

R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp. 396-400.

(3) K. C. Murdock, *J. Org. Chem.*, **33**, 1367(1968).

(4) K. Gulbins and K. Hamann, *Angew. Chem.*, **73**, 434(1961).

(5) M. L. Fielden, W. J. Welstead, and C. D. Lunsford, *Abstracts, 152nd National Meeting of the American Chemical Society*, New York, N. Y., 1966, p. 5P.

(6) W. I. Shuikin, A. D. Petrov, V. G. Glukhovtsov, I. F. Bel'skii, and G. E. Skobtsova, *Izvest. Akad. Nauk SSSR, Ser. Khim.*, **9**, 1682(1964).

(7) F. Sorm and Z. Arnold, *Coll. Czech. Chem. Commun.*, **12**, 444(1947); through *Chem. Abstr.*, **43**, 2988c(1949).

(8) A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, *Khim. Geterots. Soed.*, **1966**, 923.

(9) S. A. Morrell, U. S. pat. 2,424,184 (July 15, 1947); through *Chem. Abstr.*, **41**, P7411e(1947).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 22, 1968, from the *Research Laboratories, A. H. Robins Company, Inc., Richmond, VA 23220*

Accepted for publication September 18, 1968.

Solubility of the Parabens in Ethanol-Water Mixtures

ANTHONY N. PARUTA

Abstract □ The solubilities of *n*-alkyl parabens have been determined in binary mixtures of ethanol and water. The profiles showed a dielectric requirement value of about 29-32 for the subject compounds. The butyl derivative formed a two-phase system over a certain composition range of ethanol and water. These phases were analyzed and found to be approximately invariant with respect to the concentration of the three components indicating the formation of a solvate. The ratio of the solubility of these compounds relative to the methyl derivative is considered over the polarity range studied.

Keyphrases □ Paraben solubility—ethanol-water mixtures □ Dielectric requirements—parabens □ Dielectric constants—ethanol-water mixtures □ Polarity—paraben solubility

Previous studies on the *n*-alkyl esters of *p*-hydroxybenzoic acid have indicated cosolvency maxima at dielectric requirements (DR) (1, 4) of about 14 and 30 in a pure solvent scan and about 10 in dioxane-water mixtures (2). This study was conducted in order to substantiate the probable DR of 30 from previous work. The solvent system used, alcohol and water, provided a convenient span of dielectric constant values, *i.e.*, 24-78 and would also aid in the isolation of the solubility distribution curve in this dielectric constant range. Although a previous study utilized a solvent system encompassing the value expected, two liquid systems were formed over a wide range of composition (2).

EXPERIMENTAL

Reagents—The reagents used in this study have been previously given in recent studies (1, 2).

Procedures and Apparatus—The methodology used in determining solubility was by a gravimetric procedure which has been described previously (3). The results shown are the averages from at least three solubility runs over the total composition range.

RESULTS AND DISCUSSION

In Figs. 1 and 2 the solubilities of the parabens in milligrams per milliliter are plotted *versus* the dielectric constant of the respective

binary mixture used. As can be easily seen, the parabens show a dielectric requirement at a dielectric constant value of 30. This value substantiates the value of about 30 found for the pure solvent scan (1). It should also be noted that results are being compared utilizing the same concentration notation. The solubility profiles have been presented in the manner shown for convenience and ease of observation. For the first three members of this series of esters, a fairly linear curve is observed over a range of dielectric constants for these mixtures. This range of dielectric constants spans values of about 35-60, with slight differences in the slopes of the linear positions of these profiles. The slopes, *i.e.*, the rate of change in solubility in milligrams per milliliter per dielectric constant unit is summarized in Table I. It can be seen that as the magnitude of

