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TREATMENT OF DIMETHYL (+)-L-TARTRATE WITH SULFUR TETRAFLUORIDE*

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SUMMARY

Treatment of dimethyl (+)-L-tartrate (I) with sulfur tetrafluoride results in the formation of an intermediate, 2-fluoro-1,2-bis(methoxycarbonyl)ethyl fluorosulfite (II), which under the action of hydrogen fluoride, present in the reaction mixture, is converted into dimethyl (-)(2S:3S)-2-fluoro-3-hydroxysuccinate (III). The reaction of the latter with SF_4 leads to dimethyl meso-2,3-difluorosuccinate (IV). The structure and configurations of the compounds obtained were established by ^1H and ^{19}F NMR. Treatment of dimethyl (+)-L-tartrate (I) with sulfur tetrafluoride in the presence of excessive hydrogen fluoride gave dimethyl meso-2,3-difluorosuccinate in 96% yield.

INTRODUCTION

It has been shown [3,4] that the reaction of dimethyl (+)-L-tartrate with sulfur tetrafluoride gives dimethyl-2,3-difluorosuccinate in a yield of 23%. Attempts to isolate and identify

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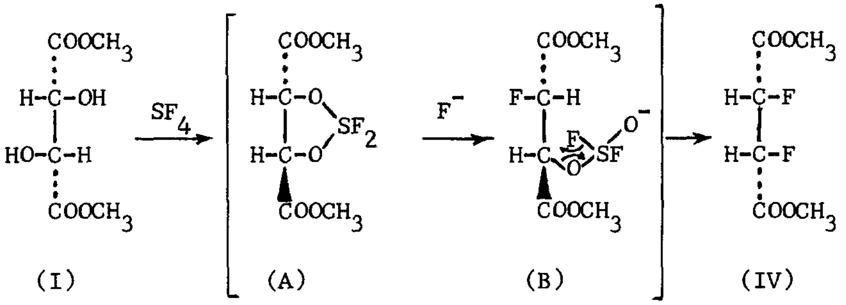
*Part III. Previous papers see [1,2]

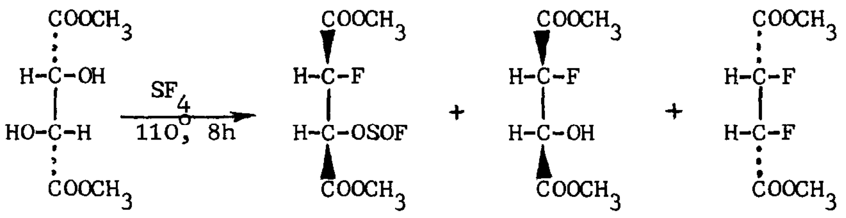
other products of this reaction were unsuccesful. Bell and Hudlicky [4,5] have found that treatment of dimethyltartrates with SF_4 occurs with inversion of configuration at one and retention of configuration at the other chiral carbon atom. They have proposed the following reaction scheme



Recently we have found [1,2] that the reactions of α-hydroxycarboxylic acids with sulfur tetrafluoride take place with the formation of trifluoromethyl fluorosulfites, which are apparently formed as a result of rearrangement of cyclic intermediates of type (A). We have also assumed possible the formation of products containing OSOF groups in the reactions of tartaric acid esters with SF_4. To study these processes, dimethyl (+)-L-tartrate has been chosen as a model substance.

RESULTS AND DISCUSSION

It has been found in this work that the reaction of dimethyl tartrate (I) with sulfur tetrafluoride actually results in the formation of 2-fluoro-1,2-bis(methoxycarbonyl)ethyl fluorosulfite (II) (Table I). Under conditions, described in previous papers [3,4] fluorosulfite (II) is the main product. In smaller quantities the mixture contains dimethyl(-)(2S:3S)-2-fluoro-3-hydroxysuccinate (III), dimethyl meso-2,3-difluorosuccinate (IV) and traces of unsaturated compounds.



(I) (II),65% (III),5% (IV),24%

The compounds obtained were isolated by vacuum distillation and identified by elementary analysis, infrared and NMR spectra. Infrared spectra of esters (II-IV) showed strong bands at 1000-1300 cm^{-1} corresponding to C-F bonds. The spectrum of fluorosulfite (II) showed characteristic absorption of S-F bond at 700-730 cm^{-1} [1,6]. In the spectrum of hydroxy ester (III) there is a strong band of hydroxy group. Difluorosuccinate (IV) gave AA'XX' patterns at NMR ^{1}H and ^{19}F. Calculation of the coupling constants gave results analogous to those previously reported for dimethyl meso-2,3-difluorosuccinate [5]. The analysis of NMR spectra of fluorosulfite (II) and hydroxy ester (III) allow assumptions to be made as to the configurations of these compounds. The values of chemical shifts and coupling constants for H and F in NMR spectra of (II) and (III) are close to the values obtained for dimethyl meso-2,3-difluorosuccinate (IV) and sharply differ from chemical shifts and coupling constants of dimethyl--D,L-2,3-difluorosuccinate [5]. This suggests erythro - configurations for fluorosulfite (II) and hydroxy ester (III). Chemical shifts and coupling constants are listed in Table II.

