Notes

Synthesis and Pharmacological Evaluation of Poly(oxyethylene) Derivatives of 4-Isobutylphenyl-2-propionic Acid (Ibuprofen)

R. Cecchi, L. Rusconi, M. C. Tanzi,* F. Danusso,

Istituto di Chimica Industriale del Politecnico, Sezione Chimica Macromolecolare e Materiali, Piazza Leonardo da Vinci 32, 20133 Milan, Italy

and P. Ferruti

Istituto Chimico dell'Università, Via Mezzocannone 4, 80134 Naples, Italy. *Received June 30, 1980*

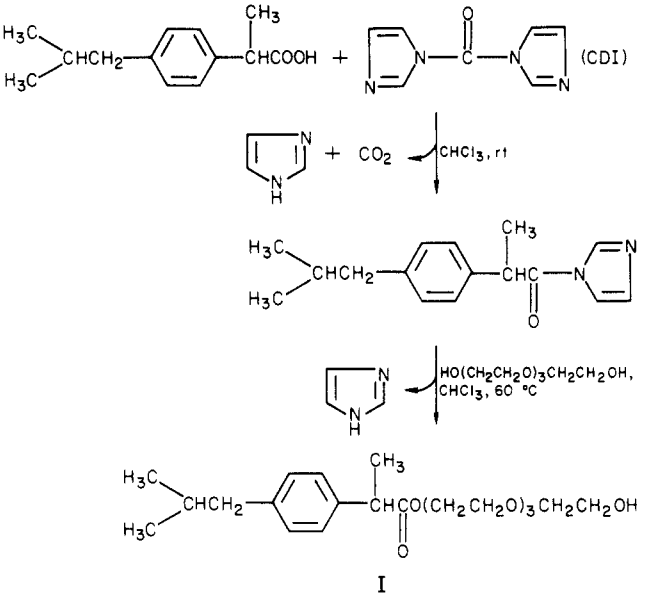
The synthesis of three oligomeric derivatives of 4-isobutylphenyl-2-propionic acid (ibuprofen), namely, the monoester of tetraethylene glycol (I) and the diesters of poly(oxyethylene) samples having molecular weights of 1000 (±50) and 2000 (±150) (II and III), has been performed via the imidazolide method. The antiinflammatory activity of I–III, and of equivalent amounts of free drug, was determined in the carrageenan-induced rat paw edema assay at different times after oral administration and found to be considerably prolonged in the case of the three derivatives. The lowest molecular weight derivative (I) also had an enhanced initial activity with regard to 4-isobutylphenyl-2-propionic acid. These results were confirmed by measuring the plasma levels of 4-isobutylphenyl-2-propionic acid in rats at different times after oral administration.

4-Isobutylphenyl-2-propionic acid (ibuprofen) is a well-known antiinflammatory drug, widely used in therapy.[1-3] The main disadvantages of 4-isobutylphenyl-2-propionic acid, and of other antiinflammatory drugs of similar structure, are a relatively short plasma half-life, resulting in a short activity duration, and a pronounced ulcerogenic potency.[3,4]

The preparation of polymeric drug adducts, in which active substances are linked to polymeric matrices by means of covalent bonds naturally hydrolyzable in the body fluids, is presently recognized[5-13] as an effective way to prolong the pharmacological activity, by a gradual release of the free drug from the macromolecular matrix. By this technique, unfavorable side effects can be minimized.[6-8]

In some instances, similar results can be obtained by reducing the matrix to an oligomeric size.[14-19] Poly(oxyethylenes) appear to be particularly convenient as oligomeric matrices, since they are easily available as fractions with well-defined molecular weights and they are known to have a good biocompatibility.[20]

Scheme I. Synthesis and Structure of the Monoester of 4-Isobutylphenyl-2-propionic Acid with Tetraethylene Glycol (I)



I

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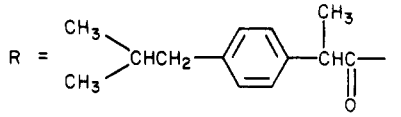
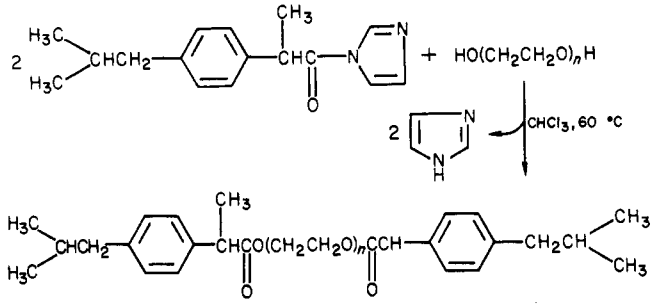
Table I. Chemical and Physical Data of Poly(oxyethylene) Derivatives of 4-Isobutylphenyl-2-propionic Acid (Ibuprofen)



compd	formula	anal.	drug,[a] % calcd	drug,[a] % found NMR	drug,[a] % found titration[b]	TLC R_f	TLC free drug[f]
I	R—O(CH_2CH_2O)$_3CH_2CH_2OH$	C, H	53.9	57	54.4[c]	0.8	absent
II	R—O(CH_2CH_2O)$_{20.3}$—R	C, H	29.9	25	27.3[d]	0.68	absent
III	R—O(CH_2CH_2O)$_{45.05}$—R	C, H	17.3	15	15.3[e]	0.47	absent

[a] Percent by weight of 4-isobutylphenyl-2-propionic acid which can be released by total hydrolysis. [b] No acidity (= free 4-isobutylphenyl-2-propionic acid) presence by alkaline titration before hydrolysis. [c] mequiv/g: calcd, 2.62; found, 2.64. [d] mequiv/g: calcd, 1.45; found, 1.32. [e] mequiv/g: calcd, 0.84; found, 0.74. [f] 4-Isobutylphenyl-2-propionic acid R_f = 0.78.

