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N-ALKYLATION OF TERTIARY ALIPHATIC AMINES BY CHLOROFORM, DICHLOROMETHANE AND 1,2-DICHLOROETHANE

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SUMMARY

The tertiary aliphatic amine imipramine is treated with chloroform, dichloromethane and 1,2-dichloroethane under mild conditions. In chloroform and dichloromethane two quaternary ammonium compounds, N-chloromethylimipraminium chloride and N-methylimipraminium chloride, are formed as well as the secondary amine desmethylimipramine. In 1,2-dichloroethane only two quaternary ammonium compounds are found.

The reaction products are quantified and isolated by means of high-performance liquid chromatography.

Routes of reactions and their importance in relation to analytical chemistry are discussed.

INTRODUCTION

Several observations on the formation of quaternary chloromethylammonium compounds when using dichloromethane as a solvent for tertiary aliphatic amines can be found in the literature¹⁻⁹. Quaternization in chloroform owing to the impurities bromochloromethane and dichloromethane has also been reported¹⁰⁻¹³. The observation of bisquaternization has also been stated⁸.

This work has been carried out to investigate the extent to which these reactions take place and to see what influence they have in analytical chemistry.

The three solvents chloroform, dichloromethane and 1,2-dichloroethane, often used for extraction, have been investigated by reaction with the model compound imipramine (IP) — a tertiary amine.

EXPERIMENTAL

Apparatus

A liquid chromatograph consisting of a Waters 6000A pump and a Waters 440 detector (254 nm) connected to an Omniscribe 5117-5 recorder was used. The sample injections were made through a Rheodyne 7120 injection valve.

The thin-layer chromatographic (TLC) and the gas chromatographic (GC)

systems as well as equipment for ultraviolet absorbance and proton magnetic resonance measurements have been described previously⁷.

The apparatus for mass spectrometric (MS) measurements has also been described^{7,10}. For the GC-MS determination of desmethylimipramine (DMI) the following chromatographic column was used: 2 m × 2 mm I.D. stainless steel packed with 3% Dexsil 300 on Gas-Chrom Q, 100-120 mesh.

Chemicals

Imipramine hydrochloride was a gift from Ciba-Geigy, Copenhagen, Denmark. N-Chloromethylimipraminium chloride and N- β -chloroethylimipraminium chloride were prepared as described in ref. 7. N-Methylimipraminium iodide was prepared by methylation of IP with methyl iodide dissolved in chloroform. All other chemicals used were of analytical grade.

High-performance liquid chromatography (HPLC)

The column (150 × 4.65 mm I.D.) was packed with LiChrosorb SI 60, 5- μ m particles, using a 2% slurry in methanol and a pressure of *ca.* 44 MPa generated by a Haskel pump 28646-4. When operated at ambient temperature with the mobile phase methanol-4 M ammonium formate (100:1.3) at a flow-rate of 1.0 ml/min, the column had 6400 theoretical plates, determined with IP, k' (capacity ratio) = 2.0.

RESULTS AND DISCUSSION

To find out to what extent a tertiary amine is transformed into quaternary ammonium compound(s), imipramine was treated with chloroform, dichloromethane and 1,2-dichloroethane. The results are shown in Table I. Chloroform from certain manufacturers contains small amounts of the very reactive bromochloromethane⁷. Therefore pure chloroform previously shown by GC⁷ to contain no bromochloro-

TABLE I
PERCENTAGE TRANSFORMATION OF IMPRAMINE INTO QUATERNARY AMMONIUM COMPOUND(S) WHEN 0.1% SOLUTIONS WERE REFLUXED OR STORED AT AMBIENT TEMPERATURE IN THE DARK

Temperature	Storage time	Solvent			
		CHCl ₃	CHCl ₃ + 0.04% CH ₂ BrCl	CH ₂ Cl ₂	CICH ₂ CH ₂ Cl
Ambient	1 day	—	0.5	10.1	3.9
	3 days	—	—	28.5	8.7
	6 days	—	1.4	58.0	17.9
	9 days	—	—	80.0	26.3
	20 days	1.0	4.0	—	—
	56 days	—	12.5	—	—
	4 years	29.5	—	—	—
Reflux	30 min	0.05	0.1	0.6	—
	60 min	0.1	0.2	1.5	—
	90 min	—	—	2.4	—
	120 min	0.2	0.5	—	—

methane and no dichloromethane was used, as well as chloroform with 0.04% of bromochloromethane added.

