Acid-catalysed Methanolysis of Methylphenylphosphinic Amides: Dependence of the Stereochemistry on the Nucleophilicity of the Departing Amine and the Acidity of the Reaction Medium [1]

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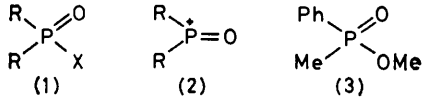
(+)-(*S*)-Methylphenylphosphinic amide (4) has been prepared and converted, by the reaction of its potassium salt with *p*-fluoronitrobenzene, into (+)-(*S*)-(*N*-*p*-nitrophenyl)methylphenylphosphinic amide (7). In methanolic 0.15M-hydrogen chloride these amides, as well as (−)-(*S*)-(*N*-phenyl)methylphenylphosphinic amide (6), give methyl methylphenylphosphinate (3) stereospecifically with inversion of configuration. At higher concentrations of hydrogen chloride, retention of configuration becomes increasingly important, and for (6) and (7) eventually exceeds inversion. At a given acidity the proportion of reaction proceeding with retention depends on the nucleophilicity of the leaving group in the amide, increasing in the order (4) < (7) < (6). These results are difficult to rationalise in terms of competing $S_N2(P)$ (inversion) and $S_N1(P)$ (racemisation) mechanisms. Possible alternative explanations involve nucleophilic catalysis by chloride ion and/or the formation of five-co-ordinate intermediates.

PHOSPHINIC acids and their derivatives (1; R = alkyl or aryl) are generally reluctant to react by dissociative $S_N1(P)$ mechanisms,[2-5] presumably because of the instability of the phosphinylium cations (2). The suggestion [6] that *N*-arylphosphinic amides (1; X = NHAr) undergo acid-catalysed hydrolysis by dissociative (*A*1 or *A*1-like) mechanisms is therefore of special interest, although our own work [7] has afforded results more in accord with associative (*A*2) mechanisms. Koizumi and his colleagues [8] recently reported that the methanolysis of



(*N*-phenyl)methylphenylphosphinic amide in acidic solution gives the methyl phosphinate (3) with predominant but not exclusive inversion of configuration at phosphorus. This was seen as compelling evidence for reaction occurring in part at least by a dissociative (*A*1) mechanism.[8] Having previously questioned the postulated dissociative character of the hydrolysis of phosphinic amides [7] we felt compelled to examine more fully the stereochemistry of methanolysis and its mechanistic interpretation. In particular, we were concerned to compare the behaviour of (*N*-phenyl)methylphenylphosphinic amide (6) with that of the related compounds (4) and (7) having leaving groups more nucleophilic (ammonia) and less nucleophilic (*p*-nitroaniline) than aniline.

Preparation of Phosphinic Amides.—(−)-(*S*)-(*N*-Phenyl)methylphenylphosphinic amide (6) (>98% one enantiomer by n.m.r. analysis †), $[\alpha]_D$ −28.5° (MeOH) was prepared from (−)-$(S)_P$-menthyl methylphenylphosphinate (5) and lithium anilide.[9] Methylphenylphosphinic amide (4) and its *N*-*p*-nitrophenyl analogue (7), neither of which has been reported previously, were obtained as racemates by reaction of methylphenylphosphinic chloride with ammonia and *p*-nitroaniline, and in optically active forms as outlined in Scheme 1. The amide (+)-(4) was obtained in high yield (78% isolated) but unfortunately suffered appreciable decomposition (most probably hydrolysis catalysed by traces of acid) on crystallisation from ethyl acetate. The final product (48%), $[\alpha]_D$ +8.3° (MeOH), contained the enantiomers of (4) in the ratio *ca.* 20 : 1 (by n.m.r. analysis †), and was contaminated with a trace (0.5%) of the corresponding phosphinic acid. The presence of the minor enantiomer may be a result of partial racemisation of the initial product rather than any lack of stereospecificity in the substitution reaction. This material was used for most of the methanolysis reactions of (4), although a small sample of enantiomerically pure amide, $[\alpha]_D$ +9.2° (MeOH), was obtained and used in one instance.

The synthesis of optically active (*N*-*p*-nitrophenyl)-methylphenylphosphinic amide (7) posed problems on account of the low nucleophilicity of the *p*-nitroanilide anion [making reaction with the menthyl phosphinate (5) unlikely] and the lability of the P–N bond in the anilide (6) (restricting the possibilities for introducing a nitro-substituent into the *N*-phenyl group). Fortunately the potassium salt of the primary amide (4) proved sufficiently nucleophilic in dioxan at 70—80 °C to displace fluoride from *p*-fluoronitrobenzene and in this way we were able to obtain a modest yield (32%) of (+)-(7), $[\alpha]_D$ +43.6° (MeOH), from (+)-(4). Only one enantiomer was apparent by n.m.r. analysis,† but because of the low solubility of (7) the spectra were not ideal and as much as 6% of the other enantiomer could have been present and escaped detection. From the

† N.m.r. spectrum recorded in the presence of the chiral shift reagent tris-[3-(2,2,2-trifluoro-1-hydroxyethylidene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$].

[1] Preliminary communication, M. J. P. Harger, *J.C.S. Chem. Comm.*, 1976, 520.

[2] P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, 1971, **93**, 6919.

[3] P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, 1971, **93**, 6924.

[4] R. J. Brooks and C. A. Bunton, *J. Org. Chem.*, 1975, **40**, 2059.

