DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(1), 61-75 (1980)

Solubility Studies of Certain 2,3 Quinolino - Phthalides

by

Fotios M. Plakogiannis,* Christos Iordanides, and Cathy Siskali-Kioulafa

*Research and Clinical Pharmacokinetics Laboratory of
Arnold & Marie Schwartz College of
Pharmacy and Health Scinces - LIU
75 DeKalb Avenue
Brooklyn, New York 11201

Abstract: The solubilities of five derivatives of 2,3 quinolino-phthalides in distilled water and in potassium chloride solutions of varying ionic strength was determined at 25°, 37°, and 51°C. The solubilities were lower in potassium chloride solutions: the over-all "salting out" coefficients were calculated for the effects of potassium chloride using the empirical Setschenow equation

$$\log \frac{S_o}{S} = KC$$

The differential heats of solutions ranged from 2kcal/mole to 7.5 kcal/mole and were determined from the slopers of the semi-logarithmic plots of the solubilities versus the reciprocal temperatures. The effect of the functional groups on the water solubilities of these compounds will be discussed.

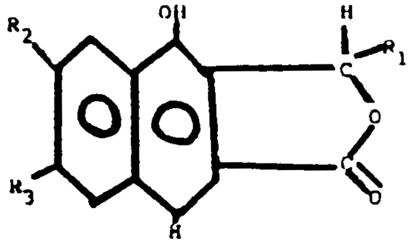
The solubilities in water of many organic compounds are reported in such general terms as "slightly soluble" or "very slightly soluble".

However, knowledge of solubilities in more precise terms, based on quantitative measurements of saturated solutions is of great pharmaceutical importance because it can influence the preparation of liquid formulations, the chemical stability, the pharmacokinetic profiles of drugs, etc. Therefore, the solubility-temperature dependencies in single aqueous systems, the effects of the ionic strength on the solubility and the heat of solutions of 2,3 quinolino-phthalide derivatives (Table 1) were evaluated.

EXPERIMENTAL

Chemicals - The synthesis and purity of compounds I-V was obtained as previously reported (1). The dissolution media and reagents were the

TABLE I - 2,3 Quinolino-phthalide Derivatives



Compound	R_1	R_2	R_3
I	φ	H	CH_3
II	φ	H	H
III	CH_3	H	CH_3
IV	CH_3	H	H
V	CH_3	CH_3	H

purest grade commerically available and were not further purified. Distilled water was used exclusively in sample preparations.

Solubility Determinations - The solubility of each compound in distilled water and in 0.5, 1.0 and 2M potassium chloride solution was determined as a function of time and temperature in the following manner. Exact quantities of each compound was added into a 100 ml volumetric flask and q.s. to 100 cc with the appropraite dissolution medium. The flasks were mechanically shaken and then suspended in constant-temperature baths[1] maintained at 25° (± 0.1), 37°(± 0.1) and 51°(± .1) respectively. The bottles were mechanically shaken periodically and samples were withdrawn at specific times intervals up to 7 days. The absorbance[2] of each solution, relative to a blank and to a standard, was measured at the appropriate wavelengths (Table 2) for each dissolution media employed.

TABLE 2 - Wavelengths of the Five Compounds

Compound	Wavelength (λ)
I	268.5
II	248
III	335.5
IV	344
V	336

---

[1] Water-Bath Shaker. Etierbach Corporation, Ann Arbor, Michigan

[2] Bausch and Lomb Spectronic 200 UV

RESULTS AND DISCUSSIONS

Concentration plateaus were reached within 4 hours and the saturation equilibrium in water and 0.5M, 1N and 2N potassium chloride solutions are summarized in Table 3. The solubilities of the compounds I-V as a function of temperature in distilled water and in potassium chloride solutions of different ionic strengths are presented in Figures 1-5 and show an expected direct relationship between the magnitude of solubility and the temperature for each solvent at each temperature. The effect of electrolyte in the

TABLE 3 - Solubility of Compounds I-V in Dissolution Media (mcg/ml)*

Compound	Temperature	Distilled Water	Potassium Chloride		
			0.5	1	2N
I	25°C	13.0	9.3	5.4	2.8
	37°C	37.0	16.5	7.0	4.2
	51°C	63.0	27.5	13.0	7.5
II	25°C	33.0	26.5	3.1	5.5
	37°C	38.5	30.0	20.0	16.0
	51°C	46.5	38.5	29.0	26.5
III	25°C	58.0	28.0	16.0	6.0
	37°C	70.0	50.0	34.0	19.5
	51°C	87.5	69.5	61.5	36.0
IV	25°C	70.0	51.0	44.0	34.2
	37°C	93.0	71.5	62.2	51.0
	51°C	119.0	104.0	81.5	67.0
V	25°C	22.0	20.0	16.6	9.05
	37°C	35.0	30.3	26.0	11.8
	51°C	49.5	41.5	35.0	16.7

