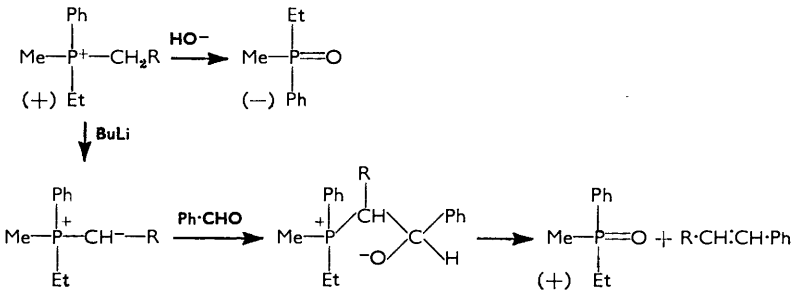
## 85. *Optically Active Phosphorus Compounds. Part II.* The Configurational Change Accompanying Transesterification.*

By M. Green and R. F. Hudson.

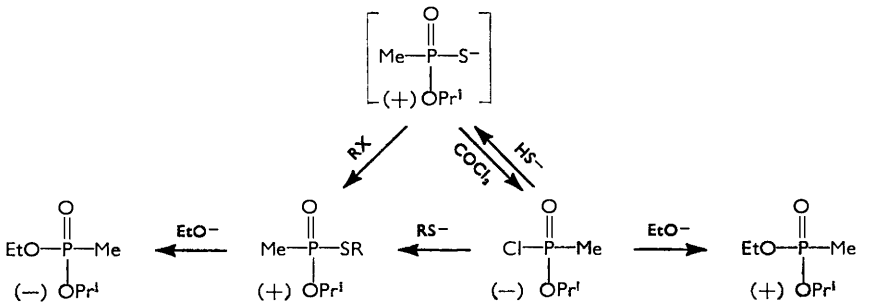
Transesterification of *O*-alkyl and *S*-alkyl esters is shown to give optically active products, which are rapidly racemised by an excess of alkoxide ions, suggesting that the reaction proceeds with inversion of configuration. This was confirmed for one reaction by comparing the rate of racemisation of methyl phenylethylphosphinate by methoxide ions with the rate of exchange of the [$^{14}$C]methoxy-group.

Convenient methods for resolving phosphorus compounds containing an asymmetric phosphorus atom into their optically active enantiomorphs have been developed recently,[1] and investigations of optical activity changes accompanying substitution have been reported. Particular success has been achieved with quaternary phosphonium compounds by Vander Werf, McEwen, and their collaborators,[2] who have shown that the corresponding phosphine oxide may be obtained stereospecifically in both (+)- and (−)-forms:




By making the reasonable assumption that the Wittig reaction [3] proceeds through a cyclic transition state and hence with retention of configuration, it follows that the displacement with hydroxide ions proceeds with stereochemical inversion. The stereospecificity of these reactions was deduced by comparing the rotations of the phosphine oxides obtained with those of the compounds originally resolved by Meisenheimer *et al.*[4]

Progress with phosphoryl and thiophosphoryl compounds has been somewhat slower, mainly because of the rapid racemisation of some of the intermediates by traces of salts or acid. Moreover, attempts to devise stereochemical cycles of the kind [5] which first established the Walden inversion of carbon compounds have been unsuccessful.




* The paper by Green and Hudson, *J.*, 1958, 3129, is considered as Part I.

[1] Aaron, Uyeda, Frack, and Miller, *J. Amer. Chem. Soc.*, 1962, **84**, 617.

[2] McEwen and Vander Werf, *J. Amer. Chem. Soc.*, 1959, **81**, 3805; Bladé-Font, McEwen, and Vander Werf, *ibid.*, 1960, **82**, 2396, 2646; Parisek, McEwen, and Vander Werf, *ibid.*, p. 5503.

[3] Wittig and Geissler, *Annalen*, 1953, **580**, 44; Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

[4] Meisenheimer, Casper, Höring, Lauter, Lichtenstadt, and Samuel, *Annalen*, 1926, **449**, 213.