[5] B. Krawiecka, J. Michalski, and Z. Skrzypczyński, *J.C.S. Chem. Comm.*, 1974, 1022.

[6] (*a*) P. Haake and D. A. Tyssee, *Tetrahedron Letters*, 1970, 3513; (*b*) D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8066.

[7] M. J. P. Harger, *J.C.S. Chem. Comm.*, 1973, 774; *J.C.S. Perkin I*, 1977, 605; M. J. P. Harger, A. J. Macpherson, and D. Pickering, *Tetrahedron Letters*, 1975, 1797.

[8] T. Koizumi, Y. Kobayashi, and E. Yoshii, *J.C.S. Chem. Comm.*, 1974, 678.

[9] A. Nudelman and D. J. Cram, *J. Amer. Chem. Soc.*, 1968, **90**, 3869; *J. Org. Chem.*, 1971, **36**, 335.

results of subsequent methanolysis experiments it seems that the product must, in fact, have been essentially a single enantiomer.

$(S)_P$-Menthyl methylphenylphosphinate (5) is known to react with lithium anilide with inversion of configuration at phosphorus to give (*S*)-(6).[9] By analogy, the preparation of the amide (4) should also yield the (*S*)-enantiomer and this in turn would give (*S*)-(7). Unequivocal proof of the *S*-configuration of the *p*-nitroanilide (+)-(7) and, by implication, of the amide

DISCUSSION

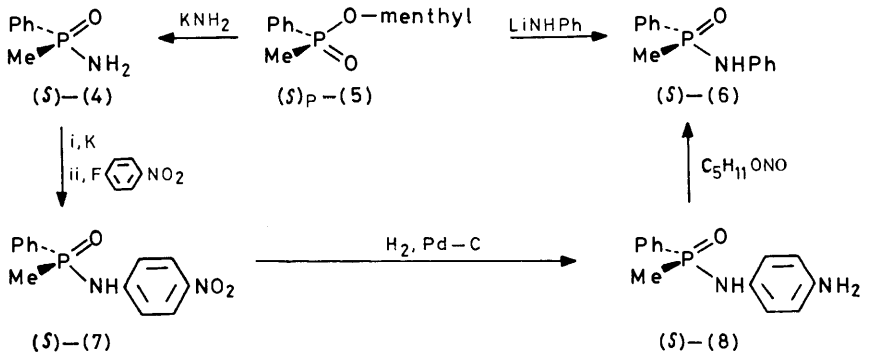
DeBruin and Perrin[10] recently reported $[\alpha]_D$ +56° (benzene) for pure (*R*)-methyl methylphenylphosphinate (3). The phosphinate we obtained from methanolysis of the anilide (−)-(*S*)-(6) in methanolic 0.15M-hydrogen chloride has $[\alpha]_D$ −56.5° (benzene) and thus appears to be the pure (*S*)-enantiomer of (3). The presence of just one enantiomer is confirmed by the n.m.r. spectrum in benzene containing $Eu(tfc)_3$; it shows only one *P*-Me resonance whereas a sample of (3) having $[\alpha]_D$ −50.7°

TABLE 1

Methanolysis of the phosphinic amides (+)-(*S*)-(4), (−)-(*S*)-(6), and (+)-(*S*)-(7); concentrations, reaction times, and specific rotations of methyl methylphenylphosphinate product

		PhMeP(O)NH_2 (4) [a]			PhMeP(O)NHPh (6)			PhMeP(O)$NHC_6H_4NO_2$ (7)		
[HCl]/M	[Amide]/M	*t*/min [b]	$[\alpha]_D^{PhH}$	$[\alpha]_D^{MeOH}$	*t*/min [b]	$[\alpha]_D^{PhH}$	$[\alpha]_D^{MeOH}$	*t*/min [b]	$[\alpha]_D^{PhH}$	$[\alpha]_D^{MeOH}$
0.015	0.007	60	−51.7	−45.4						
0.15	0.023	10	−51.9	−45.6	24	−56.5	−48.5	222	−57.2	−49.2
1.5	0.023	10	−51.7	−45.8	10	−36.9	−32.6	25	−50.7	−44.3
5.0	0.047	5	−47.9	−43.0	10	−1.1	−1.2	15	−25.8	−22.8
7.5	0.069	5	−45.0	−39.0	8	+6.6	+5.5	15	−13.4	−11.5
11.3	0.093	6 (10 °C)	−34.3	−30.4	10 (10 °C)	+11.2	+9.9	25 (10 °C)	+0.3	+0.4
ca. 14	0.116							40 (0 °C)	+3.9	+3.3

[a] Amide (4) having $[\alpha]_D$ +8.3° was used. Enantiomerically pure (4), $[\alpha]_D$ +9.2°, in 0.15M-HCl–MeOH gave MePhP(O)OMe having $[\alpha]_D$ −57.5° (PhH), −49.0° (MeOH). [b] Reaction times at 28 °C or as indicated.



SCHEME 1

(+)-(4) was obtained (Scheme 1) by reduction of the nitro-group and deamination of the product (8) to give the (−)-(*S*)-enantiomer of (6).

