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Amino-de-Alkoxylation of Methyl 2,2-Dihalocarboxylates

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Abstract: N-alkyl-2,2-dihaloamides were efficiently prepared by amino-de-alkoxylation of methyl 2,2-dihalocarboxylates, at room temperature without solvents and promoters. Excellent yields of anilides were obtained after addition of $AlCl_3$.

INTRODUCTION

The amide group is one of the fundamental chemical functionalities;[1] recently we developed efficient preparative procedures to 2,2-dihaloesters,[2] which could be starting materials for the preparation of the corresponding 2,2-dihaloamides. These compounds are useful intermediates for the synthesis of heterocyclic compounds,[3] α-chloroacryl-amides[4] and aziridine-carboxyamides;[5] they have also found application as agrochemicals,[6] fungicides[7] and amebicides.[8]

2,2-Dihaloamides have been prepared by amides acylation with acylchlorides[3e-g, 6, 7] or by chlorination of saturated N,N-dimethyl amides.[4, 9] The first route has been mainly carried out with the commercial dichloroacetyl chloride; the second one is a more versatile procedure, but gives generally unsatisfactory yields. Acetylation with methyl dihaloacetate[8] and the reaction of an aluminum amide with 2,2-dichloroesters[10] has been reported.

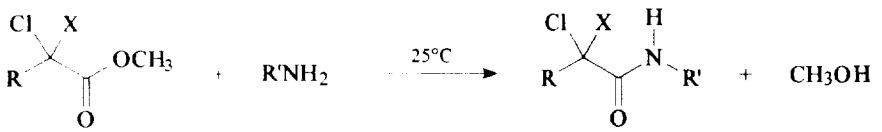
Now we report the amino-de-alkoxylation of methyl 2,2-dihalocarboxylates with aliphatic primary amines to N-alkyl-2,2-dihaloamides, at room temperature, without solvents and promoters.

RESULTS AND DISCUSSION

In the acylation of amines, esters have found less application with respect to acyl chlorides or anhydrides owing to their lower reactivity; activated esters, high pressures or bases have been used for satisfactory conversions.[11] The electronwithdrawing effect of α-halogen atoms should however increase the reactivity of the carboxylic group toward amine attack[12] to such an extent that no promotion should be required (Scheme).

Methyl 2-bromo-2-chloro-hexanoate was chosen as a test substrate and was treated with 1.5 eq. of propyl amine in a series of solvents (dimethylformamide, tetrahydrofuran, methanol, acetonitrile, methylene chloride, dimethylsulfoxide) at 25°C. Yields of N-propyl-2-bromo-2-chloro-hexanamide were good (94 %) only in methanol though after a long reaction time (42 h), whereas they were poor with the other solvents,

mainly owing to α-chloro-acryl- and α-oxo-amides formation. A significally faster amino-de-alkoxylation occurred in dimethylformamide (98% yield after 3 h) with methyl 2,2-dichloro-hexanoate, a substrate with a lower reactivity towards dehydrohalogenation.[4] In test experiments without solvent, both methyl 2-bromo-2-chloro- and 2,2-dichloro-hexanoate gave very good results in short times (3 h) with propyl amine (entries 1 and 2, Table1).



Scheme

A number of methyl α,α-dihaloesters (Table 1) was then submitted to this solventless procedure, obtaining excellent results in any case. With methyl 2-bromo-2-chloro-3-methyl-butanoate a complete conversion was obtained by adding propylamine hydrochloride to the reaction mixture. Reasonably, the acidity associated with the salt activates the carboxyl group,[13] which in this substrate is somewhat hindered by the β-branching. 2,2-Dichloro substrates always afforded higher yields with respect to the corresponding 2-bromo-2-chloro analogues, likely