* Results represent the averages of three determinations

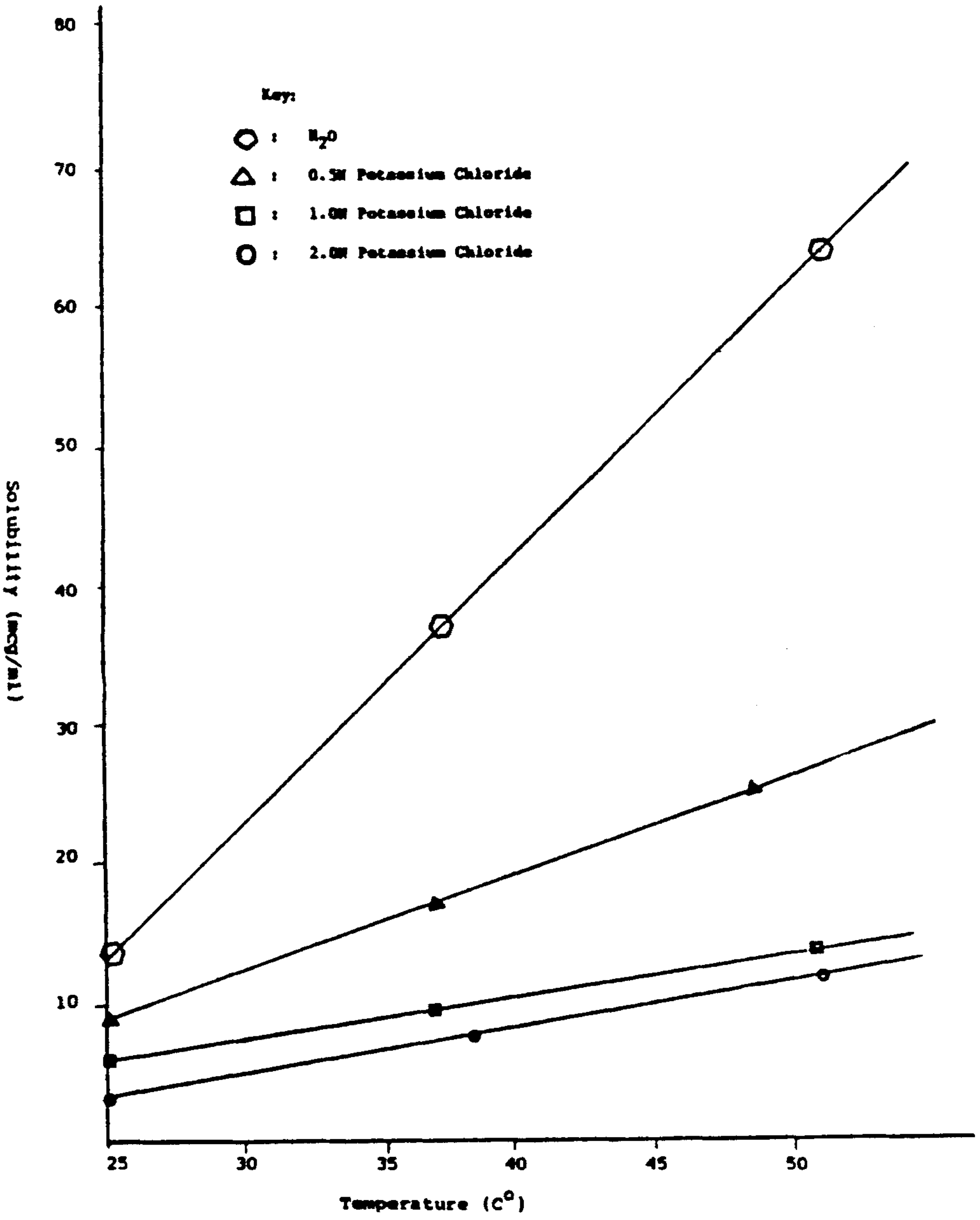


Figure 1: Solubility of compound I in dissolution media as a function of temperature