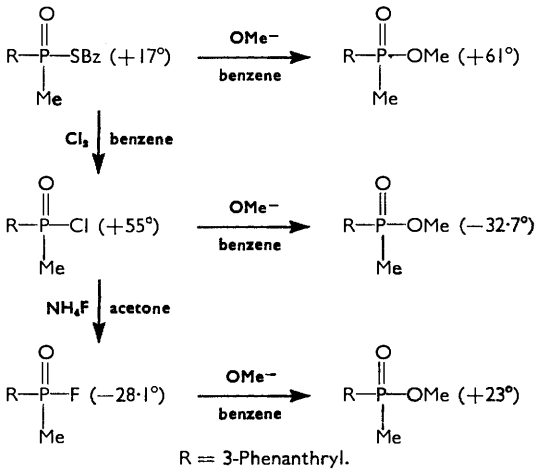
[5] See Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, p. 372.

Recently, Aaron *et al.*[1] have shown that (+)- and (−)-forms of ethyl isopropyl methylphosphonate can be prepared from (+)-isopropyl hydrogen methylphosphonothiolate by the routes illustrated, showing that at least one of these displacements involves predominant inversion of configuration.

By assuming that the two displacements involving ethoxide ions proceed with the same stereochemical change, it follows that the thiolate and the chloridate have opposite configurations, so that the reaction of the chloridate with the thiolate ion proceeds with inversion. It would also follow that, since the alkylation of the thiolic acid proceeds with retention of configuration, the reaction between sodium *O*-isopropyl methylphosphonothiolate and carbonyl chloride proceeds with inversion.

Unfortunately, in most of these reactions considerable decreases in optical purity were observed.

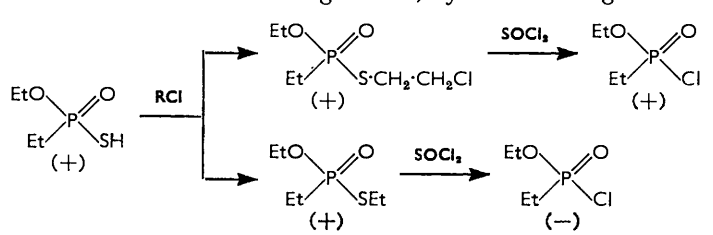
A similar series of displacements, leading to solutions of a methylphosphinate with opposite rotations, previously reported by Green and Hudson,[6] may be summarised as follows:




R = 3-Phenanthryl.

By making the reasonable assumption that reactions between anions and the phosphinic derivatives involve the same stereochemical change, it follows that all these reactions proceed with inversion of configuration. It should be noted that no definite conclusions can be drawn from this study, as the products were not isolated owing to racemisation and decomposition on distillation. These observations nevertheless provided a basis for more suitable studies and drew attention to the desirability of using less reactive intermediates for further investigations.

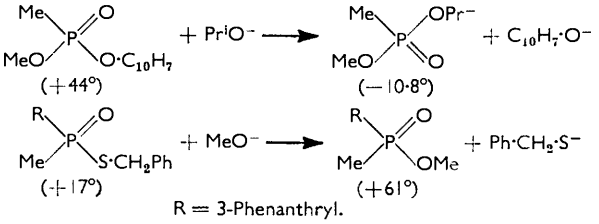
The general assumption that similar reactions proceed with similar stereochemical changes must be used with caution in view of the recent observations by Michalski and Ratajczak,[7] that (+)- and (−)-forms of a given phosphorochloridate may be obtained from different thiolates of the same configuration, by the following reactions:




[6] Green and Hudson, *Proc. Chem. Soc.*, 1959, 227.
[7] Michalski and Ratajczak, *Chem. and Ind.*, 1960, 1241.

*Transesterification.*—In view of the optical instability of the halogen derivatives, we have now concentrated on the reactions of esters.

In preliminary work it was found that the 1-naphthyloxy- and the *S*-benzyl group were rapidly removed by alkoxide ions from (+)-methyl 1-naphthyl methylphosphonate and (+)-*S*-benzyl methyl-3-phenanthrylphosphinothiolate, respectively, to give optically active esters:




R = 3-Phenanthryl.

These changes in activity could be produced by overall retention or overall inversion of configuration, since a change in sign does not necessarily indicate a change in configuration.

Some evidence in favour of the inversion mechanism is provided by the observation that *O*-methyl methyl-3-phenanthrylphosphinate was readily racemised by an excess of methoxide ions. If it is assumed that displacement of OR by OR, and OR and SR by OR′ involve the same stereochemical change, this may then be identified with inversion.

These preliminary investigations show the necessity of obtaining unequivocal information on the stereochemical change accompanying substitution at the phosphorus atom. Direct proof of inversion was obtained by comparing the rate of racemisation of methyl ethylphenylphosphinate with the rate of exchange of the methyl group (labelled with $^{14}C$) with methoxide ions. An approach of this kind was developed in the classical work of Hughes, Juliusberger, Masterman, Topley, and Weiss,[8] proving stereospecific inversion for several symmetrical exchanges at the saturated carbon atom.

