Stereochemistry of the methoxide induced rearrangement of an α-bromophosphonamidate: cleavage of the P–N and P–C bonds in the azaphosphiridine oxide intermediate[1]

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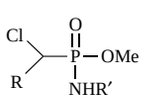
Menthyl *P*-(bromomethyl)-*N*-*tert*-butylphosphonamidate 5 has been prepared from (1*R*,2*S*,5*R*)-(−)-menthol and the S_P diastereoisomer has been isolated. This rearranges with methoxide [$Me_3(PhCH_2)N^+$ MeO^- in THF–MeOH] to give only the S_P diastereoisomer of menthyl methyl (*tert*-butylamino)-methylphosphonate 6 and very largely (95%) the S_P diastereoisomer of menthyl methyl *N*-*tert*-butyl-*N*-methylphosphoramidate 7. The configurations of these products show that when the (postulated) azaphosphiridine oxide intermediate 16 suffers ring opening by methoxide, the P–N bond is cleaved (to give 6) with inversion of configuration but the P–C bond is cleaved (to give 7) with predominant retention. These contrasting stereochemistries suggest that nucleophilic attack on the P=O group of the azaphosphiridine oxide generates a five-coordinate intermediate (not merely a transition state) that exists long enough to undergo pseudorotation.

Two types of rearrangement product are formed when an α-chlorophosphonamidate **1** reacts with methoxide, the α-aminophosphonate **3** and the phosphoramidate **4**.[2,3] In both types the α-chlorine atom has been replaced, but not directly by methoxide. Rather, it is the nitrogen atom of the amide group that has displaced chlorine, and the phosphorus atom that has acquired an extra methoxy group at the expense of the P–N or P–C bond. Some substrates give predominantly just one type of product but others (*e.g.* **1**, R = H, R′ = Bu^t) give substantial amounts of both.[2,3] The mechanism may involve initial base induced cyclisation (elimination of HC1) to give the azaphosphiridine oxide **2**. This could then break down, as a result of nucleophilic attack at phosphorus, with cleavage of the P–N bond to give **3** or the P–C bond to give **4**. There is no direct



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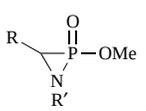

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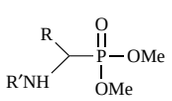

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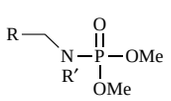

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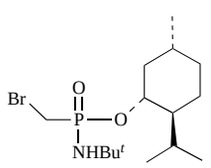
evidence for an azaphosphiridine oxide intermediate, but something other than nucleophilic attack at phosphorus is clearly rate-determining, since the reactivity of the substrate is notably insensitive to steric hindrance.[2,3] Also, the composition of the product seems to depend on the relative abilities of the α-carbon and nitrogen atoms to be displaced from phosphorus, with anionic character, by an attacking nucleophile.[3]

Little is known about azaphosphiridine oxides, the phosphorus analogues of α-lactams. Other types of three-membered ring containing a P=O group have been encountered as short-lived intermediates,[4] and some have actually been isolated.[5] Even for these, however, there is no information on the stereochemistry of nucleophilic substitution at the phosphorus atom. By contrast, stereochemical studies with four- and five-membered cyclic compounds[6] have contributed much to our understanding of nucleophilic substitution at phosphorus, especially with regard to five-coordinate intermediates and pseudorotation.[7] A stereochemical study of the rearrangement of an α-halogenophosphonamidate might therefore afford valuable information, not only on that reaction in particular but on nucleophilic substitution at phosphorus in general.

Results and discussion

Substrate

The menthyl α-bromomethylphosphonamidate **5** seemed a particularly appropriate substrate for a number of reasons. First, it should give substantial amounts of both types of rearrangement product, so that the stereochemistry of both P–N and P–C cleavage can be examined in a single reaction. Second, it and its rearrangement products (**6** and **7**) are chiral at phosphorus, as is necessary, but not at the α-C atom, which would introduce needless complexity. Third, it contains a chiral ligand (menthoxy) that, while playing no direct part in the chemistry, opens the way to (i) obtaining stereoisomers of the substrate that differ only in the configuration at phosphorus, by the separation of diastereoisomers rather than enantiomers; (ii) producing stereoisomers of each type of product that differ only in the configuration at phosphorus but which, being diastereoisomers, can be quantified relatively easily; (iii) deducing configurations at phosphorus, relative to the known configuration of the chiral ligand, by conventional X-ray crystallography.



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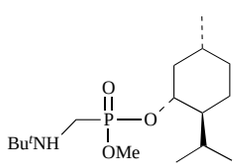

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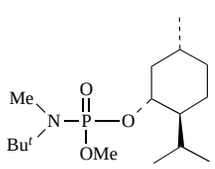

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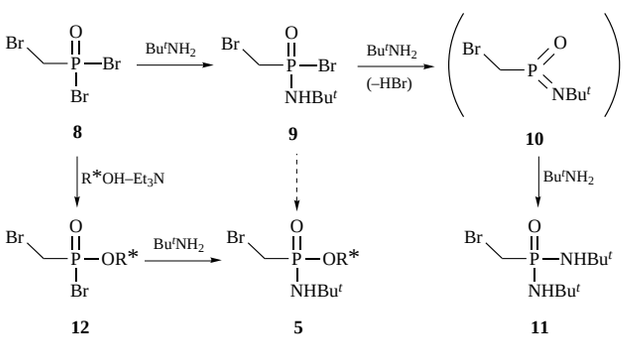
Finally, it is a bromide rather than a chloride so it should react under relatively mild conditions. This is especially important because the *P*-methoxy groups in the products render them liable to degradation, either structurally by demethylation [$>P(O)OMe + {}^{-}OMe \longrightarrow >P(O)O^{-} + Me_2O$] or configurationally by exchange [$>P(O)OMe + {}^{-}OMe' \rightleftharpoons >P(O)OMe' + {}^{-}OMe$]. The latter process would obviously compromise an investigation of the stereochemistry, but so would the former if one diastereoisomer were degraded more rapidly than the other.