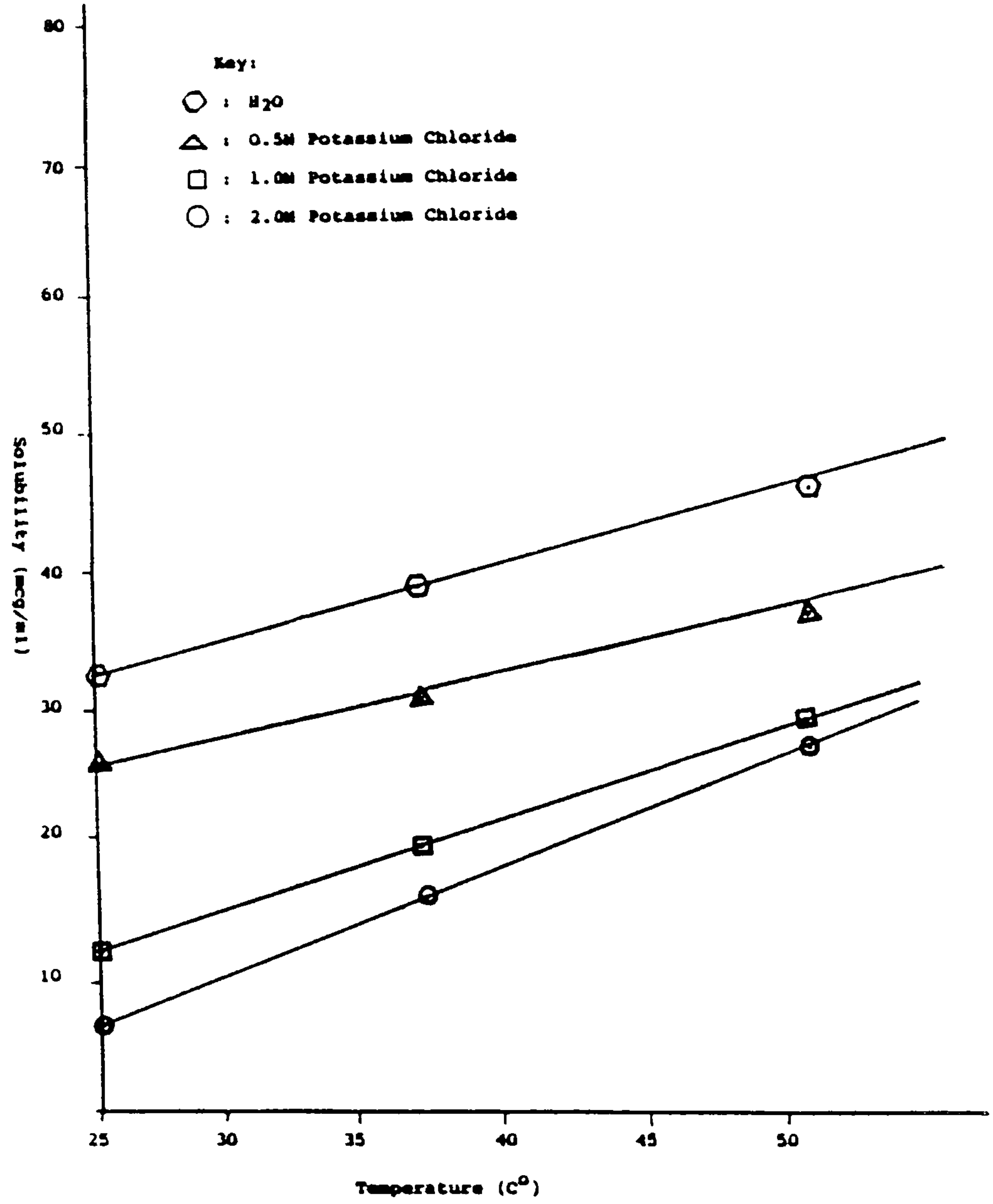


Figure 2: Solubility of compound II in dissolution media as a function of temperature