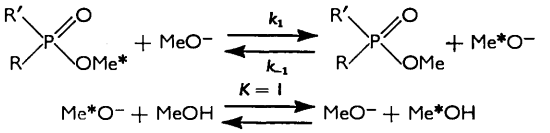
Previously, the rate of racemisation of the methiodide of methyl *p*-dimethylaminophenylmethylphosphinate[9] had been shown to proceed at a convenient rate in the presence of methoxide ions in methanol at room temperature (p. 546). The ester was stable in boiling methanol, showing that the racemisation could not be produced unimolecularly.

For further experiments, ethylphenylphosphinothiolic acid was prepared from phenylphosphinous dichloride as follows: $Ph{\cdot}PCl_2 \xrightarrow[PbEt_4]{} PhEtPCl \xrightarrow[S-AlCl_3]{} PhEtPSCl \xrightarrow[H_2O]{}$ PhEtPO·SH. This product was isolated as the dicyclohexylamine salt and resolved into the optical enantiomorphs by fractional crystallisation of the quinine salt. The (+)-dicyclohexylammonium salt gave the *S*-methyl ester (70%), $[\alpha]_D^{20}$ +10·4° (homogeneous), on reaction with methyl methanesulphonate. This was converted into the *O*-methyl ester (68%), $[\alpha]_D^{20}$ −3·49° (homogeneous), by reaction for 2 hours with exactly one equivalent of sodium methoxide in methanol at −10°. The rate of racemisation of this ester (0·62N) by sodium methoxide (0·426N) in methanol at 25·0° was measured—an E.T.L. photoelectric polarimeter (sensitivity ±0·0002°) with special temperature control was used. The pseudo-unimolecular rate constant, $k_R$, was calculated from the equation, $k_R = 2k_1 = (\ln \theta_0/\theta_t)/t$, where $\theta_0$ is the optical rotation at $t = 0$ and $\theta_t$ at time $t$, by assuming that each displacement involves stereochemical inversion with a characteristic rate constant, $k_1$ (p. 546). These measurements gave $k_1 = 6{\cdot}23$ and $6{\cdot}18 \times 10^{-5}$ sec.$^{-1}$. The alkalinity was checked during the experiment, demonstrating the absence of side reactions (*e.g.*, reaction at the methyl group, also hydrolysis by adventitious moisture).

The radioactive ester was prepared by the action of [$^{14}C$]methanol on ethylphenylphosphinyl chloride, which was prepared by the conventional route: $PhPCl_2 \xrightarrow[EtOH]{}$ $PhP(OEt)_2 \xrightarrow[EtI]{} PhEtPO{\cdot}OEt \xrightarrow[COCl_2]{} PhEtPOCl$.

[8] Hughes, Juliusburger, Masterman, Topley, and Weiss, *J.*, 1935, 1525.
[9] Coyne, McEwen, and Vander Werf, *J. Amer. Chem. Soc.*, 1956, **78**, 3061.

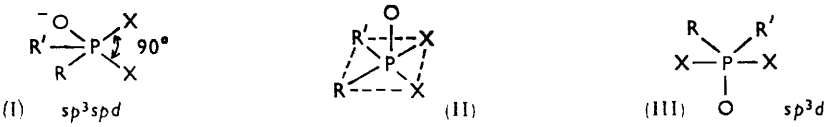
The exchange process may be represented as follows:



and the rate constant given by the equation, $k_1 = (1/\beta) \ln [a/(a - \beta x)]$, where $\beta = (A + B + S)/(A + S)$, $A$, $B$, and $S$ being the molar concentrations of ester, methoxide, and methanol, respectively, $x$ the concentration of active methanol at time $t$, and $a$ the initial concentration of active ester.

Values of $k_1 = 6{\cdot}23$ and $6{\cdot}06 \times 10^{-5}$ sec.$^{-1}$ were obtained, for the same solution of methoxide in methanol as was used in the racemisation experiments, and the same concentration of ester, at 25°. The equality, within experimental error of $k_1$ obtained by the two independent methods proves that this reaction proceeds stereospecifically with inversion of configuration.

