STUDIES ON THE SYNTHESIS OF HETEROCYCLIC COMPOUND.XII. PREPARATION OF NEW SULFUR-CONTAINING MACROCYCLES

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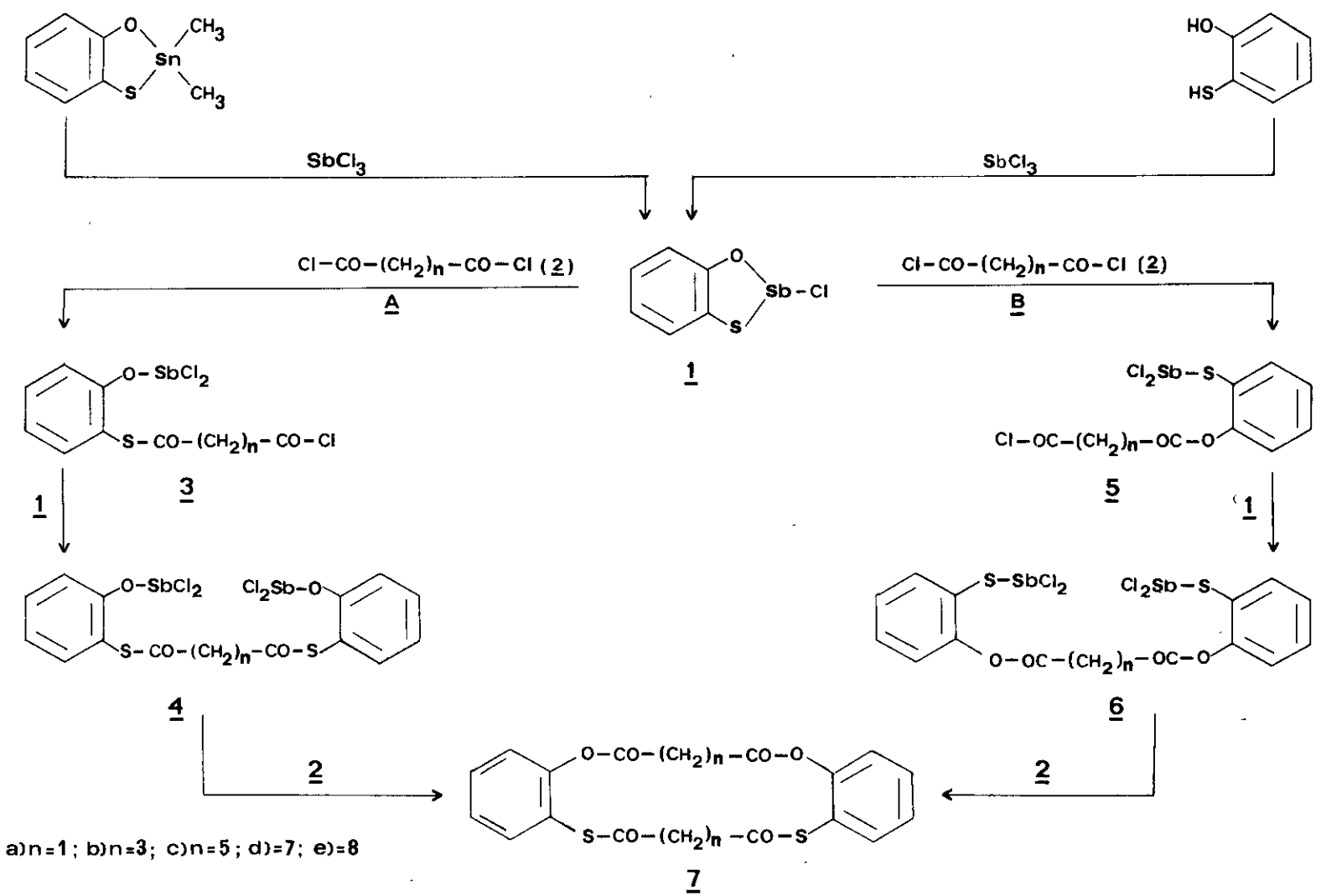
Abstract - A new series of macrocyclic sulfur-containing compounds have been prepared by treating 2-chloro-1,3,2-benzoxathiastibole with various diacyl chlorides.