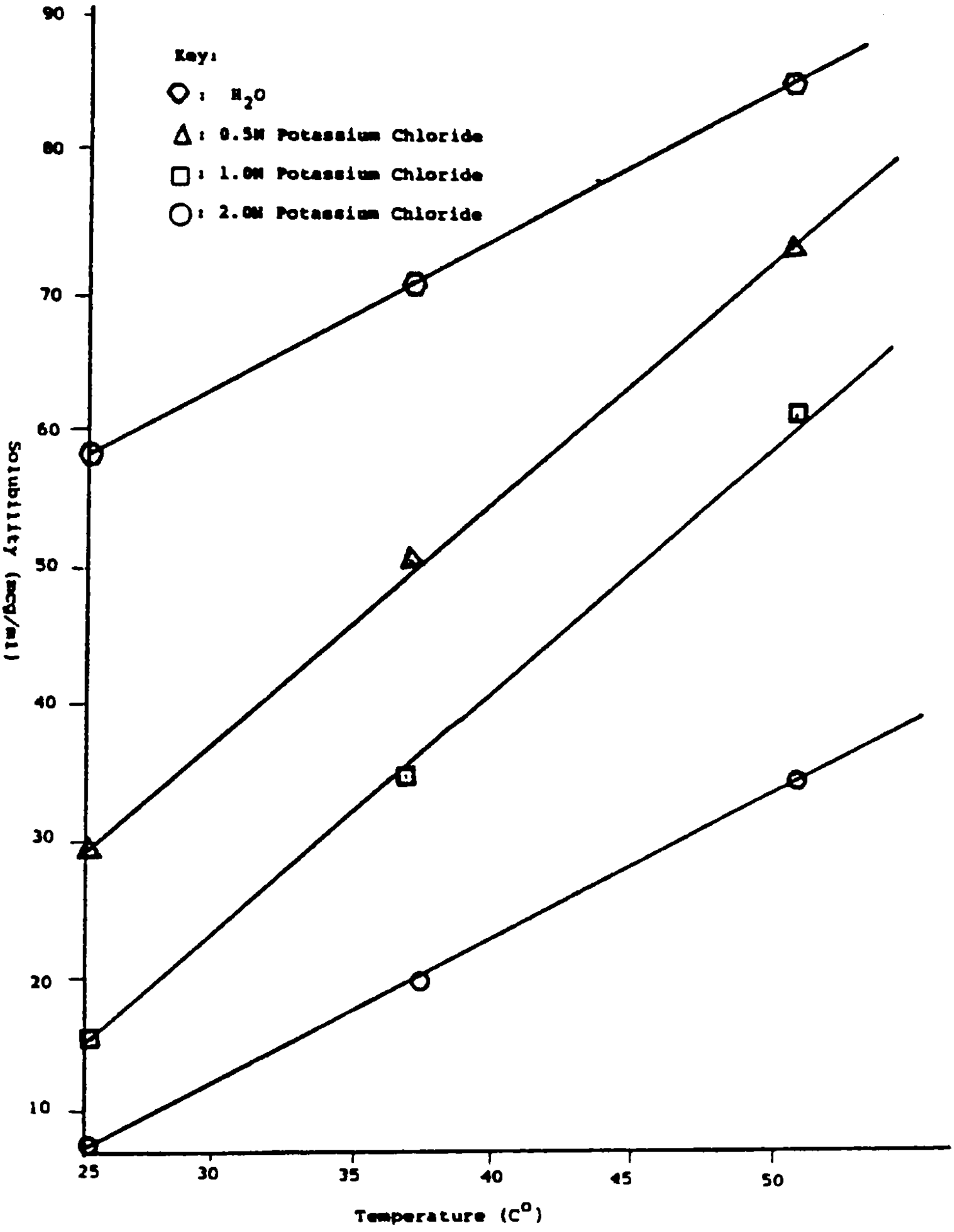


Figure 3: Solubility of Compound III in dissolution media as a function of temperature

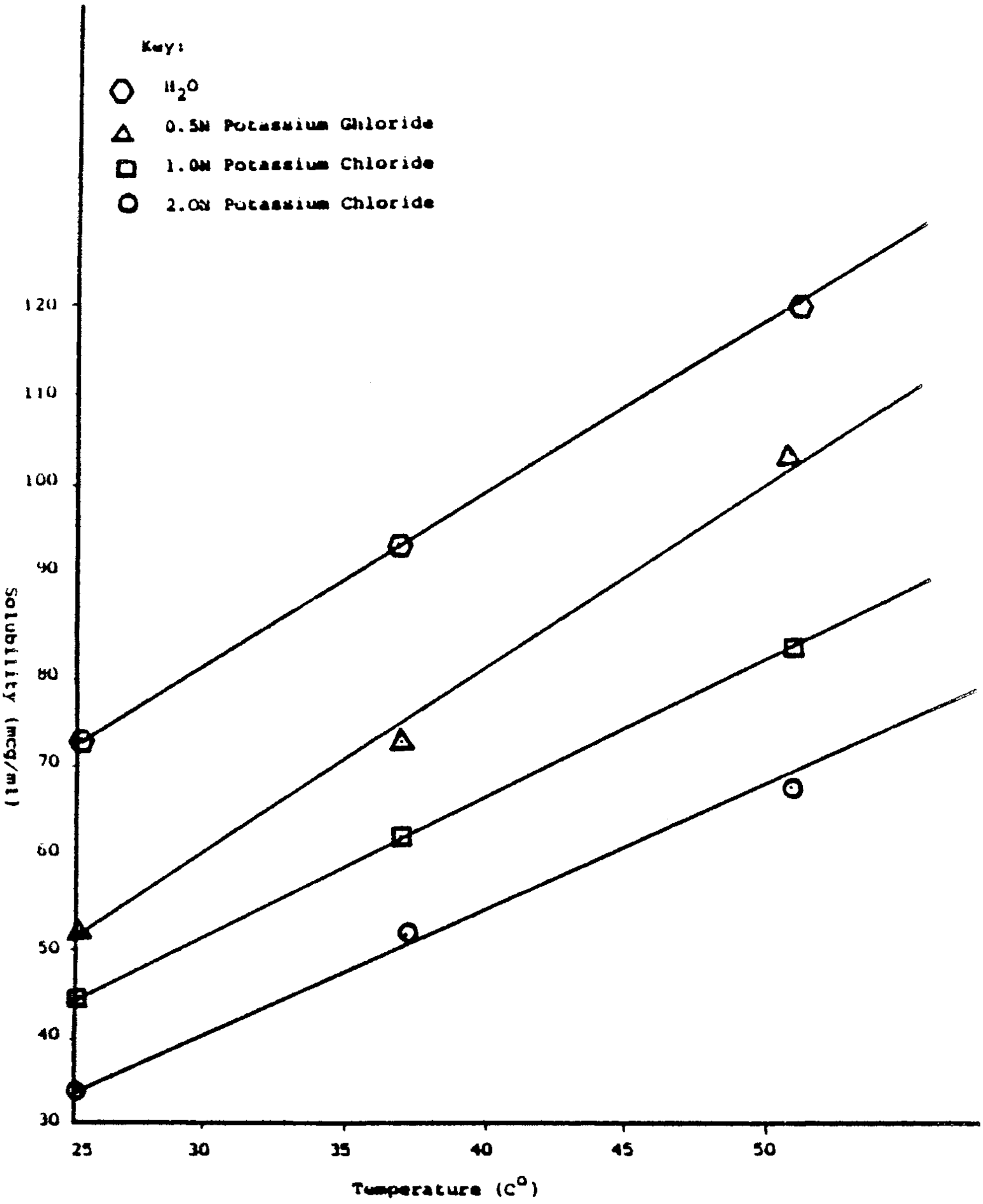


Figure 4: Solubility of compound IV in dissolution media as a function of temperature

