Some Derivatives of Morpholinophosphorodichloridate and dichloridothioate

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Morpholinophosphorodichloridate and dichloridothioate reacted with amines (2 molar equivalents) to give the amidic chlorides which were treated with nucleophilic reagents to give sixty-four derivatives. However the dichloridothioate with primary amines (1 molar equivalent) only gave diamidic thioates, the reasons for the failure to obtain the expected amidochloridothioates are briefly discussed.

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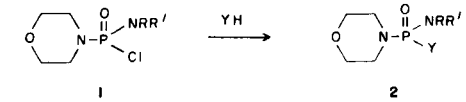
Heterocyclic compounds have proved a fertile source of pest control agents [1]; special examples of morpholine derivatives are the fungicides dodemorph, tridemorph and the molluscicide, trifenmorph [2]. In a search for new pest control agents, morpholinophosphorodichloridate was reacted with equimolar amounts of aniline, *p*-chloro- and 3,4-dichloroaniline, dimethyl and diethylamine, morpholine and isopropylamine in the presence of triethylamine to give the amidic chlorides (**1a-1g**) (Scheme 1). These, by reaction with hydrazine, sodium azide and ammonium thiocyanate gave the corresponding hydrazides **2a-7a**, azides **2d, 3g, 4i, 5g, 8b** and the isothiocyanate **4k**. The hydrazides were converted into hydrazones, the 3,5-dimethylpyrazole (**3g**) and the 3,6-dimethylpyridazine (**6b**); the compounds **3g, 6b** were obtained by prolonged heating with 2,4-pentanedione and 2,5-hexanedione. Morpholinophosphorodichloridothioate was similarly treated with dimethylamine and morpholine to give the amidochloridothioates **8a-c** and subsquent treatment with hydrazine and sodium azide gave the derivatives **10a-h, 11a-g** (Scheme 2 and Table 2).

Scheme 1

N-Substituted Morpholinophosphoramidates



1 2

	R	R′
a	H	Ph
b	H	p-ClC$_6$H$_4$
c	H	3,4-Cl$_2$C$_6$H$_3$
d	Me	Me
e	Et	Et
f	morpholino	
g	H	CHMe$_2$

R = H, R′ = Ph → Y: 2a NHNH$_2$; b NHN=CMe$_2$; c NHN=CHPh; d N$_3$; e N=PPh$_3$

R = H, R′ = p-ClC$_6$H$_4$ → Y: 3a NHNH$_2$; b NHN=CMe; c NHN=  ; d NHN=CHPh; e NHN=CHC$_6$H$_4$NO$_2$-p; f NHNHPh; g N$_3$

R = H, R′ = 3,4-Cl$_2$C$_6$H$_3$ → Y: 4a NHNH$_2$; b NHN=CMe$_2$; c NHN=CMeEt; d NHN=CHPh; e NHN=CH-C$_6$H$_4$OMe-p; f NHN=CMePh; g 3,5-dimethylpyrazolyl; h NHNHCO$_2$Et; i N$_3$; j N=PPh$_3$; k NCS

R = R′ = Me → Y: 5a NHNH$_2$; b NHN=CMe$_2$; c NHN=CHPh; d NHN=CHC$_6$H$_4$OMe-p; e NHN=CHC$_6$H$_4$NO$_2$-p; f NHN=CMePh; g N$_3$; h N=PPh$_3$

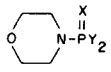
Scheme 1 (continued)

R = R′ = Et → 6a NHNH$_2$; b 3,6-dimethylpyridazinyl

R = R′ = morpholino → 7a NHNH$_2$; b NHN=CMe$_2$; c NHN=CHPh; d NHN=CHC$_6$H$_4$NO$_2$-p

R = H, R′ = CHMe$_2$ → 8a NHNHPh; b N$_3$; c N=PPh$_3$

In contrast, morpholinophosphorodichloridothioate, by reaction with equimolar amounts of primary amines, *e.g.* aniline, 3,4-dichloroaniline and isopropylamine, failed to give the expected amidochloridothioates, and low yields (*ca.* 30%) of the diamidothioates **12c-e** (Table 3) were isolated. With larger amounts of the primary amines (4 molar equivalents) the diamidothioates were obtained in higher yields (66-75%) (Table 3).



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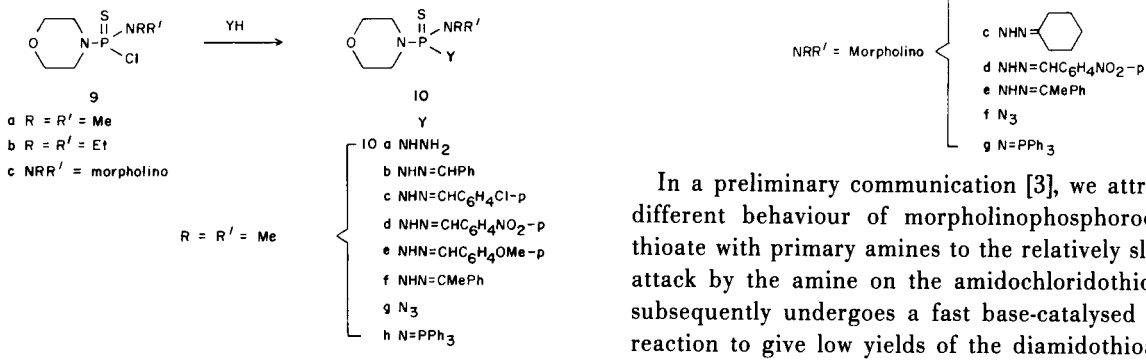
	X	Y
a	O	NHNH$_2$
b	O	NHN=CHPh
c	S	NHPh
d	S	NHC$_6$H$_3$Cl$_2$-3,4
e	S	NHCHMe$_2$
f	S	NHNH$_2$
g	S	NHN=CMe$_2$
h	S	NHN=CHPh
i	S	3,5-dimethylpyrazolyl