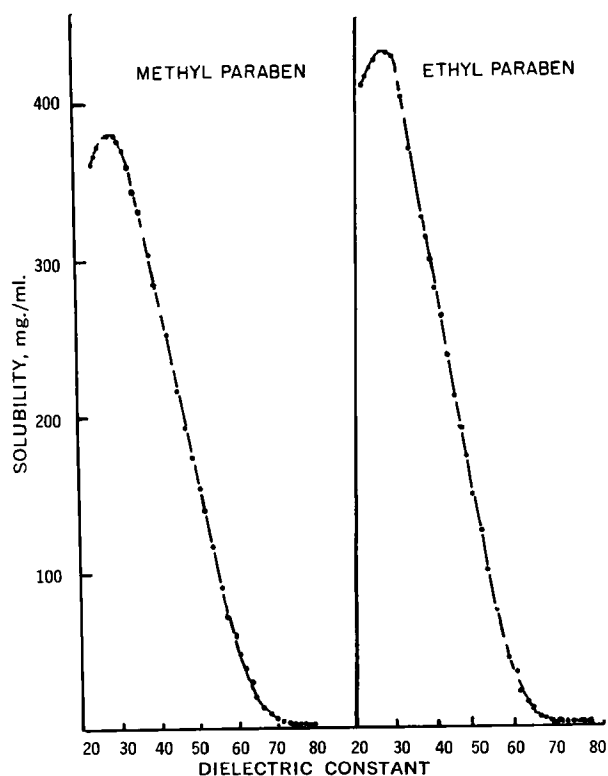


Figure 1—A plot of the solubility at 25° in mg./ml. for methyl and ethyl parabens versus the dielectric constant of the binary mixtures.

Table I—Rate of Change in Solubility for the Parabens as a Function of the Number of Carbons in the *n*-Alkyl Ester

| Paraben | No. of Carbons | Slope, mg./ml./Methylene Group |
|---------|----------------|--------------------------------|
| Methyl | 1 | 11.6 |
| Ethyl | 2 | 13.2 |
| Propyl | 3 | 16.0 |

solubility increases in going from methyl to propyl over the dielectric constant range of 24–50, the rate of change also increased in the same direction. At a dielectric constant value of 50, the magnitude of the solubility of methyl, ethyl, and propyl parabens has a common value of about 150 mg./ml.

It should be noted that the butyl derivative also shown in Fig. 2 is rather strongly deviated or is “out of step” with the other *n*-alkyl derivative. Butyl paraben also shows the formation of two liquid phases in equilibrium over a wide range of dielectric constants, *i.e.*, 39–65. The compositions of the two liquid phases is also shown in Fig. 2 and tabulated in Table II, where the molecular ratio is also shown. It might be presumed from these values that a solvate of butyl paraben is formed containing water and ethanol in equimolar quantities in this particular system or a ratio of 1:2:2.

In Fig. 3, the fraction or percent upper phase over the two-phase region for butyl paraben is plotted *versus* the composition of the binary mixtures. The positive slope indicates that the relative amount of upper phase increases as the water content of the binary mixture also increases. In this case, the upper less dense phase is mainly aqueous containing a very low content, *i.e.*, about 2 mg./ml., of butyl paraben and a content of alcohol equal to 20% by weight.

In order to contrast these solubility curves, the ratios of the solubility were considered defining methyl paraben as the base line or unity. In Fig. 4, the ratio of solubility of ethyl, propyl, and butyl paraben relative to the solubility of the methyl derivative is shown as a function of the dielectric constant or polarity. The solubility of the ethyl and propyl paraben at a dielectric constant value of about 50, and above this value the relative solubility of these derivatives is less. In other words, the relatively more polar methyl ester should

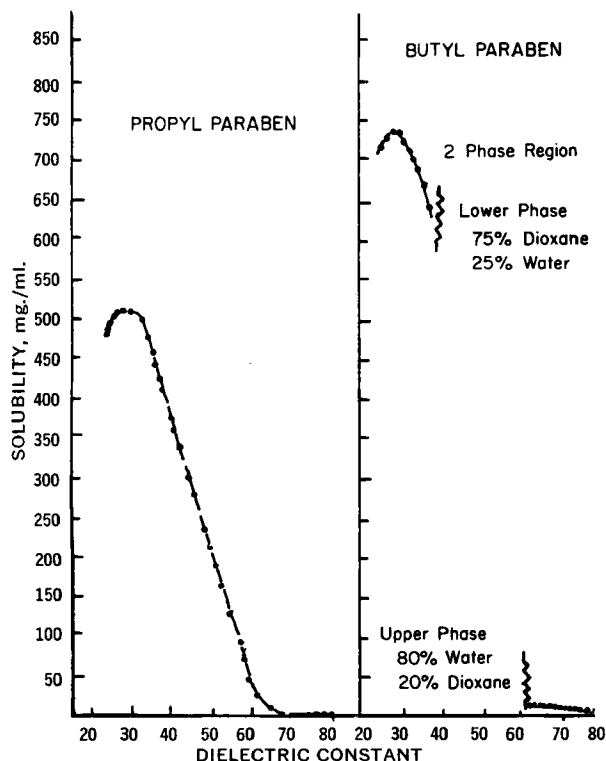


Figure 2—This plot parallels that shown in Fig. 1 for propyl and butyl paraben.