*The Transition-state Structure.*—The demonstration of a stereospecific inversion of configuration in the exchange between the methyl phosphinate and methoxide ions allows several possible transition states for this reaction to be dismissed. Thus retention of configuration would arise from the *spd*-hybridised structure (I), suggested as a possibility by Gillespie for reaction at a carbon atom,[10] which is favoured by electrostatic repulsion between the methoxide ion and the phosphoryl oxygen atom; or the square pyramidal form (II), which is less probable than a bipyramidal structure (III) on the grounds of increased electronic repulsion.[11]



Moreover, an $sp^3d$-hybridised structure (III) with axial and radial bonds equal in strength would lead to equally probable retention and inversion, as all the bonds are equivalent. Therefore, the racemisation rate and exchange rate would be equal. This structure may also be discounted.

The most probable structure is that (IV) characteristic of an $S_N2$ transition state of a saturated carbon atom with the axial bonds (*p* or *pd*) weaker than the $sp^2$ bonds in the basal plane. This configuration is supported by the longer axial bonds [12] in phosphorus pentachloride which indicate weaker bonding and imply a small contribution to the total bonding from the 3*d*-orbitals.

This transition-state structure is also supported by the absence of $^{18}O$ exchange of the phosphoryl-oxygen atom in the hydrolysis of the chlorides,[13] fluorides,[14] and esters,[15] in contrast to the exchange observed for the analogous acyl compounds.[16] It cannot,

[10] Gillespie, *J.*, 1952, 1002.
[11] Kimball, *J. Chem. Phys.*, 1940, **8**, 188.
[12] Rouault, *Compt. rend.*, 1938, **207**, 620.
[13] Dostrovsky and Halmann, *J.*, 1956, 1004.
[14] Halmann, *J.*, 1959, 305.
[15] Haake and Westheimer, *J. Amer. Chem. Soc.*, 1961, **83**, 1102.
[16] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626; Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154.

however, be differentiated from that (V) suggested by Haake and Westheimer [15] as a possible transition state structure for the acid hydrolysis of cyclic phosphates; here the entering and leaving groups lie in the basal plane, these bonds in this case being weaker than the axial bonds through $sp^3d$ hybridisation. It is interesting that Duffey has suggested that the equatorial bonds of the $sp^3d$-hybridised octahedral structure (III) are weaker than the axial bonds.[17]

It is highly likely that the energies of various transition-state structures are comparable in magnitude, owing to the influence of *d*-orbitals (or of other high-energy orbitals) and because phosphorus has a greater radius than carbon. Thus different reactions of quaternary phosphonium compounds lead to products with different configurations,[2] and the fact that phosphorus esters,[18] *e.g.*, $(RO)_2PO{\cdot}CH_2{\cdot}CO_2Et$, and amidates [19] give carbanions which readily undergo the Wittig reaction suggests that retention mechanisms are likewise possible for reactions at the phosphoryl-phosphorus atom.

## Experimental

*Ethylphenylphosphinous Chloride.*[20]—A mixture of tetraethyl-lead (64·6 g.) and phenylphosphinous dichloride (107·4 g.) was heated at 120° with stirring for 16 hr. Ethylphenylphosphinous chloride was distilled directly from the reaction mixture and after redistillation had b. p. 76°/2 mm. (yield 70%) (Found: Cl, 20·5. Calc. for $C_8H_{10}ClP$; Cl, 20·6%).

*Ethylphenylphosphinothionyl Chloride.*—Sulphur (9·6 g.) was added in small portions to a stirred suspension of anhydrous aluminium trichloride (5 g.) in ethylphenylphosphinous chloride (51·7 g.). A vigorous reaction occurred after each addition. Then the mixture was stirred at room temperature for 2—3 hr. The product was distilled directly from the mixture and after redistillation had b. p. 110°/0·5 mm. (yield 75%) (Found: Cl, 17·0. Calc. for $C_8H_{10}ClPS$: Cl, 17·35%).

*Ethylphenylphosphinothiolic Acid.*—To a stirred solution of sodium hydroxide (6·0 g.) in water (200 ml.) was added ethylphenylphosphinothionyl chloride (40·9 g.) at such a rate that the temperature did not rise above 40°. The resulting solution was set aside overnight, then extracted with ether (3 × 100 ml.), and the aqueous layer was acidified with concentrated hydrochloric acid. The product was extracted with ether (4 × 100 ml.) and dried ($MgSO_4$). The ether was removed under reduced pressure and the product converted directly into the *dicyclohexylammonium salt*, m. p. 158° (81%) (Found: C, 65·3; H, 9·4; N, 3·9. $C_{20}H_{34}NOPS$ requires C, 65·3; H, 9·3; N, 3·8%). Attempted distillation of the acid resulted in decomposition.

