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REACTIONS OF XeF_2. PART 7. SYNTHESIS OF 6-FLUOROBIOTIN METHYL ESTER

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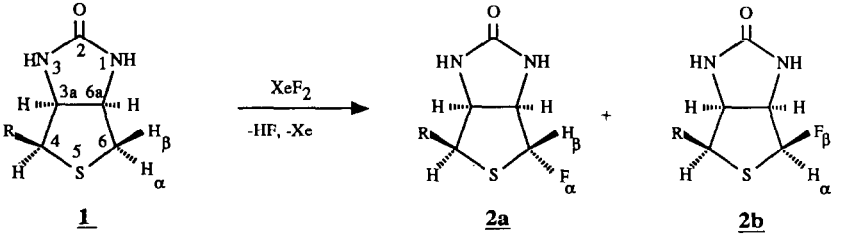
SUMMARY

The synthesis of 6-fluoro-d-biotin methyl ester and its characterization by ^1H and ^{19}F nmr and elemental analysis is described. Analogous reactions of XeF_2 with tetramisole and benzylpenicillin methyl ester were carried out but monofluorinated products could not be isolated.

RESULTS AND DISCUSSION

The α-fluorination of organosulfides [1-4] has recently been extended to sulfur-containing amino acids such as methionine, methionylglycine [5], and cysteine [6], and we now wish to describe the fluorination of biotin (vitamin H) and the attempted fluorination of tetramisole and benzylpenicillin, using XeF_2 as the fluorinating agent.

In order to avoid the formation of xenon esters [7], the methyl ester of d-biotin 1 was prepared and its reaction with XeF_2 was carried out on a 1 mmol scale in a ptfe bottle at 5-10°C in CH_3CN solution.



1 2a 2b

R = $-(CH_2)_4C(O)OCH_3$

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TABLE 1

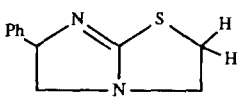
^{1}H and ^{19}F nmr data of d-biotin and 6-fluoro-d-biotin methyl ester in CD_3CN

	Chemical shift (ppm)[a]				Coupling constant (Hz)					
	δH6α	δH6β	δF6α	δF6β	H6a,H6β	H6a,H6α	F6α,H6β	F6β,H6α	F6α,H6a	F6β,H6a
1	2.94	2.75			0	4.9				
2a		5.77	-141.8		0		52.7		9.8	
2b	5.95			-154.5		4.5		58.1		14.1

[a]Chemical shifts were measured relative to internal CHD_2CN (1.93 ppm) and C_6F_6 (-162.9 ppm) and converted to the TMS and $CFCl_3$ scales.

All of the XeF_2 reacted within 90 min and the product 2a was separated by tlc, recrystallized (15% yield), and characterized by elemental analysis and ^{1}H and ^{19}F nmr (Table 1). ^{19}F nmr examination of the reaction mixture showed a 3:1 ratio of 2a:2b, and the assignment of isomeric structures is based on the vicinal coupling J(H6a,H6α) which is expected to be similar in 2b (4.5 Hz) and 1 (4.9 Hz). Occasionally, a doublet $^{3}J(F4,H3a)=10.2$ Hz of triplets $^{3}J(F4,CH_2)=20.8$ Hz was observed in the ^{19}F nmr at -123 ppm, which we assign to a third monofluorinated isomer, 4-fluoro-d-biotin methyl ester 2c.

Reaction of XeF_2 with tetramisole 3 and benzylpenicillin methyl ester 10 was also carried out since these sulfur-containing compounds have α-hydrogens. However, attempts to isolate monofluorinated products were



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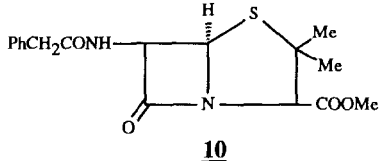

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unsuccessful. With tetramisole, ^{19}F nmr peaks in the S(IV)-F and C-F regions, as well as mass spectral evidence for tetramisole sulfoxide, indicate that fluorination and oxidation do occur, but the majority of unreacted tetramisole could be recovered by tlc. Therefore, this reaction was not pursued further. Similarly, reaction of XeF_2 with benzylpenicillin methyl ester occurred to some extent, as demonstrated by the appearance of ^{19}F nmr peaks in the S(IV)-F and C-F regions and the isolation by tlc of the corresponding sulfoxide, but a monofluorinated product could not be isolated, despite repeated attempts.