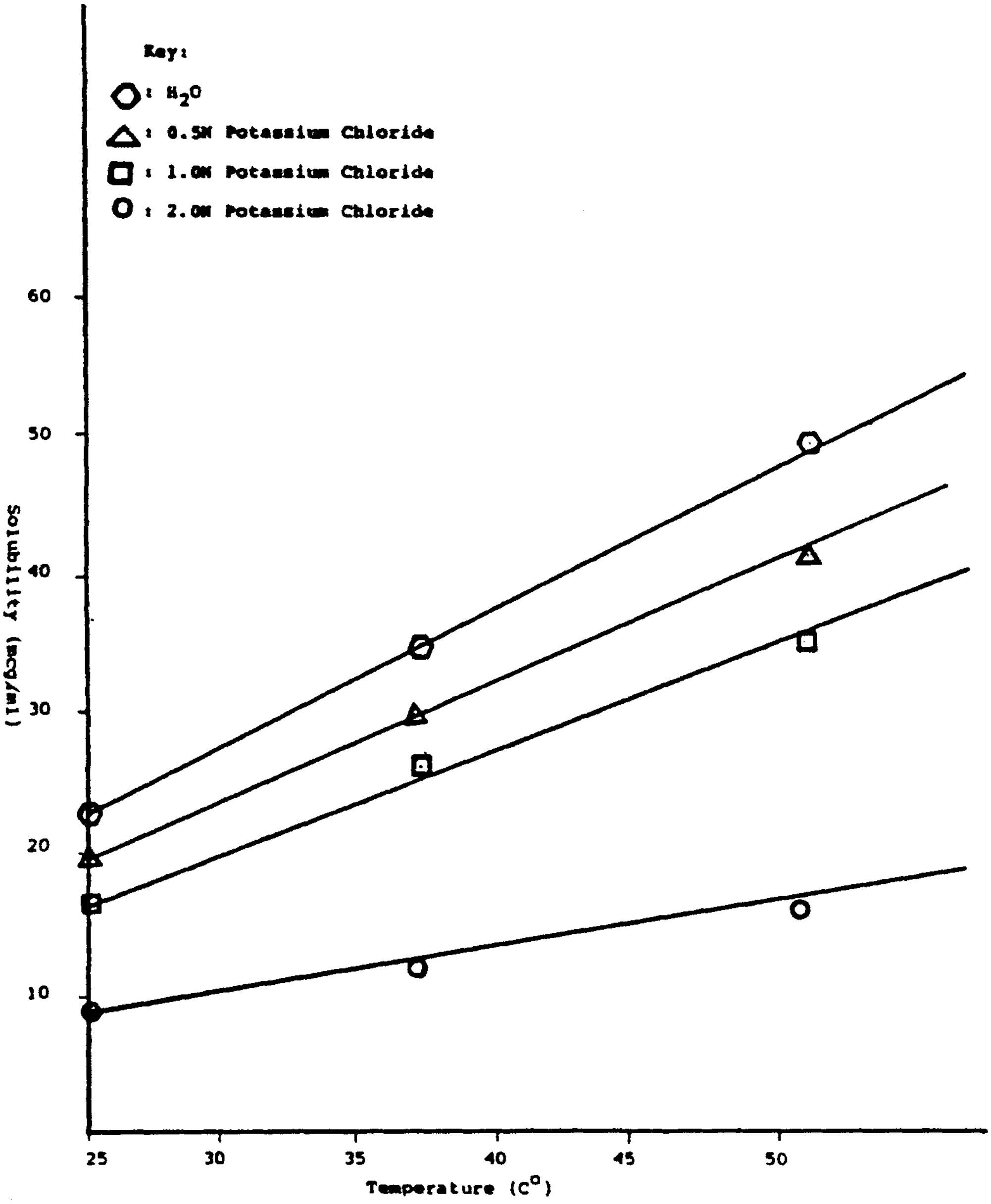


Figure 5: Solubility of compound V in dissolution media as a function of temperature

solubility of the compounds I-V at different temperatures is evident in Figure 6. It is apparent that a "salting out" phenomenon is taking place.

