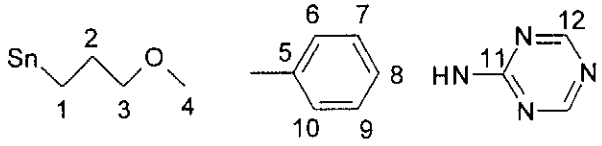



Table II $^{13}C$ and $^{119}Sn$ parameters of NMR spectra of compounds *I – VI*

| Comp. No. | $\delta(^{119}Sn)$, ppm | $\delta(^{13}C)/^nJ(^{119}Sn, ^{13}C)$, ppm/Hz | | | | $\delta(^{13}C)$, ppm other carbons | $\delta(^{13}C)$ COO, ppm |
|---|---|---|---|---|---|---|---|
| | | C1 | C2 | C3 | C4 | | |
| *I* | 14.74[a] | 12.76<br>444.8 | 25.64<br>25.4 | 75.01 | 58.47 | 114.69/C5, 149.86/C6, 132.60/C7, 132.49/C7, 116.20/C9, 115.89/C10 | 172.85 |
| *II* | 16.57[a] | 12.94<br>454.3 | 25.89<br>24.9 | 75.27 | 58.77 | 134.89/C5, 120.45/C6, 146.25/C7, 128.98/C8, 118.22/C9, 116.55/C10 | 171.61 |
| *III* | 14.29[a] | 12.65<br>454.3 | 25.73<br>25.1 | 75.09 | 58.49 | 123.30/C5, 113.72/C6, 131.87/C7, 149.88/C8. 131.87/C9, 113.72/C10 | 171.70 |
| *IV* | | 13.65 | 25.38 | 74.66 | 58.01 | 117.74/C5, 142.79/C6, 119.39/C7 132.55/C8, 119.71/C9, 131.76/C10, | 171.79 |
| | −3.31[b] | 474.4 | 25.91 | | | 164.65/C11, 167.30/C12 | |
| *V* | 16.71[a] | 15.57 | 25.49 | 75.12 | 57.99 | 135.51/C5, 140.36C6, 150.75/C7, 128.41/C8, 121.01/C9, 122.74/C10, | 170.08 |
| | 2.95[b] | 462.3 | 25.54 | | | 164.98/C11, 167.23/C12 | |
| *VI* | | 13.22 | 25.38 | 74.60 | 58.02 | 126.10/C5, 130.11/C6, 118.29/C7, 143.94/C8, 128.29/C9, 130.11/C10, | 170.0 |
| | −1.23[b] | 462.8 | | | | 164.80/C11, 167.18/C12 | |

[a]measured in $CDCl_3$, [b]measured in $(CD_3)_2SO$

Table III $^1$H parameters of NMR spectra of compounds *I – VI*

| No. | $^1$H |
|---|---|
| | ppm (multiplicity, intensity, marking) |
| *I* | 1.25(t, 6H, H1); 1.96(m, 6H, H2); 3.33(s, 9H, H4); 3.39(t, 6H, H3); 5.73(s, 2H, $NH_2$); 6.58(t, 1H, H9), 6.61(d, 1H, H10); 7.17(t, 1H, H8); 7.90(d, 1H, H7) |
| *II* | 1.27(t, 6H, H1); 1.97(m, 6H, H2); 3.35(s, 9H, H4); 3.40(t, 6H, H3); 3.69(s, 2H, $NH_2$); 6.79(t, 1H, H10); 7.16(d, 1H, H9); 7.37(s, 1H, H6); 7.43(d, 1H, H8) |
| *III* | 1.24(t, 6H, H1); 1.95(m, 6H, H2); 3.33(s, 9H, H4); 3.38(t, 6H, H3); 3.94(s, 2H, $NH_2$); 6.59(d, 2H, H6); 7.83(d, 2H, H7) |
| *IV* | 1.12(t, 6H, H1); 1.83(m, 6H, H2); 3.20(s, 9H, H4); 3.55(t, 6H, H3); 6.49(s, 4H, $NH_2$); 6.89(t, 1H, H9); 7.38(t, 1H, H8); 7.95(d, 1H, H10); 8.95(d, 1H, H7);11.25(s,1H, NH) |
| *V* | 1.19(t, 6H, H1); 1.91(m, 6H, H2); 3.28(s, 9H, H4); 3.36(t, 6H, H3); 6.35(s, 4H, $NH_2$); 7.31(t, 1H, H9); 7.49(d, 1H, H10); 8.01(d, 1H, H8); 8.25(s, 1H, H6); 11.29(s,1H, NH) |
| *VI* | 1.12(t, 6H, H1); 1.83(m, 6H, H2); 3.21(s, 9H, H4); 3.30(t, 6H, H3); 6.54(s, 4H, $NH_2$); 7.74(d, 2H, H6); 7.83(d, 2H, H7); 11.30(s,1H, NH) |

