Phosphorylated Derivatives of Cyclohexanediols and Sulphanilyl Chloride

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Summary: 1,3,- and 1,4-Cyclohexanediols (I,IV) react with phosphorus oxychloride to form the cyclic phosphorochloridate (II) and the tetrachloridate (V). These were characterized by reaction with amines to give the amidates (IIIa, b, IVa-d). (V) with diethylamine and aniline gave the amidic chlorides (VIIa,b), which with hydrazine hydrate and methanol form the amidic acid (IX) and the methoxyamidate (VIII). Sulphanilic acid (IX) with phosphorus pentachloride - phosphorus oxychloride gave the trichloride (XII), characterized as the sulphanilamides (XIIIa-d). The spectral characteristics of the various products are briefly discussed.

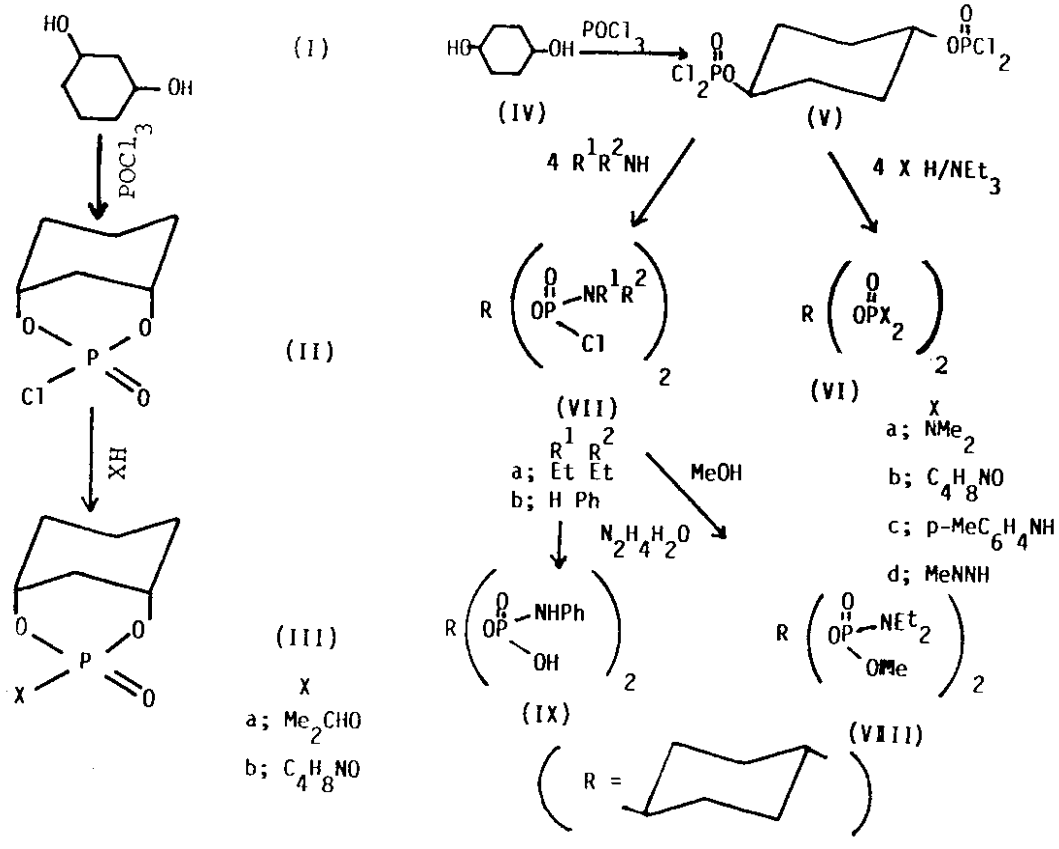
The work forms part of our general programme on the synthesis of novel organophosphorus compounds as candidate pesticides, and in particular is an extension of previous studies [1-4] on the phosphorylation of alicyclic compounds. Brown and Higson [5] reacted cis and trans-1, 2-cyclohexanediol with phosphorus oxychloride and on hydrolysis obtained 2-hydroxycyclohexyl dihydrogen phosphate, but the intermediate phosphorochloridate was not isolated. Later we showed [6] that 1,2-cyclohexanediol reacts with phosphorus oxychloride at room temperature to give the cyclic phosphorochloridate, characterized as cyclic amidates.