Bromomethylphosphonic dibromide **8** was first prepared, by controlled hydrolysis of the complex ($BrCH_2PBr_3^{+}\ AlBr_4^{-}$) formed by reaction of CH_2Br_2 with PBr_3–$AlBr_3$.[8] Our intention had been to convert this into the phosphonamidic bromide **9**, but we were unable to selectively replace just one of the Br atoms with Bu^tNH_2: even before the dibromide **8** (δ_P 1.0) had all been consumed, some of the phosphonamidic bromide (δ_P 19.2) underwent further reaction to the phosphonic diamide **11** (δ_P 15.8). This would not be expected if substitution proceeds by the normal associative $S_N2(P)$ mechanism; more likely, the high reactivity of **9** is a consequence of its ability to react by a dissociative elimination–addition mechanism with a three-coordinate P^V intermediate **10** (Scheme 1).[9] Previously, selective



Scheme 1

replacement of just one of the Cl atoms in $ClCH_2P(O)Cl_2$ with Bu^tNH_2 did not present a problem.[3] However, a better leaving group (Br instead of Cl) may accelerate the dissociative second substitution more than the associative first one, so that it does become competitive.

The alternative approach requires that the menthoxy group be introduced first (Scheme 1). The phosphonic dibromide was therefore treated with (−)-menthol and Et_3N (**8** ⟶ **12**), then with Bu^tNH_2. This gave the phosphonamidate **5** as a 54:46 mixture of diastereoisomers (^{31}P NMR and capillary GLC), together with some by-products. Crystallisation removed the impurities and afforded a small sample of a single diastereoisomer, δ_P 18.0 (diastereoisomer ratio 1:99 at least) as well as a 60:40 mixture of both, δ_p 18.3 (major) and 18.0. The EI mass spectrum of **5** did not show the molecular ion but the CI spectrum contained $(M + H)^+$ peaks at 368 and 370 (5%; ratio *ca.* 1:1) as expected. Single-crystal X-ray analysis of the single diastereoisomer of **5** revealed that it had the *S* configuration at phosphorus (Fig. 1)[1] relative to the known configuration of the menthyl group (1*R*,2*S*,5*R*).[10]

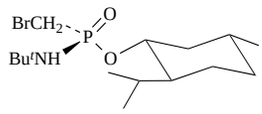


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Fig. 1

Reaction with methoxide

Preliminary experiments indicated that the α-bromomethylphosphonamidate **5**, in spite of its good leaving group, reacted with sodium methoxide in methanol only under quite forcing conditions (2 mol dm^{-3} NaOMe; 50 °C) and that product degradation (demethylation) was then quite extensive. Reaction proceeded much more readily with benzyltrimethylammonium methoxide in THF–methanol and demethylation of the products was not now a problem. All reactions were therefore carried out using a small excess of $Me_3(PhCH_2)N^{+}\ {}^{-}OMe$ (1.5 mol equiv.) as a dilute solution (0.2 mol dm^{-3} initial concentration) in THF–methanol (9:1).

For the single diastereoisomer of **5**, reaction was complete inside 4.5 h at room temperature and gave two products in a 5:1 ratio (^{31}P NMR). The major product was isolated by extraction (from diethyl ether solution) into aqueous acid and was identified as the α-aminophosphonate **6**, δ_p 28.4. The ^{1}H NMR spectrum clearly showed a methylene group with phosphorus-coupled diastereotopic protons, $\delta_H(CDCl_3)$ 2.922 (ABP, δ_A 2.941, δ_B 2.903, J_{AB} 13.9, J_{AP} 14.9, J_{BP} 15.7; CH_2P), in addition to the expected signals for P–O-menthyl (including δ_H 4.273, 1 H, dddd, J_{PH} 6.9, J_{HH} ~11, 10.7 and 4.5), P–OMe (δ_H 3.765, 3 H, d, J_{PH} 10.8) and N–Bu^t (δ_H 1.076, 9 H, s) groups. Although predominantly one diastereoisomer, minor peaks in both the ^{31}P (δ_P 28.1) and ^{1}H (δ_P 3.790, d, J_{PH} 10.7; POMe) NMR spectra indicated 4–5% of the other diastereoisomer.

The minor product, which did not extract into aqueous acid, was identified as the phosphoramidate **7**, δ_P 11.5; the ^{1}H NMR spectrum showed a phosphorus-coupled N–Me group at δ_H 2.663 (d, J_{PH} 9.6) in addition to the P–O-menthyl (δ_H includes 4.137, 1 H, dddd, J_{PH} 7.5, J_{HH} ~11, 10.6 and 4.5), P–OMe (δ_H 3.614, 3 H, d, J_{PH} 11.4) and N–Bu^t (δ_H 1.314, 9 H, s) signals. This also contained *ca.* 5% of a second diastereoisomer; δ_P 10.5; δ_H 3.628 (d, J_{PH} 11.3, POMe).

Using the 60:40 mixture of the diastereoisomers of **5**, the same two products were again formed in a 5:1 ratio, showing that the two diastereoisomers of the substrate react in essentially the same way. However, the diastereoisomer ratios of the products—43:57 for the α-aminophosphonate **6** and 41:59 for the phosphoramidate **7**—differed greatly from those seen before. This difference is important: it shows that stereospecificity (a consequence of the mechanism of reaction), not stereoselectivity (a consequence of the relative stabilities of stereoisomeric products), is chiefly responsible for the stereochemistry seen using the single diastereoisomer of the substrate.

In these experiments, the diastereoisomer ratios of the products are close to that of the substrate, but not identical. The significance of the discrepancies was investigated by repeating the reaction of the single diastereoisomer using a longer reaction time (6 h) and a much shorter one (quenched after 16 min; *ca.* 93% completion). The α-aminophosphonate product **6** from these reactions contained 12% and 1% respectively of the minor diastereoisomer, showing that it is prone to epimerisation (P–OMe exchange) under the conditions of the reaction, and suggesting that it is actually formed as just one diastereoisomer (100% stereospecificity). The phosphoramidate product **7**, on the other hand, contained 5% of the minor diastereoisomer regardless of the reaction time, implying that it is configurationally stable. Since epimerisation requires attack at phosphorus by methoxide, this is not surprising; on both steric and electronic grounds, the phosphoramidate **7** will be less susceptible to nucleophilic attack than the α-aminophosphonate **6**. Given its configurational stability, it must be that the phosphoramidate product is not formed entirely as one diastereoisomer (<100% stereospecificity).

