

BROMINATION OF 6-ACETYL-2-ETHOXY-4H-1,3,2-BENZODIOXAPHOSPHORIN 2-SULFIDE IN METHANOL AND CARBON TETRACHLORIDE

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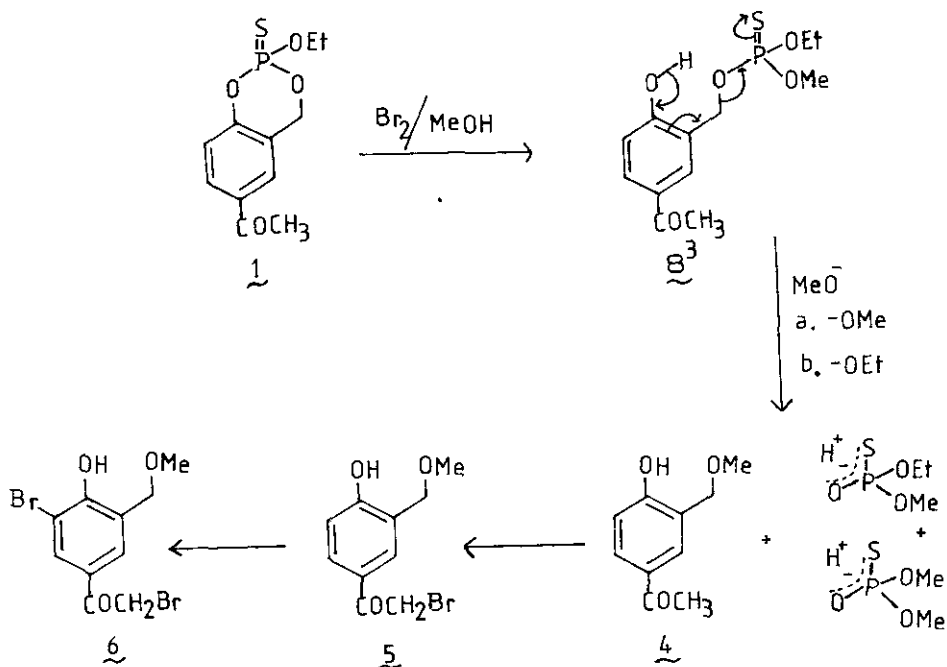
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Abstract - The reaction of 6-acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide **1**² with methanol-bromine gave 4-hydroxy-3-(methoxymethyl)acetophenone **4**⁵, ω -bromo-4-hydroxy-3-(methoxymethyl)acetophenone **5** and 5, ω -dibromo-4-hydroxy-3-(methoxymethyl)acetophenone **6**; reaction of **1** with carbon tetrachloride-bromine gave only 6-(ω -bromo)acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide **2** and 6-(ω,ω -dibromo)acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide **3**. The possible reaction mechanism is discussed.

From the study of the alcoholysis and enzymatic action of salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide) **7** Eto and Ohkawa generalized that the cyclic ester phosphorylates at first a nucleophile to produce a salicyl phosphate which then alkylates another molecule of nucleophile¹. This generalization led us to examine the behaviour of the heterocyclic ring of 6-acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide **1** towards bromine in carbon tetrachloride and also in methanol where methyl hypobromite generates both the nucleophile (MeO⁻ ion) and the electrophile (Br⁺ ion).

Treatment of **1** with a mixture of methanol-bromine at 0-5°C gave colourless crystals as the major product whose structure was clarified to be **4**. Further purification of the mother liquor gave other compounds whose structures were assigned on the basis of the spectral data as ω -bromo-4-hydroxy-3-(methoxymethyl)acetophenone **5** and 5, ω -dibromo-4-hydroxy-3-(methoxymethyl)acetophenone **6** and a mixture of ethyl methyl hydrogen phosphorothioate and dimethyl hydrogen phosphorothioate. Further bromination of **4** and **5** with one mole of bromine

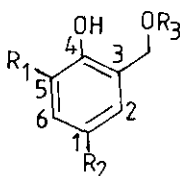
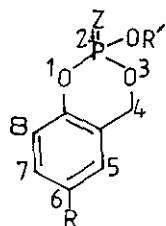
resulted in 5 and 6 respectively. These results are exhibited in scheme I along with a possible mechanism for the formation of these compounds.



Scheme I

As we have isolated 4 as the major product and no 5-bromo-4-hydroxy-3-(methoxymethyl)acetophenone 2 could be isolated from the reaction mixture, it was clear that 1 gave 4 at first which was further brominated at the 6-acetyl group preferentially to give 5 and thereafter 6⁴.