Table II—Concentrations, Solvent Composition, and Relative Numbers of Molecules for Butyl Paraben over the Range Where Two Liquid Phases Are Formed

| | Butyl | Alcohol | Water |
|--------------------------|-------|---------|-------|
| Concentration, o/o w/w | 61 | 28 | 11 |
| Solvent composition, o/o | — | 72 | 28 |
| Number of molecules | 1 | 2 | 2 |

have a higher solubility in highly polar solvents or at high dielectric constant values. As the polarity of the solvent is decreased by the addition of alcohol, the relatively less polar ethyl and propyl derivatives should possess higher solubility. The line drawn through the experimental points might be interpreted as the incremental change in solute polarity since the polarity shift in the solvent mixture is constant. Further, it is interesting to note the sigmoidal nature of the curves shown for ethyl and propyl paraben.

Butyl paraben, on the other hand, shows essentially parallel behavior relative to methyl paraben at low and high polarity. A

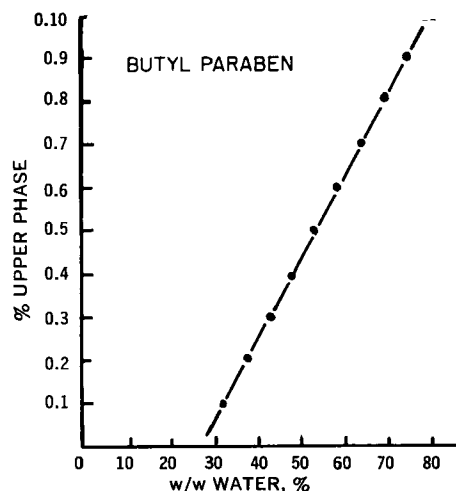


Figure 3—A plot of the phase volume ratio where the percent upper phase is shown versus the weight percent of water in the binary mixture.

dashed line has been drawn to indicate the most probable nature of the curve where true solutions formed over this polarity range. The butyl derivative again shows anomalous behavior relative to the first three members of this series. For the ethyl and propyl derivatives, however, at a dielectric constant value of about 50,

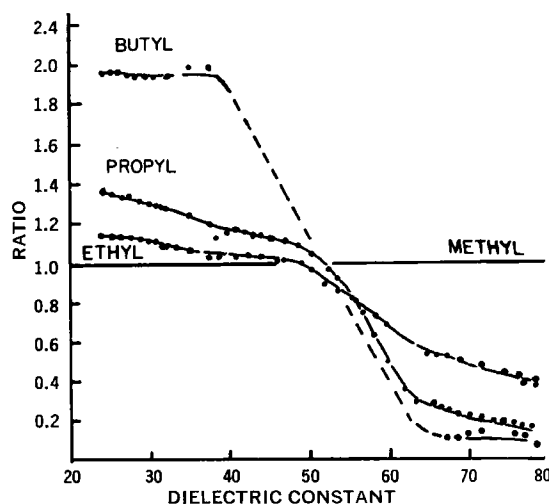


Figure 4—A plot of the ratio of the solubility of any given paraben relative to the solubility of methyl paraben versus the dielectric constant of the binary mixture.

the magnitude of the solubility is about the same and has a value of about 150 mg./ml. It can also be seen that over a narrow dielectric constant range of 49–53, which is referred to as an isodielectric point, the ratio of the solubility of these solutes is unity.

SUMMARY

Relative to the polarity of the solutes themselves it can be seen that the direction of polarity and magnitude of solubility is in the expected direction. Thus, the least polar butyl paraben has the greatest solubility in the least polar solvent mixture and vice versa. Methyl paraben, on the other hand, possesses the highest solubility in the most polar mixture, water, relative to the other members of this series. The observed nonparallelism in the case of ethyl and propyl parabens for the solubility ratio is due to the nature of the crossover solubility isotherms. The sigmoidal nature of these ratios is caused by the diminishing differences above and below the isodielectric point where the solubility curves diverge or are spread out. The magnitude of solubility for these materials can then be discriminated relative to each other where the polarity of the components of the binary mixture are sufficiently far apart.

A DR of 30 was found for these materials which substantiates the value estimated from the pure solvent scan (1).

Butyl paraben again shows anomalous behavior in these systems. This suggests the possibility of the butyl derivative in any series containing this group to be the cut-off point with regard to the periodicity of physical properties.

