The Stereochemistry of Phosphine-induced Debromination Reactions

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The stereochemistry of dehalogenation reactions with triphenylphosphine (a two-electron dehalogenating reagent) has been investigated. Both *eythro*- (or *meso*-) and *threo*- [or (±)-] dibromides give entirely *trans*-olefin, except for (±)-stilbene dibromide which gave a 36:65 *cis–trans*-mixture (the olefins formed were identified by n.m.r. spectroscopy). Authentic samples of *cis*-olefin in each case were shown *not* to isomerise to the *trans*-form under the reaction conditions. The mechanism of dehalogenation is briefly discussed in terms of initial attack of phosphine on halogen to give an intermediate ion pair. Evidence for this is available from the reaction of 1,2-dibromo-2-nitrostyrene with triphenylphosphine in methanol, which gave 2-nitro-1-phenylethyltriphenylphosphonium bromide. With *erythro*-2,3-dibromobutyric acid, dehydrohalogenation, rather than debromination, occurred to give a mixture of α-bromocrotonic and α-bromoisocrotonic acids. Attempts to extend the dehalogenation reaction to the formation of three- and six-membered rings were unsuccessful.

DEHALOGENATION of a range of 1,2-dihalides has been effected by a wide variety of reagents. Stilbene dihalides have been most thoroughly investigated, and Miller and his co-workers[1] have studied the effect of reagents and conditions on the stereochemistry of this reaction with a view to finding a system where the elimination is stereospecifically *syn* or *anti*. *meso*-Stilbene dibromide (1) gave 100% *trans*-stilbene regardless of the dehalogenating reagent used, whereas the (±)-compound (2) gave reagent-dependent mixtures of *cis*- and *trans*-alkene. The dehalogenating reagents could be divided into two groups. Two-electron reagents (*e.g.* Pt^{II}, RS^-, and I^-) followed a mainly concerted *anti*-mechanism

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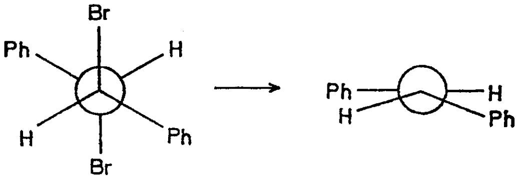
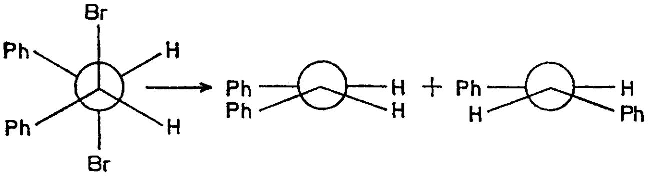
[1] (*a*) M. Mathai, K. Schug, and S. I. Miller, *J. Org. Chem.*, 1970, **35**, 1733; (*b*) W. K. Kwok and S. I. Miller, *J. Amer. Chem. Soc.*, 1970, **92**, 4599.

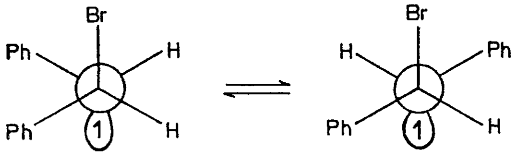
to give largely *cis*-alkene from (±)-dibromide. When a one-electron reductant (Fe^{II} or Cr^{II}) was used, (±)-dibromide gave >95% *trans*-alkene and an intermediate, equilibrating benzylic radical (3) was suggested. In view of this, tervalent phosphorus (a two-electron reagent) appeared to offer a potentially stereospecific debromination route (however see ref. 1).



(1)



(2)



(3)

$$R^1CH_AX{\cdot}CH_BXR^2 + R_3P \longrightarrow R^1CH_A{=}CH_BR^2 + R_3PX_2$$

(4) (5)

Tervalent phosphorus has been widely applied as a dehalogenating agent, phosphites being used in the majority of cases,[2,3] although phosphide anions[4] and phosphines[5] have also been studied. For the best yields (80—100%) of alkene[5,6] R^1 and R^2 in the dihalide (4) should both be strongly electron-withdrawing groups. However the major reaction pathway is still dehalogenation (50—60%) when only one group is electron-withdrawing.[3]