TABLE 1. Reactions of methyl 2,2-dihalo-carboxylates with propyl amine.[a)]

entry	R	X	R^1	amine/ester mmol/mmol	time (h)	conversion (%)	yield (%)
1	$CH_3CH_2CH_2$-	Br	$CH_3CH_2CH_2$-	1.5	3	100	94
2	$CH_3CH_2CH_2$-	Cl	$CH_3CH_2CH_2$-	1.5	3	100	99
3[b)]	$(CH_3)_2CH$-	Br	$CH_3CH_2CH_2$-	5	3	99	91
4	$(CH_3)_2CH$-	Cl	$CH_3CH_2CH_2$-	2.5	6	100	96
5	C_5H_6-	Br	$CH_3CH_2CH_2$-	1.5	.5	100	93
6	C_5H_6-	Cl	$CH_3CH_2CH_2$-	1.5	3	100	97
7	C_5H_6 CH_2-	Br	$CH_3CH_2CH_2$-	1.5	1	100	93
8	C_5H_6 CH_2-	Cl	$CH_3CH_2CH_2$-	1.5	3	100	99

a) reactions were performed on a 2 mmol scale; b) 1 eq. of propylamine hydrochloride was added.

owing to side reactions connected with the weakness of the C-Br bond; with these latter substrates long reaction times are detrimental and reaction mixtures must be worked up as soon as possible.

Subsequently the effect of the amine structure on the reaction course was examined by testing some 2,2-dihaloesters with a number of amines (Table 2).[14] According to literature, this amino-de-alkoxylation was very sensitive to amine steric hindrance,[15] good yields being obtained just from aliphatic primary amines. No amides were observed from secondary amines even from the low sterically hindered piperidine or dimethylamine,[15] with which methyl 2-bromo-2-chloro-carboxylates gave some dehydrohalogenation. Also branching on the carbon atom adjacent to the primary amine nitrogen strongly affects the transformation,[15c] *t*-butyl amine being indeed quite unreactive (Table 2, entries 3-6).

Amino-de-alkoxylation by amines carrying a β-hydroxyl group was very easy,[8b, 15c] even N-methyl 2-amino-ethanol afforded the amide in high yields (Table 2, entries 11, note c), and this was the only case we succeeded to prepare a tertiary amide.

TABLE 2. Reactions of methyl 2,2-dihalo-carboxylates with primary amines.[a)]

entry	R	X	R^1	amine/ester mmol/mmol	time (h)	conversion (%)	yield (%)
1	$CH_3CH_2CH_2$-	Br	$CH_3CH_2CH_2$-	1.5	3	100	94
2	$CH_3CH_2CH_2$-	Cl	$CH_3CH_2CH_2$-	1.5	3	100	99
3	$CH_3CH_2CH_2$-	Br	$(CH_3)_2CH$-	2.5	6	93	81
4	$CH_3CH_2CH_2$-	Cl	$(CH_3)_2CH$-	5	6	100	97
5	$CH_3CH_2CH_2$-	Br	$(CH_3)_3C$-	1.5	3	5	0
6	$CH_3CH_2CH_2$-	Cl	$(CH_3)_3C$-	1.5	3	0	0
7	$CH_3CH_2CH_2$-	Br	CH_2=$CHCH_2$-	2.5	3	100(100)[b)]	96(99)[b)]
8	$CH_3CH_2CH_2$-	Cl	CH_2=$CHCH_2$-	2.5	3	100	99
9	$CH_3CH_2CH_2$-	Br	C_5H_6 CH_2-	2.5	3	100	92
10	$CH_3CH_2CH_2$-	Cl	C_5H_6 CH_2-	2.5	3	100	99
11	$CH_3CH_2CH_2$-	Br	$HOCH_2CH_2$-[c)]	1.5	3	100	98
12	CH_3CH_2-	Br	$(CH_3O)_2CHCH_2$-	2.5	3.5	98(97)[b)]	93(95)[b)]
13	CH_3CH_2-	Br	$(C_4H_4N)CH_2$-	2.5	2	100(100)[b)]	93(94)[b)]
14	$CH_3CH_2CH_2$-	Br	C_5H_6-	1.5	3	5	0
15	$CH_3CH_2CH_2$-	Cl	C_5H_6-	2.5	3	0	0
16[d)]	CH_3CH_2-	Br	C_5H_6-	2.2	1	97	93
17[e)]	$CH_3CH_2CH_2$-	Cl	C_5H_6-	2.2	1	99	96

