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

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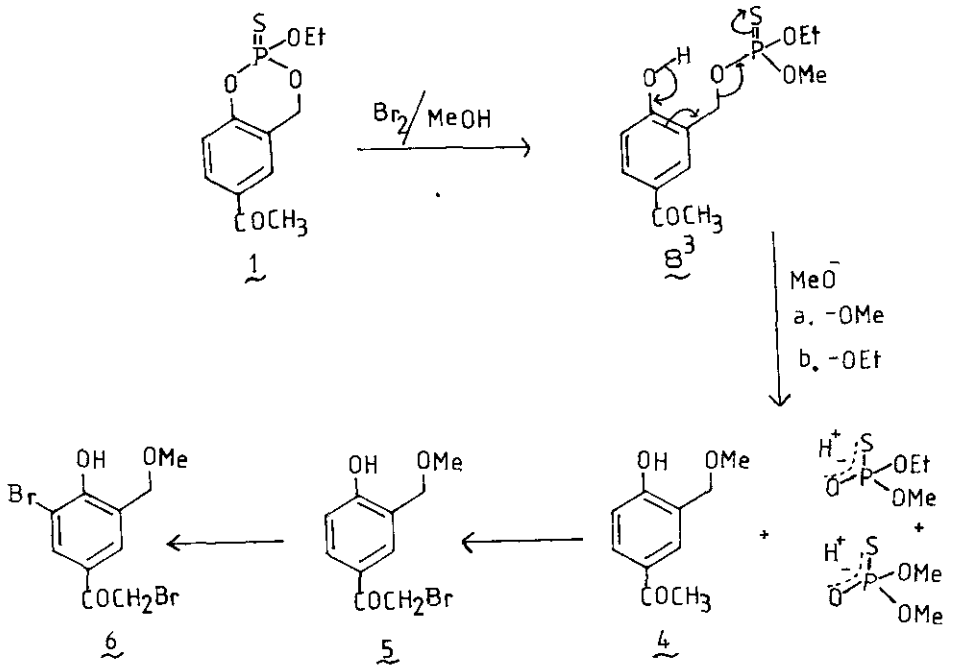
Abstract - The reaction of 6-acetyl-2-ethoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide 1[2] with methanol-bromine gave 4-hydroxy-3-(methoxymethyl)acetophenone 4[5], ω-bromo-4-hydroxy-3-(methoxymethyl)acetophenone 5 and 5,ω-dibromo-4-hydroxy-3-(methoxymethyl)acetophenone 6; reaction of 1 with carbon tetrachloride-bromine 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 nucleophile[1]. 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 clarieied 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-brome-4-hydroxy-3-(methoxymethyl)acetophenone 5 and 5,ω-dibrome-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

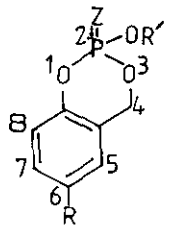
resulted in 5 and 6 respectively. These results are exhibited in scheme I along with a possible mechanism for the formation of these compounds.



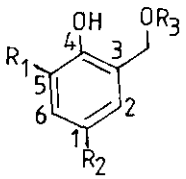
Scheme I

As we have isolated 4 as the major product and no 5-bromo-4-hydroxy-3-(methoxymethyl)acetophenone 9 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 6[4].

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
1	$-COCH_3$	Et	S
2	$-COCH_2Br$	Et	S
3	$-COCHBr_2$	Et	S
7	-H	CH_3	S



Compound	R_1	R_2	R_3
4	H	$-COCH_3$	Me
5	H	$-COCH_2Br$	Me
6	Br	$-COCH_2Br$	Me
9	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		
1	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		
2	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
3	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	$-COCH_3$		
4	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
5	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
6	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 δ8.25 & 7.88; OMe of $-CH_2OMe$ at 3.21 & 3.39 respectively.

EXPERIMENTAL

All melting points recorded are uncorrected. IR spectra were recorded on a Perkin-Elmer 237B spectrophotometer. ^{1}H NMR spectra were measured on a varian T60 instrument. Mass spectra (MS) were determined with an AEI 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 5 (25 mg), 6 (41 mg) and the highly polar compound, a mixture of ethyl methyl hydrogen phosphorothioate and dimethyl hydrogen phosphorothioate, ^{1}H NMR (CCl_4), δ: 0.97 (3H, t, J=7Hz, CH_3 of OCH_2CH_3) and 3.43 (CH_3-protons, d, J=13Hz), 3.6 (2H, m, CH_2 of OCH_2CH_3). 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 CCl_4 (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).

ACKNOWLEDGEMENT

The authors are grateful to Dr J N Baruah for his keen interest and encouragement and to the CSIR for the award of a Junior Research Fellowship to one of them (RCB).

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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 ^{1}H NMR spectra of the crude reaction mixture to see if exocyclic cleavage of P-OC_2H_5 bond occurred leaving the cyclic structure intact, but could not detect the P-O-CH_2-Ar methylene doublet to support such a (exocyclic P-OC_2H_5) bond cleavage.
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Received, 12th August, 1983