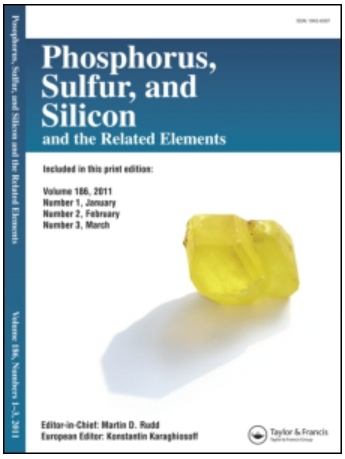

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CHOLESTERYL PHOSPHITE AND RELATED COMPOUNDS

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CHOLESTERYL PHOSPHITE AND RELATED COMPOUNDS

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The preparation of cholesteryl phosphorodichloridite (**2**) is described; this compound with aniline (2 mol. equiv.) gave the N-phenylphosphoramidochloridite (**5**) and the latter by condensation with water afforded the *N*-phenylamidophosphite (**6**).

Similarly the *N*-phenylphosphoramidochloridite (**5**) with morpholine gave the morpholidite (**7**); phenylhydrazine gave the hydrazinophosphite (**8**) and ethanol the amidoethyl phosphite (**9**). Cholesteryl phosphorodichloridite (**2**) by reaction with aniline (4 mol. equiv.) gave the N,N^1-diphenylphosphorodiamidite (**10**).

The reaction of cholesteryl phosphorodichloridite (**2**) with methanol and ethanol are discussed in relation to the analogous reactions with cholesteryl phosphorodichloridate. Boiling ethanol gave cholesterol as the only isolatable product but at room temperature a low yield of the diethylphosphite (**11**; R=Et) was obtained. The yield of the phosphite was greatly increased in the presence of base. Similarly the dichloridite **2** with boiling water gave cholesterol (**1**), but at room temperature cholesteryl phosphite **3** was isolated: the mechanistic basis for these different results is briefly discussed.

trans-4-*t*-Butylcyclohexanol with phosphorus trichloride gave the phosphorodichloridite, which was characterised by conversion to the corresponding N,N^1-diphenylphosphorodiamidite.

INTRODUCTION

Cholesterol (**1**) by the action of phosphorus trichloride and treatment with water gave cholesteryl phosphite (**3**).[1,2] This preparation was first reported[1] in 1927 and the phosphite was characterised as the anilinium salt (**4**).