a) reactions were performed on a 2 mmol scale; b) in parentheses the results on a 100 mmol scale; c) on using the N-methyl amino ethanol (2.5 eq.) amide was obtained in a 97% yield; d) 2,2-dihaloester (4.25 mmol), $AlCl_3$ (3.135 mmol) and toluene (2 ml) were added; e) 2,2-dihaloester (4.25 mmol), $AlCl_3$ (3.135 mmol) and toluene (4 ml) were added.

The nucleophilicity of aniline is so low that no amino-de-alkoxylation occurred (Table 2, entries 14-15), and we tried to promote this transformation by using $NaOCH_3$ or LiH,[16] owing to the synthetic value of the 2,2-dihaloanilides as precursors for indolones,[3a] yet with poor results. The addition of $AlCl_3$, instead, was quite satisfactory (Table 2, entries 16-17).[17]

In no case, however, the addition of promoters gave rise to the acylation of secondary amines by methyl 2,2-dihalocarboxylates.

EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a Bruker WP80 spectrometer. Mass spectra were obtained on a combined HP 5890 GC - HP 5989A MS Engine. Reagents and solvents were standard grade commercial products and

used without further purification. Methyl 2,2-dihalocarboxylates were prepared according to previous procedures.[2]

General procedure for the amino-de-alkoxylation.[18] In a round bottom flask (5 ml), fitted with a screw cap, the methyl 2,2-dihalo-carboxylate (2 mmol) and the amine (3-10 mmol; see Tables) were added. The mixture was stirred at 25 °C, and, after the time reported in Table 1 or 2, diluted with CH_2Cl_2 (10 ml) and washed with 2.5% HCl (2 x 5 ml). The organic phase was then dried over Na_2CO_3 and evaporated. The crude products were generally pure enough, and only in few cases a purification by distillation under vacuum was required; N-propyl-2-bromo-2-chloro-3-phenyl-propanamide and N-benzyl-2-bromo-2-chloro-hexanamide were purified by crystallisation from hexane.

General procedure for the preparation of anilides.[17,18] Granular $AlCl_3$ (3.135 mmol) was weighted in a schlenk tube and then crushed under inert atmosphere. Toluene (2-4 ml) and, after few minutes of stirring, aniline (9.35 mmol) were then added, while cooling the exothermic reaction in a water bath. The mixture was then thermostatted at 25°C and the methyl 2,2-dihalo-carboxylate (4.25 mmol) added. After one hour the mixture was diluted with CH_2Cl_2 (10 ml) and washed with 2.5% HCl (2 x 5 ml). The organic phase was then dried over Na_2CO_3 and evaporated. The crude products were pure enough and no further purification was generally carried out. N-phenyl-2-bromo-2-chloro-butanamide was crystallized from hexane.

N-propyl-2-bromo-2-chloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.65-1.18 (6H, m, 2 x -$CH_2C\underline{H}_3$); 1.08-1.85 (6H, m, -$CH_2(C\underline{H}_2)_2CH_3$ and -$NCH_2C\underline{H}_2CH_3$); 2.30-2.72 (2H, m, -$C\underline{H}_2CBrCl$); 3.15-3.45 (2H, m, -$C\underline{H}_2NH$-); 6.84 (1H, bs, -N$\underline{H}$). IR (neat) cm^{-1}: 3480-3330 (ν_{NH}); 1675 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 213 (15%) [M^+ - C_4H_8]; 134 (4%) [M^+ - C_4H_8 - Br]; 86 (100%) [$CONH(CH_2)_2CH_3^+$]. Found: C, 40.1; H, 6.5; N, 5.1%. $C_9H_{17}BrClNO$ requires C, 39.95; H, 6.33; N, 5.18%.