Setschenow (2) proposed an empirical relationship (Eq. 1) for the effect of an electrolyte on the solubility of a non-electrolyte:

$$\text{Log} \quad (S_0/S) = KC \qquad \text{(Eq. 1)}$$

where S_0 is the solubility of the non-electrolyte in pure solvent, S is the solubility of the non-electrolyte in an electrolyte solution of a given molar concentration C, and K is the "salting out" coefficient and is dependent upon the salt, the non-electrolyte, the solvent and the temperature.

The ratio S_0/S is equal to f, the activity coefficient of the non-electrolyte in the electrolyte solution.

Assuming that the Setschenow Equation is valid, a plot of log f versus C gives the over-all salting-out constant directly from the slope of the line; perhaps, these constants are more meaningful than individual constants calculated for each salt concentration. Accordingly, these over-all constants are presented in Table 4; a representative plot is given in Figure 7, from which it is apparent that the salting-out constants (K) are inversely proportional to the temperature.

It is apparent from Table 1 that compound IV had the greater water solubility than the other compounds and that the addition of a second methyl group in position 6 or 7 (III and V) decreased the water solubility as expected. Also, compound I with a benzyl group in the position of the methyl (R_1) showed the least solubility, whereas the removal of the methyl group from the 7-position (II) increased the water solubility. It is worth while to point out that the 6-methyl showed less water solubility than the 7-methyl which may be attributed to the greater electron density of the position of the quinoline ring.

The solubility temperature dependencies of compounds I-V are indicated in Table 5, while a representative plot is given in Figure 8. This figure

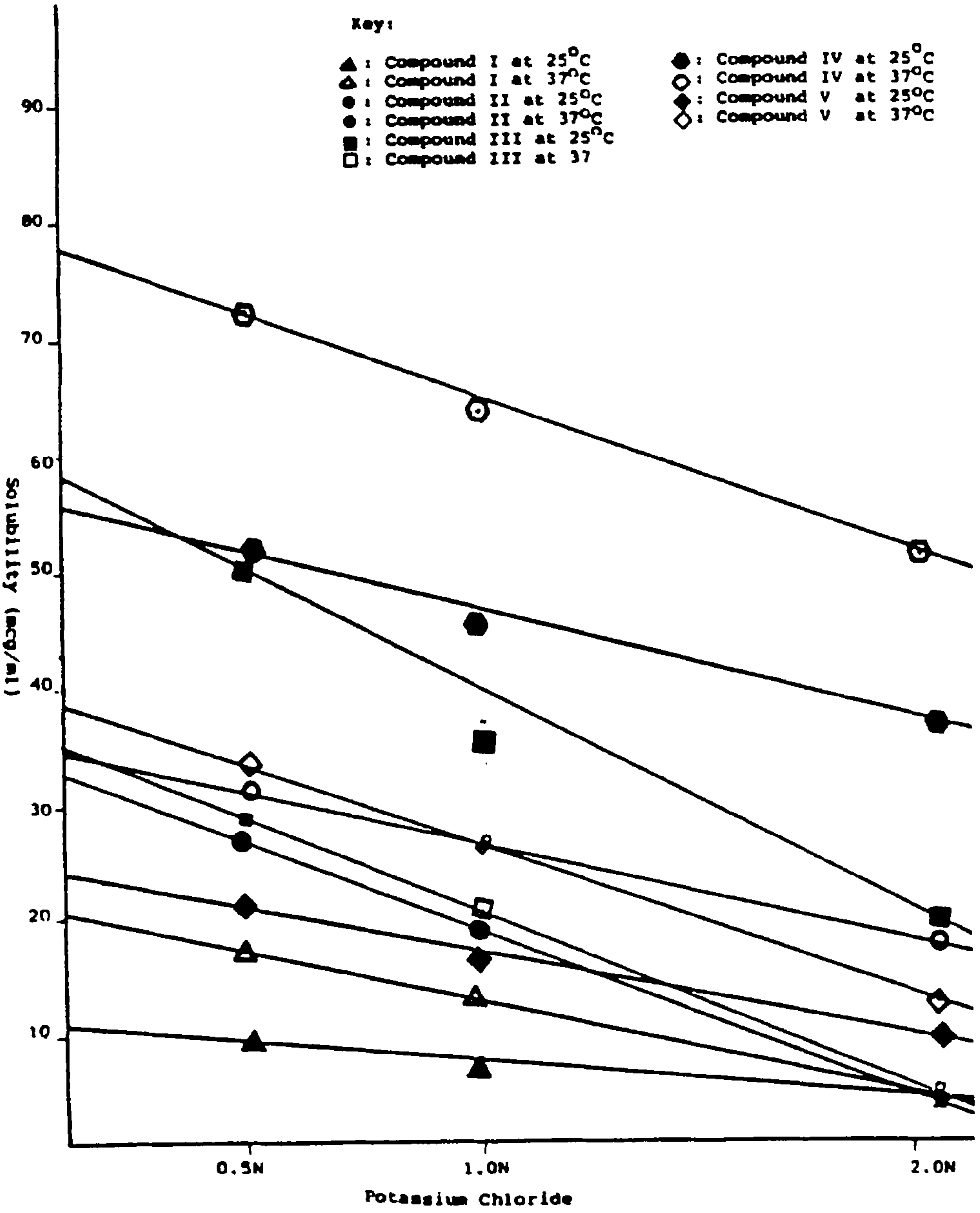


Figure 6: Effect of electrolytes in the solubility of the compounds I-V at different temperatures

