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The Quarternisation of Tertiary Amines with Dihalomethane.

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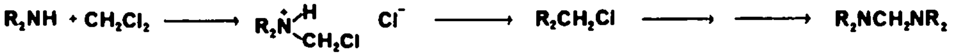
Abstract: Whereas dichloromethane is inert towards reaction with most tertiary amines under atmospheric conditions, it readily reacts with a wide variety at high pressures to produce α-chloro quaternary ammonium and even bis-ammonium salts. The reaction of dichloromethane and dibromomethane with eleven tertiary amines and properties of the products are described.

The Menschutkin reaction was reported in 1890[1] and has been the subject of extensive study at both atmospheric pressure[2] and elevated pressure[3]. The ionogenic nature of the reaction results in a particularly large pressure coefficient; values for the volume of activation typically range between -30 $cm^3\ mol^{-1}$ when measured in a polar solvent to -60 $cm^3\ mol^{-1}$ in media of low polarity[4]. The formation of bis-quaternary ammonium salts has been observed on reaction of a tertiary amine with an α,ω-dihaloalkane (1)[5] though the formation of a geminal bis-ammonium salt from a 1,1-dihaloalkane has been rarely reported.

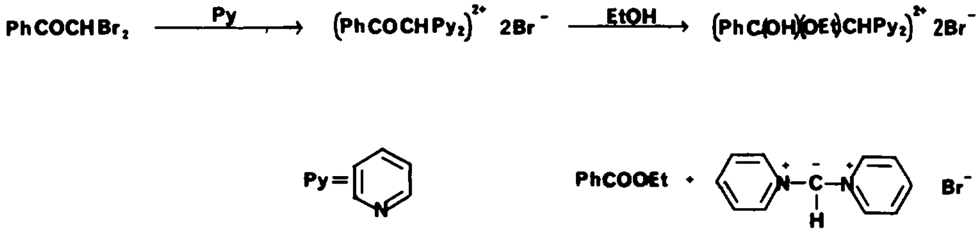
$$2R_3N \;+\; \underset{(1)}{Br(CH_2)_nBr} \longrightarrow \underset{n = 2-10}{R_3\overset{+}{N}(CH_2)_n\overset{+}{N}R_3} \quad 2Br^-$$

Diaminomethanes are products from the high pressure reaction of dichloromethane and a secondary amine. They are formed in a stepwise manner via the α-chloroammonium salts, which are not isolated[6], scheme 1. The cation ylid (2), has been successfully used in deuterium exchange studies[7] but it was generated from α,α-dibromoacetophenone and subsequent solvolytic loss of ethyl benzoate,



$R_2NH + CH_2Cl_2 \longrightarrow R_2\overset{+}{N}(H)(CH_2Cl)\ Cl^- \longrightarrow R_2CH_2Cl \longrightarrow \longrightarrow R_2NCH_2NR_2$

Scheme 1



$PhCOCHBr_2 \xrightarrow{Py} (PhCOCHPy_2)^{2+}\ 2Br^- \xrightarrow{EtOH} (PhC(OH)(OEt)CHPy_2)^{2+}\ 2Br^-$

Py =

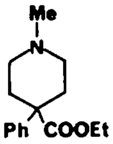
PhCOOEt +

Br⁻

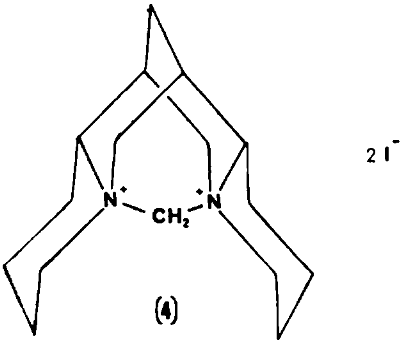
Scheme 2

(2)

scheme 2. A bis-quaternary salt generated from dichloromethane and the piperidine derivative, meperidine (3), has been inferred from the mass spectral fragmentation pattern of the amine[8]. It has recently been reported that sparteine, normally unreactive towards alkylhalides forms, exclusively, a methylene bis-ammonium salt (4) with diiodomethane[7] at pressures in excess of 20 kbar.



(3)



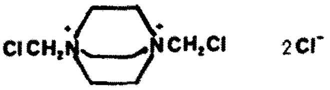
(4)

During the extraction of some alkaloid material with dichloromethane and trichloromethane the formation of artifacts, identified as quaternary salts, was observed[10]. Hansen and Nordholm studied salt formation as an unwanted byproduct of solvent extraction of tertiary aliphatic amines with trichloromethane, dichloromethane and 1,2-dichloroethene and concluded that solutions of the amines should not be stored for long periods[11]. Chloromethyltriethylammonium chloride has been prepared[12] and used as a C_1 unit in a Mannich reaction performed at 9 kbar pressure[13].