Methanolysis Reactions.—Reaction mixtures having the compositions shown in Table 1 were obtained by adding the appropriate optically active phosphinic amide to methanolic hydrogen chloride maintained at a constant temperature (usually 28 °C). After a period of time estimated to allow for more than 99.9% completion, the reaction was quenched by addition of ammonia. Preparative t.l.c. followed by distillation afforded methyl methylphenylphosphinate (3) in high yield. Its purity was established by g.l.c. and n.m.r. examination, and its optical rotation was measured in both benzene and methanol. The results are presented in Table 1.

(benzene) exhibits two signals, at δ 3.24 and 3.14, in the ratio 19 : 1. Clearly the methanolysis of (6) at low hydrogen chloride concentrations proceeds with complete inversion of configuration at phosphorus. The specific rotation of the product in methanol ($[\alpha]_D$ −48.5°) is substantially less than in benzene, and differs little from the value ($[\alpha]_D$ −47.5° in MeOH) recorded by Koizumi and his colleagues[8] for the product of reaction of the same substrate in dilute methanolic hydrogen chloride. Their deduction that methanolysis occurs with substantial (>20%) racemisation under these conditions is incorrect (as they have since acknowledged that it might be[11]) because it is based on the assumption of too large a value (−61°) for the specific rotation of pure (*S*)-(3) in methanol.

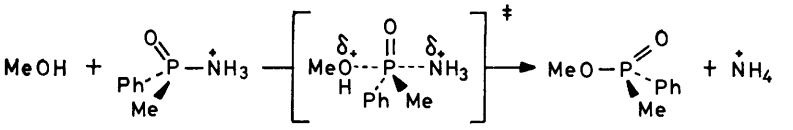
The primary amide (*S*)-(4) also reacts with complete

[10] K. E. DeBruin and D. E. Perrin, *J. Org. Chem.*, 1975, **40**, 1523.

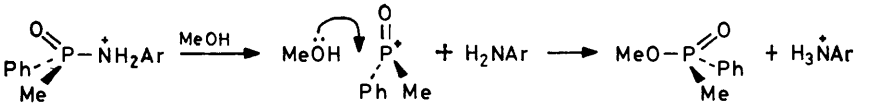
[11] T. Koizumi, Y. Kobayashi, and E. Yoshii, *Chem. and Pharm. Bull.* (*Japan*), 1976, **24**, 834.

inversion of configuration in methanolic 0.15M-hydrogen chloride. There is general agreement that primary phosphinic amides undergo acid-catalysed hydrolysis by associative ($A2$) mechanisms,[12,13] and methanolysis can hardly be less associative in character. With the assumption that associative reaction proceeds by direct $S_N2(P)$ displacement, stereospecific inversion of configuration is precisely what would be expected (Scheme 2).

The *p*-nitroanilide (7) is more interesting. It is less reactive than either (4) or (6) because, being less basic, a much smaller proportion of the molecules will be present in acid solution in their reactive *N*-protonated form. However, the low nucleophilicity of *p*-nitroaniline renders the P–N bond in the *N*-protonated substrate especially labile, and liable to break with minimal nucleophilic assistance from the solvent. Indeed, Haake and his co-workers [6] have suggested that *N*-(*p*-nitrophenyl)diphenylphosphinic amide, in contrast to the *N*-unsubstituted compound, is hydrolysed by a dissociative ($A1$) mechanism. Be that as it may, we



SCHEME 2



SCHEME 3

find that the methanolysis of (*S*)-(7) in methanolic 0.15M-hydrogen chloride is stereospecific with inversion. If reaction does follow an $A1$ pathway in methanol, the intermediate phosphinylium cation must, it seems, be trapped by solvent molecules exclusively from the side opposite to that from which the leaving group has departed (Scheme 3).

Increasing the acidity of the reaction media caused some remarkable changes. Table 2 shows the stereochemical course of the methanolysis reactions of (4), (6), and (7) as indicated by the enantiomer composition of the methyl phosphinate product.

In methanolic 1.5M-hydrogen chloride the amide (4) still reacts with complete stereospecificity but the anilide (6) and the *p*-nitroanilide (7) give phosphinate which is partially racemic. Before attaching mechanistic significance to these results it is necessary to establish that the substrates do not lose their stereochemical integrity under the reaction conditions, and that methyl methylphenylphosphinate (3) once formed is optically stable. To this end the methanolysis reactions of both (*S*)-(6) and (*S*)-(7) were repeated but with interruption (by quenching with ammonia) at 60—70% completion, and isolation of the phosphinate product and the unchanged substrate. In neither case was the optical purity of the phosphinate significantly higher than when reaction had been allowed to go to completion, and the recovered amides were still (within experimental error) enantiomerically pure. The optical stability of methyl methylphenylphosphinate (3) has been noted before [8] and was confirmed in a simple control experiment: less than 1% could have been racemised after its formation in the methanolysis reactions.

In their work with the anilide (*S*)-(6), Koizumi and his colleagues [8] likewise found that in more acidic solutions the optical purity of the methanolysis product was lower, falling to about 50% ($[\alpha]_D$ −24.3° in MeOH) in methanolic 9.4M-sulphuric acid. They inferred that reaction occurs by both $A2$ (inversion) and $A1$ (racemisation) pathways, with the latter growing in importance as the acidity of the medium increases. They recalled the term 'merged $A1$—$A2$' introduced by Haake and his co-workers [6b] to describe the mechanism of hydrolysis of (6), but we think it unlikely that those authors had in mind competing $A1$ and $A2$ processes; certainly the results of our own work [7] on the hydrolysis of alkylphenylphosphinic amides seem incompatible with such a picture. Moreover, the contribution of an $A1$ mechanism should be greater for a *p*-nitroanilide than for the corresponding anilide, yet we find that the *p*-nitroanilide (*S*)-(7) in methanolic 1.5M-hydrogen chloride affords a product which is less extensively racemised than is that from the anilide (*S*)-(6).