Scheme II. Synthesis and Structure of the Diesters of 4-Isobutylphenyl-2-propionic Acid with Poly(oxyethylenes) of M_r 1000 and 2000 (II and III)



II, n = 20.3
III, n = 45.05

The aim of this paper is to report on a way of synthesis and a preliminary evaluation of the pharmacological activity of three oligomeric derivatives of 4-isobutylphenyl-2-propionic acid (I, II, and III), in which the active principle is bound by ester bonds to the end groups of poly(oxyethylene) chains of different length (M_r 194, 1000 ± 50, and 2000 ± 150, respectively).[21]

Chemistry. The derivatives synthesized in the present work are listed in Table I. They were prepared by reacting the imidazolide of 4-isobuthylphenyl-2-propionic acid with the appropriate poly(oxyethylene) fraction in chloroform solution. 4-Isobutylphenyl-2-propionic acid imidazolide was prepared, in turn, by reacting the acid with *N,N'*-carbonyldiimidazole (CDI). The reaction conditions were adjusted in order to obtain a monoester derivative in the case of I (Scheme I) and diester derivatives in the case of II and III (Scheme II).

Compounds I and II are viscous oils insoluble in water, but soluble in a variety of organic solvents; compound III is a low-melting solid freely soluble in water. All the compounds were characterized by NMR, IR, and TLC, as well as by titration after total hydrolysis with excess of standard alkalies.

Pharmacology. Antiinflammatory Activity. The antiinflammatory activity of I, II, and III was evaluated by the carrageenan-induced rat paw edema assay, using a modification of the method described by Winter et al.[22]

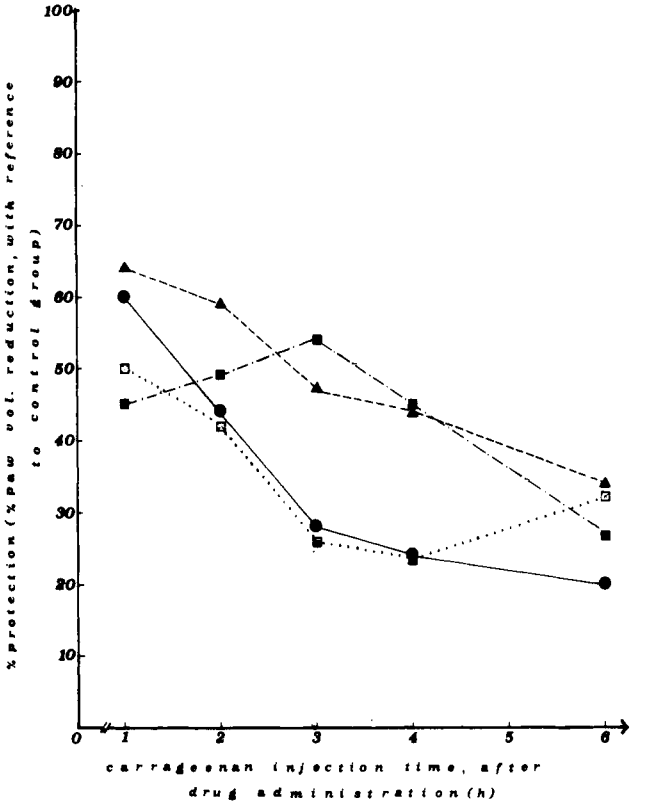


Figure 1. Male and female Wistar rats, weighing 160–200 g (12 for every compound and every measurement), fasted overnight, received 4 mL of water per os just before the subplantar injection of 0.05 mL of 1% carrageenan in saline. Ibuprofen (●–●, 100 mg/kg), MR 653 (▲–▲), MR 654 (■–■), and MR 655 (□–□), all in a dose corresponding to 100 mg/kg ibuprofen, were administered orally before carrageenan at the abscissa times. Paw volumes were measured 4 h after carrageenan injection and compared to those of a control group.

Two sets of experiments were performed. In type A experiments, the three derivatives and the free drug were orally administered (as suspensions in 0.5% gum-arabic solution) from 1 to 6 h before carrageenan injection, and the volume of the edema was measured by the plethismometric method described by Lence et al.,[23] 4 h after carrageenan. The results are shown in Figure 1.