The *erythro*- and *meso*-dibromides (Table 1) were prepared by bromination of the corresponding *trans*-alkenes in chloroform or carbon tetrachloride. (±)-Dibromides (Table 1) were prepared by bromination of the corresponding *cis*-alkenes in non-polar solvents (the proportion of *meso*-isomer has been shown to increase with increasing solvent polarity[7]). The purity of individual dibromides was established from n.m.r. data (Table 1); vicinal H–H coupling constants are larger for *erythro*- or *meso*-isomers (5—11 Hz) than for *threo*- or (±)-isomers (0—6 Hz).[7] Assigned *threo*-dibromide (4g) shows an unusually large value for $J_{1,2}$ (10·5 Hz); however the coupling constant in the *erythro*-isomer is even larger (14·7 Hz).

Debromination of *erythro*- and *meso*-dibromides with triphenylphosphine gave high yields of entirely *trans*-alkene (Table 1). Pure *trans*-alkene was also obtained from the *threo*- and (±)-isomers, except in the case of (±)-stilbene dibromide where a *cis–trans* ratio of 35 : 65 was obtained.* The stereochemistry of the alkenes formed by debromination reactions was determined from values of coupling constants of olefinic protons (Table 2) or, where this was not possible, from g.l.c. Isomerisation of either *cis*- or *trans*-stilbene was not extensive, and no trace of diethyl fumarate was found in samples of diethyl maleate subjected to typical reaction conditions.

TABLE 1

The dibromides (4; X = Br) and their debromination

(4)		R^1	R^2	$\tau(H_A)$	$\tau(H_B)$	J_{AB}/Hz	Solvent	Temp. (°C)	Time (min)	Yield of alkene (%)
a	*erythro*	Ph	NO_2	4·50(d)	3·66(d)	11	EtOAc	20	30	85 (*trans*)
b	*erythro*	3-ClC_6H_4	NO_2	4·50(d)	3·60(d)	11	EtOAc	20	30	78 (*trans*)
c	*erythro*	4-MeC_6H_4	NO_2	4·47(d)	3·59(d)	11	C_6H_6	20	30	94 (*trans*)
d	*erythro*	4-$MeO{\cdot}C_6H_4$	NO_2	4·45(d)	3·57(d)	11	EtOAc	20	30	89 (*trans*)
e	*erythro*	Me	NO_2	5·4(m)	4·04(d)	10	Et_2O	20	30	66 (*trans*)
f	*erythro*	Ph	CO_2H	*a*			EtOAc	20	180	86 (*trans*)
g	*erythro*	Ph	Bz	4·31	4·11	14·7	C_6H_6	80	15	88 (*trans*)
	threo	Ph	Bz	4·41	4·24	10·5	C_6H_6	80	15	63 (*trans*)
h	(±)	Ph	Ph	4·53(s)			Xylene	150—160	240	81 {65 (*trans*) 35 (*cis*)
	meso	Ph	Ph	4·53(s)			Xylene	150—160	240	76 (*trans*)
i	(±)	CO_2Et	CO_2Et	5·34(s)			C_6H_6	20	300	63 (*trans*)
	meso	CO_2Et	CO_2Et	5·34(s)			C_6H_6	20	300	76 (*trans*)
j	*erythro*	Me	CO_2H	5·60(m)		10·7				

[a] Insolubility precluded n.m.r. measurements.

Initial attack of phosphorus at an activated halogen

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* Miller[1] obtained entirely *trans*-stilbene from a reaction in refluxing toluene; however the higher temperature and different solvent used in our experiments may be important.

[2] S. Dershowitz and S. Proskauer, *J. Org. Chem.*, 1961, **26**, 3595.

[3] J. P. Schroeder, L. B. Tew, and V. M. Peters, *J. Org. Chem.*, 1970, **35**, 3181.

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[5] C. C. Tung and A. J. Speziale, *J. Org. Chem.*, 1963, **28**, 1521.

[6] A. J. Speziale and C. C. Tung, *J. Org. Chem.*, 1963, **28**, 1353.

[7] R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, 1968, **90**, 4429.