REFERENCES

- (1) A. N. Paruta, *J. Pharm. Sci.*, **58**, 204(1969).
- (2) *Ibid.*, **58**, 216(1969).
- (3) A. N. Paruta, B. J. Sciarone, and N. G. Lordi, *ibid.*, **53**, 1349(1964).
- (4) F. A. Restaino and A. N. Martin, *ibid.*, **53**, 636(1964).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 10, 1968, from the *College of Pharmacy, University of Rhode Island, Kingston, RI 02881*

Accepted for publication October 22, 1968.

Synthesis of Potential Hypolipidemic Agents

BIPIN B. CHAUDHARI

Abstract □ Derivatives of 2-(*p*-chlorophenoxy)-2-methylpropionic acid (I) and 2-(*p*-chlorophenylthio)-2-methylpropionic acid (II) have been synthesized for the purpose of studying their potential hypolipidemic activity.

Keyphrases □ 2-(*p*-Chlorophenoxy)-2-methylpropionic acid derivatives—synthesis □ 2-(*p*-Chlorophenylthio)-2-methylpropionic acid derivatives—synthesis □ IR spectrophotometry—structure □ NMR spectroscopy—structure □ Lipogenic activity determination—rat preputial glands

Hypocholesterolemic activity of ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate (III) in experimental animals was first reported by Thorp and Waring (1, 2) in 1962. Later, studies in humans (3, 4) showed that III possesses hypocholesterolemic as well as hypolipidemic activity. As far as hypolipidemic activity is concerned, III is capable of lowering serum triglycerides and plasma free fatty acids in humans (3–7). Recently, a group of workers at Merck and Company (8) reported that *N*-substituted amide derivatives of 2-(*p*-chlorophenoxy)-2-methylpropionic acid also exhibited good hypocholesterolemic activity with little or no undesirable side effects. Therefore, as a part of an effort to find new and potent hypolipidemic agents with a minimum of undesirable side effects, a number of compounds derived from 2-(*p*-chlorophenoxy)-2-methylpropionic acid (I) and 2-(*p*-chlorophenylthio)-2-methylpropionic acid (II) have been synthesized.

EXPERIMENTAL¹

Chemistry—Compounds I and II, and their respective acid chlorides IV and V, were prepared by the methods described in literature (9–12).

***N*-Furfuryl-2-(*p*-chlorophenoxy)-2-methylpropionamide (VI)**—To 2.90 g. (0.03 mole) furfurylamine previously cooled to 5°, 3.49 g. (0.015 mole) of IV was added dropwise with stirring over a period of 10 min. The reaction mixture was allowed to stand at room temperature for 20 hr. Then this mixture was poured onto 50 ml. of H₂O, and was extracted with 50 ml. of Et₂O. The Et₂O layer was washed with two 50-ml. portions of 5% NaHCO₃ solution and 50 ml. of H₂O. It was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give 3.50 g. of VI.

***N*-(β -Hydroxyethyl)-2-(*p*-chlorophenylthio)-2-methylpropionamide (VII)**—Reaction of V with 2-aminoethanol by the above procedure afforded VII.

2-(*p*-Chlorophenoxy)-2-methylpropionhydroxamic Acid (VIII)—A general method for converting an ester to a hydroxamic acid (13, 14) was used in this case. Thus, reaction of III² with hydroxylamine gave VIII.

3'-Hydroxy-4'-carboxy-2-(*p*-chlorophenoxy)-2-methylpropionanilide (IX)—This compound was obtained by the reaction of IV with *p*-aminosalicylic acid in THF in the presence of NaOH under similar reaction conditions as described in literature (8) for this type of amide.

***N*-Hydroxymethyl-2-(*p*-chlorophenoxy)-2-methylpropionamide (X)**—A suspension of 2.13 g. (0.01 mole) of 2-(*p*-chlorophenoxy)-2-methylpropionamide (11), 0.1 g. anhydrous Na₂CO₃, and 1.20 ml.

¹ All melting points are corrected and were taken with a Thomas-Hoover melting point apparatus. IR spectra were taken with Perkin-Elmer model 21 spectrophotometer. Elemental analyses were run by Clark Microanalytical Laboratory, Urbana, Ill. NMR spectrum was run with Varian A-60 spectrometer by Simon Research Laboratory, 164 Division Street, Elgin, Ill.

² Kindly supplied by Ayerst Laboratories, New York, NY 10017