Scheme 2

N-Substituted Morpholinophosphoramidic Thioates



In a preliminary communication [3], we attributed the different behaviour of morpholinophosphorodichloridothioate with primary amines to the relatively slow S_N2 (P) attack by the amine on the amidochloridothioate which subsequently undergoes a fast base-catalysed E_1cB (EA) reaction to give low yields of the diamidothioates **12c-e**

Table 1

N-Substituted Morpholinophosphoramidates

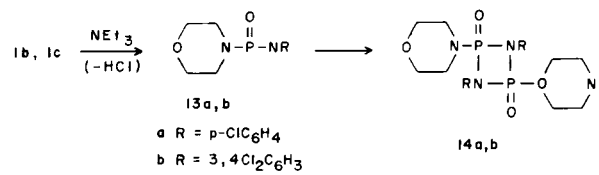
Compound No.	Yield %	Mp °C (Bp)	Recrystallised from	Molecular Formula	Analyses % Found/(Calcd.) C	H	N
1a	69	95-97	EtOAc-C_5H_{12} (1:1)	$C_{10}H_{14}ClN_2O_2P$	46.1 (46.1)	5.5 (5.4)	10.7 (10.7)
1b	64	110-113	Et_2O	$C_{10}H_{13}Cl_2N_2O_2P$	40.5 (40.7)	4.3 (4.4)	9.7 (9.5)
1c	65	123-124	C_6H_6	$C_{10}H_{12}Cl_3N_2O_2P$	36.4 (36.4)	3.7 (3.6)	8.2 (8.5)
1d	97	(80-85/0.01 mm)	—	$C_6H_{14}ClN_2O_2P$	34.2 (34.0)	6.7 (6.6)	13.3 (13.2)
1e	61	(102-106/0.05 mm)	—	$C_8H_{18}ClN_2O_2P$	45.6 (45.8)	8.9 (8.6)	13.0 (13.3)
1f	86	83-84 lit [3] 80	Et_2O	$C_8H_{16}ClN_2O_3P$	38.0 (37.7)	6.4 (6.3)	10.8 (11.0)
1g	97	oil	—	$C_7H_{16}ClN_2O_2P$	37.3 (37.1)	6.9 (7.1)	12.6 (12.4)
2a	61 (48)	oil	—	$C_{10}H_{17}N_4O_2P$	46.6 (46.9)	6.8 (6.6)	22.0 (21.8)
2b	69	210-212	Me_2CO	$C_{13}H_{21}N_4O_2P$	52.9 (52.7)	7.1 (7.1)	18.7 (18.9)
2c	67	174-176	EtOH	$C_{17}H_{21}N_4O_2P$	59.1 (59.3)	6.2 (6.1)	16.1 (16.3)
2d	59	290	Me_2CO/H_2O	$C_{10}H_{14}N_5O_2P$	45.1 (44.9)	5.3 (5.2)	26.0 (26.2)
2e	75	128-130	C_5H_{12}	$C_{28}H_{29}N_3O_2P_2$	65.8 (65.9)	5.8 (5.9)	8.2 (8.4)
3a	45 (76)	151-153	$EtOH/C_5H_{12}$	$C_{10}H_{16}ClN_4O_2P$	41.1 (41.3)	5.6 (5.5)	19.4 (19.3)
3b	55	185-188	Me_2CO	$C_{13}H_{20}ClN_4O_4P$	47.0 (47.2)	6.2 (6.05)	17.1 (16.9)
3c	69	174-178	$CHCl_3/C_5H_{12}$	$C_{16}H_{24}ClN_4O_2P$	51.6 (51.8)	6.7 (6.5)	15.0 (15.1)
3d	63	238-241	$EtOH/C_5H_{12}$	$C_{16}H_{20}ClN_4O_2P$	52.2 (52.4)	5.6 (5.45)	15.1 (15.3)
3e	66	265-268	EtOH	$C_{17}H_{19}ClN_5O_4P$	47.9 (48.2)	4.6 (4.5)	16.3 (16.5)
3f	53	161-163	EtOH	$C_{16}H_{20}ClN_4O_2P\cdot\frac{1}{2}H_2O$	51.5 (51.1)	5.4 (5.4)	14.8 (14.9)
3g	38	90-93	Et_2O	$C_{10}H_{13}ClN_5O_2P$	40.0 (39.8)	4.4 (4.3)	23.0 (23.2)
4a	55 (83)	139-141	C_5H_{12}	$C_{10}H_{15}Cl_2N_4O_2P$	36.6 (36.7)	4.6 (4.6)	17.1 (17.2)
4b	74	202-204	Me_2CO	$C_{13}H_{19}Cl_2N_4O_2P$	42.8 (42.7)	5.4 (5.7)	15.0 (15.3)
4c	94	198-200	C_6H_{12}/EtOH	$C_{14}H_{21}Cl_2N_4O_2P$	44.6 (44.3)	5.6 (5.5)	14.8 (14.8)