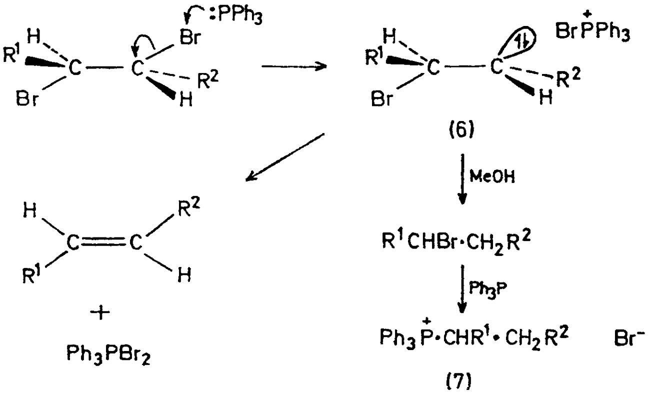
atom is well established[8] and formation of alkenes from the dibromides (4) by attack at a halogen atom could either be concerted or take place *via* an intermediate ion pair (6) (which in the *erythro*- or *meso*-cases presumably eliminates bromide before rotation). Evidence for the intermediacy of (6) was obtained from experiments in methanol, where the salt (7; $R^1 = Ph, R^2 = NO_2$) and triphenylphosphine oxide were obtained from 1,2-dibromo-1-nitro-2-phenylethane and triphenylphosphine, presumably by protonation of the intermediate carbanion followed by quarternisation (Scheme 1). The structure of the salt (7; $R^1 = Ph, R^2 = NO_2$) was confirmed by comparison with an authentic sample prepared from triphenylphosphine, β-nitrostyrene, and aqueous hydrobromic acid.[9]* No trace of crotonic acid was obtained from the reaction of *erythro*-2,3-dibromobutyric acid (8) with triphenylphosphine; instead the major product was α-bromoisocrotonic acid (9), with smaller amounts of α-bromocrotonic acid (10) (Scheme 2). Presumably both isomers (9) and (10) are formed by initial removal of an α-proton by phosphine, followed by elimination of bromide ion. A non-concerted process involving inversion and rotation is required to explain the formation of α-bromocrotonic acid by an *anti*-elimination. The reason for dehydrobromination being preferred to debromination in this reaction is not clear, since *erythro*-2,3-dibromocinnamic acid gives *trans*-cinnamic acid in high yield on treatment with triphenylphosphine.

TABLE 2

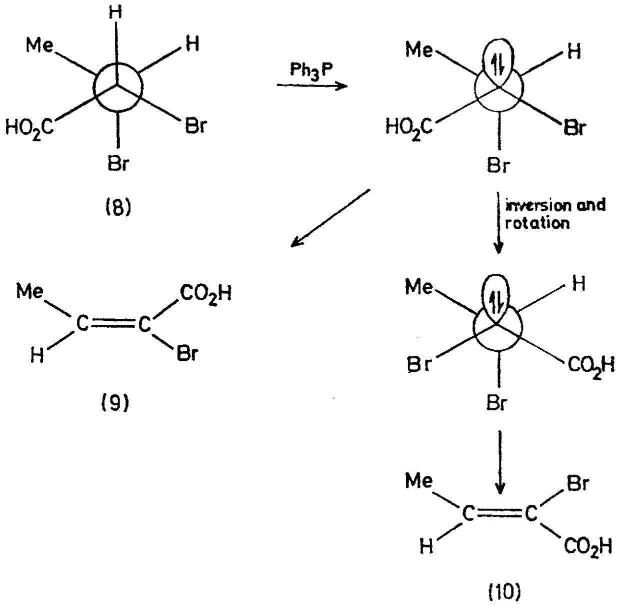
N.m.r. data for the alkenes (5)

(5)		R^1	R^2	$\tau(H_A)$	$\tau(H_B)$	J_{AB}/Hz
a	*trans*[b]	Ph	NO_2	2·00	2·42	13·5
b	*trans*[b]	3-ClC_6H_4	NO_2	2·07	2·45	13·5
c	*trans*[b]	4-MeC_6H_4	NO_2	2·01	2·43	13·5
d	*trans*[b]	4-$MeO{\cdot}C_6H_4$	NO_2	2·02	2·47	13·5
e	*trans*[b]	Me	NO_2	2·5—3·1		14·0[a]
f	*trans*[b]	Ph	CO_2H	2·24	3·56	16·0
g	*trans*[c]	Ph	Bz			
h	*trans*	Ph	Ph	2·90		
	cis	Ph	Ph	3·50		
i	*trans*	CO_2Et	CO_2Et	3·20		
	cis	CO_2Et	CO_2Et	3·76		

[a] Obtained by irradiating at the methyl frequencies. [b] Olefinic protons appeared as an AB quartet. [c] Olefinic proton signals were obscured by aromatic proton signals.