TABLE 2

Stereochemistry of hydrogen chloride-catalysed methanolysis of phosphinic amides; ratios of inversion to retention of configuration at phosphorus

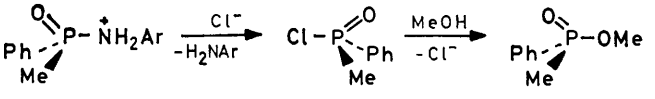
[HCl]/M	$PhMeP(O)NH_2$	PhMeP(O)NHPh	$PhMeP(O)NHC_6H_4NO_2$
0.015	100 : 0		
0.15	100 : 0	100 : 0	100 : 0
1.5	100 : 0	83 : 17	95 : 5
5.0	96.5 : 3.5	51 : 49	73 : 27
7.5	93 : 7	44 : 56	62 : 38
11.3	83 : 17	40 : 60	49.5 : 50.5
ca. 14			46.5 : 53.5

The concept of competing $A2$ (inversion) and $A1$ (racemisation) pathways becomes even less tenable when the results of experiments at higher acidities are considered (Table 2). First, methanolysis of the primary

[12] P. Haake and T. Koizumi, *Tetrahedron Letters*, 1970, 4845; *J. Amer. Chem. Soc.*, 1973, **95**, 8073.
[13] M. J. P. Harger, *J.C.S. Perkin I*, 1975, 514.

amide (4) becomes non-stereospecific. Because of the extremely high rate of reaction it has not been possible to interrupt a reaction before completion so as to exclude the possibility of partial racemisation of the substrate prior to methanolysis. If, however, the reaction of (4) is genuinely non-stereospecific some explanation other than a competing $A1$ mechanism seems to be required for an amide with a leaving group as nucleophilic as ammonia. Secondly, the reactions of the anilide (6) and the *p*-nitroanilide (7) not only reach the point of complete non-stereospecificity (corresponding to complete reaction by the $A1$ mechanism) but in sufficiently acidic media actually proceed with an excess of retention over inversion. While it is true that a high concentration of hydrogen chloride will reduce the activity of methanol in a bimolecular ($A2$) reaction, it seems inconceivable that the intermediate phosphinylium cation in any competing dissociative ($A1$) process would react with methanol to give the phosphinate with retained configuration: racemisation, inversion, or something in between are the only reasonable possibilities. An $A1$ mechanism may contribute to the observed departure from stereospecific inversion, but it cannot be the sole cause. Since a simple direct displacement [S_N2(P)] associative mechanism can only give rise to inversion it is necessary to look for some alternative mechanism which can lead to product with retention of configuration.

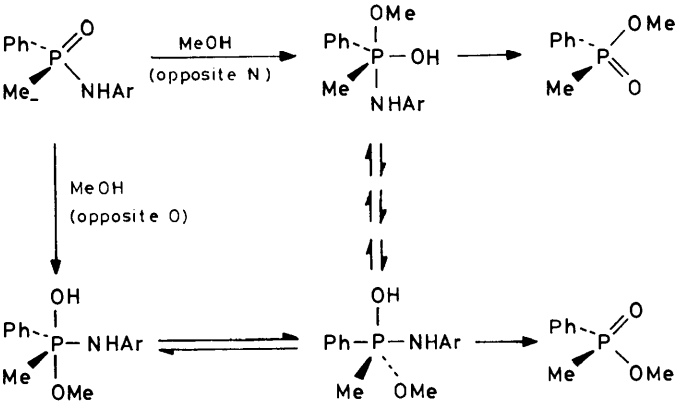
One possibility is to invoke nucleophilic catalysis by chloride ion (Scheme 4). The rates of both the un-



SCHEME 4

catalysed (inversion) and catalysed (retention) reactions would increase as the acidity of the medium increases, but because the acid is also the source of the nucleophile, the catalytic pathway would be more sensitive to the concentration of hydrogen chloride. At low concentrations of hydrogen chloride it might account for a negligibly small proportion of reaction, so that methanolysis would in effect proceed entirely by the uncatalysed pathway with inversion of configuration, while at high concentrations of hydrogen chloride it could become the major pathway and cause the majority of the product to be formed with overall retention of configuration. Seen in this light our results (Table 2) require that the catalytic mechanism plays a smaller part in the methanolysis of the *p*-nitroanilide (7) than is the case for the anilide (6) under the same reaction conditions. It could be that the greater lability of the P–N bond in the *N*-protonated form of the *p*-nitroanilide makes it less selective for nucleophilic attack by chloride ion rather than by methanol. However, the relatively stable *N*-protonated form of the primary amide (4) should then be particularly selective, whereas in fact reaction with retention of configuration is least important here. We can offer no convincing explanation, although we note that the amide (4) is more basic than (6) or (7) and its methanolysis in more concentrated methanolic hydrogen chloride might conceivably involve an extremely reactive and unselective double protonated form. Tentative support for the idea of nucleophilic catalysis is available: the presence of lithium chloride (1.35M) during the methanolysis of (*S*)-(6) in methanolic 0.15M-hydrogen chloride gives rise to phosphinate (3) in which the inversion : retention ratio has changed from 100 : 0 to 92.5 : 7.5. This change in stereochemistry could result from specific participation by chloride ion, but other factors, such as the increased polarity of the reaction medium, cannot at present be discounted. Nucleophilic catalysis might also explain why the stereochemistry of methanolysis of the anilide (*S*)-(6) seems to depend on the acid used. For example, Koizumi *et al.*[8] found that only *ca.* 18% of the product was formed with retention using [H_2SO_4] = 5.6M whereas we find about 50% retention with [HCl] = 5.0M. Such a difference is not unreasonable given that the anion derived from sulphuric acid is likely to be less nucleophilic than chloride ion with respect to a phosphinyl centre. Equally, it is possible to rationalise the more recent observation that in methanolic sulphuric acid the reaction of (*N*-cyclohexyl)methylphenylphosphinic amide [which resembles the amide (4) with respect to the nucleophilicity of the leaving group] does not deviate substantially from stereospecific inversion even at high acidities.[11]

