6.38 (H-4), and 6.63 (H-1). Irradiation at δ 4.40 reduced the H-1 and H-4 resonances to equal width at half-height.

Anal. Calcd for $C_{18}H_{24}O_4 \cdot H_2O$: C, 67.06; H, 8.13. Found: C, 67.42; H, 7.94.

Smiles Rearrangement and O-Methylation of IIIc.—A solution of 160 mg of IIIc in 10 ml of Claisen alkali was allowed to stand for 10 min, acidified, and extracted with chloroform to give a partially rearranged product. The rearranged mixture was dissolved in 10 ml of tetrahydrofuran and stored for 24 hr at 5° with excess ethereal diazomethane. Evaporation of excess reagent and solvent gave a material which upon preparative thin layer chromatography in cyclohexane–ethyl acetate (1:1) gave 60 mg of a more polar compound identified as estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 2-(2-benzoyl-4-nitro)phenyl ether 3-methyl ether (IVa) [nmr 3.70 (s, 3-OCH_3), 4.73 (m, H-11α)] and 28 mg of a less polar material identified as the isomeric 2-methyl ether 3-(2-benzoyl-4-nitro)phenyl ether IVb [nmr 3.66 (s, 2-OCH_3), 4.55 (m, H-11α)]. Neither of the two compounds could be obtained crystalline.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 3-Methyl Ether (Vc).—To a solution of 30 mg of IVa in 10 ml of acetone Jones reagent was added dropwise until the orange-brown color persisted. The mixture was allowed to stand for 20 min at room temperature, poured into water, and extracted with chloroform. Following evaporation of the solvent, the noncrystalline product Va was homogenous according to thin layer chromatography in cyclohexane–ethyl acetate (1:1). A solution of the above oil in piperidine was refluxed for 2 hr and cooled, benzene was added, and the reaction mixture was washed well with 5% sulfuric acid. Drying and evaporation of solvent gave 8 mg of a semisolid Vc which crystallized from methanol: mp 135–140°; $[\alpha]_D$ +129.7°; nmr 0.93 (s, C-18 CH_3), 3.86 (s, 3-OCH_3), 6.57 (s, H-1), and 6.62 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.91; H, 6.98.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 2-Methyl Ether (Vd).—This isomer was prepared from 14 mg of IVb exactly as described above: mp 145–147°; $[\alpha]_D$ +123.1°; nmr 0.93 (s, C-18 CH_3), 3.78 (s, 2-OCH_3), 6.44 (s, H-1), and 6.70 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.86; H, 7.72.

Estra-1,3,5(10)-triene-3,11α,17β-triol 3-(2-Benzoyl-4-nitro)-phenyl Ether 11,17-Diacetate (VIc).—The diacetate VIc was prepared from VIa as described for IIc and gave a crystalline product from ether, mp 103–105°, $[\alpha]_D$ −66.0°.

Anal. Calcd for $C_{35}H_{35}O_8N$: C, 68.63; H, 7.51. Found: C, 68.48; H, 7.24.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether 11α,-17β-Diacetate (VIIIb).—A 0.745-g sample of VIc was converted to the 2-hydroxy derivative VIIa which without purification was methylated with diazomethane to VIIb. The latter, upon cleavage with piperidine, afforded 0.23 g of VIIIb. The above reactions were carried out by procedures identical with those used in the 11β-hydroxy series. The isolated VIIIb crystallized from acetone–petroleum ether, mp 226–228°, $[\alpha]_D$ −101.7°.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.42; H, 7.83.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether (VIIIa).—A solution of 0.1 g of VIIIb in 20 ml of methanol containing 1 ml of concentrated sulfuric acid was refluxed for 15 hr. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate, dried, and evaporated to give the 0.06 g of VIIIa: crystallized from dilute methanol; mp 243–245°; $[\alpha]_D$ +25.8°; nmr 0.78 (s, C-18 CH_3), 3.85 (s, 2-OCH_3), 6.67 (s, H-4), and 7.76 (s, H-1).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.19; H, 7.98.