Product stereostructures

As anticipated, the products from the rearrangement of **5** (single diastereoisomer) were non-crystalline, so it was not possible to determine directly their configurations. For the α-aminophosphonate **6** the problem was readily solved, by treatment with

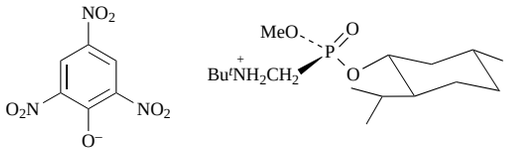
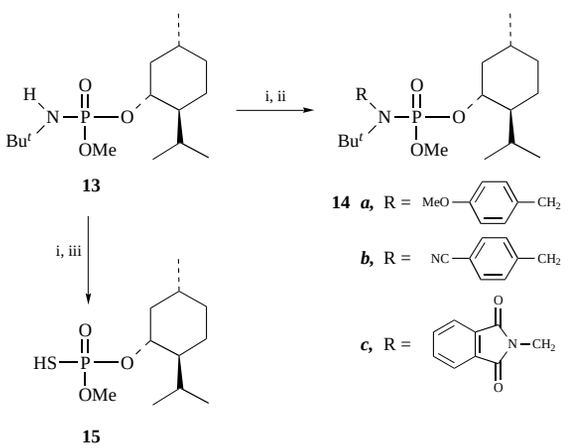


Fig. 2

picric acid. Crystallisation of the resulting salt afforded a pure sample of the dominant diastereoisomer and the configuration was determined by X-ray crystallography (Fig. 2).[1]

The phosphoramidate product **7** is a tertiary amide and there is no simple way of converting it into a crystalline derivative. That being so, the related secondary amide **13** was prepared, by treating $POCl_3$ first with (−)-menthol–Et_3N,[11] then with Bu^tNH_2 and finally with NaOMe in methanol. Repeated chromatography of the resulting mixture of the diastereoisomers of **13** (δ_P 7.2 and 6.7) eventually yielded a small sample of the lowfield diastereoisomer (δ_P 7.2; >96%). This was crystalline and on *N*-methylation (NaH in DMF; MeI) it gave the same diastereosiomer of the tertiary phosphoramidate **7** (lowfield δ_P) as was dominant in the product from the rearrangement of **5** (single diastereoisomer). Since *N*-methylation does not involve the P=O centre, the tertiary amide **7** and the secondary amide **13** must have the same configuration at phosphorus. Determination of the configuration of **13** will therefore reveal the configuration of the rearrangement product **7**. Unfortunately, despite its crystallinity, we were unable to obtain crystals of **13** that were adequate for X-ray analysis. Derivatisation of **13** thus became a necessity. To avoid any risk of compromising the configuration at phosphorus, modification of the $NHBu^t$ group was to be preferred. The derivatives **14a**–**c** were prepared (NaH



Scheme 2 *Reagents*: i, NaH in DMF; ii, RCl or RBr; iii, CS_2 then H_3O^+

in DMF; RCl or RBr) but unfortunately none was crystalline. Replacement of one of the groups attached to the P atom thus seemed unavoidable. The secondary amide **13** (>96% δ_P 7.2) was again converted into the anion (NaH in DMF), but now this was treated with CS_2 to give, after acidification, the phosphorothioic acid **15** (>96% one diastereoisomer). With dicyclohexylamine the acid formed a crystalline salt and X-ray crystallography was used to determine its stereostructure [Fig. 3(*a*)].[1] Given the mechanism of the reaction (Scheme 3), no change in the configuration at phosphorus would be expected when the Bu^tNH group is replaced by HS. More important, several examples of this type of transformation have been shown to proceed with retention of configuration at phosphorus.[12] We can therefore deduce the configuration of the amide **13** with confidence [Fig. 3(*b*), R = H], and hence the configuration of the phosphoramidate **7** (dominant diastereoisomer) formed in the rearrangement of the α-bromophosphonamidate [Fig. 3(*b*), R = Me].

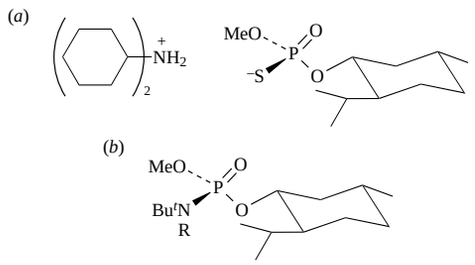
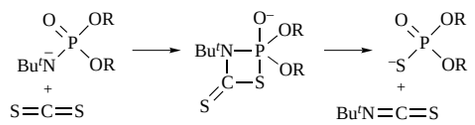


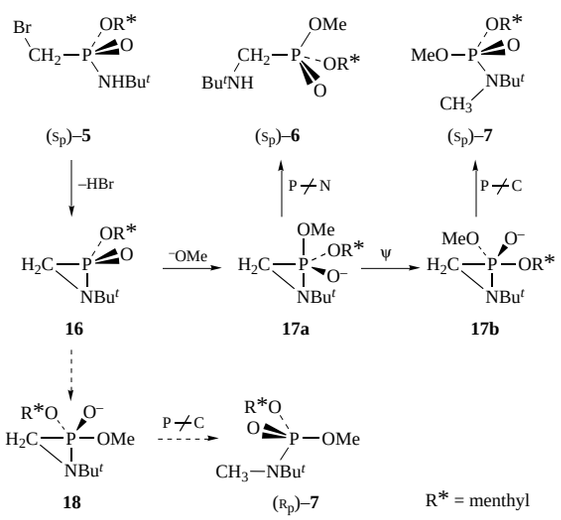
Fig. 3



Scheme 3

Reaction stereochemistry

Comparing the stereostructures of the α-bromophosphonamidate (Fig. 1) and its rearrangement products [Figs. 2 and 3(*b*)] it can be seen that methoxide cleaves the P–N bond, to form the α-aminophosphonate, with inversion of configuration at phosphorus, but the P–C bond, to form the phosphoramidate, with retention. These contrasting stereochemistries can be rationalised in terms of nucleophilic attack on the azaphosphiridine oxide intermediate **16** (Scheme 4)† if