It should be noted that fluorosulfite (II) which is an erytro- form in relation to chiral carbon atoms forms two diastereomers owing to the presence of an additional chiral center, sulfur atom, in the molecule. In the hydrolysis of fluorosulfite (II) with water an asymmetric sulfur atom is removed and an individual hydroxy ester (III) is obtained in a high yield.

TABLE I

Treatment of the esters (I - III) with sulfur tetrafluoride

Starting ester	Reaction conditions[a]		Yield of products, %		
	Temp., ^{o}C	Time, hrs	II	III	IV
Dimethyl (+)-L-tartrate (I)	20	2	98	trace	1
	60	6	80	7	8
	110	8	65	5	24
	40[b]	6	58	2	36
	90[b]	6	trace	trace	96
	20[c]	24	97	trace	trace
	110[c]	8	92	2	3
2-Fluoro-1,2-bis(methoxycarbonyl)ethyl fluorosulfite (II)	110	8	96	1	trace
	40[b]	5	44	2	50
	110[b]	8	trace	1	96
Dimethyl (-)(2S:3S)-2-fluoro-3-hydroxysuccinate (III)	60[b]	6	-	trace	97

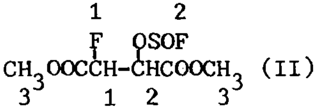
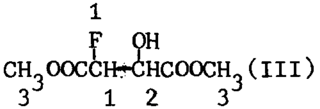
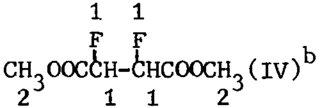
[a] 0.4 Mole SF_4 per 0.1 mole of the ester.

[b] HF (0.8 mole) was added.

[c] NaF(0.4 mole) was added.

TABLE II

^{1}H and ^{19}F NMR Data on Fluorinated Esters (II - IV)[a]

Compound	H	δ	J_{HF} vic	J_{HF} gem	J_{HH}	F	ϕ	J_{FH} vic	J_{FH} gem	J_{FF}
 $\underset{3}{CH_3}OOC\underset{1}{\overset{\overset{1}{F}}{C}}H-\underset{2}{\overset{\overset{2}{OSOF}}{C}}HCOO\underset{3}{CH_3}$ (II)	1	5.55		46.5	2.5	1	+121.7	20	46.5	6
	2	5.84	20		2.5		+122.4	20	46.5	
	3	3.78				2	-143.9 -141.1			6
 $\underset{3}{CH_3}OOC\underset{1}{\overset{\overset{1}{F}}{C}}H-\underset{2}{\overset{OH}{C}}HCOO\underset{3}{CH_3}$ (III)	1	5.25		47	2.5	1	+123.0	23	47	
	2	4.65	23		2.5					
	3	3.70								
 $\underset{2}{CH_3}OOC\underset{1}{\overset{\overset{1}{F}}{C}}H-\underset{1}{\overset{\overset{1}{F}}{C}}HCOO\underset{2}{CH_3}$ (IV)[b]	1	5.66	22.8	46.6	1.9	1	+124.5	22.8	46.6	13.8
	2	3.76								

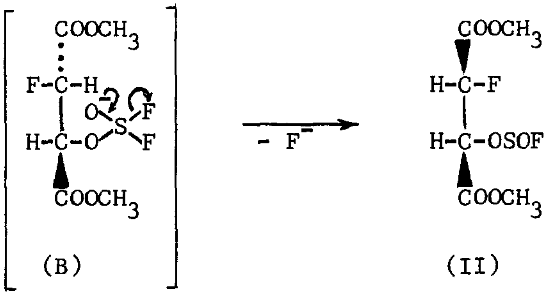
[a] Chemical shifts in ppm relative to HMDS for ^{1}H and to CF_3COOH for ^{19}F(+ for the upfield shifts). Coupling constants in Hz.

[b] The AA'XX' spectra of (IV) have been interpreted using computer-assisted iterative least-squares line-matching procedure.

It was of interest to find out whether formation of difluorosuccinate (IV) and fluorosulfite (II) in the reaction of dimethyl tartrate (I) with SF_4 is the consequence of parallel processes or whether difluorosuccinate (IV) is formed via intermediate fluorosulfite (II).

