CHAPTER III

EXPERIMENTAL

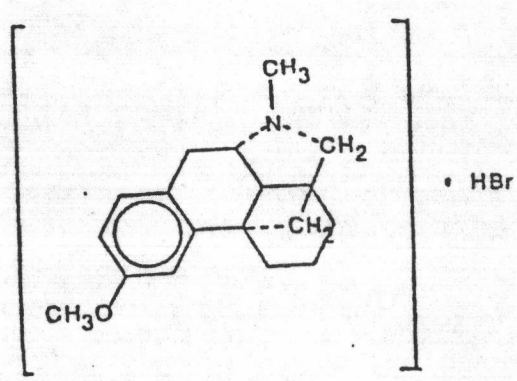
Equipments

1. Potentiograph E536 (Metrohm Herisau)
2. Glass electrode AG9100 (Metrohm Herisau)
3. Calomel electrode AG9100 (Metrohm Herisau)
4. 655 Multi-dosimat (Metrohm herisau)
5. Automatic titrator
6. Exchange unit model 3005 (501)
7. Magnetic stirrer E649 (Metrohm herisau)

Materials

Weak acidic drugs for this investigation are supplied from CHEW BROTHER & Co..

1. Dextromethorphan hydrobromide (Marsing, Denmark)



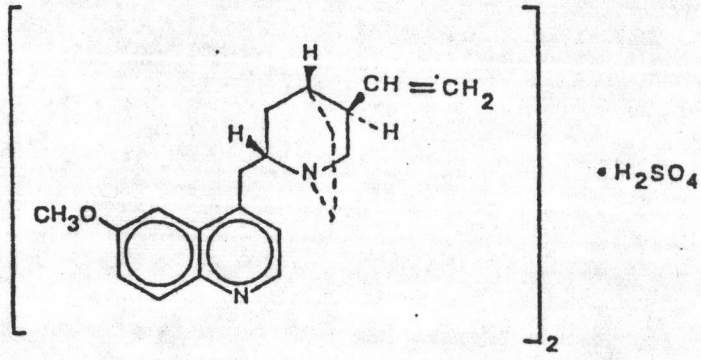
$C_{18}H_{25}NO \cdot HBr$: MW 352.31

Dextromethorphan HBr is d-form hydrobromide of racemethorphan. Occurs as the monohydrate, crystal, mp 122-124 °C, pKa 8.3

Solubility (25) : Approximately soluble in water 1.5% at 25°C. Solubility (w/w) 25% in 95% alcohol, 10% in glycerol. Soluble in propylene glycol, chloroform. Practically insoluble in ether.

pH of 1% aqueous solution : 5.2-6.5

2. Quinine sulfate (Marsing, Denmark)



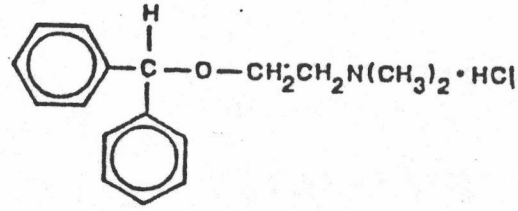
$C_{40}H_{50}N_4O_8S$: MW 746.93

pKa : 8.8

Solubility (26) : One gram dissolves in 810 ml water, 32 ml boiling water, 120 ml alcohol, 10 ml alcohol at 78 °C. Slightly soluble in chloroform, ether but freely soluble in propylene glycol. Aqueous solutions are neutral to litmus,

pH of saturated solution 6.2.

3. Diphenhydramine hydrochloride (Marsing, Denmark)

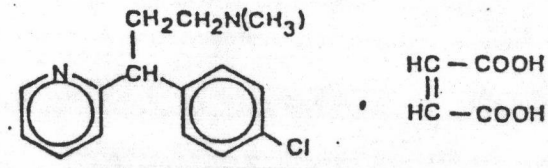


$C_{17}H_{21}NO \cdot HCl$: MW 291.82

pKa : 9.0

Solubility (27) : One gram dissolves in 1 ml water, 2 ml alcohol, 2 ml chloroform, 50 ml acetone. Very slightly soluble in benzene, ether. pH of 1% aqueous solution about 5.5

4. Chlorpheniramine maleate (Marsing, Denmark)

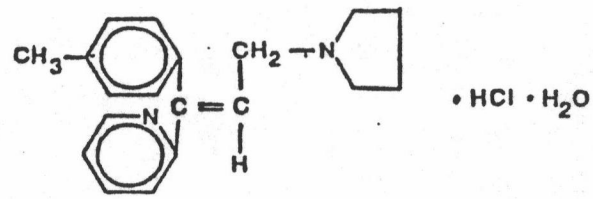


$C_{16}H_{19}ClN_2C_4H_4O_4$: MW 390.87

pKa : 9.1

Solubility (28) : One part dissolves in 3.4 parts water, in 10 parts alcohol, in 10 parts chloroform. Slightly soluble in benzene, ether. pH of 2% aqueous solution about 5

5. Triprolidine hydrochloride (Marsing, Denmark)



$C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$: MW 332.87

pKa : 6.5

Solubility (29) : Moderately soluble in water, ethanol, methanol.

Solvents and other reagents

1. Methanol AR (E-Merck lot#708K4184709) (30)

MW : 32.04, Density at 25°C : 0.7866, pKa (31) : 15.5 at 25°C, pKs (32) : 16.7 at 25 °C, ε(21) : 32.63 at 25°C. Miscible with water, ethanol, ether, benzene, ketone and most other organic solvents.