Scheme 4

a five-coordinate intermediate is involved.[7] Attack opposite the more apicophilic ring-nitrogen atom would give the phosphorane **17a**. This could collapse directly to product, by cleavage of the apical P–N bond, giving the α-aminophosphonate (S_P)-**6** with inversion of configuration. Alternatively, it could pseudorotate to the new phosphorane **17b**. This, on cleavage of the newly-apical P–C bond, would give the phosphoramidate (S_P)-**7** with retention of configuration. Granted that nitrogen is not strongly apicophilic, the possibility of some competing attack opposite carbon must also be considered. Direct breakdown of the resulting phosphorane **18**, by cleavage of the P–C bond,

† Scheme 4 shows the behaviour of the pure S_P diastereoisomer of **5**; the R_P diastereoisomer was not obtained pure, but the results for the diastereoisomer mixture (60% R_P) suggest that it reacts with comparable stereospecificity, *i.e.* (R_P)-**5** gives predominantly (R_P)-**6** (inversion of configuration) and (R_P)-**7** (retention) (Scheme 4 with OR* and O interchanged).

would in this case give the phosphoramidate (R_P)-**7** with inversion of configuration at phosphorus. The fact that the phosphoramidate was actually formed as a 95:5 mixture of diastereoisomers is therefore easily accommodated and might even have been anticipated. Of course, substitution with inversion of configuration does not actually require a phosphorane intermediate—a five-coordinate transition state will suffice—but substitution with retention of configuration surely does. And if some of the nucleophilic attack on the azaphosphiridine oxide proceeds *via* a phosphorane intermediate, the likelihood must be that all of it does. In one sense this may seem improbable: the leaving group (nitrogen or carbon) is part of a three-membered ring and its departure will afford much relief of strain. Even so, it seems a concerted pathway like that for nucleophilic substitution (S_N2) at a tetrahedral carbon is still not as favourable as the normal non-concerted addition–elimination mechanism of nucleophilic substitution at phosphorus. In fact, when the P=O group is part of a small ring there can in any case be considerable relief of strain: the ideal bond angle at phosphorus in the tetrahedral substrate is 109.5° but in a trigonal-bipyramidal phosphorane intermediate it will be only 90°, between apical and equatorial positions. Provided nucleophilic attack on the P=O group of **16** occurs opposite one of the ring atoms (N or C), the phosphorane will be formed with the ring apical, equatorial and angle strain will be much reduced.

Angle strain may also be important in determining the structures of the products, as well as their configurations. The menthoxy group (OR*) is inherently the best leaving group in the azaphosphiridine oxide **16**, yet when methoxide attacks, the P–O bond remains intact while the P–N or P–C bond breaks. Direct displacement of the menthoxy group is unlikely, since nucleophilic attack opposite the OR* group of **16** would place the three-membered ring diequatorial in the resulting intermediate (or transition state), but the menthoxy group occupies an apical position in the phosphorane **17b** and might be expected to depart. If it were to do so, however, the angle strain relieved in the formation of the phosphorane (**16** ⟶ **17**) would be reimposed in the formation of the product (**16** with OMe in place of OR*). By contrast, there will be a further easing of angle strain when **17b** forms the phosphoramidate product by cleavage of the P–C bond.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM 390 spectrometer or (where indicated) at 300 MHz on a Bruker AM-300 (Me_4Si internal standard; coupling constants, *J*, given in Hz) and ^{31}P NMR spectra (^{1}H decoupled) were recorded at 36.2 MHz on a JEOL JNM-FX90Q spectrometer (positive chemical shifts downfield from external 85% H_3PO_4). Routine mass spectra were obtained in EI or (where indicated) CI mode on a VG 16-B or Kratos Concept spectrometer and high resolution spectra were recorded by the SERC Mass Spectrometry Service at Swansea. GLC analyses were performed using a Philips capillary chromatograph (helium carrier gas; flame-ionisation detector) fitted with a 25 m × 0.22 mm column containing a 0.25 μm film of BP 5 (equivalent to SE 54) and TLC analyses were performed on silica gel 60 F_{254} (0.2 mm layer on aluminium foil). Amines were dried over KOH, CH_2Cl_2 was distilled from CaH_2, THF was distilled from sodium–benzophenone and DMF was distilled under reduced pressure from P_2O_5. Solutions of benzyltrimethylammonium methoxide in MeOH (40% w/w) were used as supplied. Light petroleum refers to the fraction with bp 60–80 °C unless otherwise indicated, and ether to diethyl ether.

Menthyl *P*-(bromomethyl)-*N*-*tert*-butylphosphonamidate 5

Based on the method of Cade,[8] the complex (δ_P 30.2) formed by addition of CH_2Br_2 (7 mol equiv.) to an equimolar mixture of PBr_3 and $AlBr_3$ was dissolved in CH_2Cl_2 and carefully hydrolysed at *ca.* −25 °C to give bromomethylphosphonic dibromide **8**; $\delta_P(CH_2Cl_2)$ 0.5; $\delta_H(CDCl_3)$ 4.13 (d, J_{PH} 4).