EXPERIMENTAL

Proton and fluorine nmr spectra were recorded on Bruker WH90 and AM300 spectrometers. Mass spectra were obtained on a Finnigan 1015 quadrupole instrument at 70 eV. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Tlc separations were carried out on silica plates. The following compounds were commercial samples: XeF_2 (PCR/SCM), d-biotin (Aldrich), DL-tetramisole hydrochloride (Aldrich), penicillin-G potassium salt (Sigma).

Preparation of d-biotin methyl ester 1

The procedure of Liu and Leonard was followed [8]. A solution of d-biotin (260 mg, 1.06 mmol) in anhydrous methanol (20 mL) containing HCl (1.4 g) was refluxed for 3 h. The solvent was evaporated and water (20 mL) was added to the residue. The mixture was neutralized with 10% sodium bicarbonate solution and extracted three times with ethyl acetate. The extract was washed with cold water and dried over sodium sulfate and the solvent evaporated to give a white solid (236 mg, 86%, mp 155-156°C) identified as d-biotin methyl ester 1 on the basis of its ^1H nmr [8] and ms: m/z 258 (M).

Preparation of 6-fluoro-d-biotin methyl ester 2

Xenon difluoride (44.5 mg, 0.26 mmol) and d-biotin methyl ester 1 (63 mg, 0.24 mmol) was mixed in a small ptfe bottle which was set on a cold plate (5-10°C) and CH_3CN (1 mL) was then added. The suspension was stirred at 10°C for 90 min during which time most of the starting compound

had reacted to form a pale yellow solution. N_2 was bubbled through the solution for 15 min and 2/3 of the solvent removed by rotary evaporator. Fresh CH_3CN was added and the mixture placed on a silica gel plate (20x20 cm) and developed by using a solvent mixture $CHCl_3$:CH_3OH = 2.6:0.4 (v/v). The major component was taken out to give a soft solid (21 mg) which was recrystallized with CH_3OH (0.15 mL) and diethyl ether (0.5 mL) to give a white solid (11 mg, mp 124-125°C) identified as 6-fluoro-d-biotin methyl ester 2a. Calcd. for $C_{11}H_{17}FN_2O_3S$: C 47.80, H 6.20. Found: C 47.82, H 6.48. The ratio of 2a:2b was 3:1 in the reaction mixture, as determined by ^{19}F nmr.

6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole 3 (tetramisole)

A solution of NaOH (0.14 g) in water (2 mL) was slowly added to tetramisole hydrochloride (0.72 g, 1 mmol) until pH 10 was reached. The desired product was extracted twice with $CHCl_3$, dried over $MgSO_4$ and solvent evaporated to give tetramisole 3 (0.57 g, mp 58-60°C). Ms: m/z 204 (M), 176 (M-C_2H_4), 148 (M-C_2H_4-N_2). ^1H nmr (300.13 MHz, $CDCl_3$): 5.45 (1H,d,d), 3.67 (1H,d,d), 3.63 (1H,m), 3.51 (1H,m), 3.35 (1H,m), 3.11 (1H,m), 2.98 (1H,d,d), 7.2-7.4 (5H).

