Phosphoric Acid Systems[1,2], Part 7. The Halogenation or Nitration of Aryl Compounds in Trialkyl Phosphates

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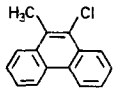
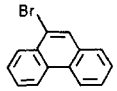
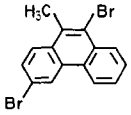
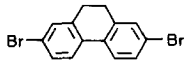
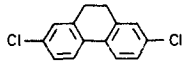
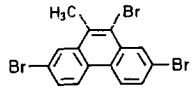
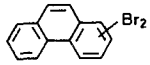
Trimethyl phosphate is a remarkable reacting solvent for halogenation reactions. No hydrogen halide is evolved during the halogenation; rather, the hydrogen halide combines very rapidly with trimethyl phosphate to form methyl halide. Indeed, the reaction is so fast that it may be assumed to proceed in a hydrogen halide-free medium. Therefore, substrates which are sensitive to hydrogen halide may be more amenable to halogenation. With this possibility in mind, the halogenation reactions listed in the Table were carried out. Some of the results of the Table show that the possibility is indeed a reality. 1,3,5-Tris[*t*-butyl]benzene on halogenation under ordinary circumstances gives the dealkylation product (5-bromo-1,3-bis[*t*-butyl]benzene from bromine in carbon tetrachloride)[3] or no reaction (bromine in acetic acid)[4] but on halogenation with the bromine/trimethyl phosphate reagent gives high yields of bromo-1,3,5-tris[*t*-butyl]-

Table. Halogenation Reactions in Trimethyl Phosphate/Phosphorus Pentoxide[a]

Product	Reaction Conditions temperature/time	Yield (%)	m.p. or b.p./torr	Molecular formula
	1. 10°/1 h 2. 25°/3 h	69	120–121°	$C_{15}H_{11}Cl$ (226.7)[b]
	25°[c]	70	62–64°	$C_{14}H_9Br$ (257.1)
	30°/16 h	74[d]	123.5°	$C_{15}H_{10}Br_2$ (350.1)
	70°/16 h	61[e]	163.5–165°	$C_{14}H_{10}Br_2$ (338.1)[b]
	70°/16 h	60[e]	142–143°	$C_{14}H_{10}Cl_2$ (249.1)[b]
	1. 25°/3 h 2. 70°/12 h	39[f]	235–237°	$C_{15}H_9Br_3$ (429.0)[b]
	50°/5 h	100[g]	93–175°	$C_{14}H_8Br_2$ (336.0)

[a] By the general procedure given. ^{1}H-N.M.R. spectra on all products were compatible with the structure proposed.

[b] Analyses (C, H or halogen) were by Galbraith Labs and were within ±0.2% of the calculated value.

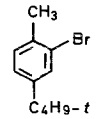
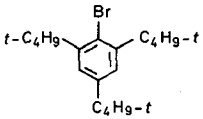
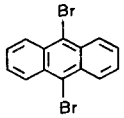
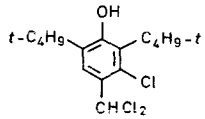
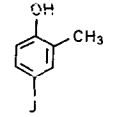
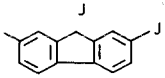
[c] On slow addition of bromine in trimethyl phosphate the 9,10-dibromo-9,10-dihydrophenanthrene first precipitated out and on stirring overnight redissolved to form 9-bromophenanthrene in a mildly exothermic reaction.

[d] From 6-bromo-9-methylphenanthrene. Thanks are due to Dr. K. N. Subbaswami for this preparation.

[e] From 9,10-dihydrophenanthrene.

[f] From 9-methyl-9,10-dihydrophenanthrene[7]. In this reaction both substitution and aromatization have taken place. The ^{1}H-N.M.R. spectrum of the product was unequivocal. The 9-methyl substituent was fixed by the structure of the starting material. ^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.90$ (s, 3, CH_3), 7.65–7.74 (d of d, H-6, $J_{6,8} = 1.1$, $J_{6,5} = 9.1$ Hz), 7.70–7.79 (d of d, H-3, $J_{3,1} = 1$, $J_{3,4} = 9.1$ Hz), 8.20–8.24 (d, H-8, $J_{8,6} = 1.1$ Hz), 8.3–8.45 (d, H-5, $J_{5,4} = 9.1$ Hz), 8.36–8.50 (d, H-4, $J_{4,5} = 9.1$ Hz), 8.56–8.6 ppm (d, H-1, $J_{1,3} = 1.1$ Hz).