DISCUSSION

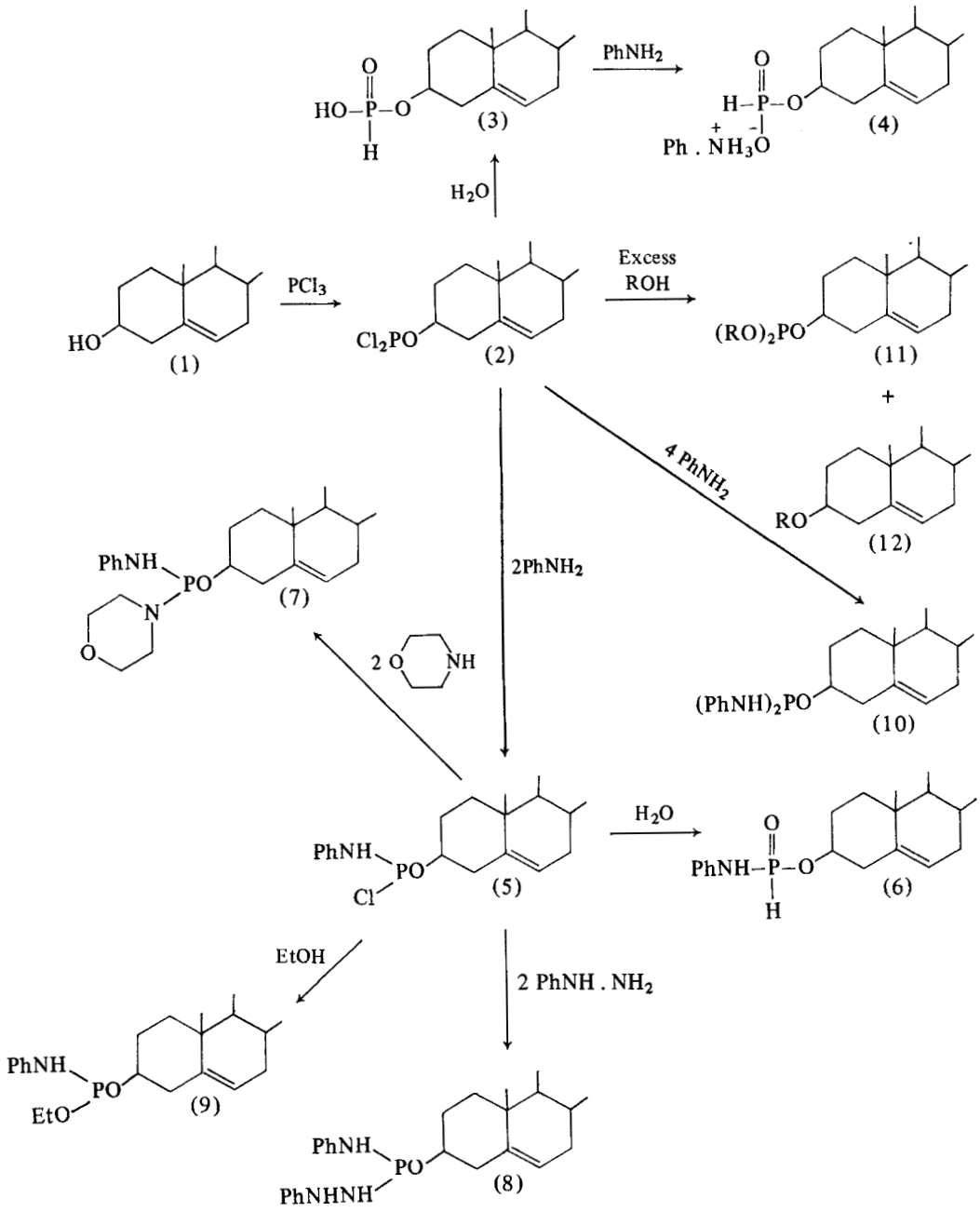
The preparation of cholesteryl phosphite (**3**) has been repeated; in addition the intermediate phosphorodichloridite (**2**) has been prepared (70% yield) by treatment of cholesterol (**1**) with an excess of phosphorus trichloride. The use of phosphorus trichloride (1 mol. equiv.) in the presence of triethylamine gave only a low yield (38%) of cholesteryl phosphorodichloridite (**2**).

To study any differences in behaviour of phosphorus III-and phosphorus V compounds, a similar set of reactions of cholesteryl phosphorodichloridite were examined to those previously studied[3,4] with cholesteryl phosphorodichloridate. The dichloridite (**2**) with aniline (2 mol. equiv.) gave the *N*-phenylamidochloridite (**5**), which by condensation with water afforded the *N*-phenylamidophosphite (**6**). Similarly morpholine gave the morpholidite (**7**), phenylhydrazine the phenylhydrazinophosphite (**8**), and ethanol the amidoethylphosphite (**9**) (Scheme 1).

Cholesteryl phosphorodichloridite (**2**) has also been converted to the N,N^1-diphenylphosphorodiamidite (**10**) by reaction with aniline (4 mol. equiv.).