SCHEME 1



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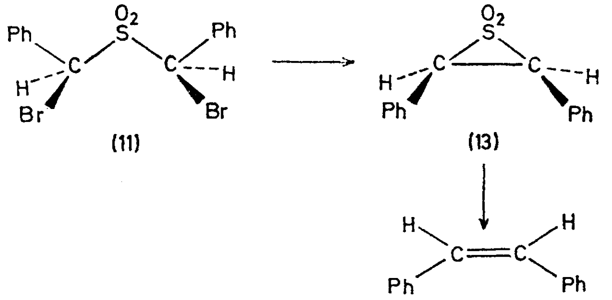

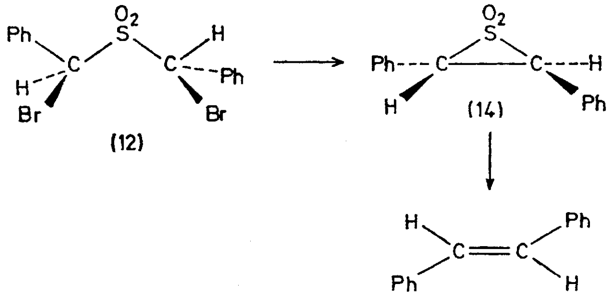

Phosphines have also been used in 1,3-debrominations. Bordwell has shown[10] that *meso*- (11) and (±)- (12) dibromo-sulphones are stereospecifically debrominated by triphenylphosphine to give high yields of *cis*- and

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* Reactions carried out under the conditions of ref. 9 afforded large amounts of polymeric material. The use of freshly distilled hydrobromic acid and ethanol as a solvent gave much higher yields of (7; $R^1 = Ph, R^2 = NO_2$).

[8] B. Miller, *Topics Phosphorus Chem.*, 1965, **2**, 133.

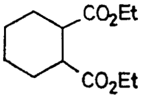
[9] H. Hoffmann, *Chem. Ber.*, 1961, **94**, 1331.

[10] F. G. Bordwell, B. B. Jarvis, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, 1968, **90**, 5298.

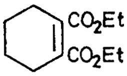
trans-stilbene, respectively, presumably *via* the episulphones (13) and (14). In view of this we investigated phosphine-induced debromination as a possible route to cyclic compounds. However, no trace of the diesters (16) and (17) could be found after refluxing the dibromo-octanedioate (15) with triphenylphosphine in benzene. Similarly neither diphenylcyclopropanone nor diphenylcyclopropenone were formed in the reaction of triphenylphosphine with the dibromide (18) under analogous conditions.

$EtO_2C\cdot CHBr\cdot[CH_2]_4\cdot CHBr\cdot CO_2Et$

(15)



(16)



(17)

$Ph\cdot CHBr\cdot CO\cdot CHBr\cdot Ph$

(18)

EXPERIMENTAL

M.p.s were taken with a Kofler micro hot-stage apparatus. I.r., mass, and n.m.r. spectra were obtained with a Perkin-Elmer model 457, an A.E.I. MS-902, and a Varian HA-100 spectrometer (tetramethylsilane as internal reference) respectively. G.l.c. was carried out on a Perkin-Elmer F-11 instrument.

1,2-*Dibromo*-1-(3-*chlorophenyl*)-2-*nitroethane*.—To 1-(3-chlorophenyl)-2-nitroethylene (5b)[11] (4·22 g, 0·023 mol) in chloroform (40 ml), bromine (3·68 g, 1·19 ml, 0·023 mol) was added dropwise at room temperature. The resulting solution was refluxed for 12 h, the chloroform was removed under reduced pressure, and the residue was recrystallised from ethanol to give 1,2-*dibromo*-1-(3-*chlorophenyl*)-2-*nitroethane* (5·5 g, 70%), m.p. 64—65°; $\nu_{max.}$ (KBr) 1565 and 1345 cm^{-1}; *m*/*e* 347(3%), 345(12), 343(17), 341(7), 220(20), 218(100), 216(73), 185(16), and 183(53) (Found: C, 28·0; H, 1·8. $C_8H_6Br_2ClNO_2$ requires C, 28·0; H, 1·7%).