In a previous paper[1] we have reported a new general method for the synthesis of macrocyclic tetraester compounds of catechol.
The reaction was effected by treating 2-chloro-1,3,2-benzodioxastibole with diacyl chlorides and it always occurred with the cleavage of the O-Sb-O bonds to give the exclusive formation of dimeric derivatives. The yields strongly depend on the ring size. Some macrocyclic polyether sulfides have been synthesized and some of their properties have been reported by Pedersen[2]. The synthesis of various macrocyclic sulfides has recently been reviewed by Brandshaw and Hui[3]. Brandshaw and his co-workers have prepared a series of macrocyclic ether-esters, thioether-esters and ether-thiolesters by treating various oligo-ethylene glycols and sulfur-containing oligo-ethylene glycols with diacyl chlorides[4]. The yields with thiol derivatives are always low even for longer reaction time. The present work extends our research on macrocycles and is intended to introduce a new method for the preparation of 2-hydroxythiophenol macrocyclic derivatives. Among various substrates containing the group O-M-S (M = Sn, P, As, Sb) previously synthesized[5], we have preferred 2-chloro-1,3,2-benzoxathiastibole 1 because the O-Sb-S bonds cleave more easily and therefore, the reaction times for the macrocyclic syntheses are remarkably shorter. In fact, the reactivity of compound 1 was affected both by the different electronic nature of both O and S atoms and by the chemical properties of M.

Scheme


SbCl3
SbCl3
Cl–CO–(CH2)n–CO–Cl (2)
A
Cl–CO–(CH2)n–CO–Cl (2)
B
1
1
1
2
2
3
4
5
6
7
a)n=1 ; b)n=3; c)n=5 ; d)=7; e)=8

We have also observed that this new method affords, analogously to the macrocyclic tetraesters of catechol[1], an increase in the yields and have established that it could be an alternative and advantageous preparation of macrocyclic sulfur-containing derivatives. 2-Chloro-1,3,2-benzoxathiastibole 1, obtained by treating 2-hydroxythiophenol or 2,2-dimethyl-1,3,2-benzoxathiastannole with antimony trichloride[5], is an excellent cyclic intermediate for the synthesis of some macrocyclic sulfur-containing derivatives. The reaction of 1 with diacyl chlorides 2 could probably occur in one of two possible paths represented by the Scheme. In fact, the strengths of Sb-O and Sb-S chemical bonds (93 and 90 Kcal/mole respectively)[6,7] have very similar values but are not such to foresee that the reaction could occur only via A. By means of the bond angles C-O-Sb > C-S-Sb in compound 1 it is possible to foresee a preferential cleavage of Sb-S , but this does not exclude the Sb-O cleavage.

Thus, the reaction should begin with the Sb-S bond cleavage (path A) to provide 3, which subsequently reacts with another molecule of 1 to give the intermediate 4. Analogously the initial cleavage of Sb-O bond would give the intermediate 6 (path B). Both intermediates 4 and 6 then lead to the formation of 7. By treating 1 (2.5 mmoles) with glutaroyl chloride 2b (1 mmoles), followed by hydrolysis with water for 10 min, the compound 7b and other two products not yet known were separated by chromatography from the reaction mixture which exhibits the characteristic bands of the OH and SH groups in the infrared spectra[8]. All compounds have been determined by their analytical and spectroscopic data which were in agreement with the proposed structures.