Table. (Continued)

Product	Reaction Conditions temperature/time	Yield (%)	m.p. or b.p./torr	Molecular formula
	25°/18 h	50[h, 6]	54–56°/0.15	$C_{11}H_{15}Br$ (227.2)
	5–10°/4 h	24	149–152°/760	C_4H_3BrS (163.0)
	65°/24 h	59 (90, crude)[i]	171.5–173.5°	$C_{18}H_{29}Br$ (325.3)
	25°/18 h	42[j]	244–245°	$C_{14}H_8Br_2$ (336.0)
	80°/18 h	11[k]	176–178°	$C_{15}H_{21}Cl_3O$ (430.0)[b]
	80°/12 h	60[8] (40, pure)	66.5–68°	C_7H_7JO (234.0)
	80°/12 h	80 (40, pure)	211–213.5°[9]	$C_{13}H_8J_2$ (418.0)

[g] By extensive chromatography, small amounts of 9,10- (m.p. 172–176°), 3,9- (m.p. 145°), and perhaps 3,9- (m.p. 142–144°) -dibromophenanthrenes were isolated.

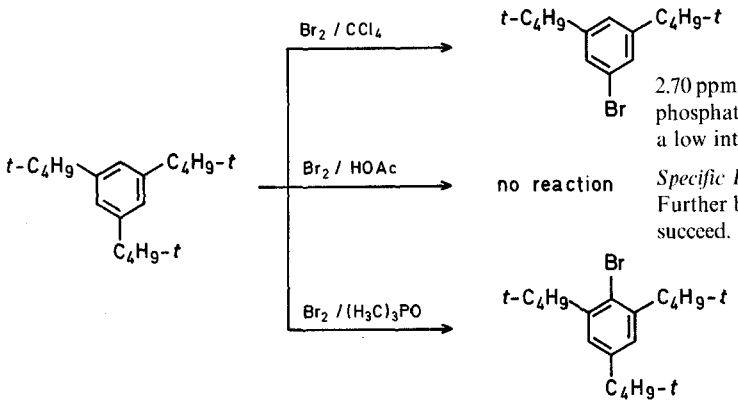
[h] The crude oil contained an impurity (not the α-bromomethyl compound) which decomposed on distillation to give hydrogen bromide and tar. The impurity was removed by treatment with ammonium hydroxide in methanol for 2 days prior to spinning band distillation.

[i] ^{1}H-N.M.R. at 25° or 0° was identical: $\delta = 1.37$ (s, 9H), 1.58 (s, 18H), 7.37 ppm (s, 2H), indicating no interference between Br and t-C_4H_9.

[j] Only one equivalent of bromine was used. Based on bromine, the yield was 84%.

[k] Unequivocal ^{1}H-N.M.R.: $\delta = 1.2$ (18H, d, 2 t-C_4H_9), 5.18 (1H, s, $CHCl_2$), 6.6 (1H, s, OH), 7.2 ppm (1H, s, arom. H).

benzene. Moreover, 2,6-bis[*t*-butyl]-4-cresol, another substrate subject to dealkylation, is exhaustively chlorinated to 2,6-bis[*t*-butyl]-3-chloro-4-dichloromethylphenol, a new compound, indicative of no dealkylation.



General observations were that bromine or chlorine in trimethyl phosphate were quite mild reagents capable of substitution into nuclei as active as, or more reactive than, benzene. Iodination could be carried out on less active substrates only with iodine monochloride but with iodine itself on phenols. Iodination, however, was more limited in its preparative scope than bromination or chlorination. Another noteworthy halogenation from the Table is the exhaustive bromination of 9-methylphenanthrene to give 2,7,10-tribromophenanthrene. The preparation succeeded because of the separation of this high melting solid from the reaction mixture. Most of the halophenanthrenes in Table were used to prepare potential antimalarials[5].

Many practical observations are to be found in the Experimental Section, and a novel nitration experiment with trimethyl phosphate and phosphorus pentoxide is described also.

General Procedure for Halogenation:

To the substrate (0.05 mol) dissolved in trimethyl phosphate (Aldrich, 100 ml), magnetically stirred, was added the halogen (0.06 mol) in trimethyl phosphate (50 ml) (rapidly if not decolorized, slowly if decolorized). This solution, protected from moisture and from light, was held first at 50° until the color noticeably lightened (usually to a cream yellow) and then at somewhere below 100° if color has not lightened. Some substitutions took overnight. After completion of the reaction, the mixture was diluted with water, filtered to remove the organic solid or extracted with hexane to remove the organic oil. Trimethyl phosphate is not soluble in hexane but is soluble in benzene or dichloromethane. Rather than extract with the latter two solvents, the trimethyl phosphate was on occasion removed at reduced (1–2 torr) pressure.