Debromination of erythro-1,2-*Dibromo*-1-*nitro*-2-*phenylethane* (4a) *with Triphenylphosphine*.—To *erythro*-1,2-dibromo-1-nitro-2-phenylethane (4a)[12] (1·54 g, 0·005 mol) in ether (100 ml), triphenylphosphine (1·31 g, 0·005 mol) in the same solvent (100 ml) was added with stirring at room temperature. Stirring was continued for 1 h. The white solid which formed was then filtered off and shown to be identical with an authentic sample of triphenylphosphine dibromide[6] by comparison of i.r. spectra. The fuming solid was added to water (100 ml) and the resulting slurry was stirred for 10 min. Extraction with ethyl acetate (100 ml), drying, and evaporation gave triphenylphosphine oxide (1·25 g, 90%), m.p. and mixed m.p. 154—155°.

The filtrate was evaporated and the yellow oily residue was recrystallised from ethanol to give *trans*-β-nitrostyrene (5a) (0·62 g, 85%), m.p. and mixed m.p. 57—58° (lit.,[13] 57—58°).

By the same procedure *erythro*-1,2-dibromo-(3-chlorophenyl)-2-nitroethane (4b), *erythro*-1,2-dibromo-(4-methylphenyl)-2-nitroethane (4c),[14] *erythro*-1,2-dibromo-(4-methoxyphenyl)-2-nitroethane (4d),[15] *erythro*-1,2-dibromodihydrocinnamic acid (4f),[16] and *erythro*- and *threo*-dibromochalcones (4g)[17] gave the corresponding alkenes and triphenylphosphine oxide. The conditions employed for debromination are summarised in Table 1; the work-up procedure in each case was that given for the reaction of compound (4a), with the following minor variations.

1-Nitroprop-1-ene (5e), obtained from the debromination of 1,2-dibromo-1-nitropropane (4e),[18] was distilled; b.p. 50—52° at 26 mmHg. *trans*-Cinnamic acid (5b), obtained from the debromination of *erythro*-1,2-dibromodihydrocinnamic acid (4f), was extracted from the reaction mixture with aqueous sodium hydroxide. The products from the reactions of (±)- and *meso*-1,2-dibromo-1,2-diphenylethane (4 h)[19] with triphenylphosphine were analysed before the work-up by g.l.c. on a 5% silicone gum rubber column at 240°. The solvent was then removed under reduced pressure, and the residue washed with water and recrystallised from ethanol to give *trans*-stilbene, m.p. 122—123° (lit.,[20] 124°).

The products from the reactions of *meso*- and (±)-diethyl dibromosuccinate (4i)[21] were also analysed by g.l.c. on a diethylene glycol succinate column at 150°, both before and after work-up. The benzene was removed under reduced pressure; the residue was washed with water, extracted with ether, and dried. Distillation gave in both cases diethyl fumarate, b.p. 95—96° at 10 mmHg (lit.,[20] 99° at 12 mmHg).

Reaction of erythro-2,3-*Dibromobutyric Acid* (4j)[22] *with Triphenylphosphine*.—Triphenylphosphine (2·62 g, 0·01 mol) in ethyl acetate (80 ml) was added to a stirred solution of *erythro*-2,3-dibromobutyric acid (4j) in ethyl acetate (150 ml) at 0° over 10 min. The temperature was allowed to rise gradually to 20° during 4 h, during which time a white precipitate formed. The solution was again cooled to 0°. The solid was filtered off, treated with water (100 ml), and extracted with ethyl acetate (150 ml). The organic layer was filtered, washed with water, dried, and evaporated to give a white solid (1·0 g) which showed two spots on t.l.c. (with similar R_F values to triphenylphosphine and triphenylphosphine oxide). Triphenylphosphine (0·8 g) was isolated as methyltriphenylphosphonium iodide (1·23 g), m.p. and mixed m.p. 182—183°, by treatment of this solid with methyl iodide in benzene.

The filtrate from the original reaction mixture was evaporated to give a white oil (2·0 g), which on treatment with aqueous 2N-sodium hydroxide (50 ml) precipitated triphenylphosphine oxide (0·4 g). The filtrate was neutralised with

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[11] N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 1940, 446.