In the foregoing discussion we have, for simplicity, imposed the restriction that associative ($A2$) substitution proceeds stereospecifically with inversion. This is appropriate for direct S_N2(P) displacement, and possible for substitution *via* a five-co-ordinate intermediate provided that species is formed by attack opposite nitrogen and collapses to product more quickly than it



SCHEME 5

undergoes permutational isomerisation. On the other hand, it is conceivable that some substitution proceeds with retention of configuration as a result of attack opposite oxygen or isomerisation of the five-co-ordinate intermediate. Scheme 5, in which the structures are intended to define the positions in space of the groups

attached to phosphorus but not necessarily their actual states of protonation, shows formally how this can come about.* We do not, however, propose to discuss our results in these terms: uncertainty as to the position (N or O) and degree (one or two) of protonation of the substrate and intermediate, and the way in which protonation is influenced by changes in the acidity of the reaction medium and the group attached to nitrogen, would make such discussion unduly speculative.

Seen as a whole, the results of the present study afford little if any evidence in support of dissociative (*A*1) mechanisms in the acid-catalysed methanolysis of alkylphenylphosphinic amides. Of themselves they give us no cause to modify our view [7] that alkyphenylphosphinic amides are hydrolysed by associative (*A*2) mechanisms.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with Perkin-Elmer 237 and 257 instruments and n.m.r. spectra (tetramethylsilane internal standard) at 60 MHz with a Varian T-60 (probe temp. 35 °C) or (as indicated) at 100 MHz with a JEOL JNM-PS-100 instrument (probe temp. 10 °C). The chiral shift reagent tris-[3-(2,2,2-trifluoro-1-hydroxyethylidene)-(+)-camphorato]europium(III) was purchased from Ryvan Chemical Co. Ltd., Southampton. Optical rotations were measured at 589 nm and 20 ± 2 °C with a cell of path length 100 mm (capacity *ca.* 0.9 ml) using a Perkin-Elmer 141 polarimeter. G.l.c. analyses were performed on a Pye 104 flame ionisation chromatograph fitted with a 1.5 m × 4 mm i.d. glass column packed with 3% silicone OV 17 on silanised 100—120 mesh Diatomite C 'Q'. Stock solutions for use in methanolysis reactions were prepared by passing dry hydrogen chloride into anhydrous AnalaR methanol; they were stored at −20 °C and standardised immediately before use.

Methyl methylphenylphosphinate (3), b.p. 106—110° at 0.6 mmHg, methylphenylphosphinic chloride, b.p. 120—130° at 2—3 mmHg, and (−)-$(S)_P$-menthyl methylphenylphosphinate, m.p. 76—78° (lit.,[15] 79—80°), $[\alpha]_D$ −92.7° (*c* 2.1 in PhH) (lit.,[15] $[\alpha]_D$ −94°), diastereoisomerically pure by n.m.r. examination, were prepared by published procedures.[15]

Methylphenylphosphinic Amide (4).—Methylphenylphosphinic chloride (2.59 g, 14.8 mmol) in dry benzene (15 ml) was added over 10 min to an ice-cold, stirred solution of ammonia (75 mmol) in ethanol (15 ml). After a further 1 h at room temperature, the precipitated solid was removed, the filtrate concentrated, chloroform (40 ml) added, and the solution washed with aqueous sodium hydrogen carbonate (10 ml). The aqueous washing was extracted with chloroform (2 × 20 ml) and the extracts were combined with the original chloroform solution. The residue remaining after evaporation was crystallised from ethyl acetate to give *methylphenylphosphinic amide* (1.03 g, 6.65 mmol, 45%), m.p. 101—103°, $\nu_{max.}$ (Nujol) 3 280, 3 225, and 3 120 (NH_2), 1 590 (NH_2 def.), and 1 175 cm^{-1} (P=O), δ ($CDCl_3$; 100 MHz) 8.0—7.2 (5 H, m, Ph), 3.43br (2 H, s, NH_2), and 1.61 (3 H, d, J_{PH} 15 Hz, Me) (Found: C, 54.0; H, 6.5; N, 9.0. $C_7H_{10}NOP$ requires C, 54.2; H, 6.5; N, 9.0%).