The amounts of quaternary compounds were determined by extraction of the organic phase with 0.01 *N* sodium hydroxide. The ultraviolet absorption of the aqueous phases were measured at 250 nm.

The results show that quaternization is fastest in dichloromethane. After *ca.* 45 min 1% of the IP is quaternized in the dichloromethane solution under reflux.

In order to find what products are formed during the reactions, the reaction mixtures were analyzed by TLC and by HPLC (Fig. 1). By analyzing the organic phase prior to and after the extraction with 0.1 *N* sodium hydroxide it was determined what peaks were possibly due to quaternary ammonium compounds, as these would be extracted to the aqueous phase.

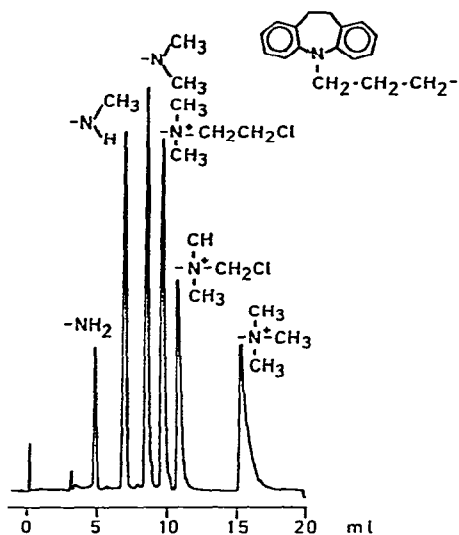


Fig. 1. Separation of imipramine and some of its derivatives on silica with methanol-4 *M* ammonium formate (100:1.3) as the mobile phase.

The reaction mixtures in chloroform and dichloromethane contained the same four components (Table II) (even after storing the chloroform solution for 4 years), and two of these were assumed to be quaternary ammonium compounds.

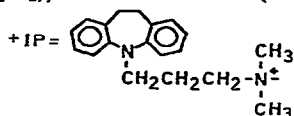
The two lipophilic compounds were found to be DMI and IP by GC-MS analysis. The two hydrophilic compounds were isolated by semi-preparative HPLC using the analytical system. The two components were shown by nuclear magnetic resonance spectroscopy and field desorption MS to be salts of the *N*-chloromethylimipraminium ion and the *N*-methylimipraminium ion.

The reaction mixture in 1,2-dichloroethane contained *N*- β -chloroethylimipraminium ions and a small amount of an unidentified quaternary ammonium compound. The reaction in 1,2-dichloroethane was not investigated any further.

The solvents in the reaction mixtures were analyzed by GC. No changes in the solutions in dichloromethane and 1,2-dichloroethane were seen. The reaction mixture

TABLE II

PRODUCTS OF THE TREATMENT OF IMPRAMINE WITH DICHLOROMETHANE (CH_2Cl_2), CHLOROFORM (CHCl_3) AND 1,2-DICHLOROETHANE ($\text{ClCH}_2\text{CH}_2\text{Cl}$)



Reagent	Reaction product				
	DMI	$\text{ClCH}_2\text{-}^+\text{IP}$	$\text{CH}_3\text{-}^+\text{IP}$	$\text{ClCH}_2\text{CH}_2\text{-}^+\text{IP}$	Other
CH_2Cl_2	+	+	+	-	-
CHCl_3	+	+	+	-	-
$\text{ClCH}_2\text{CH}_2\text{Cl}$	(+)	-	-	+	+

in chloroform showed that dichloromethane is formed when IP is added. To find out whether this was due to the amine or to the sodium hydroxide present during the extraction procedure, 0.1% solutions of triethylamine in the same three haloalkanes were analyzed similarly. Again formation of dichloromethane in chloroform was seen, while no change in the solutions in dichloromethane and 1,2-dichloroethane could be detected by this method.