TABLE 4 Salting Out Constants of Compounds I-V
at Different Temperatures

	Salting Out Constant		
Compound	25°C	37°C	51°C
I	0.49	0.40	0.29
II	0.42	0.16	0.01
III	0.45	0.30	0.19
IV	0.11	0.09	0.08
V	0.25	0.15	0.12

TABLE 5 Differential Heats of Solutions of Compounds I-V
in Dissolution Media

	Δ H-Solution Kcal mole^{-1}			
Compound	H_2O	0.5N KCl	1N KCl	2N KCl
I	7.04	6.54	6.10	5.72
II	2.20	2.00	1.85	1.70
III	2.20	2.00	1.85	1.70
IV	6.90	5.98	5.63	4.70
V	7.36	6.13	5.06	3.68

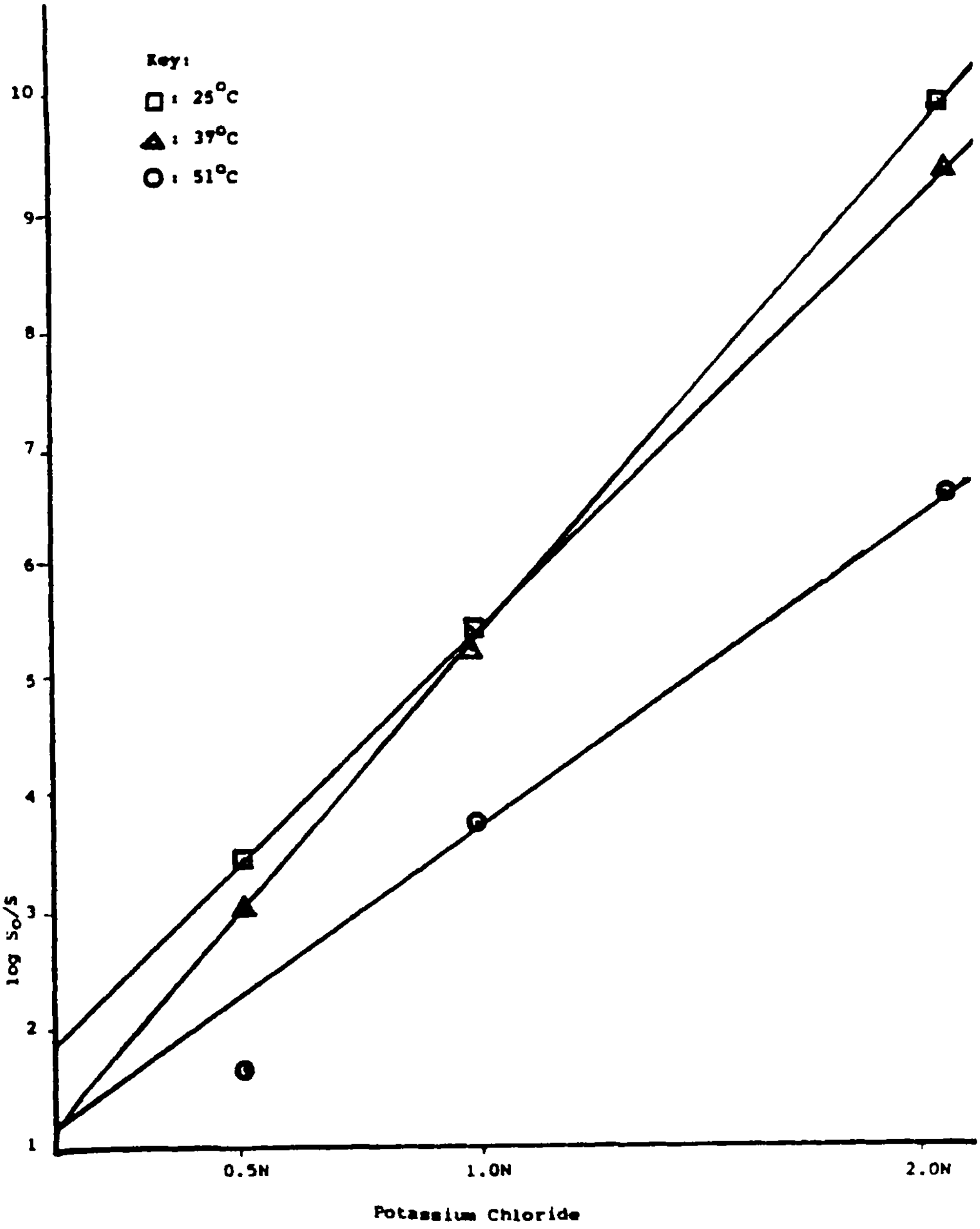


Figure 7: Dependence of K from temperature.