2,3-Dimethoxyestra-1,3,5(10)-trien-17-one-*6α,6β,9α-d*$_3$.—A solution of 50 mg of 2,3-dimethoxyestra-1,3,5(10)-trien-17-one (Ib) in 20 ml of ethyl acetate was shaken with deuterium over 100 mg of 10% palladized charcoal for 4 hr at room temperature and atmospheric pressure. Filtration of the catalyst and evaporation of solvent gave the trideuterio derivative of Ib. The nmr spectrum of the starting material Ib showed a three-proton multiplet at 2.63 representing the benzylic hydrogens, and 1-proton singlet at 6.83 and 6.63 with the former being 0.6 Hz wider at half-height. The deuterated product lacked the absorption at 2.63 but the resonances at 6.83 and 6.63 were unchanged in shape.

Registry No.—IIb, 28841-14-7; IIc, 28841-15-8; IIIa, 28897-65-6; IIIb, 28897-66-7; IIIc, 28897-67-8; IIId, 28897-68-9; IVa, 28897-69-0; IVb, 28841-16-9; Vc, 28897-70-3; Vd, 28897-71-4; VIc, 28897-72-5; VIIIa, 28897-73-6; VIIIb, 28897-74-7; 2,3-dimethoxyestra-1,3,5(10)-trien-17-one-*6α,6β,9α-d*$_3$, 28897-75-8.

New Approaches to the Preparation of Halogenated Methylenediphosphonates, Phosphonoacetates, and Malonates

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Three synthetic routes to tetraalkyl dihalomethylenediphosphonates have appeared in the literature. Low yields of tetraethyl dichloromethylenediphosphonate were obtained from the reaction of Cl_3CBr and $P(O-C_2H_5)_3$.[1] This is not a useful preparative method, however, as there are a number of products and separation is difficult. Reaction of molecular halogen with the sodium carbanion of tetraisopropyl methylenediphosphonate gave mixtures containing less than 50% of the dihalo derivative.[2] Again, separation problems render this method impractical for preparative purposes. Equation 1 describes the halogenation *via* hypohalite

$$2NaOX + H_2C(PO_3R_2)_2 \longrightarrow X_2C(PO_3R_2)_2 + 2NaOH \quad (1)$$
$$X = Cl, Br, I$$

reaction with tetraalkyl methylenediphosphonate.[2] Quantitative yields of $X_2C(PO_3R_2)_2$ are obtained when X = Cl or Br; when X = I, the product is somewhat unstable resulting in reduced yields.

Each of the above three methods could conceivably be modified to yield tetraalkyl monohalomethylenediphosphonates. Chloroform reacts with trialkyl phosphite in a complex manner; the intermediacy of $ClCH(PO_3R_2)_2$ has been postulated but never proven.[3] Direct halogenation and hypohalite halogenation have both been shown to yield at best mixtures of tetraalkyl monohalomethylenediphosphonate with the corresponding unhalogenated and dihalogenated derivatives.[2] These mixtures are exceedingly difficult to separate, rendering pure tetraalkyl monohalomethylenediphosphonates nearly inaccessible.[4]

Hata[5] has reported the preparation of monobromo derivatives of activated methylenes through the reaction of equimolar quantities of the corresponding di- and unhalogenated species. This method was not successful with diphosphonates. After extended heating (100°) of a mixture of tetraisopropyl dibromomethylenediphosphonate and tetraisopropyl methylenediphos-

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(3) A. J. Burn, J. I. G. Cadogen, and P. J. Bunyan, *J. Chem. Soc.*, 4369 (1964).
(4) O. T. Quimby, J. B. Prentice, and D. A. Nicholson, *J. Org. Chem.*, **32**, 4111 (1967).
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phonate, no change in composition could be detected by ^{31}P nmr.

Accordingly, a goal of our research became the discovery of a method for the synthesis of tetraalkyl monohalomethylenediphosphonates in high purity and high yield. This goal was realized during a study of the properties of tetraalkyl dihalomethylenediphosphonates.