The routes of reaction were investigated by heating the different compounds in acetonitrile as shown in Table III. It is seen that DMI is formed by degradation of N-chloromethylimipraminium chloride, and that the N-methylimipraminium salt is formed by methylation of IP with the N-chloromethylimipraminium ion as the methylating reagent.

TABLE III

REACTION PRODUCTS FORMED BY HEATING SOLUTIONS AT 80°C FOR 1 h

P = parent compound.

1% solutions in CH_3CN	Reaction product					
	DMI	IP	$\text{ClCH}_2\text{-}^+\text{IP}$	$\text{CH}_3\text{-}^+\text{IP}$	$\text{ClCH}_2\text{CH}_2\text{-}^+\text{IP}$	Other
IP	-	P	-	-	-	-
$\text{ClCH}_2\text{-}^+\text{IP}, \text{Cl}^-$	+	-	P	-	-	-
$\text{CH}_3\text{-}^+\text{IP}, \text{I}^-$	-	-	-	P	-	-
$\text{ClCH}_2\text{CH}_2\text{-}^+\text{IP}, \text{Cl}^-$	-	-	-	-	P	+
$\text{IP} + \text{ClCH}_2\text{-}^+\text{IP}, \text{Cl}^-$	+	P	P	+	-	-
$\text{IP} + \text{CH}_3\text{-}^+\text{IP}, \text{I}^-$	-	P	-	P	-	-
$\text{IP} + \text{ClCH}_2\text{CH}_2\text{-}^+\text{IP}, \text{Cl}^-$	-	P	-	-	P	+

N- β -Chloroethylimipraminium chloride is unable to methylate IP. The unknown compound formed in this case is also formed by heating N- β -chloroethylimipraminium chloride alone.

On basis of this the reaction scheme in Fig. 2 is suggested for the reaction between dichloromethane and IP.

Bisquaternization, which has been reported by some authors^{1,8}, was not observed in any case.

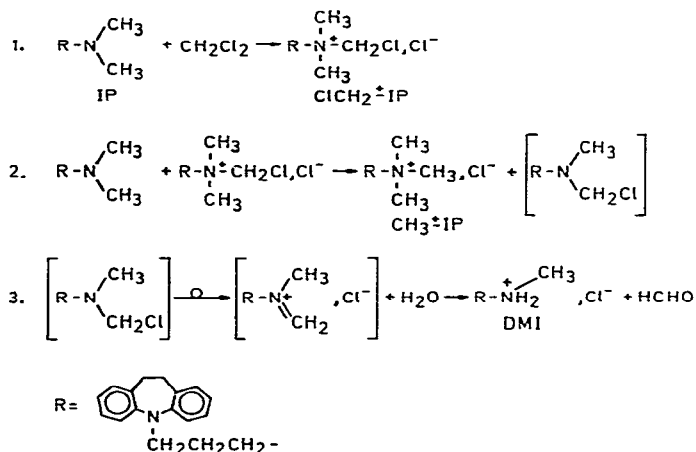


Fig. 2. The suggested reactions of imipramine in dichloromethane.

CONCLUSIONS

Dichloromethane and 1,2-dichloroethane should be used only with due care as solvents and extractants for tertiary aliphatic amines, and solutions should under no circumstances be stored. Solutions of tertiary aliphatic amines in chloroform should not be stored for long periods. The final analytical results may otherwise be invalidated depending of the method of measurement (e.g. chromatography).

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