(*N-Phenyl*)*methylphenylphosphinic Amide* (6).—A solution of aniline (2.05 g, 22.0 mmol) in dry carbon tetrachloride (20 ml) was stirred at 0 °C while methylphenylphosphinic chloride (1.75 g, 10.0 mmol) in carbon tetrachloride (8 ml) was added dropwise over 15 min. An oil separated, but became solid when chloroform (5 ml) was added. After stirring at room temperature for 40 h, water (20 ml) was added and the organic layer separated. The aqueous portion together with some insoluble material was extracted with chloroform (3 × 15 ml). The combined organic extracts were evaporated and the residue crystallised from ethyl acetate to give (*N*-phenyl)methylphenylphosphinic amide (1.78 g, 7.19 mmol, 72%), m.p. 144—146° (lit.,[16] 142°), $\nu_{max.}$ (Nujol) 3 160 (NH), 1 600 (NH def.), and 1 185 and 1 170 cm^{-1} (P=O), δ ($CDCl_3$) 8.2—7.3 (5 H, m, PPh), 7.3—6.8 (5 H, m, NPh), 6.87br (1 H, d, J_{PH} 10 Hz), and 1.79 (3 H, d, J_{PH} 15 Hz, Me).

(N-p-*Nitrophenyl*)*methylphenylphosphinic Amide* (7).—A mixture of *p*-nitroaniline (2.76 g, 20.0 mmol) and pyridine (3.16 g, 40.0 mmol) in dry benzene (15 ml) was stirred at room temperature while methylphenylphosphinic chloride (1.75 g, 10.0 mmol) in benzene (13 ml) was added dropwise. The mixture was heated under reflux for 5 h. Most of the benzene was evaporated off and the residue was dissolved in chloroform. This solution was washed with 0.25M-hydrochloric acid, aqueous 5% potassium carbonate, and water, and then concentrated to an oil. Three crystallisations from ethyl acetate afforded pale yellow (N-p-*nitrophenyl*)*methylphenylphosphinic amide* (0.80 g, 2.90 mmol, 29%), m.p. 144—146°, $\nu_{max.}$ (Nujol) 3 190 (NH), 1 600 (NH def.), 1 340 (NO_2), and 1 185 and 1 175 cm^{-1} (P=O), δ ($CDCl_3$) 8.20—6.97 (10 H, m, PPh, NH, and NAr as AA'XX' with δ_A *ca.* 8.05, δ_X *ca.* 7.08, J_{AX} *ca.* 9 Hz) and 1.85 (3 H, d, J_{PH} 14.5 Hz) (Found: C, 56.7; H, 4.9; N, 9.9. $C_{13}H_{13}N_2O_3P$ requires C, 56.5; H, 4.7; N, 10.15%).

(+)-(S)-*Methylphenylphosphinic Amide*, (*S*)-(4).—A solution of potassium amide was prepared by adding potassium (5.85 g, 0.15 g atom) to stirred anhydrous liquid ammonia (120 ml) (distilled from sodium) containing iron(III) nitrate (0.08 g) over 0.75 h. After stirring for a further 0.5 h, the flask was immersed in a bath at −50 °C and (−)-$(S)_P$-menthyl methylphenylphosphinate (14.6 g, 49.7 mmol) in tetrahydrofuran (60 ml; distilled from $LiAlH_4$) was added over 0.75 h. The mixture was allowed to warm to room temperature during 1 h and was stirred for a further 1 h. G.l.c. (3% OV 17; 230 °C) of a quenched sample showed the absence of starting material (t_R 4.3 min) and the presence of a product having the same retention time (1.8 min) as authentic (±)-(4). The reaction was quenched by stirring with ammonium chloride (9.1 g, 0.17 mol) for 20 min followed by cooling in ice and dropwise addition of water (4 ml) in tetrahydrofuran (15 ml). Most of the solvent was evaporated off under reduced pressure and aqueous 10% potassium hydrogen carbonate (60 ml) was added. The aqueous solution was washed with ether (60 ml) to remove menthol and extracted with chloroform (2 × 80 ml; 2 × 60 ml; 2 × 40 ml). The combined chloroform extracts were

* The stereochemistry of the boron trifluoride-catalysed methanolysis of phosphetan amides has recently been explained in terms of five-co-ordinate intermediates.[14] However, the special nature of the phosphetan system limits the support that can be drawn for a similar mechanism with other phosphinic amides.

[14] T. Koizumi, Y. Kobayashi, and E. Yoshii, *Tetrahedron Letters*, 1976, 2853.

[15] O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4842.

[16] C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 1928, **92**.