The ir spectra of all compounds exhibit the characteristic bands due to the O-C=O and S-C=O groups at 1760-1770 and 1710-1720 cm^{-1}, respectively. The nmr spectra exhibit three groups of signals. The aromatic portion for all compounds showed the expected peaks at 7.76-7.08 δ . For the compound 7a, the S-CO-$\underline{CH_2}$ and O-CO-$\underline{CH_2}$ groups exhibit nmr peaks at 4.16 δ and 4.04 δ as singlets respectively, and are shifted to lower fields, probably owing to the effect of two adjacent carbonyl groups.

Instead, the compounds 7b-e exhibit two superposed triplets at 2.54-2.56 δ (S-CO-$\underline{CH_2}$) and 2.63-2.73 δ (O-CO-$\underline{CH_2}$) and multiplet due to inner methylene groups at 1.17-2.34 δ . The mass spectra were most useful and have also showed the for-

mation of dimeric sulfur-containing derivatives as has been observed in the case of the macrocyclic derivatives of catechol[9].

All compounds exhibit a very low molecular ion peak and a very diagnostic peak is located at ($M^{+\cdot}/2 + 1$) and fragment peaks normally associated with the derivatives of 2-hydroxythiophenol appear in all spectra[10].

Experiments on the application of this method to the synthesis of new macrocyclic compounds and a spectrometric mass study on the mechanistic aspects of fragmentations of corresponding compounds 7 are under current investigation.

EXPERIMENTAL

All melting points were taken on an electrothermal capillary melting point apparatus and are uncorrected; ir spectra were recorded in potassium bromide pellets with a Perkin-Elmer 157G spectrophotometer; nmr spectra were determined with a Varian EM 360L spectrometer (TMS as internal reference). Mass spectra were run on a VGZAB-2F instrument operating at 70 eV. Microanalyses for CHNS were carried out on a Carlo Erba model 1106 Elemental Analyzer.

2-Hydroxythiophenol, 2,2-dimethyl-1,3,2-benzoxathiastannole, 2-chloro-1,3,2-benzoxathiastibole 1, azelaoyl chloride 2c and pimeloyl chloride 2d.

The preparation of these was carried out according to the literature procedures[5,11,12].

General method for the preparation of compounds 7.

To a rapidly stirred hot solution of 1 (5.3 mmoles) and dry benzene (25 ml), a solution of 2 (7.1 mmoles) in benzene (5 ml) was added dropwise. The heterogeneous reaction mixture was subsequently heated under reflux for an appropriate time, i.e., until the mixture had become completely homogeneous (15 min.). The benzene was then removed using a rotary evaporator to give a residue which was purified by column chromatography on silica gel using benzene-ethyl acetate (5:1) as eluent and recrystallized from methylene chloride-pentane.

7,16-Dihydrodibenzo[b,i][1,5]dioxa[8,12]dithia-cyclotetradecin-6,8,15,17-tetraone (7a). This compound was recrystallized from methylene chloride-pentane

(yield 27%), mp 186-188°C; ir : 2930, 2860,1760, 1710,1590, 1470,1450,1380, 1260, 1200, 1130, 1070, 1030, 910, 760 cm^{-1}; nmr (DMSO-d_6): 4.04 (s, 2H, OCO$\underline{CH_2}$), 4.16 (s, 2H, SCO$\underline{CH_2}$), 7.10-7.76 (m, 8H, 2xC_6H_4) δ ; ms M^+ = 388; Anal.Calcd for $C_{18}H_{12}O_6S_2$: C, 55.68; H, 3.12; S, 16.48; Found : C, 55.79; H, 3.22; S, 16.32.

