A Simple Phosphorylation Procedure for Cyclic Alcohols

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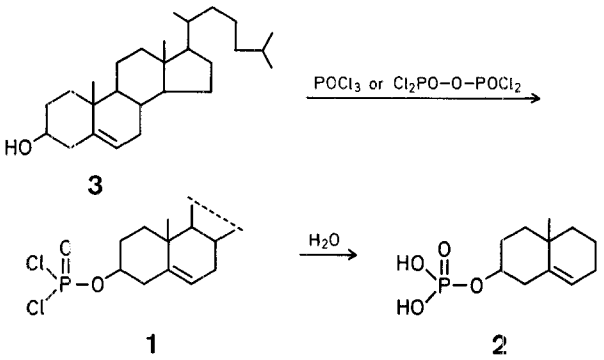
Cholesteryl phosphorodichloridate (**1**) is a useful intermediate for the preparation of cholesteryl dihydrogen phosphate (**2**) and its derivatives. The phosphorodichloridate (**1**) has been obtained from cholesterol (**3**) by treatment with phosphorus oxychloride[1], or pyrophosphoryl chloride[2].



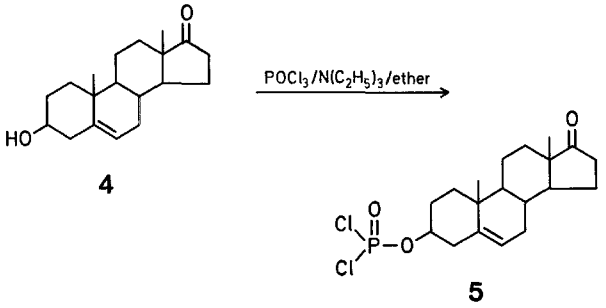
In the first method, a solution of cholesterol in pyridine is slowly added to an excess of phosphorus oxychloride in acetone at 0° (see Ref.[1]); in the second, an ethereal solution of cholesterol was added dropwise to an ethereal solution of pyrophosphoryl chloride at the same temperature (Ref.[2]).

The latter route, although the reagent is expensive[3], affords a purer product; it has been shown[2] that the phosphorus oxychloride/pyridine method gives impure phosphorodichloridate (**1**). The impurities almost certainly arise from interaction of the phosphorodichloridate with pyridine (cf. Ref.[4]) and account for the wide range of melting points (170–196°) recorded[5–9] for cholesteryl dihydrogen phosphate (**2**) obtained from the dichloridate by subsequent hydrolysis. The m.p. of cholesteryl phosphorodichloridate was rather insensitive to impurities, and the pure compound, by T.L.C. on silica gel plates developed with benzene/ether (4:1), gave a characteristic three-spot breakdown pattern (Rf 0.20, 0.42, 0.76) with considerable tailing between the spots[4].

Further work has shown that pure cholesteryl phosphorodichloridate may be obtained in excellent yield (87%) by reaction with phosphorus oxychloride *under much less polar*

conditions; namely in the presence of an equimolar quantity of triethylamine in ether. The dichloridate is only sparingly soluble in ether, and is separated from the precipitated triethylamine hydrochloride by washing with water.

This procedure has been successfully extended to the phosphorylation of 3β-hydroxy-17-oxoandrost-5-ene (**4**) to the corresponding phosphorodichloridate (**5**, 85%).



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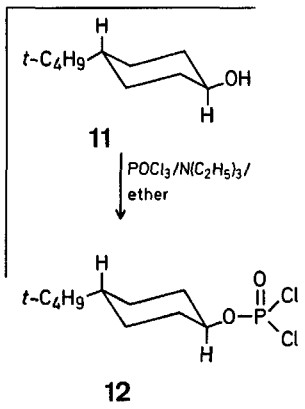
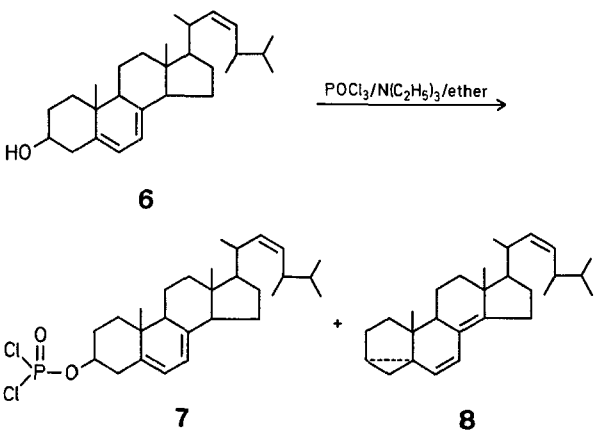
However with ergosterol, the phosphorodichloridate (**7**) was obtained in only 23% yield, while the major product