Special interest attaches to the reactions of the phosphorodichloridite (**2**) with alcohols because cholesteryl phosphorodichloridate is known[5,6] to react with boiling methanol and ethanol in the absence of base to give a mixture of the cholesteryl dialkyl phosphate (S_N2 attack at P) and the cholesteryl alkyl ether (S_N1 attack at C_3); the latter arising from anchimeric assistance of the π-electrons of the 5,6-double bond.[7] Furthermore when the reaction was carried out with more sterically hindered alcohols, e.g. isopropanol, the S_N2 reaction at phosphorus is not favoured so such alcohols give a higher proportion of the cholesteryl alkyl ether.[6]

When cholesteryl phosphorodichloridite (**2**) was similarly treated with boiling methanol, ethanol, propanol or isopropanol in the absence of base, the only isolated product was cholesterol (90% yield). On the other hand, when the reaction with ethanol was conducted at room temperature, a low yield (20%) of the diethyl phosphite (**11**; R=Et) was obtained after recrystallization of the crude product which also appeared to contain some cholesterol (**1**) and cholesteryl ethyl ether (**12**; R=Et).

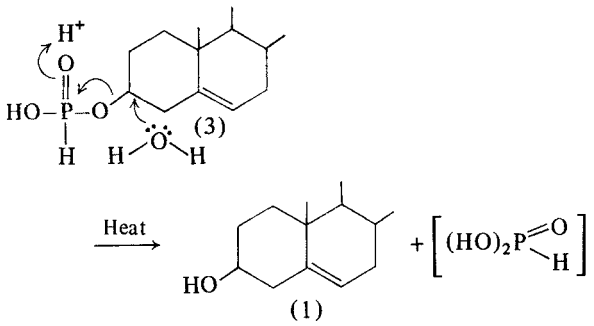


SCHEME 1

When the reaction was carried out with boiling ethanol in the presence of sodium ethoxide a good yield (80%) of the diethyl phosphite (**11**; R=Et) was obtained; the presence of base clearly favours S_N2 attack at phosphorus as has been found in previous studies[3-6] with the analogous P(V) compound, namely cholesteryl phosphorodichloridate.

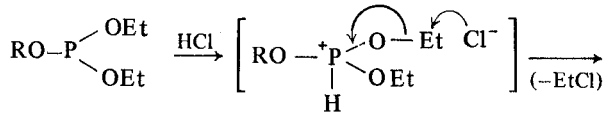
Similarly when cholesteryl phosphorodichloridite (**2**) was boiled with water only cholesterol (63%) was isolated, but at room temperature hydrolysis to

cholesteryl phosphite (3) (65%) occurred. In the absence of base, protonation of the initially formed phosphite probably accounts for the facile attack of water at the C-3-position leading to the formation of cholesterol (Scheme 2).

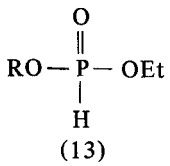


SCHEME 2

Surprisingly with ethanol comparatively little of the ethyl ether (12; R=Et) is apparently formed as compared with analogous reactions in the P(V) series where no cholesterol was isolated.[7] The substantially increased yield of cholesteryl diethyl phosphite (11; R=Et) observed in the presence of base is to be expected, since tertiary phosphites are well known[8] to suffer acid-catalysed dealkylation in the absence of base.



(11)



(13)

The dealkylation is favoured by the strong tendency of P(III) compounds to exist almost entirely in the phosphonate P(V) form (13; R=cholesteryl) due to the great strength of the P=O bond,[8] finally the ethyl phosphonate (13) is decomposed to cholesterol as previously indicated (Scheme 2), this reaction being clearly favoured by increased temperature. In support of this mechanism, cholesteryl diethyl phosphite (11; R=Et) with hydrochloric acid gave cholesterol (1).

trans-4-*t*-Butylcyclohexanol has been reacted with phosphorus trichloride to give the corresponding phosphorodichloridite; this was characterized by formation of the N,N^1-diphenylphosphorodiamidite by reaction with aniline (4 mol. equiv.). In moist air, 4-*t*-butylcyclohexyl-phosphorodichloridite was converted to the phosphorochloridite.

EXPERIMENTAL

I.r. spectra were determined as liquid films or Nujol mulls using a Perkin Elmer 237 spectrometer. N.m.r. spectra were measured with a Varian A60A spectrometer using tetramethylsilane as internal standard. The mass spectrum was measured with an A.E.I. MS9 spectrometer at 70 eV.