Helpful Remarks:

For chlorination, chlorine was bubbled into cold trimethyl phosphate until the weight increase was correct. Trimethyl phosphate is an excellent solvent for the halogens. Chlorine has been kept for a year dissolved in trimethyl phosphate protected from light.

Trimethyl phosphate contained about 3% methanol. The methanol was not removed in the above halogenations. However, phosphorus pentoxide could be added to trimethyl phosphate to remove the methanol. Trimethyl phosphate in our experience is the only non-acidic solvent that will dissolve phosphorus pentoxide. We are carrying on further experiments making use of this observation. Incidentally, halogenation may be carried out in trimethyl phosphate in which phosphorus pentoxide is dissolved, but the results were no different than using trimethyl phosphate itself.

Triethyl phosphate could be used in place of trimethyl phosphate in all halogenation reactions; it does not dissolve phosphorus pentoxide, however, nor does it work as well in iodination.

Methyl bromide was detected in the bromination reactions in trimethyl phosphate by the appearance of a sharp singlet at 2.70 ppm in the ^{1}H-N.M.R. spectrum. The commercial trimethyl phosphate showed a doublet at 3.68 ppm, $J_{P,H} = 12.4$ Hz, and a low intensity signal at 3.21 ppm (methanol).

Specific Reactions:

Further bromination of bromo-1,3,5-tris[*t*-butyl]benzene did not succeed.

Exhaustive chlorination of 2,6-bis[*t*-butyl]-4-cresol was carried out with 6 equivalents of chlorine in trimethyl phosphate added dropwise and the solution held overnight at 80° and extracted with hexane after dilution.

Nitration of Anthracene; Typical Procedure:

Trimethyl phosphate (30 ml), phosphorus pentoxide (10 g), and anthracene (5.5 g, 0.03 mol) were stirred at 23° while sodium nitrate (3.6 g, 0.03 mol) was added in portions over 30 min. The mixture was allowed to stand for 18 h and was then diluted with water (90 ml). The yellow solid was filtered off and crystallized from alcohol to give small yellow needles of *9-nitroanthracene;* yield: (71%); m.p. 144–145°.

Similarly, *9-methylphenanthrene* gave *9-methyl-10-nitrophenanthrene;* yield: 37%; m.p. 168–170°. No attempt was made to maximize these yields.

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[1] Part 1: R. G. Downey, D. E. Pearson, *J. Am. Chem. Soc.* **83**, 1718 (1961).
Part 2: R. G. Downey, D. E. Pearson, *J. Am. Chem. Soc.* **84**, 4956 (1963).
Part 3: D. E. Pearson, R. M. Stone, *J. Am. Chem. Soc.* **83**, 1715 (1961).
Part 4: C. Rai, A. W. Marcellis, *U.S. Patent* 3,703,250 (1973); the name of D. E. Pearson was added to this patent on 19. 11. 1974.
Part 5: D. E. Pearson, *J. Chem. Soc. Chem. Commun.* **1974**, 397.
Part 6: D. E. Pearson, *U.S. Patent.*

[2] Partial support of Cities Service Oil Co. is acknowledged.

[3] P. D. Bartlett, M. Roha, R. M. Stiles, *J. Am. Chem. Soc.* **76**, 2349 (1954).

[4] This laboratory obtained α-bromoacetic acid with no evidence of attack on tris-[*t*-butyl]benzene. The bromine/acetic acid reagent may be viewed as a bromination system buffered at a lower substitution potential than the bromine/trimethyl phosphate reagent. Direct bromination of 1,3,5-tris[*t*-butyl]benzene has been achieved in the presence of silver perchlorate or silver nitrate:
P. C. Myhre, *Acta Chem. Scand.* **14**, 219 (1960).
H. E. Zimmerman, J. R. Dodd, *J. Am. Chem. Soc.* **92**, 6507 (1970).

[5] L. C. Washburn, D. E. Pearson, *J. Med. Chem.* **17**, 676 (1974).

[6] P. W. Rabideau, R. G. Harvey, *J. Org. Chem.* **35**, 25 (1970).

[7] L. Stock, H. C. Brown, *J. Am. Chem. Soc.* **81**, 5615 (1959).

[8] C. M. Suter, R. D. Schultz, *J. Org. Chem.* **16**, 1117 (1974).

[9] Lit. m.p. 215°, V. T. Slyusarchuk, A. N. Novikov, *Zh. Org. Khim.* **3**, 1323 (1967); *C. A.* **67**, 99898 (1967).

Erratum

D. E. Pearson, M. G. Frazer, V. S. Frazer, L. C. Washburn *Synthesis* **1976** (9), 621–623.

Reference 1, Part 6 (p. 623) should be: D. E. Pearson, *U.S. Patent* 3,988,369, Oct. 26, 1976.