A mixture of dried (−)-menthol (2.55 g, 16.3 mmol) and Et_3N (1.58 g, 15.6 mmol) in CH_2Cl_2 (15 ml) was added over 10 min to a stirred (powerful magnet) solution of bromomethylphosphonic dibromide **8** (4.68 g, 15.6 mmol) in CH_2Cl_2 (15 ml). After 20 min more (−)-menthol–Et_3N (0.8 mmol) was added to complete the formation of **12** (two diastereoisomers, δ_P 19.0 and 17.0). Stirring was continued for a further 30 min, then *tert*-butylamine (4.66 g, 63.9 mmol) was added dropwise (exothermic) [to give product **5**, two diastereoisomers, δ_P 18.4 (major) and 18.1, ratio 54:46; several by-products]. After 20 min, all volatile material was evaporated and the residue was partitioned between toluene and water. The organic portion was dried ($MgSO_4$) and concentrated; crystallisation from EtOH–H_2O (9:1; 20 ml) gave **5** (1.53 g, 27%) as a 46:54 mixture of diastereoisomers (highfield δ_P now in excess). Recrystallisation from EtOH–H_2O (12:1; 10 ml; overnight refrigeration) gave some material (374 mg) having a diastereoisomer ratio 3:97 and this, on crystallisation from light petroleum (20 ml), gave the pure highfield (^{31}P NMR) diastereosiomer of *menthyl* P-(*bromomethyl*)-N-tert-*butylphosphonamidate* **5** (sample A), mp 155–155.5 °C; $\delta_P(CH_2Cl_2)$ 18.0; $\delta_H(CDCl_3$, 300 MHz) 4.225 (1 H, ddt, J_{PH} 8.0, J_{HH} 4.5 and 10.6), 3.278 (2 H, ABP, δ_A 3.341, δ_B 3.211, J_{AB} 13.0, J_{AP} 10.3, J_{BP} 7.1, PCH_2Br), 2.646 (1 H, d, J_{PH} 6.9, NH; exchanged with D_2O), 2.287 (1 H, m), 2.077 (1 H, d septet, J_{HH} 2.5 and 7.0), 1.663 (2 H, m), 1.55–0.75 (14 H) and 1.355 (9 H, d, J_{PH} 0.6, $PNBu^t$); *m/z* (no M^+) 354, 352 (M^+ − Me, 7%; ratio 1:1), 232, 230 (33; ratio 1:1) and 216, 214 (M^+ − Me − $C_{10}H_{18}$, 100; ratio 1:1); *m/z* (CI) 370, 368 (M + H^+, 5%; ratio 1:1), 290 (30) and 74 (100); ν_{max}(Nujol)/cm^{-1} 3220 (NH) and 1245 (P=O); t_R 14.7 min (BP 5, 210 °C) (Found: C, 48.85; H, 8.1; N, 3.8. $C_{15}H_{31}BrNO_2P$ requires C, 48.9; H, 8.5; N, 3.8%). A portion of this diastereoisomer (100% by GLC) was recrystallised from CH_2Cl_2–light petroleum and then slowly from aqueous ethanol to produce a sample for single crystal X-ray analysis.[1]

Material from the mother liquors (see above) was crystallised from light petroleum to give a sample of the *phosphonamidate* **5** as a 60:40 mixture of diastereoisomers (sample B), mp 113–115 °C; $\delta_P(CH_2Cl_2)$ 18.3 (major) and 18.0; $\delta_H(CDCl_3$, 300 MHz) 4.34–4.17 (1 H, m), 3.39–3.17 (2 H, m), 2.731 (major) and 2.650 (total 1 H; both d, J_{PH} 7.2 or 7.5, NH), 2.34–2.03 (2 H, m), 1.72–1.62 (2 H, m), 1.55–0.75 (14 H) and 1.355 and 1.351 (major) (total 9 H; both d, J_{PH} 0.7); ν_{max}(Nujol)/cm^{-1} 3300, 3260 (NH) and 1235 (P=O); t_R 14.3 (major) and 14.7 min (BP 5, 210 °C).

Reaction of menthyl *P*-(bromomethyl)-*N*-*tert*-butylphosphonamidate 5 with methoxide

A solution of the diastereoisomerically enriched bromomethylphosphonamidate **5** (sample A or B) (48 mg, 0.13 mmol) in THF (0.45 ml) was added to a mixture of methanolic benzyltrimethylammonium methoxide (40% w/w) (0.1 ml, 0.2 mmol) and THF (0.45 ml) (reaction medium: 0.2 mol dm^{-3} methoxide in 9:1 THF–MeOH). After 4.5 h (or 16 min or 6 h) the reaction was quenched (NH_4Cl) and the reaction mixture was examined by ^{31}P NMR spectroscopy to determine the ratio of the two types of rearrangement product and the diastereoisomer composition of each. Volatile material was removed, the residue was partitioned between ether and water and the ether portion was washed with aqueous NaOH and water. To separate the products the ether portion was then extracted with hydrochloric acid (1 mol dm^{-3}) and water. Concentration of the ether portion afforded menthyl methyl *N*-*tert*-butyl-*N*-methylphosphoramidate **7** (see below) and basification of the combined aqueous extracts liberated menthyl methyl (*tert*-butylamino)-methylphosphonate **6** (see below).

Menthyl methyl *N*-*tert*-butyl-*N*-methylphosphoramidate 7

The reaction of the bromomethylphosphonamidate **5** (sample B) with methoxide gave the *phosphoramidate* **7** as a 41:59 mixture of diastereoisomers, bp 74 °C (oven temp.) at 0.2 mmHg; δ_P($CDCl_3$) 11.5 and 10.5 (major); δ_H($CDCl_3$, 300 MHz) 4.20–4.08 (1 H, m), 3.628 (major) and 3.612 (total 3 H; both d, J_{PH} 11.3 or 11.4, OMe), 2.665 (major) and 2.661 (total 3 H; both d, J_{PH} 9.7 or 9.5, NMe), 2.34–2.10 (2 H, m), 1.71–1.58 (2 H, m), 1.54–0.74 (14 H) and 1.315 (9 H, s); *m/z* (CI) 320 ($M + H^+$, 48%), 264 ($M + H^+ - H_2C{=}CMe_2$, 13), 182 ($M + H^+ - C_{10}H_{18}$, 100), 166 ($M^+ - Me - C_{10}H_{18}$, 59) and 126 ($M + H^+ - C_{10}H_{18} - H_2C{=}CMe_2$, 68); ν_{max}(film)/cm^{-1} 1250 (P=O) (Found: C, 59.4; H, 10.4; N, 4.4; $M + H^+$, 320.2355. $C_{16}H_{34}NO_3P$ requires C, 60.2; H, 10.7; N, 4.4%; *M* + H, 320.2355).