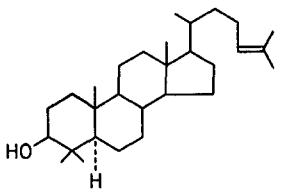


was 3,5-cycloergosta-6,8(14),22-triene (**8**). This result agrees with previous observations[2] on the ease of conversion of the dichloridate (**7**) to the triene (**8**).



6 **7** **8**

Attempts to convert lanosterol (**9**) and 5α-chloro-6β-hydroxy-17-oxoandrostane (**10**) to the corresponding phosphorodichloridates were unsuccessful; in both cases, the unchanged sterols were recovered from the reactions.



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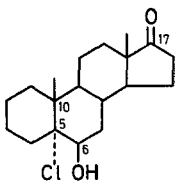

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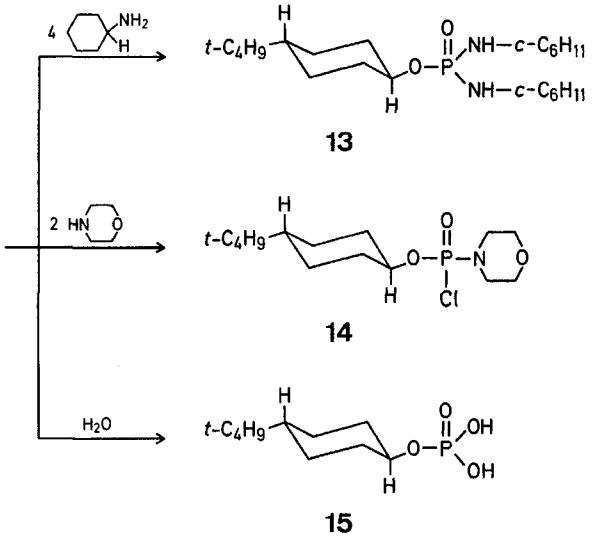
The failure is ascribed to the more hindered steric environment of the hydroxy group in these sterols as compared with cholesterol (**3**). In lanosterol (**9**), this arises from the presence of the geminal 4,4-dimethyl groups and in the androstane derivative (**10**) to the occurrence of unfavourable 1,3-diaxial interaction with 10β-methyl group.

trans-4-*t*-Butylcyclohexanol (**11**) was successfully phosphorylated to the dichloridate (**12**), an unstable oil, which was, however, characterised by conversion to the phosphate (**15**), morpholinophosphorochloridate (**14**), and dicyclohexylphosphorodiamidate (**13**).



A similar procedure, except that 2 moles of *trans*-4-*t*-butylcyclohexanol were employed, gave bis-[*trans*-4-*t*-butylcyclohexyl] phosphorochloridate.

It is therefore concluded that this represents a general phosphorylation procedure for relatively unhindered cyclohexanols and sterols, but for sterically hindered sterols, e.g. lanosterol, the more polar conditions (phosphorus oxychloride/excess pyridine/acetone) previously described (see Ref.[2]) appear to be required.

Cholesteryl Phosphorodichloridate (1):
Cholesterol (25.8 g) and triethylamine (6.8 g) in dry ether (400 ml) were added dropwise to a stirred solution of phosphorus oxychloride (10.2 g) in dry ether (150 ml) at 0°. After 2 hr at room temperature, the precipitate was filtered off, and well washed with water; yield: 28.5 g (87%); m.p. 123° (Ref.[6], m.p. 122°).

$C_{27}H_{45}Cl_2O_2P$	calc.	C 64.4	H 8.9	Cl 14.1	P 6.2
	found	64.2	9.0	14.0	6.4

I.R. (Nujol): ν_{max} = 1300 (P=O), 1020 (P—O—C), 536 and 429 (P—Cl) cm^{-1}.