[12] B. Prieks, *Annalen*, 1884, **225**, 343.

[13] D. E. Worrall, *Org. Synth.*, 1932, Coll. Vol. 1, p. 405.

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[17] R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Amer. Chem. Soc.*, 1951, **73**, 4647.

[18] E. Schmidt and G. Rutz, *Ber.*, 1928, **61**, 2142.

[19] R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *J. Amer. Chem. Soc.*, 1950, **72**, 2496; R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, 1967, **32**, 888.

[20] Heilbron's 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.

[21] H. R. Ing and W. H. Perkin, jun., *J. Chem. Soc.*, 1924, **125**, 1814.

[22] T. C. James, *J. Chem. Soc.*, 1910, **97**, 1565.

concentrated hydrochloric acid and extracted with methylene chloride to give a mixture of *cis*- and *trans*-1-bromobut-2-enoic acids (0·5 g, 58%), m.p. 80—86°, in the ratio 6 : 1 (n.m.r. spectrum). This mixture was dissolved in ethanol (5 ml) and treated with alcoholic 10% potassium hydroxide until neutral to phenolphthalein. The resulting solution slowly (2 h) deposited a white solid, which was filtered off and dried. Treatment of this solid with 2N-hydrochloric acid (25 ml), extraction with ether, drying, and evaporation gave the *trans*-acid (10) (0·08 g, 9%), m.p. 104—107° (lit.,[22] 107°), τ ($CDCl_3$) −0·80 (1H, s), 2·46 (1H, q), and 8·03 (3H, d) (*J* 8 Hz). Evaporation of the neutral filtrate gave a white solid which on treatment with dilute hydrochloric acid and extraction with ether gave the *cis*-acid (9) (0·32 g, 37%), m.p. 89—92° (lit.,[22] 92°), τ ($CDCl_3$) −1·32 (1H, s), 3·01 (1H, q), and 7·88 (3H, d) (*J* 8 Hz).

Reaction of 1,2-*Dibromo*-1-*nitro*-2-*phenylethane* (4a) *with Triphenylphosphine in Methanol*.—*erythro*-1,2-Dibromo-1-nitro-2-phenylethane (3·09 g, 0·01 mol) in methanol (100 ml) was added to triphenylphosphine (5·24 g, 0·02 mol) in methanol (500 ml) at room temperature. The resulting solution was refluxed for 40 min, cooled, and evaporated under reduced pressure. The residue was treated with ethyl acetate (200 ml) and left overnight. Filtration gave 2-nitro-1-phenylethyltriphenylphosphonium bromide (7; R^1 = Ph, R^2 = NO_2) (4·1 g, 83%), m.p. 189—191° (lit.,[9] 191°), τ ($CF_3{\cdot}CO_2H$) 4·65 (2H, m). The filtrate was evaporated and the residue chromatographed on neutral alumina to give triphenylphosphine (0·2 g), m.p. and mixed m.p. 78—79°, and triphenylphosphine oxide (2·3 g), m.p. and mixed m.p. 153—154°.

Reaction of Diethyl 2,7-*Dibromo-octanedioate* (15) *with Triphenylphosphine*.—Diethyl 2,7-dibromo-octanedioate (15) (6·29 g) was added to triphenylphosphine (4·23 g) in dry benzene (70 ml) and the mixture was refluxed for 12 h. On cooling, traces of a white solid appeared; this was filtered off and the filtrate treated with methyl iodide (5 ml) to give methyltriphenylphosphinium iodide (3·5 g), m.p. and mixed m.p. 182—183°. G.l.c. of the mother liquors from this reaction showed no trace of diethyl cyclohexane-1,2-dicarboxylate (16).

Reaction of Bis-α-bromobenzyl Ketone (18) *with Triphenylphosphine*.—The ketone (18) (3·68 g) in dry benzene (25 ml) was added to triphenylphosphine (2·62 g) in dry benzene (30 ml) and the mixture was refluxed overnight. Traces of a semi-solid salt-like substances, which could not be further purified, were precipitated; treatment of the mother liquors with methyl iodide (10 ml) gave methyltriphenylphosphonium iodide (1·4 g), m.p. and mixed m.p. 181—182°.

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