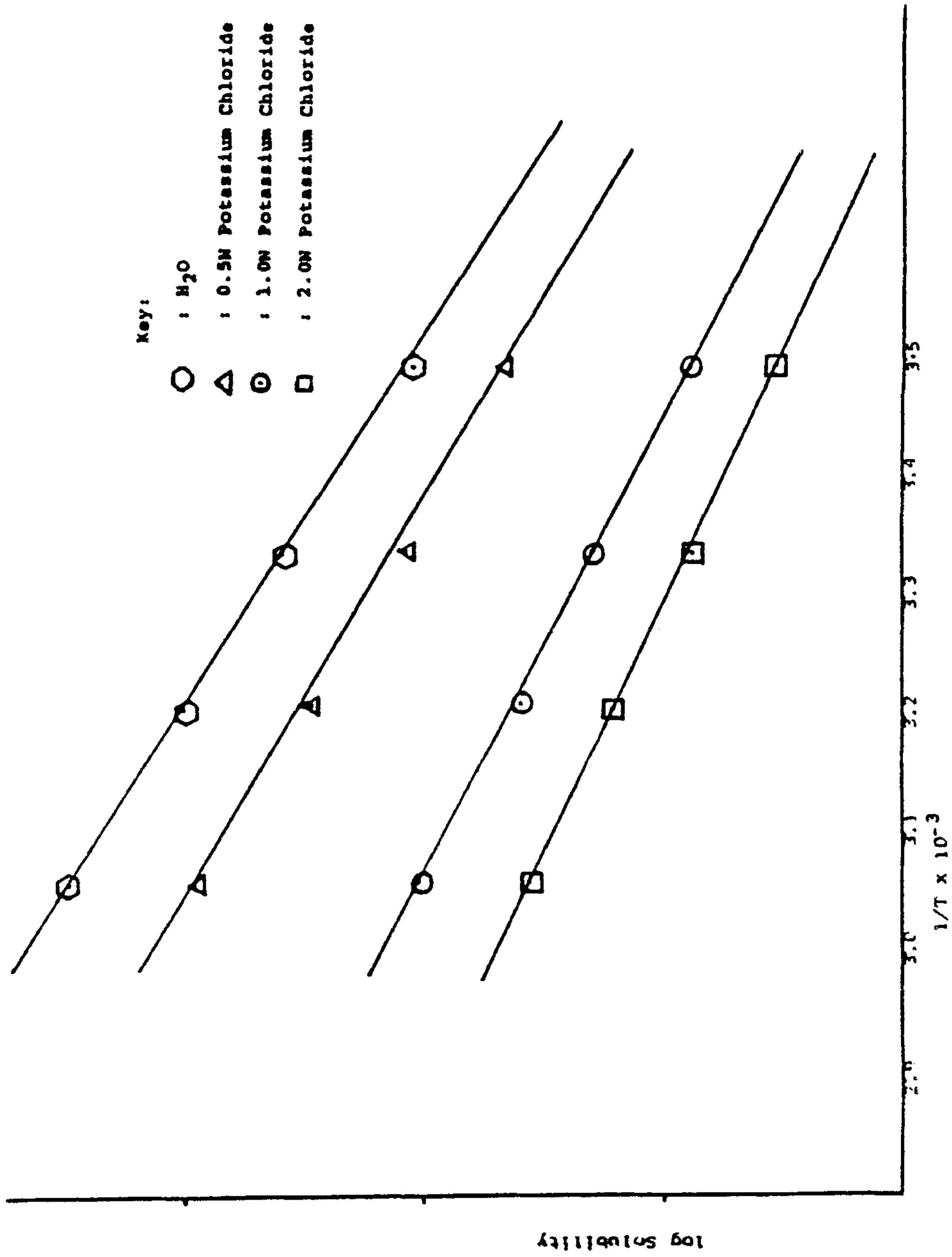


Figure 8: Log solubility of compound I versus reciprocal temperature

is a semilogarythmic plot of the solubilities against the reciprocal temperatures and their slopes yield the differential heat of solutions. Usually such curves are non-linear. However, in this case, over this limited temperature span, the plot appears linear and rough estimates of ΔH_s are possible, a phenomenon which was also observed by others, (2,3,4). These compounds have heats of solution in the 2-7.5 kcal/mole range as can be seen in Table 5.

ACKNOWLEDGEMENTS

It was presented at the 126th Annual Meeting of the American Pharmaceutical Association, Academy of Pharmaceutical Sciences Anaheim, California, April 20-27, 1979.

REFERENCES

1. C. Iordanidis and C. Siakali-Kioulafa: Tetrahedron. letter, in press.
2. K.S. Pitzer and L. Brewer, "Thermodynamics" 2nd ed. McGraw-Hill, N.Y.
3. R.I. Sedam, A.R. Cennaro and A. Osol, J. Pharm. Sci., 54, 215 (1965).
4. F.M. Plakogiannis and P. Catsovlatos, Acta Pharm. Helv. 51, 249 (1976).