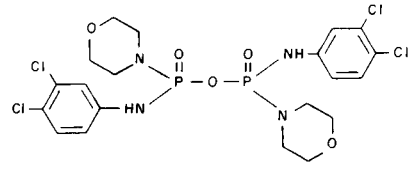
Table 1 continued

Compound No.	Yield %	Mp °C (Bp)	Recrystallised from	Molecular Formula	Analyses % Found/(Calcd.) C	H	N
4d	86	196-197	C_6H_{12}/EtOH	$C_{17}H_{20}Cl_2N_4O_2P$	49.6 (49.4)	4.8 (4.8)	13.3 (13.6)
4e	76	169-171	EtOH	$C_{18}H_{21}Cl_2N_4O_3P$	48.7 (48.8)	4.9 (4.7)	12.9 (12.6)
4f	91	221-223	EtOH	$C_{18}H_{22}Cl_2N_4O_2P$	50.5 (50.6)	5.0 (5.2)	13.2 (13.1)
4g	89	120-121	EtOH	$C_{15}H_{19}Cl_2N_4O_2P$	46.5 (46.4)	5.0 (4.9)	13.8 (14.0)
4h	75	190-191	EtOH	$C_{13}H_{19}Cl_2N_4O_4P$	39.4 (39.3)	5.0 (4.8)	13.9 (14.1)
4i	50	110-112	EtOH/H_2O	$C_{10}H_{12}Cl_2N_5O_2P$	36.0 (35.8)	3.7 (3.6)	20.8 (20.9)
4j	76	230	Et_2O	$C_{28}H_{27}Cl_2N_3O_2P_2$	58.7 (58.9)	4.6 (4.7)	7.3 (7.3)
4k	66	76-78	Et_2O	$C_{11}H_{12}Cl_2N_3O_2P$	37.3 (37.5)	3.7 (3.4)	12.0 (11.9)
5a	78 (84)	93-95	EtOH	$C_6H_{17}N_4O_2P$	34.4 (34.6)	8.0 (8.1)	26.7 (26.9)
5b	78	78-80	Me_2CO	$C_9H_{21}N_4O_2P \cdot \frac{1}{4}H_2O$	42.9 (42.8)	8.6 (8.5)	22.1 (22.2)
5c	74	110-112	EtOH	$C_{13}H_{21}N_4O_2P$	52.6 (52.7)	7.4 (7.1)	18.7 (18.9)
5d	77	115-116	EtOH	$C_{14}H_{23}N_4O_3P$	51.4 (51.5)	7.2 (7.1)	16.9 (17.1)
5e	79	195-197	EtOH	$C_{13}H_{20}N_5O_4P$	45.4 (45.7)	5.9 (5.9)	20.2 (20.5)
5f	67	122-123	EtOH	$C_{14}H_{23}N_4O_2P$	54.3 (54.2)	7.6 (7.4)	17.9 (18.1)
5g	97	oil	—	$C_6H_{14}N_5O_2P$	32.7 (32.9)	6.6 (6.4)	32.2 (32.0)
5h	68	116-117	Me_2CO	$C_{24}H_{29}N_3O_2P_2 \cdot H_2O$	61.4 (61.15)	6.4 (6.6)	8.7 (8.9)
6a	63 (65)	95-98	MeCN	$C_8H_{21}N_4O_2P$	40.5 (40.7)	9.0 (9.0)	23.4 (23.7)
6b	34	211-213	$CHCl_3/Et_2O$	$C_{14}H_{27}N_4O_2P \cdot \frac{1}{4}H_2O$	52.5 (52.7)	8.7 (7.6)	17.7 (22.4)
7a	72 (74)	140-141	EtOH	$C_6H_{19}N_4O_3P$	38.3 (38.4)	7.4 (7.6)	22.6 (22.4)
7b	66	95-97	Me_2CO	$C_{11}H_{23}N_4O_3P \cdot H_2O$	42.6 (42.8)	8.0 (8.1)	18.0 (18.2)
7c	72	135-138	EtOH	$C_{15}H_{23}N_4O_3P \cdot H_2O$	50.1 (50.5)	7.0 (7.0)	16.0 (15.7)
7d	78	205-206	EtOH	$C_{15}H_{22}N_5O_5P \cdot H_2O$	44.7 (44.9)	5.9 (6.0)	17.2 (17.5)
8a	17	108-110	EtOH	$C_{13}H_{23}N_4O_4P$	52.4 (52.3)	7.7 (7.7)	19.1 (18.8)
8b	46	40-42	Me_2CO	$C_7H_{16}N_5O_2P$	36.3 (36.05)	6.7 (6.9)	29.7 (30.0)
8c	73	135-137	PhMe	$C_{25}H_{31}N_3O_2P_2$	64.1 (64.2)	6.7 (6.8)	8.7 (9.0)

via a metaphosphate-type intermediate. With morpholinophosphorodichloridate, on the other hand, the reaction with primary amines will be relatively fast, so that the amine is consumed *before* it can initiate the base-catalysed E_1cB process and consequently the amidic chlorides **1a-c, 1g** are isolated (Scheme 1). With secondary amines, both morpholinophosphorodichloridate and the dichloridothioate gave the amidic chlorides **1d-f, 9a-c** because there is no N-H group to initiate metaphosphate formation. The results also agree with the kinetic studies of Williams and Douglas [4] who showed that phosphorothioates are more liable to undergo E_1cB reactions. The operation of competing E_1cB base-catalysed hydrolysis is demonstrated in the reaction of the primary morpholinophosphoramidic chlorides **(1a-c)** with hydrazine hydrate because the yields (*ca.* 50%) of the hydrazides **2a-4a** were appreciably lower than

the yields (*ca.* 80%) indicated in brackets in Table 1, obtained in similar reactions with anhydrous hydrazine. The base-catalysed hydrolysis with hydrazine hydrate is analogous to the well-established [5] [6] alkaline hydrolysis of primary alkyl halides and esters. This explanation is supported by the reaction of the secondary phosphoramidic chlorides **1d-e, 9a, 9c** (Schemes 1 and 2) with the hydrazine, because the yields of the hydrazides **5a-6a, 10a, 11a** are not siginficantly increased by the use of anhydrous hydrazine (Tables 1 and 2). *p*-Chloro- and 3,4-dichlorophenylmorpholinophosphoramidic chlorides **1b, 1c**, by treatment with triethylamine gave the cyclophosphazanes **14a,b** *via* the unstable imidic amides **13a,b**.