Similarly 1 was treated with a mixture of carbon tetrachloride and bromine at 25°C and the red solid obtained from this reaction was subjected to preparative thin layer chromatography to give 6-(ω -bromo)acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide 2 and 6-(ω,ω -dibromo)acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide 3. Their structures were established on the basis of spectral data. The bromination reaction in carbon tetrachloride was found to be slow at 0-5°C but was accelerated at 25°C.



Compound	R	R'	Z
<u>1</u>	-COCH ₃	Et	S
<u>2</u>	-COCH ₂ Br	Et	S
<u>3</u>	-COCHBr ₂	Et	S
<u>1</u>	-H	CH ₃	S

Compound	R ₁	R ₂	R ₃
<u>4</u>	H	-COCH ₃	Me
<u>5</u>	H	-COCH ₂ Br	Me
<u>6</u>	Br	-COCH ₂ Br	Me
<u>2</u>	Br	-COCH ₃	Me

 Table 1. Physical data for compounds 1-6

Compound	MS M ⁺ (m/e)	IR ν _{C=O} cm ⁻¹ (KBr)	¹ H NMR in δ(ppm), (J Hz), (CDCl ₃)					Mp °C	Yield %
			4CH ₂	5H	7H	8H	-COCH ₃ Proton		
<u>1</u>	272	1678	5.31 d (14)	7.70 d (1.5)	7.88 dd (8,1.5)	7.03 d (8)	2.43 s 3H		
<u>2</u>	351	1691	5.31 d (13)	7.76 d (1.5)	7.94 dd (8,1.5)	7.09 d (8)	4.24 s 2H	75	85.00
<u>3</u>	430	1684	5.13 d (13)	7.90 d (1.5)	8.10 dd (8,1.5)	7.07 d (8)	6.40 s 1H	94	10.00
			ArCH ₂ OMe	2H	6H	5H	-COCH ₃		
<u>4</u>	180	1655	4.64 s 2H	7.74 d (1.5)	7.84 dd (8.5,1.5)	6.87 d (8.5)	2.30 s 3H	86	51.00
<u>5</u>	259	1670	4.50 s 2H	7.73 d (1.5)	7.85 dd (8.5,1.5)	6.83 d (8.5)	4.10 s 2H	Semi solid	13.12
<u>6</u>	338	1682	4.55 s 2H	8.0 d (1.5)	7.69 d (1.5)	-	4.20 s 2H	90-91	16.40

OH protons for 5 & 6 at δ 8.25 & 7.88; OMe of -CH₂OMe at 3.21 & 3.39 respectively.

EXPERIMENTAL

All melting points recorded are uncorrected. IR spectra were recorded on a Perkin-Elmer 237B spectrophotometer. ¹H NMR spectra were measured on a varian T60 instrument. Mass spectra (MS) were determined with an AEL MS 30 spectrometer. Methanol used in the reactions was 98% (glc) pure.

Reaction of compound 1 with bromine in methanol

To a solution of **1** (200 mg) in dry methanol (10 ml) at 0°C was added a cold solution of bromine (250 mg) in methanol (10 ml) slowly in small portions while keeping the temperature of the mixture at 0-5°C. The reaction mixture was stirred for 30 min at this temperature. The solvent was evaporated in vacuo to dryness to give colourless crystals of **4** (73 mg : yield 51%).

The mother liquor was subjected to preparative silica gel TLC (1:9 ethyl acetate:benzene) to give compound **2** (25 mg), **6** (41 mg) and the highly polar compound, a mixture of ethyl methyl hydrogen phosphorothioate and dimethyl hydrogen phosphorothioate, ¹H NMR (CCl₄), δ: 0.97 (3H, t, J=7Hz, CH₃ of OCH₂CH₃) and 3.43 (CH₃-protons, d, J=13Hz), 3.6 (2H, m, CH₂ of OCH₂CH₃). Bromination of **4** and **5** was carried out in similar way.

Reaction of compound 1 with bromine in carbon tetrachloride

To a solution of **1** (200 mg) in dry carbon tetrachloride (10 ml) was gradually added a solution of bromine (250 mg) in CCl₄ (10 ml) and the solution was stirred at 25°C for 30 min. The reaction mixture was worked up in similar way as described above to give compound **2** (219 mg) and **3** (31 mg) after preparative TLC (silica gel; benzene).

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2. M.Eto, "Organophosphorous Pesticides:Organic and Biological Chemistry", CRC Press, Inc., p. 254 (1974).
3. We could isolate a very small amount of **8** just to record the mass spectra. The prominent molecular ion peak was found at M⁺ 304.
4. We have recorded the ¹H NMR spectra of the crude reaction mixture to see if exocyclic cleavage of P-OC₂H₅ bond occurred leaving the cyclic structure intact, but could not detect the P-O-CH₂-Ar methylene doublet to support such a (exocyclic P-OC₂H₅) bond cleavage.
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