N-propyl-2,2-dichloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.72-1.18 (6H, m, 2 x -$CH_2C\underline{H}_3$); 1.10-1.78 (6H, m, -$CH_2(C\underline{H}_2)_2CH_2$- and -$NCH_2C\underline{H}_2CH_3$); 2.28-2.58 (2H, m, -$C\underline{H}_2CCl_2$); 3.12-3.50 (2H, m, -$C\underline{H}_2NH$-); 6.85 (1H, bs, -N$\underline{H}$). IR (neat) cm^{-1}: 3475-3200 (ν_{NH}); 1685 (amide I); 1530 (amide II). MS (EI, 70 eV) *m/z*: 169 (36%) [M^+ - C_4H_8]; 134 (5%) [M^+ - C_4H_8 - Cl]; 86 (100%) [$CONH(CH_2)_2CH_3^+$]. B.p. 78-80 °C (0.01mmHg). Found: C, 47.9; H, 7.5; N, 6.4%. $C_9H_{17}Cl_2NO$ requires C, 47.80; H, 7.58; N, 6.19%.

N-propyl-2-bromo-2-chloro-3-methyl-butanamide

^{1}H NMR δ ($CDCl_3$): 0.80-1.15 (3H, t, -$C\underline{H}_3$); 0.95 (3H, d, -$CHC\underline{H}_3$); 1.24 (3H, d, -$CHC\underline{H}_3$); 1.40-1.80 (2H, m, -$NCH_2C\underline{H}_2CH_3$); 2.90 (1H, m, -$C\underline{H}CClBr$); 3.10-3.50 (2H, m, -$C\underline{H}_2NH$); 6.95 (1H, bs, -N$\underline{H}$). IR (neat) cm^{-1}: 3100-3480 (ν_{NH}); 1670 (amide I); 1525 (amide II). MS (EI, 70 eV) *m/z*: 213 (18%) [M^+ - C_3H_6]; 134 (3%) [M^+ - C_3H_6 - Br]; 86 (100%) [$CONH(CH_2)_2CH_3^+$]. B.p. 89-90 °C (0.2mmHg). Found: C, 37.6; H, 5.8; N, 5.3%. $C_8H_{15}BrClNO$ requires C, 37.45; H, 5.89; N, 5.46%.

N-propyl-2,2-dichloro-3-methyl-butanamide

^{1}H NMR δ ($CDCl_3$): 0.75-1.08 (3H, t, -$CH_2C\underline{H}_3$); 1.10 (6H, d, -$CH(C\underline{H}_3)_2$); 1.55 (2H, m, -$NCH_2C\underline{H}_2CH_3$); 2.85 (1H, m, -$C\underline{H}CCl_2$); 3.14-3.48 (2H, m, -$C\underline{H}_2NH$); 6.90 (1H, bs, -N$\underline{H}$). IR (neat) cm^{-1}: 3120-3475 (ν_{NH}); 1670 (amide I); 1530 (amide II). MS (EI, 70 eV) *m/z*: 169 (18%) [M^+ - C_3H_6]; 134 (4%) [M^+- C_3H_6 - Cl]; 86 (100%) [$CONH(CH_2)_2CH_3^+$]. Found: C, 45.4; H, 7.0; N, 6.5%. $C_8H_{15}Cl_2NO$ requires C, 45.30; H, 7.13; N, 6.60%.