The compound **1c**, by partial hydrolysis with aqueous pyridine afforded the pyrophosphoramide **15**; this method has been extensively used in the synthesis of pyrophosphoramides [7]. The ir spectrum showed a band at 870 cm^{-1} which was assigned to the P-O-P stretching absorption in agreement with previous observations [7]; the ^{31}P nmr spectrum exhibited two signals δ −5.5, +8.5 ppm which demonstrates the existence of diastereoisomers [8].

The phosphinimines **4j, 5h, 9h, 10g** also gave two signals in the ^{31}P nmr spectra with a coupling constant, $J_{pp} \cong$

Table 2

N-Substituted Morpholinophosphoramidic Thioates

Compound No.	Yield %	Mp °C (Bp)	Recrystallised from	Molecular Formula	Analyses % Found/(Calcd.) C	H	N
9a	79	(80-85/0.1 mm)	—	$C_6H_{14}ClN_2OPS$	31.6 (31.5)	5.8 (6.1)	12.5 (12.3)
9b	61	(121-126/0.05 mm)	—	$C_8H_{18}ClN_2OPS$	37.2 (37.4)	6.8 (7.0)	11.1 (10.9)
9c	92	101-103	EtOH	$C_8H_{16}ClN_2O_2PS$	35.7 (35.5)	6.2 (6.0)	10.2 (10.4)
10a	78 (88)	63-65	MeOH	$C_6H_{17}N_4OPS$	32.0 (32.1)	7.8 (7.6)	24.7 (25.6)
10b	89	127-129	MeOH	$C_{13}H_{21}N_4OPS$	49.9 (50.0)	6.8 (6.7)	17.8 (17.9)
10c	78	139-141	MeOH	$C_{13}H_{20}ClN_4OPS$	45.1 (45.0)	5.7 (5.8)	16.1 (16.2)
10d	88	150-151	MeOH	$C_{13}H_{20}N_5O_3PS$	43.5 (43.7)	5.6 (5.6)	19.8 (19.6)
10e	69	107-108	MeOH	$C_{14}H_{23}N_4O_2PS$	49.0 (49.1)	6.6 (6.7)	16.4 (16.4)
10f	65	104-106	MeOH	$C_{14}H_{23}N_4OPS$	51.3 (51.5)	7.2 (7.1)	17.4 (17.2)
10g	52	oil	—	$C_6H_{14}N_5OPS$	30.4 (30.6)	5.8 (5.95)	29.5 (29.8)
10h	68	133-134	C_5H_{12}	$C_{24}H_{29}N_3OP_2S$	61.2 (61.4)	6.0 (6.1)	9.1 (9.0)
11a	90 (93)	94-95	MeOH	$C_9H_{19}N_4O_2PS$	36.0 (36.1)	7.0 (7.1)	21.3 (21.05)
11b	90	121-122	Me_2CO	$C_{11}H_{23}N_4O_2PS$	43.1 (43.1)	7.6 (7.5)	18.4 (18.3)
11c	88	112-113	EtOH	$C_{14}H_{27}N_4O_2PS$	48.4 (48.6)	8.0 (7.8)	16.5 (16.2)
11d	96	165-167	EtOH	$C_{15}H_{22}N_5O_4PS$	45.4 (45.1)	5.5 (5.5)	17.3 (17.5)
11e	97	130-131	EtOH	$C_{16}H_{25}N_4O_2PS$	52.2 (52.2)	7.0 (6.8)	14.9 (15.2)
11f	61	77-78	Me_2CO/H_2O	$C_8H_{16}N_5O_2PS$	34.7 (34.65)	6.0 (5.8)	25.0 (25.3)
11g	88	195-196	EtOH	$C_{26}H_{31}N_3O_2PS$	60.7 (61.0)	6.8 (6.1)	8.1 (8.2)

Table 3

N-Substituted Morpholinophosphoramidates and Diamidothioates

Compound No.	Yield %	Mp °C (Bp)	Recrystallised from	Molecular Formula	Analyses % Found/(Calcd.) C	H	N
12a	65	132-134	EtOH	$C_4H_{14}N_5O_2P\cdot H_2O$	22.5 (22.5)	7.2 (7.6)	33.0 (32.9)
12b	61	199-202	C_6H_6	$C_{18}H_{22}N_5O_2P\cdot H_2O$	55.3 (55.5)	5.9 (6.2)	17.7 (18.0)
12c	66	215	EtOAc	$C_{16}H_{20}N_3OPS$	57.4 (57.6)	6.2 (6.0)	12.5 (12.6)
12d	70	162	EtOH	$C_{16}H_{16}Cl_4N_3OPS$	40.6 (40.8)	3.3 (3.4)	8.9 (8.9)
12e	75	112-113	MeOH	$C_{10}H_{24}N_3OPS\cdot\frac{1}{4}H_2O$	44.6 (44.5)	9.0 (9.1)	15.3 (15.6)
12f	73	oil	—	$C_4H_{14}N_5OPS$	22.4 (22.75)	6.8 (6.6)	33.0 (33.2)
12g	88	110-112	Me_2CO	$C_{10}H_{22}N_5OPS$	40.9 (41.2)	7.5 (7.6)	23.9 (24.1)
12h	80	151-152	EtOH	$C_{18}H_{22}N_5OPS$	55.6 (55.8)	5.9 (5.7)	18.3 (18.1)
12i	65	138-140	MeOH	$C_{14}H_{22}N_5OPS$	49.5 (49.5)	6.5 (6.5)	20.8 (20.6)