A large range of mono- and bis-ammonium salts using dihalomethane as the electrophile have now been characterised and the effect of pressure on the salt formation studied. As usual the activity of the halide increases in the order Cl < Br < I.

Results and Discussion

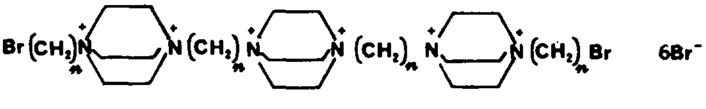
Trimethylamine, quinuclidine and 1,4-diazobicyclo[2.2.2]octane (DABCO) were dissolved in excess dichloromethane at 30°C. Over a period of a few days almost quantitative yields of the quaternary chloromethyl ammonium salts were produced. Quinuclidine and trimethylamine formed only one salt: chloromethylquinuclidinium chloride and chloromethyltrimethylammonium chloride respectively. In contrast DABCO and dichloromethane resulted in a mixture of ammonium salts, 1-chloromethyl-1-azonia-4-azobicyclo[2.2.2]octane chloride and 1,4-bis(chloromethyl)-1,4-diazoniabicyclo[2.2.2]octane dichloride (5). Diethylmethylamine, triethylamine, tri-n-butylamine, N-methylmorpholine and pyridine do not react with dichloromethane to form salts at atmospheric pressure.



(5)

The quaternisation of a selection of tertiary amines with dibromomethane occurred at atmospheric pressure to give, in most cases, good yields of the bromomethyl ammonium salt, Table 1. With dichloromethane the more forcing conditions provided by pressure were generally required for reaction to occur, Table 2. It was notable that pyridine consistently reacted to give a bis-pyridinium salt and even when a large excess of electrophile was present a substantial quantity of this salt was produced, Table 3. The rate of formation of the bis-pyridinium salt was considerably faster than the rate of formation of the (mono-)pyridinium salt. The displacement of the second halide atom appears to be activated by an α-ammonium group, facilitating the formation of the bis-ammonium salt. However in the case of, for example, chloromethyltrimethylammonium chloride, the substitution of the second halide atom is severely restricted by the steric enviroment of the reaction centre which may be compared to a neopentyl system. The formation of a bis-ammonium salt was induced by high pressure in the cases of trimethylamine and dichloromethane and triethylamine and dibromomethane where the halomethyl ammonium salts were exclusively produced at atmospheric pressure. The use of high pressure is well known to facilitate sterically hindered reactions[4].

A brief study was made of the reactivity of α,ω-dibromoalkanes of various chain lengths in the Menschutkin reaction, Table 4. The product distribution appears complex and probably results from a combination of steric and electronic factors; this is undergoing further study. It was hoped that the condensation of DABCO and a dihaloalkane would result in some high molecular weight products. This was the case when 1,4-dibromobutane or 1,5-dibromopentane were employed, the major product being the polyelectrolyte (6). The formation of polymers by reaction of alkyldiamines and dichloroalkanes has been reported[14] however the use of primary or secondary amines and subsequent elimination of hydrogen chloride led to the recovery of neutral products only. A diquaternary ammonium salt of DABCO and benzyl chloride is known[15] but oligomers such as (6) appear to be novel.



(6) $n = 4,5$

Pressure had little effect on the distribution of products in the reaction between diiodomethane and a selection of amines, Table 5.

Experimental

The high pressure equipment consisted of a double-walled cylindrical pressure vessel (Psika Ltd.) fitted with a piston powered by a 100-tonne hydraulic ram, the whole being contained in a press frame. Samples of up to 5 ml of the reaction mixture were encapsulated in a poly(tetrafluoroethylene) cylindrical cell closed with a sliding stopper. This was placed within the high pressure vessel which was filled with hydraulic fluid (Plexol 244) and the desired pressure applied. A calibrated strain gauge directly connected to the cylinder monitored the pressure, the temperature was controlled by an external heating jacket. Pressures up to 12 kbar and temperatures up to 80°C could be employed.