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. T.l.c. was carried out on Silica gel G plates developed with iodine vapour. Microanalyses were carried out by Butterworth Microanalytical Consultants Ltd., Teddington, England.

Cholesteryl Phosphorodichloridite (2)

Cholesterol (1) (5 g) was gradually added to phosphorus trichloride (20 ml) at 0°. A vigorous reaction occurred with evolution of hydrogen chloride, and the mixture was stirred at room temperature for 15 min. Cooling (−80°) followed by filtration, and washing with cold anhydrous acetone, gave *the phosphorodichloridite* (2) (4.6 g., 70%), m.p. 121–124° (Found: C, 66.5; H, 9.1; P, 6.2. $C_{27}H_{45}Cl_2OP$ requires C, 66.5; H, 9.2; P, 6.4%). ν_{max} 1020 (P–O–C), 485 (P–Cl) cm^{-1}. NMR ($CDCl_3$) δ: 0.63 (18-Me), 0.93 (21-Me), 1.00 (19-Me), 3.75 (m, 3α-H), 5.50 (m, 6β-H).

Cholesteryl phosphorodichloridite (m.p. 120°, 38%) was also obtained by condensation of cholesterol with phosphorus trichloride in tetrahydrofuran in the presence of triethylamine.

Cholesteryl Phosphite (3)

Cholesteryl phosphorodichloridite (2) (2 g) was treated with water (25 ml) at room temperature for 5 hr. The solid was recrystallized from benzene-ether to give *cholesteryl phosphite* (3) (1.2 g, 65%), m.p. 158–159° (lit.[1] 158°). (Found: C, 72.3; H, 10.7. Calc. for $C_{27}H_{47}O_3P$: C, 72.0; H, 10.5%). ν_{max} 2480 (P–OH), 2320 (P–H), 1220 (P=O), 1020 (P–O–C) cm^{-1}.

Cholesteryl N-Phenylphosphoramidochloridite (5)

Cholesteryl phosphorodichloridite (2g) in dry chloroform (30 ml) was stirred with aniline (0.76 g, 2 mol. equiv.) in dry chloroform (1 ml). After 30 min, the precipitate of aniline hydrochloride (0.52 g) was filtered off, and the filtrate was evaporated under reduced pressure to give the *N-phenylphosphoramidochloridite* (5) (1.7 g, 76%), m.p. 147–149° (m.m.p. with cholesterol = 135–140°). (Found: C, 72.6; H, 9.5; N, 2.4. $C_{33}H_{52}ClNOP$ requires C, 72.8; H, 9.4; N, 2.6%). ν_{max} 3160 (NH), 1605, 1500 (arom C=C), 1005 (P–O–C) cm^{-1}. NMR ($CDCl_3$) δ: 0.67 (18 Me), 0.82 (26/27-Me), 0.93 (21-Me), 1.02 (19-Me), 3.75 (m, 3α-H), 4.20 br (C_6H_5NH), 5.50 (m, 6β-H), 6.90–7.40 (C_6H_5NH). The signal at δ 4.20 was removed by treatment with D_2O. This compound gave a positive test for Cl and could also be obtained using petroleum ether (b.p. 40–60°) or tetrahydrofuran as solvent.

Cholesteryl N,N¹-Diphenylphosphorodiamidite (**10**)