*Partial Optical Resolution of Ethylphenylphosphinothiolic Acid.*—The acid (75 g.) and anhydrous quinine (128·5 g.) were dissolved in hot acetone (1·5 l.). Addition of light petroleum (b. p. 40—60°) in 100-ml. portions every 24 hr. resulted in gradual crystallisation of the quinine salt in fractions (1) 0·5 g., (2) 46 g., (3) 3 g., (4) 83 g., and (5) 20 g. The free acid was liberated by dissolving each fraction in an excess of N-sodium hydroxide and extracting the liberated quinine with ether. The partially resolved acid was isolated by acidification of the aqueous layer and extraction with ether (4 × 100 ml.). The ether extract was dried ($MgSO_4$) and evaporated under reduced pressure. Dicyclohexylammonium salts from the above fractions had (2) $[\alpha]_D^{20}$ −6·6° (*c* 6), (3) $[\alpha]_D^{20}$ +6·5° (*c* 5), (4) $[\alpha]_D^{20}$ +1·3° (*c* 5), and (5) $[\alpha]_D^{20}$ +1·1° (*c* 5; all in MeOH). The infrared spectra of potassium bromide discs of the optically active dicyclohexylammonium salts were identical with those of the analytical sample.

(+)-S-*Methyl Ethylphenylphosphinothiolate.*—Methyl methanesulphonate (1·10 g.) and dicyclohexylammonium ethylphenylphosphinothiolate (3·67 g.; $[\alpha]_D^{20}$ +1·3°) in dry benzene (50 ml.) were boiled for 10 hr. The cold solution was extracted with water (3 × 20 ml.), dried ($MgSO_4$), and evaporated, and the residue was distilled. The *product* (68%) had b. p. 120°/0·3 mm., $n_D^{20}$ 1·5755, $[\alpha]_D^{20}$ +10·4° (homogeneous) (Found: P, 15·2; S, 15·8. $C_9H_{13}OPS$ requires P, 15·5; S, 16·0%).

[17] Duffey, *J. Chem. Phys.*, 1949, **17**, 196.
[18] Wadsworth and Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
[19] Wadsworth and Emmons, *J. Amer. Chem. Soc.*, 1962, **84**, 1316.
[20] Kharasch, Jensen. and Weinhouse, *J. Org. Chem.*, 1949, **14**, 429.

(−)-*Methyl Ethylphenylphosphinate.*—Sodium (0·46 g.) was dissolved in dry methanol (100 ml.). To this solution at −10° (+)-*S*-methyl ethylphenylphosphinothiolate {4·00 g.; $[\alpha]_D^{20}$ +10·4° (homogeneous)} was added dropwise. After 2 hr. at −10°, the mixture was neutralised with methanolic hydrochloric acid, and the methanol was removed. The residue was dissolved in benzene (100 ml.), washed with water (1 × 50 ml.), dried ($MgSO_4$), and recovered. Distillation gave the *product* (68%), b. p. 106—108°/0·8 mm., $n_D^{20}$ 1·5225, $[\alpha]_D^{20}$ −3·49° (homogeneous) (Found: C, 58·7; H, 7·6. $C_9H_{13}O_2P$ requires C, 58·7; H, 7·1%).

*Diethyl Phenylphosphonite.*—Operations were conducted in nitrogen. To a solution of sodium ethoxide (from sodium, 23 g.) in absolute ethanol (500 ml.) was added dropwise, with ice-cooling and stirring, phenylphosphinous dichloride (89·5 g.). Then the mixture was stirred overnight at room temperature. Sodium chloride was filtered off and the filtrate concentrated. Distillation of the residue gave the product, b. p. 76—78°/0·5 mm. (73%) (Found: C, 60·3; H, 7·5. Calc. for $C_{10}H_{15}O_2P$: C, 60·6; H, 7·6%).

*Ethyl Ethylphenylphosphinate.*—Ethyl iodide (10 g.) was added to diethyl phenylphosphonite (60 g.) in a 2-l. flask fitted with a condenser, and the mixture was heated. The vigorous reaction was allowed to proceed for ~10 min. The mixture was then distilled, to give the product, b. p. 100°/0·5 mm. (85%) (Found: C, 60·2; H, 7·8; P, 15·6. Calc. for $C_{10}H_{15}O_2P$: C, 60·6; H, 7·6; P, 15·6%).