8,9,19,20-Tetrahydro-7H,18H-dibenzo [b,k] [1,7] dioxa[10,16]dithia-cyclooctadecin-6,10,17,21-tetraone (7b). This compound was recrystallized from methylene chloride-pentane (yield 22%), mp 216-218°C; ir : 2980, 2930, 2870, 1770, 1710, 1580, 1470, 1430, 1380, 1260, 1200, 1140, 1070, 1030, 940, 750 cm^{-1}; nmr (DMSO-d_6) : 1.99-2.34 (m, 4H, 2xCH_2), 2.69 (t, 4H, 2xOCO$\underline{CH_2}$), 2.73 (t, 4H, 2xSCO$\underline{CH_2}$), 7.04-7.59 (m, 8H, 2xC_6H_4) δ ; ms M^+ = 444; Anal.Calcd for $C_{22}H_{20}O_6S_2$: C, 59.46; H, 4.54; S, 14.41; Found : C, 59.56; H, 4.51; S, 14.28.

8,9,10,11,21,22,23,24-Octahydro-7H,20H-dibenzo[b,m][1,9] dioxa[12,20]dithia-cyclodocosin-6,12,19,25-tetraone (7c). This compound was recrystallized from methylene chloride-pentane (yield 38%), mp 175-177°C; ir : 2920, 2860, 1770, 1720, 1590, 1470, 1440, 1370, 1260, 1200, 1130, 1070, 1030, 950, 750 cm^{-1}; nmr ($CDCl_3$) : 1.38-2.06 (m, 12H, 6x$\underline{CH_2}$), 2.56 (t, 4H, 2xOCO$\underline{CH_2}$), 2.73 (t, 4H, 2xSCO$\underline{CH_2}$), 7.09-7.60 (m, 8H, 2xC_6H_4) δ ; ms M^+ = 500; Anal.Calcd for $C_{26}H_{28}O_6S_2$: C, 62.39; H, 5.64; S, 12.80; Found : C, 62.41; H, 5.68; S, 12.63.

8,9,10,11,12,13,23,24,25,26,27,28-Dodecahydro-7H,22H-dibenzo [b,o][1,11]dioxa [14,24]-dithia-cyclohexacosin-6,14,21,29-tetraone (7d). This compound was recrystallized from methylene chloride-pentane (yield 40%), mp 134-136°C; ir : 2970, 2880, 1760, 1720, 1590, 1470, 1450, 1380, 1300, 1270, 1200, 1120, 1070, 1020, 950, 760 cm^{-1}; nmr ($CDCl_3$) : 1.23-2.02 (m, 20H, 10x$\underline{CH_2}$), 2.54 (t, 4H, 2xOCO$\underline{CH_2}$), 2.63 (t, 4H, 2xSCO$\underline{CH_2}$), 7.08-7.62 (m, 8H, 2xC_6H_4) δ ; ms M^+ = 556; Anal.Calcd for $C_{30}H_{36}O_6S_2$: C, 64.73; H, 6.52; S, 11.51; Found : C, 64.68; H, 6.48; S, 11.33.

8,9,10,11,12,13,14,24,25,26,27,28,29,30-Tetradecahydro-7H,23H-dibenzo [b,p][1,12]-dioxa[15,26] dithia-cyclooctacosin-6,15,22,31-tetraone (7e). After chromatography a very viscous liquid was obtained (yield 30%); ir : 2940, 2860, 1770, 1710, 1590, 1470, 1450, 1370, 1290, 1270, 1200, 1120, 1070, 1030, 950, 760 cm^{-1} ; nmr ($CDCl_3$) : 1.17-2.03 (m, 24H, 12x$\underline{CH_2}$), 2.55 (t, 4H, 2xOCO$\underline{CH_2}$), 2.65 (m, 4H, 2xSCO$\underline{CH_2}$), 7.14-7.77 (m, 8H, 2xC_6H_4) δ ; ms M^+ = 584; Anal.Calcd for $C_{32}H_{40}O_6S_2$: C, 65.74; H, 6.90; S, 10.95; Found : C, 65.83; H, 6.83; S, 10.71.

REFERENCES AND NOTES

A* preliminary account of this work was presented at the XIII Convegno Nazionale di Chimica Organica della Società Chimica Italiana, Milano 12-16 Sett.1982.

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Received, 24th November, 1982