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.

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Synthesis of Potential Hypolipidemic Agents

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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.

EXPERIMENTAL[1]

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 H_2O, and was extracted with 50 ml. of Et_2O. The Et_2O layer was washed with two 50-ml. portions of 5% $NaHCO_3$ solution and 50 ml. of H_2O. It was dried over anhydrous Na_2SO_4 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 III[2] 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 Na_2CO_3, and 1.20 ml.

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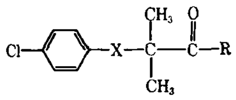
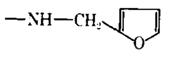
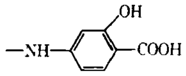
[1] All melting points are corrected and were taken with a Thomas-Hoover melting point apparatus. IR spectra were taken with Perkin-Elmer model 21 spectrophotometer. Elemental analyses were run by Clark Microanalytical Laboratory, Urbana, Ill. NMR spectrum was run with Varian A-60 spectrometer by Simon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

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

Table I—Derivatives of 2-(*p*-Chlorophenoxy)-2-methylpropionic Acid and 2-(*p*-Chlorophenylthio)-2-methylpropionic Acid



No.	X	R	Yield, %	Recrystn. Solvent	M.p., °C.	Anal., % Calcd.	Anal., % Found
VI	O		73	*n*-Heptane	62–63	C, 61.34 H, 5.45 Cl, 12.09 N, 4.76	61.13 5.58 12.05 4.73
VII[a]	S	—NH—CH_2CH_2OH	33	*n*-Heptane	63–64	C, 52.67 H, 5.85 N, 5.12	52.67 5.85 5.00
VIII	O	—NHOH	61	MeOH-H_2O	129–130	C, 52.30 H, 5.23 Cl, 15.46 N, 6.09	52.48 5.38 15.42 5.80
IX	O		29	MeOH-H_2O	178–179	C, 58.38 H, 4.58 N, 4.00	58.19 4.66 4.06
X	O	—NH—CH_2OH	82	Toluene	107–108	C, 54.23 H, 5.75 Cl, 14.57 N, 5.75	54.44 5.95 14.53 5.78
XI	S=O	—OH	61	EtOH	138–139	C, 49.10 H, 4.46 S, 12.99	48.93 4.38 13.39

[a] Structure confirmed by NMR spectroscopy.

(0.015 mole) of 37% formaldehyde solution was stirred and heated under reflux for 5 hr. After cooling to room temperature the desired product was isolated in a similar manner as described for Compound VI.

2-(*p*-Chlorophenylsulfinyl)-2-methylpropionic Acid (XI)—To a solution of 2.30 g. (0.01 mole) of II in 10 ml. Me_2CO was slowly added 5.70 g. (0.05 mole) of 30% H_2O_2. The reaction flask was tightly stoppered and kept at room temperature for 2 days. A white solid (1.80 g.) was precipitated from the reaction mixture.

Pharmacology—*Measurement of In Vitro Lipogenic Activity in Rat Preputial Glands*[3]—Lipogenic activity was measured by the method similar to that of Griesemer and Thomas (15). But, instead of a human skin, the authors have used rat preputial glands (16) as a model to study lipogenesis.In brief, the effect of test compounds on the incorporation of radioactive acetate into lipids by rat preputial glands was studied. Whole preputial glands (from which fatty fluid had been thoroughly expressed) from a given rat were employed as matched pairs with one as a control and other treated with a test compound. These glands were placed in a Krebs-Ringer phosphate buffer at pH 7.4 containing radioactive hydrogen as sodium acetate under an O_2 atmosphere at 37° for 3 hr. Initial concentration of 5×10^{-3} moles/l. of a test compound with 0.1% polysorbate 80[4] as an emulsifier was employed during incubation. The lipid obtained by solvent extraction after hydrolysis was assayed in a Packard scintillation counter.[5] Because of the limited studies, conclusive data on lipogenic activity of these compounds is not available at present. However, the studies do indicate that Compounds I, II, VII, and the oxygen analog of VII (12) were able to inhibit lipid biosynthesis (*in vitro*). While Compounds X and XI were found inactive as far as hypolipidemic activity was concerned, Compounds II, VII, and the oxygen analog of VII were found more potent in inhibiting lipid biosynthesis than Compound I.

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[4] Tween 80, Atlas Chemical Co., Wilmington, Del.

[5] Packard Instrument Co., La Grange, Ill.