Table 1 Tertiary amines quarternised with dibromomethane. Reactant ratio, 2 (amine): 1 (dibromomethane)

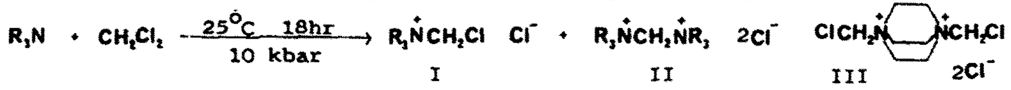
$$R_3N + CH_2Br_2 \xrightarrow{MeCN} \underset{I}{R_3\overset{+}{N}CH_2Br\ \ Br^-} + \underset{II}{R_3\overset{+}{N}CH_2\overset{+}{N}R_3\ \ 2Br^-}$$

Amine	Conditions °C	hr	p/bar	% Product I	II	% Yield
Trimethylamine	30	3	1	100	-	85
Triethylamine	70	44	1	100	-	81
Triethylamine	30	144	5000	7	93	
Tri-n-butylamine	70	44	1	-	-	
Diethylmethylamine	30	51	1	100	-	87
N-methylmorpholine	30	51	1	100	-	20
Quinuclidine	30	3	1	100	-	100
DABCO*	30	28	1	100		85
Pyridine	70	72	1	-	100	72
N,N-dimethylaniline	70	139	1	44	56	
Isoquinoline	70	17	1	49	51	

* Reactant ratio 1 DABCO : 2 CH_2Br_2

In a typical experiment triethylamine (1 ml) and dichloromethane (4 ml) were mixed and pressurised overnight at 10 kbar and 30°C. On release of the pressure, solid material was observed. This was separated from any remaining reactants by filtration under a nitrogen atmosphere, washed with diethyl ether, recrystallised by precipitation from absolute ethanol on addition of dry diethyl ether and dried in a vacuum desiccator. Analysis was performed by ^1H n.m.r., Table 6, and halide determined by silver titration to a conductometric end point. The results of the analyses were in accord with the expected products, except for the iodide salts, where reduced solubility resulted in inconsistent figures for halide content of the salt. In these cases ^1H n.m.r. spectroscopy (in DMSO-d_6) indicated the product present.

Table 2 Tertiary amines quarternised with excess dichloromethane at high pressure. The error limit quoted corresponds to one standard deviation from a mean of three determinations.



Amine	% Product I	% Product II	% Product III	% Chloride Calculated	% Chloride Observed
Trimethylamine	84	16		(cpI) 24.61 (cpII) 34.91	26.27⁺ ± 0.73
Triethylamine	100	-		19.05	19.81 ± 0.81
Tri-n-butylamine	100	-		13.11	13.11 ± 0.19
Diethylmethylamine	100	-		20.60	20.50 ± 0.56
N-methylmorpholine	100	-		19.05	20.33 ± 0.51
Quinuclidine	100	-		18.08	17.87 ± 0.54
pyridine	-	100		29.17	29.29 ± 0.80
DABCO	12		88	(cpI) 17.99	17.82 ± 0.36
DABCO*	83		17	(III) 25.14	24.37⁺ ± 0.31
DBU	-	-			
Quinoline	-	-			
N,N-dimethylaniline	-	-			

+ Determination on crude product mixture.
* Reactant ratio 1:1 in MeCN solvent.

Table 3 Quarternisation of pyridine with dibromomethane.

$$\text{Py} + CH_2Br_2 \xrightarrow[72\text{hr} \quad 50\%\text{MeCN}]{70^\circ C \quad 1\text{ bar}} \underset{\text{I}}{\text{Py}\overset{+}{}CH_2Br\ Br^-} + \underset{\text{II}}{\overset{+}{\text{Py}}CH_2\overset{+}{\text{Py}}\ 2Br^-}$$

Reactant ratio Pyridine	Reactant ratio CH_2Br_2	% Product I	% Product II
2	1	-	100
1	2	2	98
1	10	30	70
1	50*	67	33

* No solvent present.

Table 4 Tertiary amines quarternised with dibromomalkanes. Reactant ratio, 1 (amine) : 2 (dibromoalkane)

$$R_3N + Br(CH_2)_nBr \xrightarrow{30^{\circ}C\ \ 1\ bar} \underset{I}{R_3\overset{+}{N}(CH_2)_nBr\ \ Br^-} + \underset{II}{R_3\overset{+}{N}(CH_2)_n\overset{+}{N}R_3\ \ 2Br^-}$$

Amine	n	Time hr	% Product I	II	% Yield
Triethylamine*	1	95	100	-	82
	2	95	20	80	
	3	28	69	31	
	4	22	72	28	
	5	22	36	64	
Quinuclidine*	1	3	100	-	78
	2	3	78	22	
	3	3	59	41	
	4	3	80	20	
Pyridine+,‡	1	66	2	98	
	2	17	21	79	
	3	2.5	37	63	
	4	1	24	76	
	5	2	6	97	
DABCO‡	1	28	100	-	85
	2	28	100	-	99
	3	1	5	95	
	4	1	oligomer	(6)	
	5	1	oligomer	(6)	

* Reaction performed in EtOH (30 - 50%, weight of solvent as a fraction of total weight)
\+ Reaction performed at 70°C
‡ Reaction performed in MeCN (30 - 50%)