Cholesteryl phosphorodichloridite (**2**) (2g) in dry chloroform (30 ml) was gradually added to a solution of aniline (1.52 g, 4 mol. equiv.) in chloroform (10 ml). The mixture was stirred for 16 hr and the precipitate of aniline hydrochloride filtered off. The filtrate, after evaporation under reduced pressure and crystallization from chloroform-acetonitrile, gave the *phosphorodiamidite* (**10**) (1.8 g, 73%), m.p. 154–157°. (Found: C, 77.7; H, 9.8; N, 4.4. $C_{39}H_{57}N_2OP$ requires C, 78.0; H, 9.6; N, 4.6%). ν_{max} 3350, 3160 (NH), 1620, 1610, 1500 (arom C=C), 1050 (P–O–C) cm^{-1}. NMR ($CDCl_3$) δ: 0.66 (18-Me), 0.82 (26/27-Me), 0.91 (21-Me), 3.76 (*m*, 3α-H), 4.40 ($2C_6H_5NH$), 5.50 (m, 6β-H), 6.90–7.50 (10 ArH). The signal at δ 4.40 was removed by D_2O treatment. The aliphatic-aromatic proton ratio was approximately 4.7:1.

Cholesteryl Aniliniumphosphite (**4**)

Cholesteryl phosphite (1 g) was reacted with aniline (1 ml) in toluene (50 ml) as previously described. Crystallization (toluene) gave the *aniliniumphosphite* (**4**) (0.9 g), m.p. 156–158° (lit.[1] 170°). (Found: C, 72.7; H, 10.2; N, 2.4. Calc. for $C_{33}H_{54}NO_3P$: C, 72.9; H, 10.0; N, 2.6%). ν_{max} 2310 (P–H), 1215 (P=O), 1015 (P–O–C) cm^{-1}.

Reaction of Cholesteryl Phosphorodichloridite (**2**) *with Boiling Water*

Cholesteryl phosphorodichloridite (1 g) was boiled under reflux with water (50 ml) for 20 min. The mixture was cooled (0°) and the precipitate (0.75 g) filtered off. T.l.c. (toluene – EtoAc, 5:1) showed two major spots: cholesterol (**1**) (R_F 0.50) and cholesteryl phosphite (**3**) remaining on the base line and two minor spots (R_F 0.35 and 0.64). The solid, after two recrystallizations from ethanol, gave cholesterol (0.5 g, 63%), m.p. 146°.

Cholesteryl Diethylphosphite (**11**; R=Et)

Cholesteryl phosphorodichloridite (**2**) (2 g) and sodium ethoxide (0.56 g, 2 mol. equiv.) in petroleum ether (b.p. 30–40°, 50 ml) was boiled under reflux for 3 hr. Cooling gave a solid precipitate, this was filtered off and the filtrate evaporated under reduced pressure. The residue was extracted with chloroform (40 ml), filtered, and the filtrate concentrated to ⅓ its original volume. Cooling and crystallization of the solid from chloroform-acetonitrile gave the *diethylphosphite* (**11**; R=Et) (1.6 g 80%), m.p. 125–127°. T.l.c. (toluene-EtoAc 5:2) showed one spot (R_F 0.35). (Found: C, 73.3; H, 11.0; P, 5.9. $C_{31}H_{55}O_3P$ requires C, 73.5; H, 10.9; P, 6.1%). ν_{max} 1050, 1020 (P–O–C) cm^{-1}. N.m.r. ($CDCl_3$) δ: 0.66 (18-Me), 0.78 (26/27-Me), 0.86 (21-Me), 1.00 (19-Me), 3.50 (4H, m, $(CH_3CH_2O)_2P$), 3.80 (3α-H), 5.40 (6β-H), J_{P-H} 7.60 Hz. Cholesteryl diethyl phosphite (m.p. 126–129°, 50%) was also obtained from a similar reaction with ethanol-pyridine at room temperature.

Reaction of Cholesteryl Phosphorodichloridite (**2**) *with Alcohols*

(a) *With Methanol*

(i) *at the b.p.*

Cholesteryl phosphorodichloridite (2 g) was boiled under reflux with dry methanol (50 ml) for 30 min. Concentration of the solution under reduced pressure and cooling gave cholesterol (**1**) (1.46 g, 90%), m.p. 149°.