17-Oxoandrost-5-ene-3β-yl Phosphorodichloridate (5):
3β-Hydroxy-17-oxoandrost-5-ene (3 g) and triethylamine (3 g) were similarly reacted with phosphorus oxychloride (1.6 g) in

ether (75 ml) to give the phosphorodichloridate; yield: 3.5 g (85%); m.p. 115°.

$C_{19}H_{27}Cl_2O_3P$	calc.	C 56.3	H 6.7	P 7.6
	found	56.2	6.8	7.6

I.R. (Nujol): $\nu_{max} = 1280$ (P=O), 980 (P—O—C) cm^{-1}.

Ergosteryl Phosphorodichloridate (7):
Ergosterol (13.1 g) and triethylamine (3.4 g) were similarly treated with phosphorus oxychloride (5.1 g) in ether (250 ml) to give the phosphorodichloridate; yield: 4.5 g (23%); m.p. 84° (Ref.[2], m.p. 84°).

Evaporation of the ethereal filtrate and recrystallization of the residual solid from acetone afforded 3,5-cycloergosta-6,8(14),22-triene; yield: 6.5 g (60%); m.p. 99–101° (Ref.[2], m.p. 102°).

U.V. (cyclohexane): $\lambda_{max} = 261$ nm ($\varepsilon = 23000$).

***trans*-4-*t*-Butylcyclohexyl Phosphorodichloridate (12):**
trans-4-*t*-Butylcyclohexanol (15.6 g) and triethylamine (10.1 g) in ether (150 ml) were reacted with phosphorus oxychloride (15.3 g) in ether (65 ml) to give the phosphorodichloridate as an oil; yield: 13.6 g. Attempted distillation under reduced pressure caused decomposition.

I.R. (Nujol): $\nu_{max} = 1315$ (P=O), 1030 (P—O—C) cm^{-1}.

***trans*-4-*t*-Butylcyclohexyl Disodium Phosphate (corresponding to 15):**
The crude phosphorodichloridate **12** (1 g) was boiled under reflux with water (100 ml) for 8 hr. Evaporation of the reaction mixture under reduced pressure, and treatment with hot sodium carbonate solution gave the disodium salt of **15** as a white powder; yield: 0.7 g; m.p. 268–270°.

$C_{10}H_{19}Na_2O_4P$	calc.	C 42.9	H 6.8	P 11.1
	found	42.6	6.9	10.7

***trans*-4-*t*-Butylcyclohexyl Morpholinophosphorochloridate (14):**
The phosphorodichloridate **12** (400 mg) was gently warmed with morpholine (400 mg) in acetonitrile (20 ml) for 5 min. The product crystallized on cooling; yield: 180 mg; m.p. 117–119°.

$C_{14}H_{27}ClNO_3P$	calc.	C 51.9	H 8.4	N 4.3	P 9.6
	found	51.6	8.8	4.0	9.3

***trans*-4-*t*-Butylcyclohexyl-N,N'-dicyclohexylphosphorodiamidate (13):**
The phosphorodichloridate **12** (500 mg) was boiled with cyclohexylamine (1 g) in acetonitrile (25 ml) for 5 min. The product crystallized on cooling; yield: 450 mg; m.p. 134–137°.

$C_{22}H_{43}N_2O_2P$	calc.	C 66.3	H 10.9	N 7.0	P 7.8
	found	65.9	10.5	7.1	8.3

I.R. (Nujol): $\nu_{max} = 1215$ (P=O), 1030 (P—O—C) cm^{-1}.

Bis-[*trans*-4-*t*-butylcyclohexyl] Phosphorochloridate:
trans-4-*t*-Butylcyclohexanol (31.2 g) and triethylamine (22.2 g) in ether (300 ml) were similarly treated with phosphorus oxychloride (15.3 g) in ether (300 ml) to give the phosphorochloridate as colorless needles; yield: 29 g; m.p. 127–128° (from ethanol).

$C_{20}H_{28}ClO_3P$	calc.	C 61.1	H 9.7	P 7.9
	found	61.3	10.0	7.8

I.R. (Nujol): $\nu_{max} = 1300$ (P=O), 1045 (or 1003) (P—O—C) cm^{-1}.

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