The present paper examines the reactions of 1,3- and 1, 4-cyclohexanediols (I,IV) with phosphorus oxychloride: (I) reacted with the reagent (1 mol) in the presence of a tertiary base (pyridine or triethylamine) to give a high yield of the cyclic phosphorochloridate (II) (Scheme 1 and Table 1). The product is an indication of the ease of cyclic phosphorylation of cis-diols [7] and the stabilization of the cis (diaxial) isomer of (I) due to intramolecular (O...H-O)hydrogen bonding making this the favoured conformation. Compound (11) was characterized by reaction with morpholine and isopropanol to give the derivatives (IIIa, b); in the latter reaction the ring was not opened in contrast to previous observations [6], possibly because the reaction was carried out at room temperature.

1, 4-Cyclohexanediol (IV), which exists predominantly in the diequatorial conformation, reacted with phosphorus oxychloride (2 moles) in the presence of triethylamine to give the tetrachloridate (V). (V) was condensed with amines (4 moles) in the presence of triethylamine to give the tetra-amidates (VIa-c). Under similar conditions, anhydrous NN-dimethylhydrazine afforded the tetrahydrazide (VId), but attempted reaction with hydrazine hydrate was unsuccessful probably due to competing hydrolysis.

Reaction of (V) with dimethylamine or aniline under similar conditions only afforded the amidic chlorides (VIIa, b), presumably this is due to the larger steric size of these amines inhibiting the $S_N2(P)$ reaction.

Scheme I



The structures of the products (VIIa, b) were supported by their formation in higher yields (60%) when the reactions were repeated using less amine (2 moles). Further confirmation of structure came from the reaction of VIIa with methanol to give the methoxy derivative (VIII); attempted conversion of VIIb to the corresponding hydrazide by reaction with excess hydrazine hydrate was unsuccessful and only the N-phenylphosphoramidic acid (IX) was isolated. The latter is a consequence of the operation of the base-catalysed (E_1cB) hydrolysis reaction which is known [8,9] to be extremely facile with primary phosphoramidic chlorides.

Sulphanilamides are well-known antibacterial drugs [10] and it appeared interesting to prepare some phosphorylated derivatives for biocidal screening. Aniline was reacted with phosphorus oxychloride to give N-phenylphosphoramidic dichloride [11] (X), which was treated with chlorosulphonic acid at low temperature (-10 to 0°). The product, on the basis of TLC and mass spectral data, appeared to be a mixture of the desired phosphorosulphanilyl chloride (XII) and sulphanilic acid (XI) (Scheme 2 and Table 2). These observations indicate that chlorosulphonation is accompanied by some P-N bond cleavage; this is not surprising since the P-N bond strength (116 kcal/mol) is less than the S-N bond strength (176kcal/mol) [12]. Further, Shode [13] found that benzenesulphonanilides undergo smooth chlorosulphonation with chlorosulphonic acid at low temperatures (-10 to 8°), but when the reaction temperature exceeded 10°, N-S bond cleavage occurred. N^4-(Dichlorophosphoro) sulphanilyl chloride (XII) was, however, prepared in excellent yield by reaction of sul-