Reaction of sodium sulfide and tetraisopropyl dichloromethylenediphosphonate produced compound I in 25–50% yield (eq 2). Although the mechanism of the reaction is not clear, it is obvious that both nucleophilic displacement and reduction are involved.

$$2Na_2S + 2Cl_2C[PO_3(i\text{-}C_3H_7)_2]_2 \longrightarrow [(i\text{-}C_3H_7)_2O_3P]_2CHSSCH[PO_3(i\text{-}C_3H_7)_2]_2 + 4NaCl \quad (2)$$

When sodium hydrosulfide was employed in reaction 2 in place of Na_2S, an immediate precipitate of sulfur was observed upon addition of the first portion of NaSH. Following the addition of 1 equiv of NaSH to 1 equiv of the dichloromethylenediphosphonate, nearly quantitative yields of elemental sulfur and tetraisopropyl chloromethylenediphosphonate were isolated, as described in eq 3. Addition of a second equivalent of

$$NaSH + R_2O_3PCPO_3R_2 \longrightarrow NaX + \downarrow S + R_2O_3PCPO_3R_2 \quad (3)$$

NaSH resulted in reduction of the second halogen to form the methylenediphosphonate (eq 4).

$$NaSH + R_2O_3PCPO_3R_2 \longrightarrow NaX + S\downarrow + R_2O_3PCPO_3R_2 \quad (4)$$

Table I describes the variation in yield of monohalomethylenediphosphonates with reaction temperature

TABLE I

REDUCTION OF TETRAALKYL DIHALOMETHYLENEDIPHOSPHONATES WITH SODIUM HYDROSULFIDE

—$R_2O_3PCX_2PO_3R_2$— R	X	Reaction temp, °C	Yield of $R_2O_3PCH(X)PO_3R_2$,[a] %
i-C_3H_7	Cl	25	94
i-C_3H_7	Cl	0	84
i-C_3H_7	Br	25	77
i-C_3H_7	Br	0	95
C_2H_5	Cl	25	49
C_2H_5	Cl	0	91
C_2H_5	Br	25	51
C_2H_5	Br	−10	78
C_2H_5	Br	−25	82

[a] Per cent yields were obtained from electronic integration of a ^{31}P nmr spectrum. Reaction conditions were identical except for the variation in temperature. See Experimental Section for details.

where the alkyl groups are ethyl and isopropyl and the halogens are chlorine and bromine. In general, it can be concluded that to obtain maximum yields a lower reaction temperature must be employed for ethyl esters than for isopropyl esters and for bromo derivatives than for chloro derivatives.

The ability of other reducing agents to convert dihalomethylenediphosphonates to monohalomethylenediphosphonates was briefly explored. The results of these experiments are collected in Table II. As can

TABLE II

MISCELLANEOUS REDUCTIONS OF DIHALOMETHYLENEDIPHOSPHONATES

Reducing agent	—$R_2O_3PCX_2PO_3R_2$— R	X	% $R_2O_3PCH(X)PO_3R_2$[a]
NaCN + NaOH	C_2H_5	Br	54
$SnCl_2$	C_2H_5	Br	84
NaCN + NaOH	C_2H_5	Cl	53
$(C_2H_5)_3SiH$	i-C_3H_7	Cl	Low[c,d]
Na_2SO_3[b]	i-C_3H_7	Cl	54

[a] Reactions were run in aqueous methanol at 25°. Equimolar quantities of reagents were employed. Yields were determined by electronic integration of a ^{31}P nmr spectrum. [b] Sodium bicarbonate was added to buffer the solution. [c] A ^{31}P nmr spectrum of the reaction mixture indicated ~5% reaction. [d] Benzene was employed in place of water as solvent for this reaction.

be seen none of these materials was found to be superior to NaSH with the possible exception of $SnCl_2$. In the reduction of tetraethyl dibromomethylenediphosphonate, subzero reaction temperatures were required with NaSH to achieve yields comparable to those obtained with $SnCl_2$ at 25°.