We have studied the reaction of dimethyl (+)-L-tartrate (I) with sulfur tetrafluoride under various conditions (Table I). When treated with SF_4 at 20°, instead of 110°, dimethyl tartrate (I) was found to give fluorosulfite (II) in a 98% yield. Formation of difluoro ester (IV) practically did not occur.

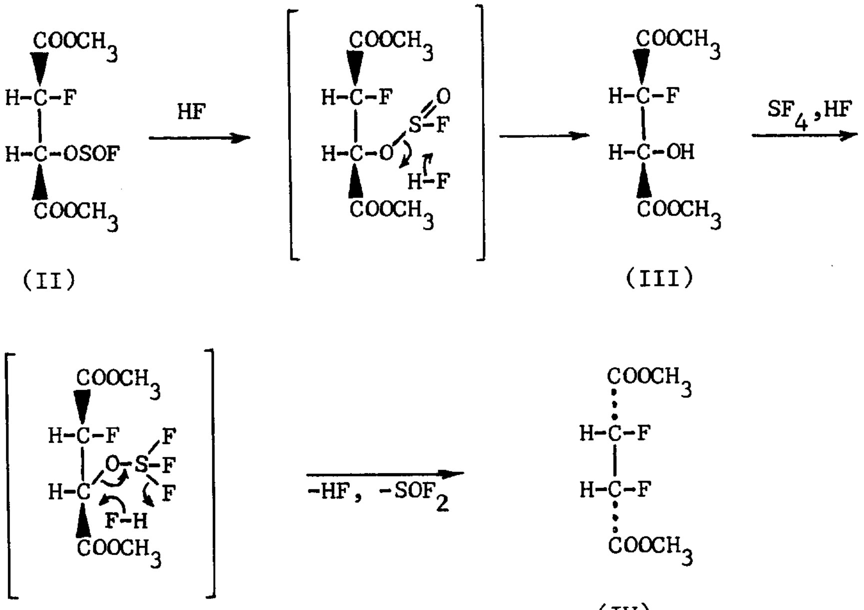
Thus, the first step of the reaction of dimethyl tartrate(I) with SF_4, the formation of intermediate fluorosulfite (II), apparently proceeds as follows. Cyclic intermediate (A) probably is actually converted by S_N2 reaction into anion (B) with inversion of configuration at one of chiral carbons atoms. However, the rearrangement of anion (B) into difluoro ester (IV) resulting from a four-center displacement of sulfuroxy group by fluorine does not occur as the authors of papers [4,5] supposed. Instead, the removal of F^- and formation of fluorosulfite (II) take place.



For a further conversion of fluorosulfite (II) into difluoro ester (IV), the quantity of hydrogen fluoride in the reaction mixture was found to be a determining factor.

Like other fluorosulfites previously reported [1,2], fluorosulfite (II) fails to react with SF_4 in the absence of hydrogen fluoride. But the reaction of (II) with sulfur tetrafluoride in the presence of excessive HF gives difluoro ester (IV) in a high yield.

We have recently shown [1] that trifluoroalkyl fluorosulfites react with hydrogen fluoride yielding the corresponding alcohols. Similarly, treatment of fluorosulfite (II) with HF gives a 97% yield of individual dimethyl (-)(2S:3S)-2-fluoro-3-hydroxysuccinate (III). The latter, on being heated with SF_4 in the presence of HF, will form dimethyl meso-2,3-difluorosuccinate (IV) in 97% yield. Thus both these reactions occur with retention of configuration. The conversion of hydroxy ester (III) into difluoro ester (IV) may take place in accordance with the scheme described elsewhere [7].



(II)

(III)

(IV)

Processes established in this work give an opportunity to effectively influence the results of the reactions of tartaric acid esters with sulfur tetrafluoride. Thus, on treatment of dimethyl and diethyl (+)-L-tartrates with SF_4 in mild conditions and in the presence of NaF, acceptor of hydrogen fluoride, corresponding fluorosulfites are formed in 95-97% yields. The latter, as shown above, are easily hydrolyzed with water, giving dimethyl and diethyl 2-fluoro-3-hydroxysuccinates, respectively. The products of replacement of both hydroxy groups in dimethyl and diethyl tartrates by fluorine atoms can be obtained in quantitative yields while heating these esters with SF_4 in the presence of excessive hydrogen fluoride.