2. Ethanol (E-Merck lot#645K3324383) (33)

MW : 46.07, Density of 95% ethanol at 25°C : 0.810, pKa (31) : 15.5 at 25°C, pKs (32) : 19.1 at 25°C, ε (21) : 24.3 at 25°C. Miscible with water and with many organic liquids

3. Propylene glycol (Vidhyasom, lot#003229) (34)

MW : 76.09, dl-Form, Hygroscopic, viscous liquid, density at 25 °C : 1.036, pKa (31) at 25 °C : 15.1, pKs (32) : 17.2 at 25 °C, $\mathcal{E}$ (21) : 32.0 at 25 °C. Miscible with water, acetone, chloroform. Soluble in ether

4. Potassium hydrogenphthalate AR (E-Merck, lot#2430379)

5. Sodium hydroxide AR (Vidhyasom Co., LTD., lot#000328)

6. Potassium chloride AR (E-Merck, lot#1398804)

7. Glacial acetic acid AR (E-Merck, lot#535K1080663)

8. Perchloric acid AR (E-Merck, lot#2445490)

9. Acetic anhydride (obtained from department of pharmaceutical chemistry, Chulalongkorn University)

10. Mercuric acetate AR (E-Merck, lot#CC400410)

11. Crystal violet (Chroma-Gesallschaft Schmid Gmbh & Co.,lot#TB345)

12. p-Naphthalbenzein (British Drug House, lot#3030650),

13. Distilled water.

Preparation of Sodium Hydroxide Standard Solution

Dissolved 10 gm of sodium hydroxide in 20 ml of carbondioxide - free water. The supernatant was decanted after precipitated sodium carbonate had settled out. 8 ml of this liquid was pipetted into 1 litre volumetric flask and then diluted with carbondioxide - free water to the volume. The solution of 0.1 N sodium hydroxide was standardized with potassium hydrogen phthalate and end point volume was determined by potentiometry (parallel tangents method).

Preparation of Potassium Hydrogenphthalate Standard Solution

Dissolved potassium chloride in the carbondioxide - free water, and diluted to give a final concentration 0.100 M

Dissolved potassium hydrogen phthalate, accurately weighed with suitable quantities to its molecular weight) to produce 0.005 M in the solution of 0.100 M potassium chloride in order to control ionic strength of solution, warmed if necessary to effect solution. Transfer 50.0 ml of this solution to a 100 ml beaker.

Preparation of Weak Acidic Drugs in Mixed Solvent

All weak acidic drugs were accurately weighed with suitable quantities to produce 0.005 M Dissolved

them with portion of distilled water, warmed if necessary to effect solution. Added the organic solvent (ethanol, methanol or propylene glycol) with suitable volumes (according to the percentage of organic solvents required in mixed solvents). Allowed the solution to room temperature and adjust to the volumes with distilled water. Tranfer 50.0 ml of this solution to a 100 ml beaker.

Titration of Weak Acidic Drugs with 0.1 N Sodium Hydroxide

Titrated 50.0 ml of weak acidic drugs solutions with 0.1 N sodium hydroxide standard solution. The electrode were submerged into titrated solution for 5 minutes prior to commencement of titration to assure that electrode were in equilibrium with a magnetic bar and magnetic stirrer after each addition of titrant and the pH value was measured when the equilibrium was reached.

Non-aqueous Titration

Weak acidic drugs were titrated in non-aqueous system as described in the United State Pharmacopoeia XX; triprolidine HCl (3), dextromethorphan HBr (35), quinine sulfate (4), chlorpheniramine maleate (36) and diphenhydramine HCl (37).

Determination of equivalence volumes

Equivalence volumes of the titration in mixed solvent were obtained from extrapolation of linear plots according to equation (11), (14) and (20). The variables to be calculated and plotted were shown in Table 1. Computer programs, as shown in appendix,were employed for the calculations and the extrapolations were obtained from linear regression method.

Percentage purity of weak acidic drugs were calculated as followed:

$$\% \text{ purity} = \frac{Ve \times N \times Eq.wt.A \times 100}{Wt.A}$$

where Ve was end point volume (ml)

N was normallity of titrant (meq/ml)

Eq.wt was eqivalence weight of sample A (mg/meq)

Wt.A was weighed of sample A (mg)

Table 1 Expression of Variables in Gran's Plot

Function Plotted	Variables	
	Y-axis	X-axis
1. Monoprotic acid		
1.1 Before equivalence point	$G[H^+]$	G
	$V[H^+]$	V
1.2 After equivalence point	$KwVt/[H^+]$	V
2. Diprotic acid		
2.1 Before 1st equivalence point	$G[H^+]$	G
	$V[H^+]$	V
2.2 Before 2nd equivalence point	$[H^+](G-Ve_1N)$	G
	$[H^+](V-Ve_1)$	V
2.3 After equivalence point	$KwVt/[H^+]$	V

Note : * $G = VN + (V + Vo)\{[H^+] - [OH^-]\}$

Table 2 Selected pKa Values of Weak Acidic Drugs

Weak Acidic Drugs	pKa (38)
Triprolidine Hydrochloride	6.5
Dextromethorphan Hydrobromide	8.3
Quinine Sulfate	8.8
Diphenhydramine Hydrochloride	9.0
Chlorpheniramine maleate	9.2