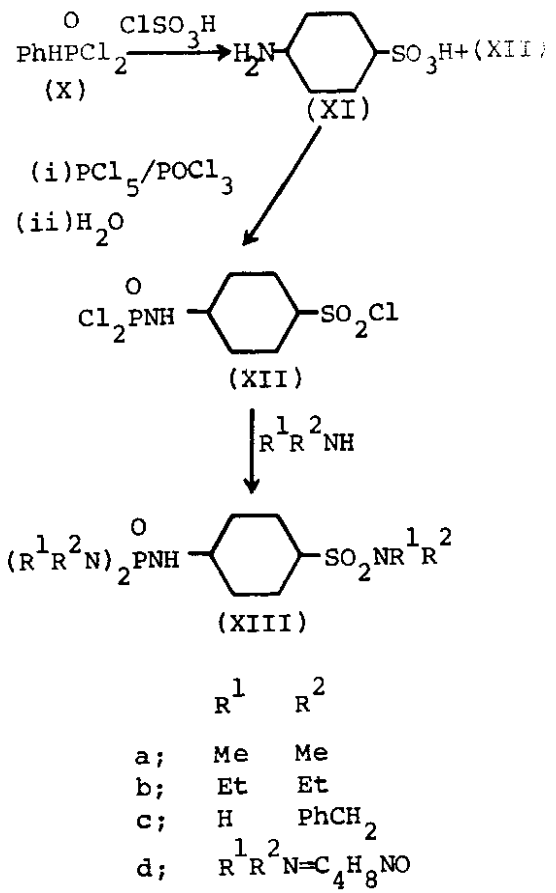
Table-1: Physical data of the phosphorylated cyclohexanediols

Compd. No	M.P. °C	Yield %	Formula	Analysis % Calc. (Found) C	H	N	MS(CI) M^+
II	oil	89	$C_6H_{10}ClO_3P$	36.6 (36.4)	5.1 (5.1)	- -	197
IIIa	oil	25	$C_9H_{17}O_4P$	49.1 (48.8)	7.7 (7.8)	-	220
IIIb	oil	42	$C_{10}H_{18}NO_4P$	48.6 (48.8)	7.3 (7.4)	5.7 (5.7)	247
V	50-2	76	$C_6H_{10}Cl_4O_4P_2$	20.6 (20.4)	2.8 2.9	- -	349
VIa	65	55	$C_{14}H_{34}N_4O_4P_2$	43.7 (43.5)	8.8 (9.0)	14.6 (14.5)	384
VIb	78-9	50	$C_{22}H_{42}N_4O_8P_2$	47.8 (47.6)	7.7 (7.9)	10.1 (10.0)	552
VIc	127	36	$C_{34}H_{42}N_4O_4P_2$	64.5 (64.7)	6.7 (6.8)	8.8 (8.9)	316
VId	oil	65	$C_{14}H_{38}N_8O_4P_2$	37.8 (37.6)	8.6 (8.8)	25.2 (25.0)	444
VIIa	oil	38	$C_{14}H_{30}Cl_2N_2O_4P_2$	39.7 (40.0)	7.1 (7.3)	6.6 (6.8)	453
VIIb	126-8	50	$C_{18}H_{22}Cl_2N_2O_4P_2$	46.7 (46.9)	4.8 (5.0)	6.0 (6.0)	462
VIII	oil	62	$C_{16}H_{36}N_2O_6P_2$	46.4 (46.6)	8.7 (8.9)	6.8 (7.0)	414
IX	115-6	70	$C_{18}H_{24}N_2O_6P_2$	50.7 (50.6)	5.6 (5.7)	6.6 (6.5)	427

phanilic acid (XI) with a mixture of phosphorus pentachloride and phosphorus oxychloride as described by Bieber and Kane [14].

(XII) was condensed with amines (6 mols) to give the sulphanilamides (XIIIa-d). Attempts were made to obtain selective replacement of one or two of the chlorine atoms of XII by treatment with aniline (1 or 2 mole) in presence of triethylamine. These experiments were unsuccessful and gave complex mixtures of products.

All the compounds were characterized by analysis and mass spectral



Scheme 2

data (Tables 1 and 2), together with IR and PMR spectra. With the phosphorylated cyclohexanediols (Table 1), electron impact (EI) mass spectra exhibited extensive fragmentation, however the chemical ionization (CI) procedure afforded the molecular ions (M^+). With the phosphorylated sulphanilamides (Table 2), on the other hand, EI mass spectra showed the M^+ ions.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded as thin films or nujol mulls with a Perkin Elmer spectrophotometer. PMR spectra were obtained with a Varian HA-80 spectrometer using TMS as internal standard. Mass spectra were determined with a VG micromass 16F spectrometer operating at 60eV.