Table 4

Compound No.	Spectroscopic Data NMR (DMSO-d_6) δ
2b	7.3-7.15 (m, aromatics, 5H), 6.1 (d, PONHPh, 1H), 5.3 (s, NHN=CMe_2, 1H), 3.55-3.1 (m, morpholine, 8H), 1.95 (s, N=CMe_2, $6H_2$)
4e	7.95 (s, $Cl_2C_6H_3NH$, 1H), 7.6 (s, N=CH, 1H), 7.35-6.85 (m, aromatics, 7H), 6.25 (d, NHN=CH, 1H), 3.85 (s, OMe, 3H), 3.80-3.1 (m, morpholine, 8H)
5f	7.70-7.25 (m, aromatics, 5H), 6.65 (d, NH, 1H), 3.75-3.1 (m, morpholine, 8H), 2.70 (d, NMe_2, 6H), 2.15 (s, C-*Me*, 3H)
5d	8.4 (d, NH, 1H), 7.75 (s, N=CH, 1H), 7.6-6.75 (m, aromatics, 4H), 3.75 (s, O*Me*, 3H), 3.65-3.1 (m, morpholine, 8H), 2.6 (d, NMe_2, 6H)
5e	9.85 (d, NH, 1H), 9.35-8.6 (m, aromatics, 4H), 7.9 (s, N=CH, 1H), 3.75-3.1 (m, morpholine, 8H), 2.8 (d, NMe_2, 6H)
7b	6.10 (d, NH, 1H), 3.81-3.2 (m, morpholine, 8H), 1.7 (d, N=CMe_2, 6H)
7c	8.45 (d, NH, 1H), 7.9 (s, N=CH, 1H), 7.5-7.0 (m, aromatics, 5H), 3.75-3.45 (m, morpholine, 16H)
7d	9.05 (d, NH, 1H), 8.25-7.55 (m, aromatics, 4H), 7.9 (s, N=CH, 1H), 3.75-3.15 (m, morpholine, 16H)
8a	7.2-6.7 (m, aromatics, 5H), 6.5 (d, $PO(NH)_2$, 2H), 6.2 (s, NHPh), 3.45-3.1 (m, CH, morpholine, 9H), 1.2 (s, 2 × *Me*, 6H)
10b	7.65 (s, N=CH, 1H), 7.60-7.25 (m, aromatics, 5H), 6.95 (d, NH, 1H), 3.75-3.2 (m, morpholine, 8H), 2.7 (d, NMe_2, 6H)
10e	7.6 (s, N=CH, 1H), 7.55-6.75 (m, aromatics, 4H), 7.15 (d, NH, 1H), 3.75 (s, OMe, 3H), 3.65-3.0 (m, morpholine, 8H), 2.7 (s, NMe_2, 6H)
11b	6.0 (d, NH, 1H), 3.7-3.05 (m, morpholine, 16H), 1.65 (d, N=CMe_2, 6H)
11d	8.3-7.55 (m, aromatics, 4H), 7.35 (s, N=CH, 1H), 6.95 (s, NH, 1H), 3.75-3.15 (m, morpholine, 16H)
12d	7.30-6.95 (m, aromatics, 6H), 5.10 (d, 2 × NH, 2H), 3.7-3.15 (m, morpholine, 8H)
12i	5.95 (s, pyrazolyl, 2H), 3.70-3.20 (m, morpholine, 8H), 2.30 (d, 4 × *Me*, 12H)

Table 4 continued

Compound No.	Spectroscopic Data MS
1a	260 (M^+), 245, 217, 202, 173, 167, 138, 122, 86, 77
1c	328 (M^+), 293, 242, 167, 161, 86
1d	212 (M^+), 169, 154, 153, 126, 86
1f	270 (M^+), 238, 184, 152, 86
1g	227 (M^+), 213, 211, 195, 86, 44
2a	256 (M^+), 225, 93, 86, 57, 41
2b	296 (M^+), 239, 181, 154, 139, 93, 86, 72, 56, 42
2c	344 (M^+), 239, 181, 154, 112, 93, 86, 65, 42
2d	267 (M^+), 252, 224, 210, 180, 153, 139, 93, 86, 77, 56, 43
2e	501 (M^+), 409, 324, 322, 279, 262, 201, 183, 91, 65, 41
3a	290 (M^+), 259, 173, 133, 128, 126, 98, 86
3b	330 (M^+), 275, 273, 217, 206, 190, 188, 173, 153, 127, 99, 86
3c	370 (M^+), 273, 244, 188, 153, 147, 127, 112, 96, 86, 85
3d	378 (M^+), 273, 218, 215, 190, 188, 165, 153, 127, 119, 90, 86, 85
3e	423 (M^+), 393, 337, 273, 258, 218, 190, 188, 174, 165, 153, 129, 99, 86
3f	366 (M^+), 259, 173, 133, 126, 107, 86
4a	324 (M^+), 293, 161, 131, 86
4b	364 (M^+), 307, 203, 161, 86, 85
4c	388 (M^+), 307, 244, 222, 161, 86
4d	413 (M^+), 327, 307, 222, 161, 86
4e	442 (M^+), 356, 307, 161, 86
4f	427 (M^+), 341, 307, 222, 161, 86, 85
4i	335 (M^+), 293, 174, 161, 86
4j	569 (M^+), 483, 409, 161, 86
5a	208 (M^+), 176, 150, 133, 119, 92, 86
5b	248 (M^+), 205, 192, 177, 160, 148, 133, 119, 106, 86
5c	296 (M^+), 252, 208, 192, 177, 148, 133, 106, 86
5d	326 (M^+), 240, 192, 177, 160, 144, 86
5e	341 (M^+), 255, 192, 177, 134, 86
5f	310 (M^+), 267, 253, 225, 192, 177, 161, 148, 133, 119, 106, 86
5g	219 (M^+), 204, 189, 177, 175, 132, 86
5h	453 (M^+), 409, 323, 202, 86