dried (Na_2SO_4) and evaporated, and the residue triturated with ether (2 × 20 ml) to give a solid (*ca.* 6 g) having an n.m.r. spectrum essentially the same as that of (±)-(4). Some decomposition (probably hydrolysis) occurred on crystallisation from ethyl acetate giving a product contaminated with material only sparingly soluble in chloroform. This product was dissolved in aqueous 5% sodium hydrogen carbonate (8 ml) and 2M-sodium hydroxide (6 ml) and the solution extracted repeatedly with chloroform. The extracts were combined and evaporated, and the residue crystallised, with only gentle heating and rigorous exclusion of moisture, from ethyl acetate. (*S*)-Methylphenylphosphinic amide (3.67 g, 23.6 mmol, 48%), $[\alpha]_D$ +8.3° (*c* 2.2 in MeOH), m.p. 98—104°,* was identified by comparison of its i.r. and n.m.r. spectra with those of the authentic (±)-amide (4). G.l.c. (3% OV 17; 200 °C) showed a single peak (t_R 3.8 min), but the presence of some methylphenylphosphinic acid impurity (0.5%) was indicated by an additional peak [t_R 1.5 min; PhMeP(O)OMe] when a sample was treated with diazomethane. From the 100 MHz n.m.r. spectrum in $CDCl_3$ containing $Eu(tfc)_3$ (18 mg per 24 mg of amide) it was seen that the signal at δ 1.61 (3 H, d, J_{PH} 15 Hz, Me) had shifted to δ 2.24 (d, J_{PH} 15 Hz) and δ 2.14 (d, J_{PH} 15 Hz), ratio *ca.* 20 : 1, and that the relative intensity of the higher-field resonance increased on addition of (±)-amide. A sample of enantiomerically pure (≥99% by n.m.r.) (*S*)-methylphenylphosphinic amide, $[\alpha]_D$ +9.2° (*c* 2.8 in MeOH), m.p. 90—98°,* contaminated with methylphenylphosphinic acid (1.7% by g.l.c.), was obtained by crystallisation (twice) of a part of the above product from benzene–chloroform (3 : 1).

(−)-(S)-(N-*Phenyl*)*methylphenylphosphinic Amide*, (*S*)-(6).—This was prepared from (*S*)$_P$-menthyl methylphenylphosphinate and an excess of lithium anilide;[9] the product (40%) had m.p. 162—164° (lit.,[6b] 163.5—165.5°) and $[\alpha]_D$ −28.5° (*c* 2.12 in MeOH) (lit.,[6b] $[\alpha]_D$ −28°) after chromatography and crystallisation from ethyl acetate. The n.m.r. spectrum in $CDCl_3$ included δ 1.79 (3 H, d, J_{PH} 15 Hz, Me) which was shifted to δ 2.63 by $Eu(tfc)_3$ (20 mg per 28 mg of amide). Addition of (±)-(6) caused a new resonance (d, J_{PH} 15 Hz) to appear at δ 2.46; this had not previously been present.

(+)-(S)-(N-p-*Nitrophenyl*)*methylphenylphosphinic Amide*, (*S*)-(7).—A fine suspension of potassium (0.98 g, 25 mg atom) was prepared by allowing a mixture of the molten metal and dioxan (20 ml) to cool while stirring vigorously. Solid (+)-(*S*)-methylphenylphosphinic amide (*ca.* 95% one enantiomer) (1.32 g, 8.5 mmol) was added (gas evolved) and the mixture stirred at room temperature for 10 min and at 80—90 °C for 20 min. The temperature was reduced to 70—80 °C and *p*-fluoronitrobenzene (4.23 g, 30 mmol) in dioxan (10 ml) was added over 5 min. After a further 25 min at 70—80 °C the mixture was allowed to cool and the reaction was quenched by addition of ammonium chloride (1.60 g, 30 mmol) followed, dropwise, by water (1 ml) in dioxan (10 ml). More water (40 ml) was added, the pH checked (pH *ca.* 9), and the mixture extracted with chloroform (60 and 3 × 40 ml). Concentration of the extracts gave a brown oil. The aqueous portion was acidified to pH 2 and extracted again to give a further small amount of oil. The combined oils were chromatographed on alumina (135 g) (elution with ether containing an increasing proportion of methanol; 150 ml fractions). T.l.c. (alumina; 4% methanol in ether) showed that fractions 12—18, eluted with 4—5% methanol in ether, contained material having the same R_F value (0.1) as authentic (±)-(7); these were combined and evaporated. The residue was dissolved in dichloromethane (5 ml) and ether (15 ml) was added to precipitate a khaki solid (1.05 g). A further precipitation followed by two crystallisations from ethyl acetate afforded a less coloured sample of (*S*)-(*N*-*p*-nitrophenyl)methylphenylphosphinic amide (0.76 g, 2.7 mmol, 32%), $[\alpha]_D$ +43.6° (*c* 1.7 in MeOH), m.p. 183.5—185°, identified by comparison of its i.r. and n.m.r. spectra with those of the authentic (±)-amide (7). The n.m.r. spectrum ($CDCl_3$) included a signal at δ 1.92 (3 H, d, J_{PH} 15 Hz, Me), shifted to δ 3.13 when $Eu(tfc)_3$ (10 mg per 14 mg of amide) was added. Addition of (±)-(7) gave rise to a new resonance at δ 3.36 (d, J_{PH} 15 Hz); this had not previously been visible, although the limited solubility of the amide and the broadness of the peaks in the spectrum could have allowed as much as 6% of the minor enantiomer to escape detection.

Confirmation of the S-*Configuration of* (+)-(N-p-*Nitrophenyl*)*methylphenylphosphinic Amide* (7).—A solution of (+)-(*N*-*p*-nitrophenyl)methylphenylphosphinic amide (0.061 g, 0.22 mmol) in ethanol (3 ml) was stirred with 10% palladium–charcoal (0.010 g) under hydrogen for 3 h at room temperature. Most of the solvent was removed under reduced pressure and dioxan (2 ml) was added. The resulting solution was added dropwise over 30 min to a stirred solution of pentyl nitrite (0.040 g, 0.35 mmol) in dioxan (5 ml) at 100 °C. Preparative t.l.c. (alumina; 7% methanol in ether) of the red-brown oil remaining after evaporation of volatile material afforded (*N*-phenyl)-methylphenylphosphinic amide, R_F 0.42, m.p. 142—146°, i.r. and n.m.r. spectra as for the authentic amide (6), in low yield. The optical rotation, $[\alpha]_D$ −25° (*c* 0.9 in MeOH), showed this to be the (*S*)-enantiomer of (6), and further purification was not attempted. Since (+)-(7) was prepared from (+)-(4) without breaking or making of bonds to the chiral phosphorus, (+)-(4) must also have the *S*-configuration.