*Ethylphenylphosphinyl Chloride.*—Ethyl ethylphenylphosphinate (50 g.) in carbon tetrachloride (50 ml.) was added dropwise, with ice-cooling and stirring, to a saturated solution of carbonyl chloride in carbon tetrachloride (200 ml.), through which a rapid stream of carbonyl chloride was passed. When the addition was complete (½ hr.), the mixture was left at room temperature overnight. The excess of carbonyl chloride and carbon tetrachloride was removed, and the residue was distilled. The product (80%) had b. p. 101°/0·3 mm. (Found: C, 51·0; H, 5·5; Cl, 19·0. Calc. for $C_8H_{10}ClOP$: C, 50·8; H, 5·3; Cl, 18·8%).

*Methyl Ethylphenylphosphinate.*—Ethylphenylphosphinyl chloride (12·0 g.) in ether (25 ml.) was added dropwise, with ice-cooling and stirring, to a solution of triethylamine (6·44 g.) and methanol (2·55 g.) in dry ether (75 ml.). The mixture was then stirred overnight at room temperature. The amine hydrochloride was filtered off and the solvent removed. The residue was distilled, to give the product, b. p. 106—107°/0·8 mm., $n_D^{23}$ 1·5218, identical in infrared spectrum with that prepared from the *S*-methyl ester.

[$^{14}$C]*Methyl Ethylphenylphosphinate.*—The procedure described above was used, with [$^{14}$C]methanol. The product had a specific activity of 2·14 mc/mole and $n_D^{23}$ 1·5218.

S-*Methyl Ethylphenylphosphinate.*—The same procedure was used as described above for the *O*-methyl ester. Ethylphenylphosphinyl chloride (32·7 g.) was added to methanethiol (13 g.) and triethylamine (17·5 g.) in dry ether (200 ml.). The product had b. p. 120°/0·3 mm., $n_D^{20}$ 1·5757, and an infrared spectrum identical with that prepared from ethylphenylphosphonothiolic acid described above.

*Reaction of Sodium Isopropoxide with* (+)-*Methyl* 1-*Naphthyl Methylphosphonate* [21] (I).—(*a*) A solution of the ester (I) (0·166 g.; $[\alpha]_D^{20}$ +44°) in propan-2-ol (2 ml.) was added to an ice-cold 0·1406M-solution of sodium isopropoxide in isopropanol (5 ml.). The mixture was then made up to 10 ml. with propan-2-ol; $\alpha = -0·13°$. This corresponds to a specific rotation $[\alpha]_D^{20}$ −11·4° for isopropyl methyl methylphosphonate, on the basis of quantitative conversion.

(*b*) The reaction was repeated with 1·2 g. of ester and 0·12 g. of sodium in propan-2-ol (5 ml.). The mixture was kept for 2—3 min., then poured into dry ether (500 ml.). The precipitate was filtered off, the ether removed, and the residue distilled. A fraction, b. p. 40°/0·05 mm. (0·12 g.), $n_D^{20}$ 1·4125, $[\alpha]_D^{20}$ −10·8° (in benzene), was isopropyl methyl methylphosphonate.

*Isopropyl Methylphosphonate.*—A solution of propan-2-ol (1·5 g.) and diethylaniline (3·73 g.) in ether (50 ml.) was added to methyl methylphosphonochloridate (3·2 g.) in ether (50 ml.) at 0° with stirring. The mixture was set aside overnight, the precipitate filtered off, the ether removed, and the residue distilled; the *product* had b. p. 40°/0·05 mm., $n_D^{20}$ 1·4120 (Found: C, 39·7; H, 8·6; P, 19·7. $C_5H_{13}O_3P$ requires C, 39·5; H, 8·6; P, 19·7%).

*Reaction of* (+)-S-*Benzyl Methyl*-3-*phenanthrylphosphinothiolate* [21] (II) *with Sodium Methoxide.*—(*a*) A solution (0·65M) of sodium methoxide in methanol (0·16 ml.) was added to a solution of the ester (II) (0·1003 g.; $[\alpha]_D^{20}$ +11·3°) in benzene (7 ml.). The mixture was then made up to 10 ml.; it had $\alpha$ +0·32° (1 dm.). The calculated activity (for absence of reaction)

[21] Green and Hudson, *J.*, 1958, 3129.

is +0·12°. If complete conversion into methyl methyl-3-phenanthrylphosphinate is assumed, $[\alpha]_D^{20}$ +43·3° (in benzene) is the calculated value of the specific rotation of the product.