N-propyl-2-bromo-2-chloro-2-phenyl-acetamide

^{1}H NMR δ ($CDCl_3$): 0.98 (3H, t, $-CH_2C\underline{H}_3$); 1.61 (2H, m, $-NCH_2C\underline{H}_2CH_3$); 3.37 (2H, m, $-C\underline{H}_2NH$); 6.90 (1H, bs, $-N\underline{H}$); 7.20-8.00 (5H, m, $-C_6\underline{H}_5$). IR (neat) cm^{-1}: 3335-3480 (ν_{NH}); 1675 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 210 (33%) [M^+ - Br]; 124 (20%); 86 (61%) [$CONH(CH_2)_2CH_3^+$]; 43 (100%) [$NH(CH_2)_2CH_3^+$]. B.p. 140-141 °C (0.3 mmHg). Found: C, 45.5; H, 4.5; N, 5.0%. $C_{11}H_{13}BrClNO$ requires C, 45.47; H, 4.51; N, 4.82%.

N-propyl-2,2-dichloro-2-phenyl-acetamide

^{1}H NMR δ ($CDCl_3$): 0.95 (3H, t, $-CH_2C\underline{H}_3$); 1.50 (2H, m, $-NCH_2C\underline{H}_2CH_3$); 3.33 (2H, m, $-C\underline{H}_2NH$); 6.88 (1H, bs, $-N\underline{H}$); 7.23-7.97 (5H, m, $-C_6\underline{H}_5$). IR (neat) cm^{-1}: 3460-3280 (ν_{NH}); 1680 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 210 (3%) [M^+ - Cl]; 124 (11%); 86 (56%) [$CONH(CH_2)_2CH_3^+$]; 43 (100%) [$NH(CH_2)_2CH_3^+$]. Found: C, 53.7; H, 5.2; N, 5.5%. $C_{11}H_{13}Cl_2NO$ requires C, 53.68; H, 5.32; N, 5.69%.

N-propyl-2-bromo-2-chloro-3-phenyl-propanamide

^{1}H NMR δ ($CDCl_3$): 0.88 (3H, t, $-CH_2C\underline{H}_3$); 1.50 (2H, m, $-NCH_2C\underline{H}_2CH_3$); 3.24 (2H, m, $-C\underline{H}_2NH$); 3.72 (H, d, $-CBrCl\underline{C}H(H)\ C_6H_5$); 4.18 (H, d, $-CBrClCH(\underline{H})C_6H_5$); 6.75 (1H, bs, $-N\underline{H}$); 7.32 (5H, m, $C_6\underline{H}_5$). IR (nujol) cm^{-1}: 3455-3290 (ν_{NH}); 1675 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 224 (100%) [M^+- Br]; 165 (22%); 91 (5%) [$C_7H_7^+$]. M.p. 60-62 °C. Found: C, 47.4; H, 5.1; N, 4.5%. $C_{12}H_{15}BrClNO$ requires C, 47.32; H, 4.96; N, 4.60%.

N-propyl-2,2-dichloro-3-phenyl-propanamide

^{1}H NMR δ ($CDCl_3$): 0.86 (3H, t, $-CH_2C\underline{H}_3$); 1.42 (2H, m, $-NCH_2C\underline{H}_2CH_3$); 3.34 (2H, m, $-C\underline{H}_2NH$); 3.78 (2H, s, $-CCl_2C\underline{H}_2\ C_6H_5$); 7.32 (5H, m, $-C_6\underline{H}_5$). IR (nujol) cm^{-1}: 3450-3285 (ν_{NH}); 1670 (amide I); 1525 (amide II). MS (EI, 70 eV) *m/z*: 224 (100%) [M^+- Cl]; 165 (26%); 91 (6%) [$C_7H_7^+$]. Found: C, 55.3; H, 5.9; N, 5.4%. $C_{12}H_{15}Cl_2NO$ requires C, 55.40; H, 5.81; N, 5.38%.