Extension of this synthetic method to other related systems was briefly examined. Table III records the results of the interaction of dihalomalonates and dihalophosphonoacetates with various reducing agents. High yields of monohalo derivatives could be obtained with the proper reducing agent in all cases examined. Triethyl bromophosphonoacetate was not further purified as we were not able to separate it from the dibromo starting material by vacuum distillation.

In the preparation of dihalomalonates and dihalophosphonoacetates it was found convenient to employ a hypohalite halogenation procedure.[2] Purified yields of triethyl dihalophosphonoacetates and diethyl dihalomalonates ranged from 60 to 80%. This halogenation procedure appeared to be superior to reported methods.[6-8] Halogenation of salts of malonic acid by hypohalites has been reported[9] and Bell, *et al.*,[10] have suggested participation of OBr^- bromination when this ion was present as a catalyst for Br_2 bromination of diethyl malonate.

Experimental Section

Melting and boiling points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. The

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(10) R. P. Bell, D. H. Everett, and H. C. Longuet-Higgins, *Proc. Roy. Soc., Ser. A*, **186**, 443 (1946).

TABLE III

REDUCTION OF DIHALOPHOSPHONOACETATES AND DIHALOMALONATES

Dihalo	Reducing agent	Monohalo	% yield	Temp, °C
$Cl_2C(COOC_2H_5)_2$	Na_2SO_3	$ClCH(COOC_2H_5)_2$	82	20
	NaSH		5	−15
$Cl_2C(COOC_2H_5)PO_3(C_2H_5)_2$	Na_2SO_3	$ClCH(COOC_2H_5)PO_3(C_2H_5)_2$	98	20
	SnF_2		<5	0
$Br_2C(COOC_2H_5)_2$	NaSH	$BrCH(COOC_2H_5)_2$	12	−20
	SnF_2		97	0
$Br_2C(COOC_2H_5)PO_3(C_2H_5)_2$	NaSH	$BrCH(COOC_2H_5)PO_3(C_2H_5)_2$	<5	0
	SnF_2		75	0

TABLE IV

PHYSICAL AND ANALYTICAL DATA FOR DIHALOPHOSPHONOACETATES AND DIHALOMALONATES

Compd	Registry no.	Yield,[a] %	C, % Calcd	C, % Found	H, % Calcd	H, % Found	P, % Calcd	P, % Found	Mol wt, % Calcd	Mol wt, % Found	Bp (mm), °C	$n^{25}D$
$Cl_2C(COOC_2H_5)_2$	20165-81-5	59	36.7	36.7	4.4	4.4			229	230	87 (2.4)	1.4404
$Br_2C(COOC_2H_5)_2$	631-22-1	68	26.4	26.9	3.1	2.9			318	310	76–80 (0.3)	1.4830
$Cl_2C(COOC_2H_5)PO_3(C_2H_5)_2$[b]	5823-12-1	80	32.8	32.1	5.1	5.3	10.6	10.8	293	280	115–118 (0.05)	1.4540
$Br_2C(COOC_2H_5)PO_3(C_2H_5)_2$[c]	28845-75-2	79	25.2	24.7	3.9	4.0	8.1	8.1	382	370	125–128 (0.06)	1.4916

[a] Distilled yield. [b] ^{31}P nmr, δ −7.5. [c] ^{31}P nmr, δ −7.0.