EXPERIMENTAL

NMR spectra were taken on Tesla BS-497 NMR Spectrometer at 100 MHz for ^1H and 94.075 MHz for ^{19}F using HMDS as internal and CF_3COOH as external standards and d_6-acetone as solvent. Gas-liquid chromatography was carried out on ПАХВ-07 Chromatograph with thermal conductivity detector and helium as a carrier gas. The flow rate was 60 ml/min. Stainless steel column (3m×6mm) with 15% of silicon FS-1265 on Chromosorb W(AW-DMCS). Infrared spectra were taken on Specord IR-75 Infrared Spectrometer with KBr optics.

Chemicals

Sulfur tetrafluoride was prepared according to the literature [8]. Solvents and chemicals were of commercial grade. Dimethyl and diethyl (+)-L-tartrates were redistilled and had melting and boiling points described in the literature [3,4].

Treatment of dimethyl (+)-L-tartrate (I) with SF_4

Following the procedure described in the literature [3,4] dimethyl tartrate (I) and excess of about 3 equivalents of sulfur tetrafluoride (with addition of HF or NaF, if necessary) were treated in stainless steel cylinders at selected temperatures (Table I). Volatile products were removed and the liquids from the cylinders were stirred in polyethylene flasks with NaF in anhydrous methylene chloride for 3 hours. Percentage composition of the mixture was determined by GLC method. The mixture was filtered and the solvent was removed. Compounds (II) and (IV) were separated by vacuum distillation. <u>2-Fluoro-1,2-bis (methoxycarbonyl)ethyl fluorosulfite (II)(nc)</u>, b.p. 110-112°/6mm, d^{21}1.4572, $n^{17}D$ 1.4270. Analysis: Found: F, 15.19, 15.32; S, 12.85, 13.21. $C_6H_8F_2O_6S$ requires F, 15.45; S, 13.00. <u>Dimethyl meso-2,3-difluorosuccinate (IV)</u>, b.p. 97-99°/ 7mm, $n^{18}D$ 1.4040. Lit. b.p. 50-56°/ 0.06mm [4].

<u>Dimethyl (-)(2S:3S)-2-fluoro-3-hydroxysuccinate (III)</u>

a) A mixture of fluorosulfite (II) (0.05 mole) and water (0.06 mole) was stirred for 5 hours at 20°. The products were mixed with 10 ml of benzene. Hydroxy ester (III) was isolated by evaporation and vacuum distillation at 97-98°/ 1mm. The yield was 97%. d^{20}1.3463, $n^{18}D$ 1.4328, $[\alpha]_D^{21} = -10.2°$. Analysis: Found: F, 10.14, 10.26. $C_6H_9FO_5$ requires F, 10.55.

b) Fluorosulfite (II) (0.05 mole) and anhydrous hydrogen fluoride (0.3 mole) were treated for 7 hours in a stainless steel cylinder at 60°. Volatile products were removed at 30° and the liquid was stirred for 2 hours with NaF in methylene chloride. Vacuum distillation at 96-98°/ 1mm gave hydroxy ester (III) (95%).

<u>Treatment of fluorosulfite (II) and hydroxy ester (III) with SF_4</u>

Both (II) and (III) were separately treated with SF_4 (with or without additional HF) following the procedure described above for the reactions of dimethyl tartrate with SF_4 (Table I).

Diethyl 2,3-difluorosuccinate

The mixture of diethyl (+)-L-tartrate (0.1 mole), sulfur tetrafluoride (0.4 mole) and HF (0.8 mole) was heated in a stainless steel cylinder for 5 hours at 90°. Working up in the manner described above gave diethyl 2,3-difluorosuccinate (97%), b.p. 96-98°/ 5mm, $n^{17}D$ 1.4069. Lit. b.p. 98°/ 4mm [3].

2-Fluoro-1,2-bis(ethoxycarbonyl)ethyl fluorosulfite (nc)

The mixture of diethyl (+)-L-tartrate (0.1 mole), sulfur tetrafluoride (0.3 mole) and NaF (0.4 mole) was treated as described above. The yield of 2-fluoro-1,2-bis(ethoxycarbonyl) ethyl fluorosulfite 92% , b.p. 95-98°/ 1mm, $n^{17}D$ 1.4214. Analysis: Found: F, 12.24, 12.88; S, 11.28, 11.67. $C_8H_{12}F_2O_6S$ requires F, 13.87; S, 11.75.

Diethyl 2-fluoro-3-hydroxysuccinate

2-Fluoro-1,2-bis(ethoxycarbonyl)ethyl fluorosulfite (0.05 mole) and water (0.06 mole) were treated as described above for the hydrolysis of fluorosulfite (II). The yield of diethyl 2-fluoro-3-hydroxysuccinate 97% , b.p. 144-146°/ 16mm, $n^{20}D$ 1.4232. Lit. b.p. 144-145°/ 15mm [3].

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