Table IV Structurally important absorptions in the IR spectra of compounds *I – VI*

| No. | State | ν(COO), $cm^{-1}$ | | | $\nu_{as}$(COC), $cm^{-1}$ |
|---|---|---|---|---|---|
| | | $\nu_{as}$(COO) | $\nu_s$(COO) | Δν(COO)[d] | |
| *I* | c[a] | 1618 | 1355 | 263 | 1102 |
| | n[b] | 1630 | 1356 | 274 | 1114, 1104 |
| *II* | c | 1624 | 1355 | 269 | 1097 |
| | n | 1629 | 1354 | 275 | 1114, 1098 |
| *III* | c | 1616 | 1349 | 267 | 1103 |
| | n | 1610 | 1337 | 273 | 1117, 1107 |
| *IV* | c | 1605 | 1355 | 250 | 1100 |
| | s[c] | 1609 | 1351 | 258 | 1112, 1089 |
| *V* | c | 1600 | 1343 | 257 | 1098 |
| | s | 1605 | 1344 | 261 | 1111, 1088 |
| *VI* | c | 1614 | 1349 | 265 | 1103 |
| | s | 1618 | 1343 | 275 | 1110, 1100 |

[a]solution in $CHCl_3$; [b]neat; [c]susp. in parafin oil; [d]$\Delta\nu(COO) = \nu_{as}(COO) - \nu_s(COO)$

IR Spectra

The IR spectra of the studied compounds were measured on a Perkin-Elmer 684 instrument as neat liquids, paraffin mulls and solutions in $CHCl_3$ in the region of 4000 – 350 $cm^{-1}$. The values of the structurally significant absorptions are collected in Table IV.

## Discussion

By the procedures described above, six new substituted tris(3-methoxypropyl)tin benzoates were prepared and characterized, which should be briefly commented. Esters *IV – VI* can be prepared either by linking the 4,6-diamino-1,3,5-triazin-2-yl group to the nitrogen atom of ester *I – III*, or by starting with the preparation of N-(4,6-diamino-1,3,5-triazin-2-yl)aminobenzoic acids followed by their esterification with the corresponding organotin(IV) compound. From the stand point of the yield, the first route would be more advantageous. However, during the substitution of esters *I – III* they are decomposed, and so is the tris(3-methoxypropyl)tin(IV) group. Therefore it is necessary to use the second route.

NMR Spectra

The chemical shift $\delta(^{119}Sn)$ of the prepared esters in chloroform solutions lies in a relatively narrow range from 16.54 ppm to 14.29 ppm and in dimethylsulfoxide solutions from 2.95 ppm to –3.31 ppm. The upfield shift of the signals in the dimethylsulfoxide is about 15 ppm (see ester *V*, where the shift was determined in both solutions), which is probably due to the weak coordination of the central tin atom by the solvent molecule. All the measured values of $\delta(^{119}Sn)$ lie within the interval characteristic of the five-coordinated tin atom in comparable tributyltin(IV) compounds [14]. For the evaluation of the shape of tin coordination polyhedron it is especially necessary to take into account the values of the chemical shift $\delta(^{13}C)$ of the carbon in the carboxyl group and the interaction constant $^1J(^{119}Sn, ^{13}C)$. The value of this interaction constant reflects, in a first approximation, the electron density at the C1 carbon atom of the tin alkyl substituents and correlates with the angle of C–Sn–C [13]. In the studied esters this interaction constant lies within a narrow range of 444.8 – 474.4 Hz, which corresponds to the C–Sn–C angle within the range of 119° – 122°.