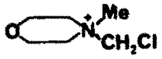
Table 5 Tertiary amines quarternised with diiodomethane. Reactant ratio 2 amine : 1 diiodomethane

$$R_3N + CH_2I_2 \xrightarrow{28^{\circ}C} \underset{I}{R_3\overset{+}{N}CH_2I\ \ I^-} + \underset{II}{R_3\overset{+}{N}CH_2\overset{+}{N}R_3\ \ 2I^-}$$

Amine	Time/hr	Pressure	Solvent‡	% Product I	II	% Yield
Trimethylamine	2	1 bar	30% MeCN	100	-	97
	2	5 kbar	10% MeOH*	-	-	
Triethylamine	4	1 bar	40% MeCN	100	-	61
	19	5 kbar	40% MeCN	100	-	100
Quinuclidine	2	1 bar	50% MeCN	100	-	98
	2	5 kbar	30% MeOH	100	-	100
Pyridine+	18	1 bar	-	-	100	50

‡ Solvent measured as a percentage of the total mass of the reaction mixture
* Reaction mixture carbonised under pressure
\+ Reaction performed at 50°C

Table 6 ^{1}H n.m.r. data of the ammonium salts in D_2O.
(Varian T60 n.m.r. spectrometer.)

$(Me_3NCH_2Cl)^+$	Cl^-	3.3 (9H, s), 5.1 (2H, s)
$(Et_3NCH_2Cl)^+$	Cl^-	1.3 (9H, t), 3.4 (6H, q), 5.0 (2H, s)
$(Et_2MeNCH_2Cl)^+$	Cl^-	1.35 (6H, t), 3.1 (3H, s), 3.5 (4H, q), 5.1 (2H, s)
$(Bu_3NCH_2Cl)^+$	Cl^-	0.8-2.0 (21H, m), 3.4 (6H, bt), 5.1 (2H, s)
	Cl^-	3.3 (3H, s), 3.6 (4H, bt), 4.1 (4H, bt), 5.3 (2H, s)
	Cl^-	1.8-2.4 (7H, m), 3.6 (6H, bt), 4.9 (2H, s)
$\overset{+}{Py}CH_2\overset{+}{Py}$	$2Cl^-$	7.5 (2H, s), 8.3 (4H, t), 8.8 (2H, t), 9.6 (4H, d)
	Cl^-	3.0-3.8 (12H, m), 5.1 (2H, s)
	$2Cl^-$	4.2 (12H, s), 5.5 (4H, s)

References.

1. N. Menschutkin, Z. Phys. Chem., (1890), 6, 41.
2. E. M. Arnett and R. Reich, J. Am. Chem. Soc., (1980), 102, 5892.
   C. D. Johnson, I. Roberts and P. G. Taylor, J. Chem. Soc., Perkin Trans. II, (1981), 409.
3. W. J. leNoble and Y. Ogo, Tetrahedron, (1970), 26, 4119.
4. N. S. Isaacs, Liquid Phase High Pressure Chemistry, Wiley, Chichester (1981).
5. H. Z. Sommer and L. L. Jackson, J. Org. Chem., (1970), 35(5), 1558.
   H. Z. Sommer, H. I. Lipp and L. L. Jackson, J. Org. Chem., (1971), 36(6), 824.
   K. Murai and C. Kimura, Kogyo Kagaku Zasshi, (1971), 74(9), 1842; Chem. Abs., (1972), 76, 13398.
   M. Yamada, T. Sakakibara, T. Takamoto and R. Sudoh, Bull. Chem. Soc. Jpn., (1977), 50(8), 2174.
6. K. Matsumoto, S. Hashimoto, Y. Ikemi and S. Otani, Heterocycles, (1984), 22(6), 1417.
7. R. A. Olofson, D. M. Zimmerman and R. C. Schnur, J. Labelled Cps., (1972), 8(3), 397.
8. A. Vincze and L. Gefen, Isreal J. Chem., (1978), 17, 236.
9. J. Jurczak, Tenth AIRAPT International High Pressure Conference, University of Amsterdam, 1985.
10. J. D. Phillipson and N. G. Bisset, Phytochemistry (1972), 11, 2547.
    A. H. Beckett and H. M. Ali, J. Chromatography, (1979), 177, 255.
11. S. H. Hansen and L. Nordholm, J. Chrom., (1981), 204, 79.
12. D. A. Wright and C. A. Wulff, J. Org. Chem., (1970), 35(12), 4252.
13. K. Matsumoto, Angew. Chem. Int. Ed. Engl., (1982), 21, 922.
14. T. J. Suen, A. Senior, D. L. Swanson and Y. Jen, J. Polymer Sci., (1960), 45, 289.
15. S. H. Pine, J. Cheney, B. Catto and J. D. Petersen, J. Org. Chem., (1974), 39(2), 130.