Table 4 continued

Compound No.	Spectroscopic Data MS (continued)
6a	237 (M^+), 134, 120, 86, 72
6b	315 (M^+), 219, 205, 203, 177, 163, 135, 108, 94, 86, 72
7a	250 (M^+), 234, 219, 193, 176, 134, 101, 86
7c	338 (M^+), 252, 232, 220, 205, 193, 175, 86
7d	383 (M^+), 297, 232, 217, 205, 192, 175, 158, 130, 86
8a	298 (M^+), 191, 107, 86
8b	233 (M^+), 218, 147, 86
8c	470 (M^+), 393, 218, 148, 86
9a	228 (M^+), 193, 171, 152, 98, 86
9b	256 (M^+), 223, 221, 186, 170, 152, 138, 86
9c	270 (M^+), 238, 184, 152, 86
10b	312 (M^+), 268, 242, 236, 226, 208, 193, 161, 133, 108, 86
10c	346 (M^+), 302, 260, 229, 193, 174, 164, 137, 108, 86
10d	357 (M^+), 327, 313, 271, 240, 208, 193, 174, 161, 149, 121, 108, 86
10f	326 (M^+), 282, 240, 193, 174, 164, 133, 118, 108, 86
10g	236 (M^+), 194, 179, 160, 149, 128, 108, 86
10h	469 (M^+), 425, 383, 355, 326, 294, 277, 235, 193, 159, 117, 86
11a	226 (M^+), 235, 202, 148,1 18, 86
11b	306 (M^+), 374, 264, 250, 235, 220, 204, 188, 165, 148, 136, 118, 102, 86
11c	346 (M^+), 260, 250, 235, 228, 215, 202, 192, 176, 165, 150, 118, 86
11d	399 (M^+), 313, 281, 235, 216, 192, 165, 150, 118, 86
11e	368 (M^+), 282, 250, 235, 215, 202, 192, 164, 118, 104, 86
11f	277 (M^+), 245, 235, 191, 160, 86
11g	511 (M^+), 425, 393, 304, 274, 260, 218, 193, 118, 86
12a	195 (M^+), 165, 134, 87, 86
12b	371 (M^+), 266, 207, 180, 164, 130, 118, 103, 92, 86
12c	333 (M^+), 240, 215, 154, 122, 93, 86, 77, 56
12c	469 (M^+), 309, 222, 198, 161, 126, 86
12e	265 (M^+), 207, 175, 147, 86, 58
12f	211 (M^+), 180, 150, 115, 86
12g	291 (M^+), 234, 220, 150, 135, 101, 86
12h	387 (M^+), 284, 268, 236, 181, 150, 120, 104, 86, 77
12i	339 (M^+), 253, 242, 186, 159, 147, 127, 97, 86

Table 4 continued

Compound No.	Spectroscopic Data continued IR (ν max cm^{-1})
1a	3120 (NH), 1600 (arom C=C), 1265 (P=O), 1100 (C-O-C)
1b	3170 (NH), 1605 (arom C=C), 1260 (P=O), 1100 (C-O-C), 975 (P-N)
1c	3200 (NH), 1600 (arom C=C), 1280 (P=O), 1090 (C-O-C)
1e	1255 (P=O), 1095 (C-O-C)
2a	3360, 3160 (NH), 1600 (arom C=C), 1240 (P=O), 1100 (C-O-C)
2b	3240 (NH), 1600 (arom C=C), 1240 (P=O), 1100 (C-O-C)
2c	3240 (NH), 1600 (arom C=C), 1245 (P=O), 1105 (C-O-C)
2d	3150 (NH), 2140 (N_3), 1600 (arom C=C), 1250 (P=O), 1105 (C-O-C)
3g	3180 (NH), 2150 (N_3), 1600 (arom C=C), 1250 (P=O), 920 (P-N)
4a	3340, 3260 (NH), 1600 (arom C=C), 1255 (P=O),
4b	3220 (NH), 1600 (arom C=C), 1260 (P=O), 1100 (C-O-C)
4d	3260 (NH), 1600 (arom C=C), 1290 (P=O), 1100 (C-O-C)
4i	3240 (NH), 2160 (N_3), 1600 (arom C=C), 1290 (P=O), 1100 (C-O-C)
4j	3240 (NH), 1600 (arom C=C), 1260 (P=O), 1090 (C-O-C)
5b	3150 (NH), 1265 (P=O), 1090 (C-O-C)
5c	3320 (NH), 1600 (arom C=C), 1260 (P=O), 1080 (C-O-C)
5g	2140 (N_3), 1250 (P=O), 1080 (C-O-C)
5h	1600 (NH), 1250 (arom C=C), 1080 (C-O-C)
6a	3320, 3170 (NH), 1190 (P=O), 1090 (C-O-C), 960 (P-N)
7b	3250 (NH), 1250 (P=O), 1090 (C-O-C)
8a	3400, 3200 (NH), 1600 (arom C=C), 1200 (P=O), 1090 (C-O-C)
9a	1090 (C-O-C), 730 (P=S)
10b	3200 (NH), 1600 (arom C=C), 1080 (C-O-C), 720 (P=S)
10g	2160 (N_3), 1090 (C-O-C), 760 (P=S)
11b	3210 (NH), 1080 (C-O-C), 740 (P=S)
12g	3180 (NH), 1080 (C-O-C), 720 (P=S)

20 Hz, in good agreement with the previous results [8].

The ir spectra (Table 4) agree with reported data [9]. The phosphoryl stretching absorption band for the hydrazides generally appeared at a lower frequency than in the amidic chlorides; the range (760-720 cm^{-1}) for the thiophosphoryl absorption is in good agreement with our previous work [10].

The mass spectra of the phosphoramidic hydrazides and hydrazones showed the molecular ions, in contrast to the analogous sulphonyl derivatives which usually did not show the molecular ions [11].