The value of the chemical shift $\delta(^{13}C)$ of carbon in the carboxyl group of the studied esters was found within the range of 170.0 – 172.85 ppm. The magnitude of this shift reflects the bonding ability of this carboxyl group. The ethyl ester of benzoic acid (with $\delta(^{13}C)$(COO) equal to 166.8 ppm) is an example

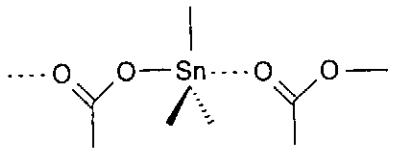
of monodentate carboxyl group, whereas sodium benzoate (with $\delta(^{13}C)(COO)$ equal to 175.5 ppm) can represent an example of bidentate carboxyl group. It is obvious that the values of the chemical shift $\delta(^{13}C)$ of the studied esters (170.0 – 172.85 ppm) lie close to the middle of the above-mentioned range. Therefore, it is necessary to characterize the carboxyl group as anisobidentate [14], which means an intermediate ordering between monodentate and bidentate carboxyl group. The chemical bonding of such a group is represented by one strong and one weak Sn–O bond, while the NMR spectrum detects a dynamic equilibrium of both these bonds.

IR Spectra

The character of bonding of the carboxyl group can be evaluated with a high probability from the value of the stretching vibration of carboxyl group ν(COO), i.e. from the difference between the positions of asymmetric and symmetric vibrations of this group $\Delta\nu(COO) = \nu_{as}(COO) - \nu_{s}(COO)$ [17]. Organic esters of carboxylic acids with monodentate-type carboxyl ligand possess the values of $\Delta\nu(COO)$ over 400 $cm^{-1}$. Typically monodentately bonded stannyl esters with more polar COO-Sn bond exhibit the values around 350 $cm^{-1}$ [16]. On the other hand, carboxylates with the bidentate bonding type, like silver benzoate, show the values of $\Delta\nu(COO)$ around 150 $cm^{-1}$. The prepared esters *I* – *VI* exhibit the values of $\Delta\nu(COO) = 250-275$ $cm^{-1}$, i.e. much lower than those of monodentate carboxyl groups, but substantially higher than those of bidentate COO ligands. Therefore it is necessary in this case to take the bonding of carboxyl group as anisobidentate. Because practically similar values of $\Delta\nu$ were observed both for their solutions in chloroform and for the esters in solid state or as a neat liquid (melt), it is possible to assume that the carboxyl ligand has an anisobidentate character both in the chlororm solution and in the pure state.

It is necessary to mention also the values of antisymmetric stretching vibrations of the ether group in 3-methoxypropyl substituents of the tin atom $\nu_{as}(COC)$. In the compounds of $Mep_2SnCl_2$ and $MepSnCl_3$ it was observed that in the solid state there is a strong interaction between the oxygen atom of the ether group and the central tin atom [8]. This interaction could result in a decrease in the value of $\nu_{as}(COC)$. Such a shift was observed in the IR spectra of the above-mentioned compounds [7]. In the esters of *I* – *VI* in chloroform solutions, we have observed only one band of $\nu_{as}(COC)$ at ~1100 $cm^{-1}$, at the samples measured in the melt or in the solid state we observed two close bands with the difference in their positions of 10 – 23 $cm^{-1}$. A possible reason for this effect can be the interaction of etheric oxygen atom of the substituent with central tin atom in the neat state, which competes with the interaction of the weakly bonded oxygen atom of the carboxyl group.

Therefore we can conclude that in chloroform solutions and evidently also in the neat state of the studied organotin(IV) esters the coordination polyhedron of the central tin atom has a shape of the trigonal bipyramide with three carbon atoms of methoxypropyl groups in the equatorial plane and with oxygen atoms of the carboxyl groups in the apical positions.



Solubility

The determination of solubility of the prepared organotin(IV) esters showed that the solubility of aminobenzoates *I – III* is lower than the solubility of the analogous chloride by about one order. The solubility of *N*-substituted aminobenzoates *IV – VI* is still lower, but it is sufficiently high for biological testing.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