N-isopropyl-2-bromo-2-chloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.78-1.10 (3H, m, $-CH_2C\underline{H}_3$); 1.20 (6H, d, $-CH(C\underline{H}_3)_2$); 1.20-1.74 (4H, s, $-CH_2(C\underline{H}_2)_2CH_3$); 2.25-2.70 (2H, m, $-C\underline{H}_2BrCl$); 4.10 (1H, m, $-NC\underline{H}(CH_3)_2$); 6.60 (1H, bs, $-N\underline{H}$). IR (neat) cm^{-1}: 3320-3480 (ν_{NH}); 1670 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 213 (16%) [M^+ - C_4H_8]; 134 (4%) [M^+ - C_4H_8 - Br]; 86 (100%) [$CONHCH(CH_3)_2^+$]. B. p. 88-89 °C (mmHg 0.2). Found: C, 39.8; H, 6.3; N, 4.9%. $C_9H_{17}BrClNO$ requires C, 39.95; H, 6.33; N, 5.18%.

N-isopropyl-2,2-dichloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.78-1.12 (3H, m, $-CH_2C\underline{H}_3$); 1.25 (6H, d, $-CH(C\underline{H}_3)_2$); 1.25-1.90 (4H, m, $-CH_2(C\underline{H}_2)_2CH_3$); 2.30-2.65 (2H, m, $-C\underline{H}_2CCl_2$); 4.10 (1H, m, $-NC\underline{H}(CH_3)_2$); 6.60 (1H, bs, $-N\underline{H}$). IR (neat) cm^{-1}: 3320-3480 (ν_{NH}); 1680 (amide I); 1525 (amide II). MS (EI, 70 eV) *m/z*: 169 (18%) [M^+- C_4H_8]; 134 (5%) [M^+ - C_4H_8 - Cl]; 86 (100%) [$CONHCH(CH_3)_2^+$]. Found: C, 47.7; H, 7.8; N, 6.4%. $C_9H_{17}Cl_2NO$ requires C, 47.80; H, 7.58; N, 6.19%.

N-allyl-2-bromo-2-chloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.80-1.10 (3H, m, $-CH_2C\underline{H}_3$); 1.10-1.80 (4H, m, $-CH_2(C\underline{H}_2)_2CH_3$); 2.40-2.70 (2H, m, $-C\underline{H}_2CBrCl$); 3.90 (2H, m, $-C\underline{H}_2NH$); 5.15-5.42 (2H, m, $-CH=C\underline{H}_2$); 5.50-6.20 (H, m , $-C\underline{H}=CH_2$); 6.90 (1H, bs, $-N\underline{H}$). IR (neat) cm^{-1}: 3240-3480 (ν_{NH}); 1740 (amide I); 1530 (amide II). MS (EI, 70 eV) *m/z*: 211 (23%) [M^+ - C_4H_8]; 188 (11%) [M^+ - Br]; 84 (100%) [$CONHCH_2CH=CH_2^+$]. Found: C, 40.2; H, 5.8; N, 5.1%. $C_9H_{15}BrClNO$ requires C, 40.25; H, 5.63; N, 5.22%.

N-allyl-2,2-dichloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.78-1.15 (3H, m, $-CH_2C\underline{H}_3$); 1.20-1.70 (4H, m, $-CH_2(C\underline{H}_2)_2CH_3$); 2.30-2.60 (2H, m, $-C\underline{H}_2CCl_2$); 3.80-4.10 (2H, m, $-C\underline{H}_2NH$); 5.00-5.45 (2H, m, $-CH=C\underline{H}_2$); 5.60-6.10 (1H, m, $-C\underline{H}=CH_2$); 6.90

(1H, bs, -NH). IR (neat) cm^{-1}: 3350-3490 (ν_{NH}); 1680 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 167 (18%) [M^+ - C_4H_8]; 132 (9%) [M^+ - C_4H_8 - Cl]; 84 (100%) [$CONHCH_2CH{=}CH_2^+$]. Found: C, 48.4; H, 6.6; N, 6.1%. $C_9H_{15}Cl_2NO$ requires C, 48.23; H, 6.75; N, 6.25%.

