Some Biological Properties of 2-(4-Isobutylphenyl)-propionic Acid

Sir:

We have previously described some of the biological properties of ibufenac (4-isobutylphenylacetic acid) (1), an anti-inflammatory, analgesic antipyretic compound, which subsequently has proved to be effective in the treatment of rheumatoid arthritis and other rheumatic diseases.

Since then we have prepared and investigated the biological properties of a large number of other substituted phenylalkanoic and alkenoic acids and derivatives. The highest pharmacological activity is found in substituted 2-phenylpropionic acids, and 2-(4-isobutylphenyl)-propionic acid, ibuprofen (British Pharmacopoeia Commission approved name), has been selected for further studies. Some of the properties of this compound are given below.

Ibuprofen, a colorless crystalline stable solid, m.p. 75–77°, is relatively insoluble in water, but readily soluble in most organic solvents.

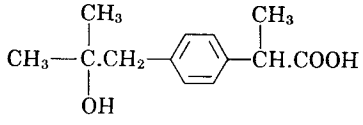
The anti-inflammatory, analgesic, and antipyretic potencies of this compound compared with ibufenac and acetylsalicylic acid are shown in Table I. Three of the experimental methods used have been described previously (1), the other is a modification of a mouse-writhing technique in which intraperitoneal acetylcholine was used as the writhing agent. In all tests the compounds were administered orally in 10% mucilage of acacia in graded doses. From the results in Table I it will be noted that ibuprofen is approximately 4 to 8 times more active than ibufenac.

TABLE I—ANTI-INFLAMMATORY, ANALGESIC, AND ANTIPYRETIC ACTIVITIES OF IBUPROFEN AND IBUFENAC AFTER ORAL ADMINISTRATION (ACETYLSALICYLIC ACID = 1)

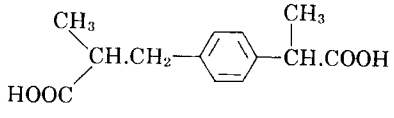
	Anti-Inflammatory Activity UV Erythema	Analgesic Activity—Mouse Writhing	Analgesic Activity—Inflamed Rat's Paw	Anti-pyretic Activity Yeast-Fevered Rat
Ibufenac	2–4	2	2–4	4
Ibuprofen	16–32	16–32	8–16	20

The resolution of ibuprofen has been effected with (−)-1-phenylethylamine, and no difference has been detected in the anti-inflammatory potency of the two enantiomorphs in the guinea pig ultraviolet erythema test. Shen and his colleagues (2), have however found in related compounds, *e.g.*, 2-(3-chloro-4-cyclohexylphenyl) propionic acid, that a large part of the anti-inflammatory activity resides in the *dextro* isomer.

The principal urinary metabolites of ibuprofen in man have been isolated and characterized by infrared and nuclear magnetic resonance spectra as I and II. It may be significant that both of these metabolites were found to be *dextro*-rotatory.



I



II

No appreciable species differences have been found in the blood level/time curves after single oral doses of ibuprofen. In the dog, rat, and guinea pig, peak levels of the drug occurred at or before 1.5 hr. When six healthy men took a dose of 200 mg. after overnight fasting, the mean plasma concentrations at 0.75, 1.5, 3, and 6 hr. were 15.0, 14.0, 7.4, and 2.3 mcg./ml., respectively. The amount of drug in the serum or plasma of animals was measured by the method previously described (3). The same method was used for human plasma, except that the amount of drug was assayed by thin-layer chromatography. Experiments in which the ^{14}C-labeled drug was administered orally to dogs indicated that ibuprofen is well absorbed. Clinical studies are in progress and will be reported later.

(1) Adams, S. S., Cliffe, E. E., Lessel, B., and Nicholson, J. S., *Nature*, **200**, 271(1963).
(2) Shen, T. Y., reported in *Chem. Eng. News*, **45** (7), 10(1967).
(3) Adams, S. S., and Cliffe, E. E., *J. Pharm. Pharmacol.*, **17**, 173(1965).

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Received August 17, 1967.
Accepted for publication September 14, 1967.