(*b*) A further equivalent of sodium methoxide was added to this solution, which was then left overnight. Its optical activity became zero.

*Rate of Exchange of Methoxide Ions with* (−)-*Methiodide of Methyl* p-*Dimethylaminophenylmethylphosphinate.*[9]—Preliminary measurements established a slow reaction at room temperature, and complete racemisation at 80° in 2 hr. with 0·05N-methanolic sodium methoxide. The rate of racemisation was determined as follows; a Hilger microptic polarimeter fitted with a 1 dm. tube, in an air thermostat-bath, was used.

Ester 0·054M; sodium methoxide 0·075M.; 15°. Solvent, methanol.

| Time (hr.) | 0 | 0·5 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| α (−) | 0·57° | 0·48° | 0·38° | 0·29° | 0·20° | 0·14° | 0·11° | 0·07° | 0·05° |

$k_2 = 3{\cdot}4$ l. mole$^{-1}$ hr.$^{-1}$.

*Rate of Exchange of Methoxide Ions with* (−)-*Methyl Ethylphenylphosphinate, Measured Polarimetrically.*—(−)-Methyl ethylphenylphosphinate (0·5 ml.; $[\alpha]_D^{20}$ −3·49°) was added to a solution (4·5 ml.) of sodium methoxide in absolute methanol made up by weight. The mixture was shaken and *ca.* 3 ml. were introduced by means of a hypodermic syringe into the cell (2·5 ml.) of the polarimeter (E.T.L. model). This was modified by inserting Teflon washers between the body and the aluminium block which holds the cell, and by drilling channels into the block through which water at a constant temperature could be circulated. Readings were taken at regular intervals, and the pseudo-unimolecular rate constant was calculated from the equation derived below.

The initial concentration of sodium methoxide in the reaction mixture was measured acidimetrically (phenolphthalein indicator), and the concentration checked during the experiment.

*Rate of Isotopic Exchange of Methoxide Ions with* (−)-*Methyl Ethylphenylphosphinate.*—(*a*) *Method.* A mixture of [$^{14}$C]methyl ester (0·5 ml.) and inactive ester (2·0 ml.) was added to the solution (22·5 ml.) of sodium methoxide in methanol, contained in a tube of 30-ml. capacity, held in a thermostat at 25·0°. The tube was rapidly shaken for a few moments, and a polyisoprene stopper through which the needle of a hypodermic syringe had been forced was fitted to the open end.

At known times, *ca.* 3—4 ml. of solution were withdrawn by fixing a syringe to the needle attached to the reaction vessel, releasing the syringe, attaching a second needle, and delivering the solution into a small tube containing *ca.* 0·3 g. of benzoic acid to neutralise the alkali. The tube was then cooled in liquid nitrogen and attached to a vacuum-pump. The methanol was distilled into a second bulb cooled in liquid nitrogen, with a plug of glass wool to protect the distillate.

The samples were counted by making up 1-ml. portions to 20 ml. with toluene containing the scintillator, in a "Tricarb" model scintillation counter, the optimum counting range (~$10^4$—$10^5$ counts/min.) being used. The initial activity of the solution was obtained by withdrawing a sample of the mixture and counting this directly, making the appropriate adjustment for the dilution of methanol by the ester, and a correction for the change in volume of mixing (see below). The pseudo-unimolecular rate constant was calculated by the rate equation given in the following section.

(*b*) *Calculation of rate constants.* (i) Polarimetrically. Suppose that each act of reaction leads to inversion of configuration, and at time 0, we have $A$ dextrorotatory and $B$ lævorotatory molecules. At time $t$ the corresponding numbers are given by $A - X$ and $B + X$, respectively, since $X$ (+)-molecules have been converted into the (−)-form. The rate of the forward reaction is then given by $dX/dt = k_2Y(A - B - 2X)$, where $Y$ is the concentration of sodium methoxide. At $t = 0$, the optical activity, $\alpha_0 = C(A - B)$, and, at time $t$, $\alpha = C(A - B - 2X)$. Thus, $-d\alpha/dt = -2dX/dt$, so that $d\alpha/dt = 2k_2\alpha$, *i.e.*, $Yk_2 = (1/2t) \ln (\alpha_0/\alpha) \equiv k_1$.