N-benzyl-2-bromo-2-chloro-hexanamide

^1H NMR δ ($CDCl_3$): 0.78-1.10 (3H, m, $-CH_2CH_3$); 1.25-1.80 (4H, m, $-CH_2(CH_2)_2CH_3$); 2.42-2.78 (2H, m, $-CH_2CBrCl$); 4.55 (2H, d, $-C_6H_5CH_2NH$); 7.10 (1H, bs, -NH); 7.25 (5H, m, $-C_6H_5$). IR (nujol) cm^{-1}: 3240-3460 (ν_{NH}); 1685 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 261 (3%) [M^+ - C_4H_8]; 238 (74%) [M^+ - Br]; 149 (3%) [$CONHCH_2C_6H_5^+$]; 91 (100%) [$C_7H_7^+$]. M.p. 42-43 °C. Found: C, 49.0; H, 5.3; N, 4.6%. $C_{13}H_{17}BrClNO$ requires C, 49.00; H, 5.38; N, 4.40%.

N-benzyl-2,2-dichloro-hexanamide

^1H NMR δ ($CDCl_3$): 0.79-1.10 (3H, m, $-CH_2CH_3$); 1.50-1.74 (4H, m, $-CH_2(CH_2)_2CH_3$); 2.34-2.65 (2H, m, $-CH_2Cl_2$); 4.52 (2H, d, $-C_6H_5CH_2NH$); 7.12 (1H, bs, -NH); 7.24 (5H, m, $-C_6H_5$). IR (neat) cm^{-1}: 3230-3460 (ν_{NH}); 1655 (amide I); 1510 (amide II). MS (EI, 70 eV) *m/z*: 238 (60%) [M^+ - Cl]; 182 (2%) [M^+ - Cl - C_4H_8]; 91 (100%) [$C_7H_7^+$]. Found: C, 57.1; H, 6.2; N, 5.1%. $C_{13}H_{17}Cl_2NO$ requires C, 56.95; H, 6.25; N, 5.11%.

N-(2-hydroxyethyl)-2-bromo-2-chloro-hexanamide

^1H NMR δ ($CDCl_3$): 0.94 (3H, s, $-CH_3$); 1.20-1.78 (4H, m, $-CH_2(CH_2)_2CH_3$); 1.70 (1H, bs, -OH); 2.44-2.79 (2H, m, $-CH_2CBrCl$); 3.50 (2H, q, $-CH_2NH$); 3.78 (2H, m, $-CH_2OH$); 7.28 (1H, bs, -NH). IR (neat) cm^{-1}: 3640-3140 (ν_{OH} and ν_{NH}); 1680 (amide I); 1530 (amide II). MS (EI, 70 eV) *m/z*: 217 (15%) [M^+ - C_4H_8]; 136 (4%) [M^+ - C_4H_8 - Br]; 88 (100%) [$CONH(CH_2)_2OH^+$]; 60 (10%) [$NH(CH_2)_2OH^+$]. Found: C, 35.2; H, 5.5; N, 5.0%. $C_8H_{15}BrClNO_2$ requires C, 35.25; H, 5.55; N, 5.14%.

N-(2-hydroxyethyl)-N-methyl-2-bromo-2-chloro-hexanamide

^1H NMR δ ($CDCl_3$): 0.81 (3H, t, $-CH_3$); 1.08-1.84 (4H, m, $-CH_2(CH_2)_2CH_3$); 2.00 (1H, bs, -OH); 2.40-2.71 (2H, m, $-CH_2CBrCl$); 2.45 (3H, s, $-CH_2NCH_3$) 3.66 (2H, m, $-CH_2NCH_3$); 3.90 (2H, m, $-CH_2OH$). IR (neat) cm^{-1}: 3620 (ν_{OH}); 1645 (amide I). MS (EI, 70 eV) *m/z*: 285 (4%) [M^+]; 256 (100%) [M^+ - CH_2OH]; 174 (47%); 102 (89%) [$CONCH_3(CH_2)_2OH^+$]; 74 (67%) [$CH_3N(CH_2)_2OH^+$]. Found: C, 37.8; H, 6.0; N, 4.7%. $C_9H_{17}BrClNO_2$ requires C, 37.72; H, 5.98; N, 4.89%.