The reaction of **5** (sample A) with methoxide gave the *phosphoramidate* **7** as a 95:5 mixture of diastereoisomers; δ_P($CDCl_3$) 11.5 (major) and 10.5; δ_H($CDCl_3$, 300 MHz) for major component: 4.137 (1 H, dddd, J_{PH} 7.5, J_{HH} ~11, 10.6, 4.5), 3.614 (3 H, d, J_{PH} 11.4, OMe), 2.663 (3 H, d, J_{PH} 9.6, NMe), 2.31–2.11 (2 H, m), 1.70–1.60 (2 H, m), 1.53–0.79 (14 H, m) and 1.314 (9 H, s); ν_{max}(film)/cm^{-1} 1250 (P=O).

Authentic samples of the phosphoramidate **7** were also prepared, by methylation of menthyl methyl *N*-*tert*-butylphosphoramidate **13**. Thus **13** (mixture of diastereoisomers) (98 mg, 0.32 mmol) was stirred with NaH (18 mg, 0.75 mmol) in DMF (0.75 ml) for 2.7 h. Methyl iodide (136 mg, 0.96 mmol) was then added. After 1 h, volatile material was removed and the residue was partitioned between light petroleum and water. The organic portion was dried ($MgSO_4$) and concentrated to give the *phosphoramidate* **7** as a 58:42 mixture of diastereoisomers with the lowfield (^{31}P NMR) diastereoisomer in excess. In like manner, the sample of **13** (>96% one diastereoisomer) recovered unchanged from its reaction with NaH–CS_2 (see below) gave the *phosphoramidate* **7** as a 98:2 mixture of diastereoisomers with the lowfield (^{31}P NMR) diastereoisomer dominant; δ_H($CDCl_3$) 3.628 and 3.612 (major) (3 H, d, J_{PH} 11.3 or 11.4, OMe).

Menthyl methyl (*tert*-butylamino)methylphosphonate 6

The reaction of the bromomethylphosphonamidate **5** (sample B) with methoxide gave the α-*aminophosphonate* **6** as a 43:57 mixture of diastereoisomers; δ_P($CDCl_3$) 28.4 and 28.1 (major); δ_H($CDCl_3$, 300 MHz) 4.33–4.21 (1 H, m), 3.791 (major) and 3.765 (total 3 H; both d, J_{PH} 10.6 or 10.8, OMe), 2.922 and 2.920 (major) (total 2 H; ABP pattern or d, J_{PH} 15.2, PCH_2N), 2.22–2.07 (2 H, m), 1.72–1.61 (2 H, m), 1.51–1.28 (2 H, m), 1.26–0.68 (13 H; includes NH) and 1.085 (major) and 1.078 (total 9 H; both s); *m/z* 319 (M^+, 13%), 304 ($M^+ - Me$, 39), 182 ($M^+ - C_{10}H_{17}$, 18) and 166 ($M^+ - Me - C_{10}H_{18}$, 100); ν_{max}(film)/cm^{-1} 3280 (NH) and 1245 (P=O). Treatment with picric acid in benzene and crystallisation from CH_2Cl_2–ether–light petroleum afforded the *picrate*, mp 158–163 °C; δ_P($CDCl_3$) 17.0 (major) and 16.2 (diastereoisomers); δ_H($CDCl_3$, 300 MHz) 8.886 (2 H, s), 4.37–4.16 (1 H, m), 3.676 (major) and 3.649 (total 3 H; both d, J_{PH} 11.3 or 11.4, OMe), 3.50–3.30 (2 H, m), 2.12–1.84 (2 H, m), 1.70–0.69 (16 H) and 1.475 (9 H, s) (Found: C, 48.3; H, 6.7; N, 10.1. $C_{22}H_{37}N_4O_{10}P$ requires C, 48.2; H, 6.8; N, 10.2%).

The reaction of **5** (sample A) with methoxide gave the α-*aminophosphonate* **6** as a 95:5 mixture of diastereoisomers; δ_P($CDCl_3$) 28.4 (major) and 28.1; δ_H($CDCl_3$, 300 MHz) major diastereoisomer: 4.273 (1 H, dddd, J_{PH} 6.9, J_{HH} ~11, 10.7 and 4.5), 3.765 (3 H, d, J_{PH} 10.8, OMe), 2.922 (2 H, ABP, δ_A 2.941, δ_B 2.903, J_{AB} 13.9, J_{AP} 14.9, J_{BP} 15.7, PCH_2N), 2.26–2.06 (2 H, m), 1.73–1.60 (2 H, m), 1.58–0.75 (15 H; includes NH) and 1.076 (9 H, s); ν_{max}(film)/cm^{-1} 3290 (NH) and 1245 (P=O). Treatment with picric acid in benzene afforded, after crystallisation from ether–light petroleum, a single diastereoisomer of the *picrate*, mp 118.5–120.5 °C; δ_P($CDCl_3$) 16.4; δ_H($CDCl_3$, 300 MHz) 8.889 (2 H, s), 4.259 (1 H, dddd, J_{PH} 6.8, J_{HH} ~11, 11 and 5), 3.692 (3 H, d, J_{PH} 11.3, OMe) 3.360 (2 H, ABP, δ_A 3.391, δ_B 3.329, J_{AB} ~J_{AP} ~J_{BP} ~15), 2.13–2.02 (1 H, m), 1.916 (1 H, m), 1.72–1.58 (2 H, m), 1.30–0.70 (14 H) and 1.470 (9 H, s). A portion of this diastereoisomerically pure picrate was allowed to crystallise slowly from ether–light petroleum to give a sample suitable for single crystal X-ray analysis.[1]