Phosphorylation of 1,3-cyclohexanediol (I)

To a stirred suspension of (I) (9.3 g) and triethylamine (22.4 ml) at 0° was added dropwise a solution of phosphorus oxychloride (7.35 ml) in ether (25 ml). The mixture was stirred at room temperature for 3 hours, the triethylamine hydrochloride was filtered off and the solvent evaporated under reduced pressure to give the phosphorochloride (II). IR ν_{max} : 1300 (P=O), 990 (P-O-C), 660 (P-Cl) cm^{-1}. (A similar yield of the same product was obtained using pyridine instead of triethylamine).

Reaction of (II) with isopropanol

A lution of (II) (3.93 g) and triethylamine (2.8 ml) in acetone (25 ml) was stirred with isopropanol (3.1 ml) at room temperature for 8 hours to give the cyclic isopropylphosphate (IIIa) (1.3 g). IR ν_{max}: 1280 (P=O), 1080 (P-O-C) cm^{-1}. PMR [$(CD_3)_2CO$]: δ 3.80-3.20 (1 H, m, $C\underline{H}Me_2$), 1.8-0.9 (16 h, m, cyclohexyl H, CH_3).

Reaction of (II) with morpholine

Morpholine (1.75 g) was added dropwise to a stirred solution of II (3.93 g) and triethylamine (2.8 ml) in THF (30 ml) at 0°. The mixture was stirred at room temperature for 6 hours to give IIIb (3.1 g). IR ν_{max} 1300 (P=O), 980 (P-O-C), 800 (P-N) cm^{-1}. PMR [$(CD_3)_2CO$]: δ 4.5-4.2 (2H, m, cyclohexyl-1, 3 H),

Table-2: Physical data of the phosphorylated sulphanilamides

Compd. No	M.P. °C	Yield %	Formula	Analysis % Calc. (Found) C	H	N	MS (EI) M^+
XIIIa*	219-20	55	$C_{12}H_{23}N_4OPS$	43.1 (43.1)	6.9 (6.8)	16.8 (16.9)	344
XIIIb	152-3	65	$C_{18}H_{35}N_4O_3PS$	51.7 (51.5)	8.4 (8.3)	13.4 (13.3)	418
XIIIc	152	57	$C_{27}H_{29}N_4O_3PS$	62.3 (62.1)	5.6 (5.5)	10.8 (10.6)	520
XIIId	140-2	70	$C_{18}H_{29}N_4O_6PS$	47.0 (47.1)	6.3 (6.4)	12.2 (12.0)	460

*PMR (DMSO-d_6) δ: 7.67-7.12 (4H, m, ArH), 5.2 (1H, d, NH, J_{p-NH} 10.7 Hz). 1.20 (18H, m, CH_3). The signal at δ5.2 was removed by D_2O treatment.

3.60-3.1 (8 H, m, morpholine H), 1.90-1.10 (8 H, m, cyclohexyl H).

Phosphorylation of 1,4-cyclohexanediol (IV)

To a stirred solution of (IV) (9.3 g) and triethylamine (22.4 ml) in acetonitrile (150 ml) at O°, was gradually added a solution of phosphorus oxychloride (14.7 ml) in acetonitrile (25 ml). The mixture was stirred at room temperature for 3 hours to give the tetrachloridate (V). IR ν_{max}:1300 (P=O), 980 (P-O-C), 660 (P-Cl) cm^{-1}

Preparation of the tetrasubstituted derivatives of (V) (Compounds VIa-d)

A mixture of the amine (0.04 mol) and triethylamine (0.04 mol) in acetonitrile (25 ml) was added dropwise to a stirred solution of (V) (0.01 mol) in acetonitrile (20 ml). The mixture was stirred at room temperature for 3 hours, the amine hydrochloride was filtered off and the solvent evaporated in vacuo. The solid products were purified by trituration with water and recrystallization from methanol to give VIa-c. The liquid product (VId) was purified by extraction with ether and washing with water.