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The ir spectra were measured as Nujol mulls with a Perkin Elmer 257 spectrophotometer. The ^1H nmr spectra were obtained with a Varian HA80 spectrometer using TMS as internal standard. The ^{31}P nmr spectra were measured with a Bruker HFX-90 spectrometer operating at 36.43 MHz, chemical shifts are expressed on the δ scale with upfield shifts negative; the external standard was 85% phosphoric acid. Mass spectra were recorded with a VG micromass 16F spectrometer operating at 70 eV. Camlab Polygram silica gel tlc plates sensitized to uv 254 nm were used. Microanalyses were carried out by ICI Ltd (Pharmaceuticals Division), Alderley Park, Cheshire, England.

Yields, crystallization solvents, melting points and analytical data for most of the compounds are listed in Tables 1-3, and spectroscopic data in Table 4.

Morpholinophosphorodichloridate.

Morpholine was phosphorylated with phosphorus oxychloride as previously described [12] [13] to give the phosphorodichloridate (90%), 70-80°/0.2 mm (lit [12] 110°/5 mm, lit [13] 65-68°/0.1 mm); ir: 1280 (P=O) 1090 (C-O-C) cm^{-1}; ms: 204 (M^+), 169, 118, 86.

Morpholinophosphorodichloridothioate.

Morpholine was reacted with thiophosphoryl chloride as previously described [14] to give the dichloridothioate (69%), bp 78-85°/0.1 mm, mp 40-41° (lit [14] 100-102°/1.5 mm); tlc (ethanol): showed one spot, R_F 0.80; ir: 1080 (C-O-C), 740 (P=S) cm^{-1}; ms: 219 (M^+), 184, 162, 149, 133, 86.

Dimorpholinophosphorochloridate.

Morpholine was reacted with phosphorus oxychloride as previously described [15] to give the phosphorochloridate (86%), mp 83-84° (lit [15] 80°); tlc (ethanol) showed one spot, R_F 0.62; ir: 1250 (P=O), 1090 (C-O-C) cm^{-1}.

Dimorpholinophosphorochloridothioate.

Morpholine (17.4 g) and triethylamine (20.2 g) in ether (150 ml) was added dropwise to a stirred solution of thiophosphoryl chloride (16.9 g) in ether (150 ml) at 0°. After 12 hours, the precipitate was filtered off and the filtrate evaporated to give the chloridothioate (25 g, 90%), mp 101-103°; tlc (ethanol) showed one spot, R_F 0.83; ir: 1080 (C-O-C), 740 (P=S) cm^{-1}; ms: 270 (M^+), 238, 184, 152, 86.

Anal. Calcd. for $C_8H_{16}ClN_2O_2PS$: C, 35.5; H, 6.0; N, 10.4. Found: C, 35.7; H, 6.3; N, 10.2.

N-Substituted Morpholinophosphoramidic Chlorides **1a-1g** (Scheme 1 and Table 1). General Procedure.

The amine (0.1 mole) was gradually added to a stirred ethereal solution of morpholinophosphorodichloridate (0.1 mole) and triethylamine (0.1 mole) at room temperature (with aromatic amines) or at −15° (with aliphatic amines). After 24 hours, the filtrate was evaporated under reduced pressure to give either a solid which was purified by recrystallization or a liquid, purified by vacuum distillation.

N-Substituted Morpholinophosphoramidic Hydrazides and Hydrazones **2a-7a**. General Procedure.

The morpholinophosphoramidic chloride (0.02 mole) was reacted with hydrazine hydrate (0.05 mole) in acetonitrile for 12 hours. Addition of ice-water gave a solid, which was purified by recrystallization. In the case of hydrazides obtained from primary amines, the yields were substantially increased when anhydrous hydrazine was used (*e.g.* **2a-3a**, Table 1). The various hydrazones (Scheme 1) were obtained by warming the hydrazide with the appropriate carbonyl compound (1 molar equivalent) in methanol (½ hour). The hydrazinothioates **10a, 11a, 12f** were similarly prepared.

N-Substituted morpholinophosphoramidic Azides **2d, 3g, 4i, 5g, 8b** (Scheme 1).

The morpholinophosphoramidic chloride (0.02 mole) was reacted with sodium azide (0.04 mole) in aqueous acetone for 3 hours. The mixture was poured onto ice-water to give a product purified by recrystallization or solvent extraction. Treatment of the azide with triphenylphosphine (1 molar equivalent) in boiling benzene (24 hours) gave the triphenylphosphinimines **2e, 4j, 5h, 8c**. The azidothioates **10h, 11g** (Scheme 2) were similarly prepared. The ^{31}P nmr showed two signals: δ 12.75 (P=O), 9.22 (P-N), (**4j**); 12.55 (P=O), 9.6 (P-N) (**5h**); 62.37 (P=S), 10.5 (P-N) (**10h**), J_{PP} 20 Hz.

N-(3,4-Dichlorophenyl)morpholinophosphoramidic-3′,5′-dimethylpyrazole (**4g**) (Table 1).

N-(3,4-Dichlorophenyl)morpholinophosphoramidic hydrazide (**4a**, 1g) was refluxed with 2,4-pentanedione (0.31 g) in benzene (30 ml) for 5 hours. Evaporation of the solution under reduced pressure gave an oil, which solidified on trituration with petroleum ether. After recrystallization, tlc (cyclohexane-ethanol 2:1) showed one spot, R_F 0.75; ir: 3100 (NH), 1600 (arom C=C), 1280 (P=O), 1100 (C-O-C) cm^{-1}; ms: 388 (M^+), 294, 227, 161, 86. The 3,6-dimethylpyridazine derivative **6b** was similarly obtained using 2,5-hexanedione.

Ethyl *N*-(3,4-Dichlorophenyl)morpholinophosphoramidic Carbazate (**4h**).