Menthyl methyl *N*-*tert*-butylphosphoramidate 13

(*a*) A mixture of (−)-menthol (3.13 g, 20 mmol) and Et_3N (2.02 g, 20 mmol) in light petroleum (25 ml) was added over 20 min to a cooled (ice bath) and stirred solution of phosphorus oxychloride (3.07 g, 20 mmol) in light petroleum (15 ml). The mixture was stirred at room temperature for 3.5 h and the precipitate (Et_3NHCl) was removed by filtration (moisture excluded). The filtrate was concentrated to give menthyl phosphorodichloridate (5.06 g, 93%);[11] δ_P(CH_2Cl_2) 5.5; ν_{max}(film)/cm^{-1} 1290 (P=O), 990 and 970. (*b*) *tert*-Butylamine (2.66 g, 36.4 mmol) in benzene (5 ml) was added dropwise over 5 min to a cooled (ice bath) and stirred solution of the crude phosphorodichloridate (4.97 g, 18.2 mmol) in benzene (20 ml). After 10 min the mixture was warmed to room temperature and stirred for a further 2 h. The precipitate (Et_3NHCl) was removed by filtration and the filtrate was concentrated to give *menthyl* N-tert-*butylphosphorochloramidate* (5.35 g, 95%) as an oil that slowly solidified; δ_P($CDCl_3$) 10.5 (major) and 9.8 (diastereoisomers; ratio 65:35) (impurity ~10%); δ_H($CDCl_3$) 4.63–4.13 (1 H, m), 3.23 (1 H, br, NH), 2.43–0.70 (18 H) and 1.33 (9 H, s). This material was used without purification. (*c*) A solution of the impure phosphorochloramidate (4.3 g, 14 mmol) in light petroleum (bp 40–60 °C) (8 ml) was stirred and cooled (ice bath) while a 2 mol dm^{-3} solution of NaOMe in MeOH (14 ml; 2 mol equiv.) was added. After 10 min the remaining methoxide was quenched (NH_4Cl) and volatile material was removed. The residue was partitioned between light petroleum and water and the organic portion was dried ($MgSO_4$) and concentrated to give the crude product (3.6 g, 85%); δ_P(CH_2Cl_2) 7.2 (major) and 6.7 (diastereoisomers; ratio 60:40). Crystallisation from light petroleum (bp 40–60 °C) at −40 °C gave *menthyl methyl* N-tert-*butylphosphoramidate* **13**, mp 73–76 °C (diastereoisomer ratio now 53:47, lowfield δ_P still in excess); δ_H($CDCl_3$, 300 MHz) 4.22–4.09 (1 H, m), 3.683 and 3.670 (major) (total 3 H; both d, J_{PH} 11.3 or 11.4, OMe), 2.483 and 2.436 (major) (total 1 H; both d, J_{HH} 7.3 or 7.1, NH; exchanges with D_2O), 2.39–2.08 (2 H, m), 1.72–1.59 (2 H, m), 1.54–0.77 (14 H) and 1.275 (major) and 1.271 (total 9 H; both d, J_{PH} 0.7 or 0.8); *m/z* 305 (M^+, 1%), 290 ($M^+ - Me$, 8), 168 ($M^+ - C_{10}H_{17}$, 50), 152 ($M^+ - Me - C_{10}H_{18}$, 100) and 112 ($M^+ - C_{10}H_{17} - H_2C{=}CMe_2$, 60); ν_{max}(Nujol)/cm^{-1} 3220 (NH) and 1240 (P=O) (Found: C, 58.9; H, 10.3; N, 4.4; M^+, 305.2127. $C_{15}H_{32}NO_3P$ requires C, 59.0; H, 10.6; N, 4.6%; *M*, 305.2120).

Chromatography of a 60:40 mixture of the diastereoisomers of **13** [rotating silica layer (chromatatron), eluent 1:1 ethyl acetate–light petroleum (bp 40–60 °C)] followed by the repeated chromatography of enriched fractions afforded a small sample (3% yield) that was >96% the lowfield (^{31}P NMR) diastereoisomer.

***N*-Alkyl derivatives of menthyl methyl *N*-*tert*-butylphosphoramidate 13**

Although the phosphoramidate **13** was crystalline, all attempts to grow crystals suitable for X-ray studies were unsuccessful. Several derivatives were prepared as summarised below, but none of them was obtained in a crystalline form.

(*a*) The phosphoramidate **13** (mixture of diastereoisomers) (153 mg, 0.5 mmol) was stirred with NaH (31 mg, 1.3 mmol) in DMF (1 ml). After 1.3 h, 4-methoxybenzyl chloride (235 mg, 1.5 mmol) was added and the mixture was stirred for a further 30 min. The excess NaH was quenched with methanol (60 μl) and solvent was removed. The residue was partitioned between ether and water and the organic portion was dried (Na_2SO_4) and concentrated. Chromatography [silica layer; 1:3 EtOAc–

light petroleum (bp 40–60 °C); R_f 0.21] afforded *menthyl methyl*-N-(4-*methoxybenzyl*)-N-tert-*butylphosphoramidate* **14a** (171 mg, 79%) as a semi-solid (completely molten above 50 °C); $\delta_P(CH_2Cl_2)$ 11.9 (major) and 10.8 (diastereoisomers; ratio 60:40); $\delta_H(CDCl_3)$ 7.07 (4 H, AA′BB′, δ_A 7.32, δ_B 6.82, J_{AB} 9), 4.5–3.9 (1 H, m), 4.20 (2 H, br d, J_{PH} 13, $PNCH_2Ar$), 3.76 (3 H, s, OMe), 3.63 (3 H, d, J_{PH} 11, POMe), 2.5–0.8 (18 H) and 1.30 (major) and 1.28 (total 9 H; both s, NBu^t); *m/z* (CI) 426 ($M + H^+$, 11%), 368 (10), 288 ($M + H^+ - C_{10}H_{18}$, 17) and 230 (100). (**CAUTION**: An attempt to dry 4-methoxybenzyl chloride over molecular sieves for 24 h resulted in decomposition with a build-up of pressure in the container; it was therefore used without drying).

(*b*) Similar alkylation of the phosphoramidate **13** with 4-cyanobenzyl bromide gave, after chromatography, *menthyl methyl* N-(4-*cyanobenzyl*)-N-tert-*butylphosphoramidate* **14b** (17%) as a glass; $\delta_P(CH_2Cl_2)$ 11.4 and 10.4 (diastereoisomers; ratio 50:50); $\delta_H(CDCl_3)$ 7.51 (4 H, br s), 4.42 and 4.40 (total 2 H; both d, J_{PH} 12 or 13, $PNCH_2Ar$), 4.12 (1 H, m), 3.66 (3 H, d, J_{PH} 11, POMe), 2.45–0.65 (18 H) and 1.29 and 1.27 (total 9 H; both s); *m/z* (CI) 421 ($M + H^+$, 80%), 405 ($M^+ - Me$, 17), 365 ($M + H^+ - H_2C{=}CMe_2$, 10), 306 (36), 283 ($M + H^+ - C_{10}H_{18}$, 100) and 267 ($M^+ - Me - C_{10}H_{18}$, 75); ν_{max}(film)/cm^{-1} 2220 (C≡N).