(ii) *at room temperature*

The phosphorodichloridite (2 g) was stirred with dry methanol (50 ml) for 16 hr. T.l.c. (toluene–EtoAc 5:2) showed two spots: cholesterol (R_F 0.51) and one at the base line, possibly cholesteryl phosphite (**3**). Concentration and several recrystallizations gave cholesterol (1.1 g, 70%), m.p. 149°. The mother-liquor appeared to decompose on chromatography (silica gel) and t.l.c. of some fractions showed 9 spots.

(b) *With Ethanol*

(i) *at the b.p.*

Again the main product isolated was cholesterol (90%).

(ii) *at room temperature*

The phosphorodichloridite (2 g) was stirred with absolute ethanol (30 ml). After 6 hr., the solution was evaporated *in vacuo* and the residue treated with petroleum ether (50 ml) at 35°. Evaporation under reduced pressure and trituration of the residue with acetonitrile gave a solid (1.5 g). T.l.c. (toluene–EtoAc 5:2) gave 3 spots (R_F 0.94, 0.51, and 0.36) assigned as cholesteryl ethyl ether (12; R=Et), cholesterol (1), and cholesteryl diethyl phosphite (**11**; R=Et). Two recrystallizations from ether gave cholesteryl diethyl phosphite (320 mg 20%), m.p. 128–130° (R_F 0.35). ν_{max} 1060, 1025 (P–O–C) cm^{-1}.

Cholesteryl N-Phenylamidophosphite (**6**)

Cholesteryl N-phenylphosphoramidochloridite (**5**) (0.8 g) was stirred with water (50 ml) for 6 hr; the precipitate was filtered off and washed with cold acetone (25 ml). Recrystallization from ether-benzene-acetonitrile gave the *phenylamidophosphite* (**6**), (0.5 g), m.p. 151–153° (Cl was absent) (Found: C, 75.6; H, 10.1; N, 3.1. $C_{33}H_{52}NO_2P$ required C, 75.4; H, 9.9; N, 2.7%).

Cholesteryl N-Phenylamidoethyl Phosphite (**9**)

Cholesteryl *N*-phenylphosphoramidochloridite (1.0 g) was boiled under reflux with absolute ethanol (20 ml) for 2 hr. Evaporation under reduced pressure gave a pale yellow oil which was crystallized from acetonitrile-chloroform to give a solid (0.7 g). T.l.c. (toluene–EtoAc 5:2) showed 3 spots (R_F 0.95, 0.52 and 0.32). The first spot is due to cholesteryl ethyl ether, the second due to traces of cholesterol, and last to the required product. Two recrystallizations from (i) benzene-ether-acetone and (ii) ether gave *cholesteryl N-phenylamidoethylphosphite* (**9**) (0.2 g), m.p. 128–131° (R_F 0.32). (Found: C, 75.7; H, 10.3; N, 2.8. $C_{35}H_{56}NO_2P$ requires C, 75.95; H, 10.1; N, 2.5%). ν_{max} 3180 (NH), 1600, 1510 (arom C=C), 1225 (P=O), 1020, 1005 (P–O–C) cm^{-1}.

The same product (m.p. 127–130°) was obtained (79% yield) by carrying out the reaction at room temperature for 8 hr.

Cholesteryl N-Phenylphenylhydrazinophosphite (**8**)

Cholesteryl N-phenylphosphoramidochloridite (**5**) (1.0 g) was

reacted with phenylhydrazine (0.4 g, 2 mol. equiv.) in chloroform (30 ml) at room temperature for 9 hr. The solid was filtered off, and was washed with ice-water, cold dilute HCl, and acetonitrile. Recrystallization from ethanol gave the *phenylhydrazidite* (**8**) (0.45 g, 40%), m.p. 140–143°. T.l.c. (toluene–EtoAc 5 : 2) showed one spot (R_F 0.30) (Found: C, 76.3; H, 9.5; N, 6.6. $C_{39}H_{58}N_3OP$ requires C, 76.1; H, 9.4; N, 6.8%). ν_{max} 3200, 3120 (NH) 1610, 1505 (arom C=C), 1040 (P–O–C) cm^{-1}. The mass spectrum did not show the molecular ion (M^+, 615); the two highest fragment ions were cholesterol (M^+, 386) and cholestadiene (368). The loss of the fragment (PhNH · P=N–NHPh was indicated by the presence of the ion (M^+, 229) which was further degraded by loss of phenyl (M^+, 154) and of PhNH (135).