Reaction of tetramisole with XeF_2

In a typical reaction, tetramisole 3 (56 mg, 0.27 mmol) in CH_3CN (0.8 mL) was added with stirring to solid XeF_2 (49 mg, 0.29 mmol) in a ptfe bottle cooled to 5°C on a cold plate. The solution turned yellow within 1 min and further stirring for 35 min gave a brown solution. Removal of solvent by rotary evaporator left behind an oily solid which was dissolved in $CDCl_3$ for ^1H and ^{19}F nmr examination. Using shorter reaction times and pre-cooled CH_3CN, gave orange solutions which turned deep yellow. On other occasions the solvent CH_3CN was replaced with CH_2Cl_2.

The majority of starting compound 3 was recovered by tlc but attempts to isolate fluorinated tetramisole by tlc were unsuccessful. ^{19}F nmr examination of the reaction mixture did, however, show the presence of six fluorinated products 4-9: 4 (0.8%) δF-93.15; 5 (0.8%) δF-93.27; 6 (2.1%) δF_a-71.38, δF_b-85.31, $J(F_aF_b)$=209.4; 7 (2.1%) δF_a-73.50, δF_b-86.59, $J(F_aF_b)$=209.7; 8 (0.7%) δF_a-87.4, δF_b-92.2, $J(F_aF_b)$=174.2; 9 (0.9%)

δF_a-95.9, δF_b-108.1, δF_c-119.9, $J(F_aF_b)$=178.7, $J(F_aF_c)$=9.5, $J(F_bF_c)$=0. We assume that 4 and 5 are monofluorinated diastereomers containing the -SCF- group, 6 and 7 are difluorinated diastereomers containing the $-SCF_aF_b-$ group, 8 is a difluorinated $-SCF_aF_b-$ derivative (not diastereomeric), and 9 is a trifluorinated $-SCF_aF_bCF_c-$derivative. The reaction mixture also showed a minor peak at +37 ppm in the S(IV)-F region; a peak at m/z 220 in the mass spectrum is assigned to tetramisole sulfoxide. In view of the low yield of monofluorinated products, this reaction was not pursued further.

Benzylpenicillin methyl ester 10

Benzylpenicillin methyl ester 10 was prepared by the method of Bell et al. [9]. A suspension of penicillin G potassium salt (0.78 g, 2.1 mmol) in anhydrous DMF (4.4 mL) was stirred at 25°C with CH_3I (1.5 mL) for 3 h, N_2 was passed through the solution for 20 min and reaction mixture allowed to stand overnight. It was poured slowly into 12 mL of ice-water with vigorous stirring. The oil was washed twice with cold water and kept in water until it solidified. The liquid was decanted and saturated with NaCl until a second solid crop was obtained. Both solids were combined and dissolved in CH_2Cl_2 and the CH_2Cl_2 solution was washed with NaCl-saturated water and dried with Na_2SO_4. The solvent was removed and the residual oil triturated with absolute diethyl ether. A white solid precipitated and was washed twice with diethyl ether and pumped to dryness. The product, benzylpenicillin methyl ester 10 (0.46 g, 63%, mp 89-90°C) was identified by IR, nmr [9] and ms: m/z 348 (M).

Reaction of XeF_2 with benzylpenicillin methyl ester 10

This reaction was carried out with various modifications, but without positive identification of the desired product.

Attempts to isolate a fluorinated product by tlc were unsuccessful. A search of the ^{19}F nmr spectra of various reaction mixtures did show a number of doublet peaks at δF-144.4 (J=12 Hz), δF-176.0 (J=50 Hz), δF-182.7 (J=45 Hz) and δF-184.7 (J=44 Hz), and up to six minor singlet peaks in the sulfur(IV) fluoride region from +44 to +17 ppm, in addition to BF_4^- and $SiF_6^=$, but only starting material 10 and the sulfoxide (see below) could be isolated by tlc, and the reaction was not pursued further.

Benzylpenicillin methyl ester sulfoxide 11

The sulfoxide 11 was identified in the reaction mixture after reaction of XeF_2 with 10. It was separated by tlc and identified by ^1H nmr [10] and ms: m/z 364 (M), 346 ($M-H_2O$).

ACKNOWLEDGEMENT

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