(*c*) Similar alkylation of the phosphoramidate **13** with *N*-(bromomethyl)phthalimide (reaction allowed to proceed overnight) gave, after chromatography (silica layer; ethyl acetate; R_f 0.52), *menthyl methyl* N-tert-*butyl*-N-(*phthalimidomethyl*)-*phosphoramidate* **14c** (39%) as an oil; $\delta_P(CDCl_3)$ 10.8 (major) and 9.9 (diastereoisomers; ratio 63:37); $\delta_H(CDCl_3)$ 7.78 (4 H, m), 5.34–5.10 (2 H, m, NCH_2N), 4.22 (1 H, m), 3.74 (3 H, d, J_{PH} 12, POMe), 2.47–0.55 (18 H) and 1.42 (major) and 1.40 (total 9 H; both s); *m/z* (CI) 465 ($M + H^+$, 65%), 449 ($M^+ - Me$, 20), 409 ($M + H^+ - H_2C{=}CMe_2$, 8), 327 ($M + H^+ - C_{10}H_{18}$, 69), 311 ($M^+ - Me - C_{10}H_{18}$, 100) and 271 ($M + H^+ - H_2C{=}CMe_2 - C_{10}H_{18}$, 55); ν_{max}(film)/cm^{-1} 1770 and 1710 (C=O).

O-Menthyl *O*-methyl phosphorothioate 15

The phosphoramidate **13** (mixture of diastereoisomers) (765 mg, 2.5 mmol) was stirred with NaH (103 mg, 4.3 mmol) in DMF (4.6 ml). After 1.7 h, CS_2 (0.76 g, 10 mmol) was added (deep red colour) and the mixture was left overnight. The excess NaH was quenched with MeOH (100 μl). Solvent was removed and the residue was partitioned between water and ether. The aqueous portion was acidified (HCl) to pH ≤ 1 and the liberated free phosphorothioic acid **15** was extracted into light petroleum. Purification of the acid by crystallisation of its ammonium salt from CH_2Cl_2–light petroleum (bp 40–60 °C) failed to remove a by-product (15%; believed to be **15** with O in place of S, resulting from reaction of the phosphoramidate anion with CO_2 instead of CS_2). The triethylammonium salt of **15**, $\delta_P(CH_2Cl_2)$ 58.3 and 58.0 (diastereoisomers) (by-product δ_P 0.3) was therefore prepared and partitioned between CH_2Cl_2 and water; the by-product passed into the aqueous phase allowing the pure acid **15** (545 mg, 82%) to be liberated from the organic phase. Crystallisation from light petroleum (bp 40–60 °C) at −20 °C afforded O-*menthyl* O-*methyl phosphorothioate* **15** as an equal mixture of diastereoisomers, mp 65–75 °C; $\delta_P(CDCl_3)$ 61.0 and 60.6; $\delta_H(CDCl_3)$ 7.57 (1 H, br s, OH), 4.53–4.05 (1 H, m), 3.73 (3 H, d, J_{PH} 13, OMe) and 2.40–0.67 (18 H); ν_{max}(Nujol)/cm^{-1} 3600–1800 (several maxima; OH) and 820 (P=S).

A portion of the phosphoramidate **13** (52 mg, 0.17 mmol) having >96% the lowfield diastereoisomer (^{31}P NMR) was treated as above to give the *phosphorothioic acid* **15** [>96% one diastereoismer, $\delta_P(CDCl_3)$ 61.2] and some unreacted substrate (12 mg) which was converted into **7** by *N*-methylation (see above).

Dicyclohexylammonium *O*-menthyl *O*-methyl phosphorothioate

The phosphorothioic acid **15** (mixture of diasteroisomers) was treated with dicyclohexylamine in light petroleum (bp 40–60 °C). Crystallisation of the product from light petroleum (bp 40–60 °C) gave *dicyclohexylammonium* O-*menthyl* O-*methyl phosphorothioate* as an equal mixture of diastereoisomers, mp 151–154 °C; $\delta_P(CDCl_3)$ 56.7 and 56.0; $\delta_H(CDCl_3$, 300 MHz) 8.85 (2 H, br s, $^+NH_2$), 4.25–4.05 (1 H, m), 3.612 and 3.600 (total 3 H; both d, J_{PH} 13.2 or 13.0, OMe), 3.12–2.93 (2 H, m) and 2.47–0.77 (38 H); *m/z* [negative ion FAB (NOBA matrix)] 265 (100%); ν_{max}(Nujol)/cm^{-1} 3200–2140 (NH) (Found: C, 61.6; H, 10.1; N, 3.0. $C_{23}H_{46}NO_3PS$ requires C, 61.7; H, 10.4; N, 3.1%). Similarly, the phosphorothioic acid **15** [>96% one diastereoisomer, $\delta_P(CDCl_3)$ 61.2] was converted into the *dicyclohexylammonium salt*; crystallisation from light petroleum (bp 40–60 °C) afforded a sample that was ⩾99.5% one diastereoisomer, $\delta_P(CDCl_3)$ 55.9; $\delta_H(CDCl_3$, 300 MHz) 8.82 (v br, $^+NH_2$), 4.117 (1 H, dddd, J_{PH} ~10, J_{HH} ~10, 10 and 4.3), 3.612 (3 H, d, J_{PH} 13.3, OMe), 3.11–2.95 (2 H, m), 2.49–2.38 (1 H, m), 2.256 (1 H, m), 2.17–2.04 (4 H, m), 1.89–1.76 (3 H, m) and 1.75–0.79 (29 H). This sample was allowed to crystallise slowly from a mixture of ether, CH_2Cl_2 and light petroleum to give a crystal suitable for X-ray analysis.[1]

Acknowledgements

We thank the SERC for a research studentship (to R. S.-M.) and for access to the Mass Spectrometry Service at Swansea.

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Paper 6/04093D
Received 11*th June* 1996
Accepted 11*th September* 1996