TABLE V

PHYSICAL AND ANALYTICAL DATA FOR MONOHALO DERIVATIVES

Compd[b]	Registry no.	Bp (mm), °C	$n^{25}D$	^{31}P nmr,[a] δ (ppm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	P, % Calcd	P, % Found	Mol wt, % Calcd	Mol wt, % Found
$[(i\text{-}C_3H_7)_2O_3P]_2CHCl$	20107-67-9	105–108 (0.05)	1.4465	−11.5 (d, J = 18.2 Hz)	41.3	41.2	7.7	7.9	16.4	16.5	378.5	365
$[(i\text{-}C_3H_7)_2O_3P]_2CHBr$	10596-20-6	140 (0.03)	1.4528	−11.5 (d, J = 17.5 Hz)	37.0	37.1	6.8	7.5	14.65	14.8	423	400
$[(C_2H_5)_2O_3P]_2CHBr$	28845-79-6	127–128 (0.08)	1.4682	−13.0 (m)	29.4	29.1	5.8	5.7	16.9	16.8	367	355
$(C_2H_5)_2O_3P(C_2H_5OOC)CHCl$	7071-12-7	120–124 (0.1)	1.4448	−12.0 (m)	37.1	36.8	6.2	6.2	12.1	12.2	258.5	255
$(C_2H_5OOC)_2CHCl$	14064-10-9	62 (0.1)			43.2	43.9	5.7	6.0			194.5	195
$(C_2H_5OOC)_2CHBr$	685-87-0	87–88 (0.2)	1.4500		37.8	37.5	4.9	4.9			223	235

[a] Chemical shifts relative to 85% H_3PO_4. [b] ^1H nmr spectra were found to be consistent with the assigned structure.

phosphorus nmr spectra were measured using spinning 9-mm glass tubes with a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm. Side-band calibration was used. Varian HA-100 and HR-60 spectrometers were used to obtain the proton spectra. Molecular weights were obtained by vapor pressure osmometry.

Tetraalkyl dihalomethylenediphosphonates were prepared according to the method of Quimby, *et al.*[2] Triethyl dihalophosphonoacetates and diethyl dihalomalonates were also prepared by the hypohalite procedure[2] without significant modification. Table IV reports yields, analyses, and physical characteristics of these materials.

Monohalo derivatives of methylenediphosphonate, phosphonoacetate, and malonate esters were all prepared by the same general procedure. The preparation of tetraisopropyl chloromethylenediphosphonate is considered typical and is given in detail below. Physical characteristics and elemental analyses of the monohalo derivatives prepared by this procedure are collected in Table V. Other information pertinent to their syntheses can be found in Tables I, II, and III.

Tetraisopropyl Chloromethylenediphosphonate.—A solution of sodium hydrosulfide (28 g, 0.5 mol) in 200 cc of water was slowly added to tetraisopropyl dichloromethylenediphosphonate (206.7 g, 0.5 mol) in 200 cc of methanol. The temperature was maintained at 25° throughout the addition. Precipitation of sulfur was noted with the initial addition of NaSH. After addition was complete, the solution was stirred for *ca.* 0.5 hr and then filtered to remove the sulfur (14.8 g, 92.5%). The filtrate was extracted with $CHCl_3$ and the organic portion was dried over Na_2SO_4. Removal of solvent left 185.6 g of a colorless liquid (98%). A ^{31}P nmr spectrum indicated 95% purity. Vacuum distillation gave the pure title compound (see Table V for further details).

Reaction of Sodium Sulfide and Tetraisopropyl Dichloromethylenediphosphonate. Preparation of $[(i\text{-}C_3H_7)_2O_3P]_2CHSSCH[PO_3(i\text{-}C_3H_7)_2]_2$ (I).—Equimolar quantities of Na_2S (39 g, 0.5 mol) and tetraisopropyl dichloromethylenediphosphonate (206.7 g, 0.5 mol) were combined at room temperature in a water–methanol solvent. The resulting mixture was stirred 3 hr at 25° and the temperature was raised to 75° and maintained there for 1 hr. The product was isolated by $CHCl_3$ extraction. After removal of the solvent, the remaining liquid was dissolved in petroleum ether. Compound I crystallized from this solution on cooling. It was recrystallized from hexane–petroleum ether (bp 30–60°) (yield 25–50%, mp 99.5–101.5°): δ −15.2 (d, J = 19 Hz). The ^1H nmr spectrum was consistent with the structure proposed for I.

Anal. Calcd for $C_{26}H_{58}O_{12}P_4S_2$: C, 41.6; H, 7.8; P, 16.5; S, 8.5; mol wt, 750.8. Found: C, 41.5; H, 7.7; P, 16.5; S, 8.8; mol wt, 750.

Registry No.—I, 28845-76-3.

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