The phosphoramidic chloride **1c** (1 g) was reacted wtih ethyl chloroformate (0.34 g) and triethylamine (0.31 g) in benzene (25 ml) for 12 hours. The mixture was treated with ice-water (100 ml) and the precipitate purified by recrystallization; tlc (ethanol) showed one spot, R_F 0.87; ir: 3210 (NH), 1710 (C=O), 1600 (arom C=C), 1250 (P=O), 1080 (C-O-C) cm^{-1}; ms: 396 (M^+), 381, 322, 310, 293, 161, 86; nmr (deuteriochloroform): δ 7.45 (s, $NHC_6H_3Cl_2$, 1H), 7.3-6.8 (m, aromatics, 3H), 5.45 5.25 (m, $NHNH$-CO_2Et, 2H), 4.2-4.05 (q, CH_2CH_3, 2H), 3.65-3.15 (m, morpholine, 8H), 1.22 (t, CH_2CH_3, 3H).

N-(3,4-Dichlorophenyl)morpholinophosphoramidic Isothiocyanate (**4k**) (Table 1).

The phosphoramidic chloride **1c** (1 g) was stirred with ammonium thiocyanate (0.52 g) in acetonitrile (30 ml) for 12 hours. Removal of the precipitate and evaporation of the filtrate gave an oily solid. Purified by trituration with ether and recrystallization to give the isothiocyanate; ir: 3160 (NH), 2040 (NCS), 1600 (arom C=C), 1250 (P=O), 1080 (C-O-C) cm^{-1}; ms: 351 (M^+), 294, 201, 186, 161, 125.

Morpholinophosphoramidic Chloridothioates **9a-9c** (Scheme 2 and Table 2) from Secondary Amines.

To a stirred solution of morpholinophosphorodichloridothioate (0.04 mole) in ether (100 ml), the secondary amine (0.04 mole) and triethylamine (0.04 mole) in ether (100 ml) was added dropwise at 0°. The mixture was stirred for 12 hours at room temperature and filtered. The filtrate was evaporated and the product purified by recrystallization or vacuum distillation.

Attempted Preparation of Morpholinophosphoramidic Chloridothioates from Primary Amines.

Morpholinophosphorodichloridothioate (5 g, 0.023 mole) was similarly reacted with aniline (2.2 g, 0.23 mole) and triethylamine (2.3 g, 0.023 mole) in ether (100 ml) for 12 hours; tlc (ethanol) of the crude product (5 g) showed two spots, R_F 0.80, 0.60; ms: 333, 219, 191, 154, 162, 149, 133, 86.

The product appears to be a mixture of morpholinophosphorodichloridothioate and the diphenyldiamidothioate **12c** (Scheme 3). The crude product was washed with water and recrystallized (ethyl acetate) to give the compound **12c** 2.2 g (29%), tlc (petroleum ether-ethyl acetate 1:1) showed one spot, R_F 0.60; ir: 3250 (NH), 1600 (arom C=C), 1075 (C-O-C), 720 (P=S) cm^{-1}; ms: 333 (M^+).

Analogous experiments in which morpholinophosphorodichloridothioate was similarly treated with 3,4-dichloroaniline and isopropylamine afforded low yields of the diamidates **12d** (31%), **12e** (26%). Repetition of these experiments using larger quantities of the amines (4 molar equivalents) gave improved yields of the diamidates (Table 3).

1,3-Di(*p*-chlorophenyl)-2,4-dimorpholino-2,4-dioxocyclophosphazane (**14a**).

N-(*p*-Chlorophenyl)morpholinophosphoramidic chloride (**1b**) (5.9 g) was refluxed with triethylamine (6 ml) in acetonitrile (40 ml) for 5 hours. After cooling, the precipitate of triethylamine hydrochloride was filtered off and the filtrate evaporated. The gummy residue was triturated with distilled water and crystallized from methanol to give the cyclophosphazane (2.8 g, 55%), mp 250-252°; ir: 1600, 1500 (arom C=C), 1270 (P=O), 1100 (C-O-C), 940 (P-N) cm^{-1}; ms: 516 (M^+), 430, 173, 155, 86.

Anal. Calcd. for $C_{20}H_{24}Cl_2N_4O_4P_2$: C, 46.4; H, 4.7; N, 10.8. Found: C, 46.5; H, 4.7; N, 10.6.

1,3-Di(3′,4′-dichlorophenyl)-2,4-dimorpholino-2,4-dioxocyclophosphazane(**14b**).

This was similarly prepared from compound **1c** (62%), mp 280-282°; ir: 1600 (arom C=C), 1290 (P=O), 1090 (C-O-C) cm^{-1}; ms: 584 (M^+), 498, 292, 217, 161, 86.

Anal. Calcd. for $C_{20}H_{22}Cl_4N_4O_4P_2$: C, 41.0; H, 3.75; N, 9.6. Found: C, 41.1; H, 3.8; N, 9.3.

P^1,P^2-Di(3,4-dichlorophenyl) P^1,P^2-dimorpholinopyrophosphoramide (**15**).

The amidic chloride **1c** (1.5 g) was dissolved in 10% aqueous pyridine (50 ml) and the solution left for 12 hours. Addition of ice-water gave an emulsion which was extracted with chloroform (2 × 20 ml). Evaporation of the solvent gave an oil, which solidified on trituration with petroleum ether (bp 40-60°). Recrystallization from methanol gave the pyrophosphoramide (0.4 g, 30%), mp 180-182°; ir: 3200, 3180 (NH), 1600 (arom C=C), 1300 (P=O), 1100 (C-O-C), 870 (P-O-P) cm^{-1}; ^{31}P nmr: δ 5.5, 8.5 ppm.

Anal. Calcd. for $C_{20}H_{24}Cl_4N_4O_5P_2$: C, 39.7; H, 4.0; N, 9.3. Found: C, 39.5; H, 4.0; N, 9.0.

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