Cholesteryl N,N¹-Diphenylhydrazinophosphite

Cholesteryl phosphorodichloridite (**2**) (2.0 g) was reacted with phenylhydrazine (4 mol. equiv.) in anhydrous chloroform (40 ml) at room temperature for 6 hr. After cooling filtration removed phenylhydrazine hydrochloride (0.7 g); the filtrate was evaporated under reduced pressure. The product was crystallized from ethanol to give the *N,N¹-diphenylhydrazinophosphite* (1.0 g), m.p. 161–164° (Found: C, 74.1; H, 9.2; N, 9.1. $C_{39}H_{59}N_4OP$ requires C, 74.3; H, 9.4; N, 8.9%). ν_{max} 3250, 3190 (NH), 1610, 1505 (arom C=C), 1060 (P–O–C) cm^{-1}.

Cholesteryl N-Phenylphosphoroamidomorpholidite (7)

Cholesteryl *N*-phenylamidophosphorochloridite (0.36 g) was reacted with morpholine (0.12 g, 2 mol. equiv.) in ether (20 ml) at room temperature for 4 hr. and at 4° overnight. Filtration gave a solid which was triturated with ice water to remove morpholine hydrochloride. The residue was recrystallized from acetonitrile-chloroform to give the *N-phenylaminomorpholidite* (**7**) (0.3 g, 76%), m.p. 160–163° (Found: C, 72.1; H, 9.5; N, 4.9. $C_{37}H_{55}N_2O_2P$ requires C, 72.25; H, 9.3; N, 4.7%). ν_{max} 3160 (NH), 1610 (arom C=C), 1055 (P–O–C) cm^{-1}.

4-t-Butylcyclohexylphosphorodichloridite

4-*t*-Butylcyclohexanol (10 g) was gradually added to ice-cold phosphorus trichloride (15 ml) with stirring. The reaction was stirred a further 15 min at room temperature and cooled to −80°. The precipitate was filtered off and washed with cold dry acetone to give the *phosphorodichloridite* (1.5 g), m.p. 45–48°. (Found: C, 47.1; H, 7.5; P, 12.0. $C_{10}H_{19}Cl_2OP$ requires C, 46.7; H, 7.4; P, 12.1%). ν_{max} 1020, 980 (P–O–C) cm^{-1}. The phosphorodichloridite, after standing in moist air, gave 4-*t*-butylcyclohexylphosphorochloridite, m.p. 130°C. (Found: C, 50.4; H, 8.6. $C_{10}H_{20}ClO_2P$ requires C, 50.3; H, 8.4%).

4-t-Butylcyclohexyl N,N¹-diphenylphosphorodiamidite

4-*t*-Butylcyclohexylphosphorodichloridite (0.5 g) was reacted with aniline (4 mol. equiv.) in petroleum ether (bp. 40–60°, 10 ml) with stirring at room temperature for 12 hr. Cooled the reaction mixture (0°) and filtered off the aniline hydrochloride. The filtrate, after evaporation and recrystallization of the residual solid from pentane, gave the *N,N¹-diphenylphosphorodiamidite* (0.20 g, 26%), m.p. 112–114°. (Found: C, 71.1; H, 8.4; N, 7.4. $C_{22}H_{31}N_2OP$ requires C, 71.35; H, 8.4; N, 7.6%). ν_{max} 3140, 3090 (NH), 1609, 1505 (arom C=C), 1000, 975 (P–O–C) cm^{-1}. T.l.c. (EtoAc-petroleum ether (60–80°) 1 : 2) showed one spot (R_F 0.65).

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