(ii) Exchange. Representing the exchange process as:

$$AX^* + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AX + X^* \qquad X^* + HX \overset{K=1}{\rightleftharpoons} HX^* + X$$

$$(a - x)\ Y \qquad A \quad y \qquad y \quad S \qquad (x - y)\ B$$

since the concentration of the tracer is very low, we have, from the neutralisation, $y = Yx/(S + Y)$, so that $dx/dt = k_1Y(a - \beta x)$, where $\beta = (A + Y + S)/(Y + S)$. Integration gives $k_2Y = k_1 = (1/\beta t) \ln [a/(a - \beta x)]$, which approximates to the first-order equation, $k_1 = (1/t) \ln [a/(a - x)]$, when $\beta \longrightarrow 0$, and in the present case the divergence is only $\pm 0{\cdot}2\%$ over the first 30% of the reaction (*i.e.*, within the experimental error). The rate constants, given in the following sections, were therefore calculated for the first 30% of the reaction from the simple first-order equation.

(*c*) *Results.* (i) Polarimetric measurements. In the following experiments, the ester (0·5 ml., 0·572 g.) was added to a 0·48N-solution (4·5 ml.) of methanolic sodium methoxide. The concentration of sodium methoxide was found to be 0·426N immediately after mixing. In each experiment, the angle of rotation was measured every 5 min. and a graph drawn of angle against time, from which the following values are taken:

*Run A.* Temperature 25°.

| Time (min.) | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|
| α | 0·440° | 0·404° | 0·372° | 0·345° | 0·320° | 0·300° | 0·278° |
| Time (min.) | 70 | 80 | 90 | 100 | 110 | 120 | 130 |
| α | 0·257° | 0·238° | 0·222° | 0·206° | 0·190° | 0·176° | 0·163° |

The pseudo-unimolecular rate constant was obtained graphically: $k_1 = 6{\cdot}23 \times 10^{-5}$ sec.$^{-1}$.

*Run B.* Temperature 25°.

| Time (min.) | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|
| α | 0·340° | 0·318° | 0·297° | 0·276° | 0·255° | 0·235° | 0·216° |
| Time (min.) | 70 | 80 | 90 | 100 | 110 | 120 | 130 |
| α | 0·201° | 0·187° | 0·174° | 0·162° | 0·152° | 0·142° | 0·132° |

$k_1$ (graphically) $= 6{\cdot}17 \times 10^{-5}$ sec.$^{-1}$.

Titration of 1 ml. of reaction mixture with 0·1N-HCl:

| Time (hr.) | 0 | 1·5 | 2·25 | 3·25 | 24 |
|---|---|---|---|---|---|
| Titration (ml.) | 4·26 | 4·24 | 4·22 | 4·22 | 4·18 |

(ii) Exchange measurements. In the following experiments, active ester (0·5 ml.) and inactive ester (2·0 ml.) were mixed with sodium methoxide solution (22·5 ml.), resulting volume 24·75 ml. Sodium methoxide in the reaction mixture = 0·426N; ester = 0·62M.

*Run A.* Temperature 25·0°.

| Time (min.) | 11 | 25·75 | 45·5 | 71·5 | 91·5 | 118 | 411·5 | ∞* | ∞ |
|---|---|---|---|---|---|---|---|---|---|
| Activity ($10^3$ counts/min.) | 5·76 | 12·9 | 22·3 | 32·4 | 40·2 | 49·6 | 108 | (128·7) | 141·5 |

$k_1$ (graphically) $= 6{\cdot}23 \times 10^{-5}$ sec.$^{-1}$.

*Run B.* Temperature 25·0°.

| Time (min.) | 20 | 38 | 59 | 85·5 | 117·5 | 158·5 | 443 | ∞* | ∞ |
|---|---|---|---|---|---|---|---|---|---|
| Activity ($10^3$ counts/min.) | 9·5 | 17·6 | 26·1 | 35·6 | 46·0 | 58·9 | 105·3 | (123·7) | 135·6 |

$k_1$ (graphically) $= 6{\cdot}60 \times 10^{-5}$ sec.$^{-1}$.

∞* represents the activity of an aliquot portion, and ∞ represents the calculated value of the total activity in an aliquot part of *distilled methanol* after allowance for the dilution on mixing of the ester and alcoholic sodium methoxide.

We are grateful for assistance from Dr. J. R. Catch, A.E.R.E., Amersham, in the preparation of the labelled ester, and from Dr. R. Collet, of the Hôpital Cantonal, Geneva, for counting the samples.

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