Methanolysis of Phosphinic Amides.—The appropriate optically active amide (0.25—0.50 mmol) dissolved in a small volume of methanol was added to methanolic hydrogen chloride maintained at 28 °C (or as shown in Table 1) to give a reaction mixture of the required composition (Table 1). Reaction was allowed to continue for a time (Table 1) estimated to give >99.9% completion and was then quenched by cooling and addition of a small excess of methanolic 6M-ammonia. Precipitated ammonium chloride was removed and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (10—25 ml) and the solution filtered and evaporated under reduced pressure. Methyl methylphenylphosphinate was isolated by preparative t.l.c. on alumina [developing solvent 4% methanol in ether for experiments involving amides (*S*)-(4) and (*S*)-(6) (phosphinate R_F 0.4, aniline R_F 0.7) and 6% methanol in ether for experiments involving (*S*)-(7) (phosphinate R_F 0.5, *p*-nitroaniline R_F 0.75)], and was purified by bulb-tube distillation; b.p. 115—125° (oven temp.) at 8 mmHg. The purity was established by n.m.r. examination and by g.l.c. on 3% OV 17 at 175 °C (phosphinate t_R 5.0 min, aniline t_R 1.05 min) or 210° (phosphinate t_R 1.9 min, *p*-nitroaniline t_R 4.7 min), and the identity confirmed by comparison of the i.r. spectrum with that of authentic (±)-methyl methylphenylphosphinate. The

* The wide melting range is probably due to the presence of phosphinic acid impurity.

optical rotation was measured in benzene and in methanol (*c* 1.5—2.5) (Table 1) and in several cases the enantiomeric composition was confirmed by n.m.r. spectroscopy at 60 MHz; typically, a sample of the phosphinate having $[\alpha]_D$ −50.7° (benzene) exhibited δ 1.33 (3 H, d, J_{PH} 15 Hz) which was shifted by addition of $Eu(tfc)_3$ (29 mg per 24 mg of phosphinate) to δ 3.24 (d, J_{PH} 15 Hz) and 3.14 (d, J_{PH} 15 Hz); ratio *ca.* 19 : 1. [At 100 MHz $Eu(tfc)_3$ caused unacceptable broadening of the peaks.] The optical stability of methyl methylphenylphosphinate under the conditions, and for the lengths of time, of the methanolysis reactions was confirmed by maintaining a sample in methanolic 5.2M-hydrogen chloride at 28 °C; the rotation ($[\alpha]_D$ −45.4°) of the solution decreased by only *ca.* 1% per hour.

Interrupted Methanolysis of Phosphinic Amides.—The method was as described above except that reaction was quenched by addition of ammonia after an estimated 1.5—2.0 half lives and the extent of reaction was determined by n.m.r. examination of the mixture of product and starting material. Phosphinate (3) and unchanged amide (6) (R_F 0.3 in 4.5% methanol in ether) or (7) (R_F 0.25 in 6% methanol in ether) were isolated by preparative t.l.c. (alumina). The phosphinate was purified and characterised as before. The amide was purified by precipitation from dichloromethane with ether, its purity confirmed by m.p. determination, i.r. and n.m.r. spectroscopy, and g.l.c. on 3% OV 17 at 240 °C [(6), t_R 10.3 min] or 285° [(7), t_R 11.3 min], and its optical rotation determined. The results are summarised as follows:

(*S*)-(6) with [HCl] = 0.16M; t = 2.4 min (65% completion)

(3), $[\alpha]_D$ −55.9° (PhH), −49.0° (MeOH); recovered (6), $[\alpha]_D$ −27.6° (MeOH)

(*S*)-(6) with [HCl] = 1.5M; t = 0.4 min (60% completion)

(3), $[\alpha]_D$ −38.5° (PhH), −33.0° (MeOH); recovered (6), $[\alpha]_D$ −27.85° (MeOH)

(*S*)-(7) with [HCl] = 1.5M; t = 3.0 min (70% completion)

(3), $[\alpha]_D$ −49.5° (PhH), −44.0° (MeOH); recovered (7), $[\alpha]_D$ +41.8° (MeOH)

(*S*)-(7) with [HCl] = 5.0M; t = 0.6 min (75% completion)

(3), $[\alpha]_D$ −30.9° (PhH), −27.1° (MeOH); recovered (7), $[\alpha]_D$ +41.3° (MeOH)

Methanolysis of (N-Phenyl)methylphenylphosphinic Amide in the Presence of Lithium Chloride.—The methanolysis of (−)-(*S*)-(6) in methanolic 0.15M-hydrogen chloride was repeated with lithium chloride (1.35M) present in solution. The residue remaining after evaporation (reduced pressure) of methanol from the quenched reaction mixture was dissolved in water (5 ml) and extracted with dichloromethane (3 × 10 ml). Methyl methylphenylphosphinate was isolated from the organic extracts and purified in the usual way; it had $[\alpha]_D$ −47.7° (PhH), −42.1° (MeOH).

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