N-(2,2-dimethoxyethyl)-2-bromo-2-chloro-butanamide

^1H NMR δ ($CDCl_3$): 1.10 (6H, t, $-CH_3$); 2.52 (2H, q, $-CH_2CBrCl$); 3.40 (6H, s, 2 x $-OCH_3$); 3.34-3.58 (2H, m, $-CH_2NH$); 4.44 (1H, t, $-CH(OCH_3)_2$); 7.06 (1H, bs, -NH). IR (neat) cm^{-1}: 3260-3460 (ν_{NH}); 1685 (amide I); 1520 (amide II). MS (EI, 70 eV) *m/z*: 258 (5%) [M^+ - C_2H_4]; 132 (4%) [$CONHCH_2(OCH_3)_2^+$]; 75 (100%) [$CH(OCH_3)_2^+$]. Found: C, 32.2; H, 5.1; N, 4.7%. $C_8H_{15}BrClNO_3$ requires C, 33.30; H, 5.24; N, 4.85%.

N-(2-pyridyl-methyl)-2-bromo-2-chloro-butanamide

^1H NMR δ ($CDCl_3$): 1.14 (3H, t, $-CH_3$); 2.60 (2H, q, $-CH_2CBrCl$); 4.61 (2H, d, $-CH_2NH$); 7.10-7.82 (4H, m, $-C_5H_4N$); 8.55 (1H, bs, -NH). IR (neat) cm^{-1}: 3140-3480 (ν_{NH}); 1675 (amide I); 1540 (amide II). MS (EI, 70 eV) *m/z*: 264 (6%) [M^+ - C_2H_4]; 211 (13%) [M^+ - C_2H_4 - Br]; 175 (2%); 135 (100%) [$CONHC_5H_4N^+$] Found: C, 41.2; H, 4.2; N, 9.6%. $C_{10}H_{12}BrClN_2O$ requires C, 41.19; H, 4.15; N, 9.61%.

N-phenyl-2-bromo-2-chloro-butanamide

^1H NMR δ ($CDCl_3$): 1.22 (3H, t, $-CH_3$); 2.68 (2H, q, $-CH_2CH_3$); 7.08-7.72 (5H, m, $-C_6H_5$); 8.50 (1H, bs, -NH). IR (nujol) cm^{-1}: 3440-3240 (ν_{NH}); 1710 (amide I); 1605 (amide II). MS (EI, 70 eV) *m/z*: 275 (25%) [M^+]; 196 (4%) [M^+ - Br]; 160 (2%); 132 (6%), 120 (100%) [$CONHC_6H_5^+$]. M.p. 41-42 °C. Found: C, 43.4; H, 4.0; N, 5.2%. $C_{10}H_{11}BrClNO$ requires C, 43.43; H, 4.01; N, 5.06%.

N-phenyl-2,2-dichloro-hexanamide

^{1}H NMR δ ($CDCl_3$): 0.92 (3H, t, -C<u>H</u>$_3$); 1.24-1.74 (4H, m, -CH_2(C<u>H</u>$_2$)$_2$$CH_3$); 2.35-2.74 (2H, m, -C<u>H</u>$_2$$CCl_2$); 7.04-7.78 (5H, m, C_6<u>H</u>$_5$); 8.46 (1H, bs, -N<u>H</u>). IR (neat) cm^{-1}: 3450-3285 (ν_{NH}); 1670 (amide I); 1525 (amide II). MS (EI, 70 eV) *m/z*: 259 (16%) [M^+]; 203 (20%) [M^+ - C_4H_8]; 168 (4%) [M^+ - C_4H_8 - Cl]; 120 (60%) [$CONHC_6H_5^+$]; 92 (30%) [$NHC_6H_5^+$]. Found: C, 55.5; H, 5.7; N, 5.5%. $C_{12}H_{15}Cl_2NO$ requires C, 55.40; H, 5.81; N, 5.38%.

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