Application of a similar procedure using diethylamine afforded only the diethylamidic chloride (VIIa). IR ν_{max}: 1280 (P=O), 990 (P-O-C), 800 (P-N), 650 (P-Cl) cm^{-1}. PMR ($CDCl_3$): δ 3.5-3.1 (10 H, m, cyclohexane-1, 4H, NCH_2), 2.1-1.8 (8H, m, cyclohexane H), 1.20 (12 H, t, NCH_2CH_3).

Similarly, reaction of (V) with aniline gave the phenylamidic chloride (VIIb). IR ν_{max} 3390 (NH), 1600 (arom C=C). 1180 (P=O), 1050

(P-O-C), 810 (P-N), 660 (P-Cl) cm^{-1}. PMR ($CDCl_3$): δ 8.5 (2H, s, NH), 7.85-6.90 (10 H, m, ArH), 3.3-3.10 (2H, m, cyclohexyl 1,4 H), 1.8-1.6 (8H, m, cyclohexyl H). The signal at δ 8.5 was removed by D_2O treatment.

Reaction of (VIIa) with methanol

(VIIa) (1.6 g) was stirred with a solution of methanol (0.5 g) and triethylamine (1.1 ml) in acetone (10 ml) at room temperature for 6 hours to give VIII. IR: ν_{max} 1280 (P=O), 980 (P-O-C), 800 (P-N) cm^{-1}.

Reaction of (VIIb) with hydrazine hydrate

(VIIb) (1.9 g) was stirred with a mixture of hydrazine hydrate (0.62 g) and triethylamine (1.7 ml) in acetonitrile (30 ml) at room temperature for 6 hours to give the N-phenylphosphoramidic acid (IX). IR: ν_{max} 3480 (OH), 3320 (NH), 1200 (P=O), 1600 (arom C=C), 1040 (P-O-C), 810 (P-N) cm^{-1}. PMR (DMSO $-d_6$): δ 9.82 (2H, s, OH), 9.20 (2H, s, NH), 7.80-6.85 (10H, m, ArH), 3.5-3.2 (2H, m, cyclohexyl 1, 4H), 1.80-1.48 (8H, m, cyclohexyl H).

N-Phenylphosphoramidic dichloride (X)

Reaction of aniline with phosphorus oxychloride as previously described [11] gave (X) (81%), recrystallized from benzene as needles, m.p. 86 - 87° (lit. [11] 87°).

Attempted chlorosulphonation of (X)

(X) (5 g) was gradually added to chlorosulphonic acid (4.8g) in an ice -salt bath (-15°), the mixture was stirred at -15 to 0° for 2 hours and then poured onto ice. The precipitate was collected and washed with ice-water to give a solid, m.p. 280°; yield 25%. Sodium fusion test was positive for Cl N, P and S. MS: 307 (M^+ for XII), 272 (M-Cl), 223, 208, 172 (M^+ for XI), 138, 129, 92. TLC (EtOH) showed two spots R_F 0.23, 0.68; the product appears to be a mixture of (XI) and (XII).

N^4-(Dichlorophosphoro) sulphanilyl chloride (XII)

Sulphanilic acid (XI) was refluxed with a mixture of phosphorus chloride and phosphorus oxychloride as previously described [14] to give (XII) m.p. 155 - 157° (lit. [14] 155°); yield 91% (Found:C, 23.3; H, 1.7; N, 4.6%. $C_6H_5Cl_3NO_3PS$ requires: C, 23.2; H, 1.6; N, 4.5%); IR ν_{max}: 3160 (NH), 1600 (arom C=C), 1250 (P=O), 1360, 1180 (SO_2) cm^{-1}. MS: 307 (M^+), 272 (M-Cl), 223, 208 ($M-SO_2Cl$), 172, 126, 92. TLC (EtOH) showed one spot, R_f 0.67.

Reaction of (XII) with amines

(XII) (0.01 mol) was stirred with a solution of the amine (0.06 mols) in ether (30 ml) at room temperature for 3 hours. The precipitate was collected, washed with water (to remove the amine hydrochloride) and purified by recrystallization from ethanol, to give (XIIIa-d).

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