Type B experiments were confined to I. This derivative was orally administered 1 h before carrageenan injection, and the edema volume was then measured at different times from 2 to 8 h after carrageenan. Two doses of I were

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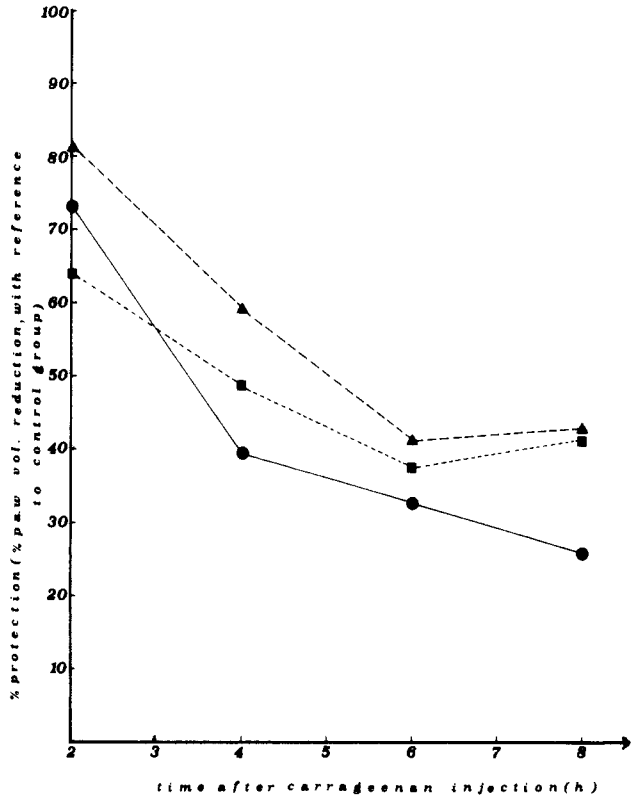

Figure 2. Twenty-eight male Wistar rats, weighing 130–150 g, fasted overnight, random assigned to four groups, received 4 mL of water per os just before the subplantar injection of 0.05 mL of 1% carrageenan in saline. Ibuprofen (●–●, 50 mg/kg), and MR 653 (▲–▲, dose corresponding to 50 mg/kg ibuprofen; ■–■, dose corresponding to 30 mg/kg ibuprofen) were administered orally 1 h before carrageenan injection. Paw volumes were measured at the abscissa times, after carrageenan injection, and compared to those of the control group.

tested, 1 equiv corresponding to the 4-isobutylphenyl-2-propionic acid ED_{50} and the other corresponding to 60% of the 4-isobutylphenyl-2-propionic acid ED_{50}. For comparison, some rats were treated with free 4-isobutylphenyl-2-propionic acid in a dose corresponding to its ED_{50}. The results are shown in Figure 2.

Both sets of experiments show that the oligomeric derivatives exhibit a more sustained action in the time after carrageenan injection compared with the free drug. Furthermore, the initial activity of I was considerably higher than that of an equivalent dose of 4-isobutylphenyl-2-propionic acid.

Pharmacokinetic Data. Plasma drug levels of 4-isobutylphenyl-2-propionic acid after derivative and free drug oral administration, in blood samples drawn from the sublingual vein of rats according to ref 24, were gas chromatographically determined at different times according to ref 25. The results are shown in Figure 3.

As can be observed, a close correspondence was found with the results of the antiinflammatory activity assay. In particular, the plasma concentrations of 4-isobutylphenyl-2-propionic acid from I are at least twice those

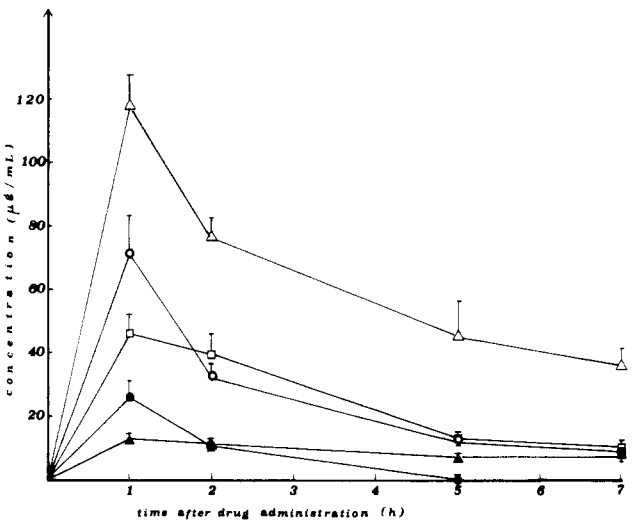

Figure 3. Ibuprofen plasma levels in male Wistar rats weighing 180–220 g, after oral administration of ibuprofen (●, 19.2 mg/kg; ○, 58.8 mg/kg), MR 653 (△, dose corresponding to 58.8 mg/kg ibuprofen), MR 654 (□, dose corresponding to 38.8 mg/kg ibuprofen), MR 655 (▲, dose corresponding to 19.2 mg/kg ibuprofen). Plotted values are the mean ± SE of $N = 5$.

corresponding to an equivalent dose of free drug.

Preliminary Toxicity Data. The oral LD_{50} of the three derivatives was determined in mice and found to be higher than 2000 mg/kg. The ulcerogenic potency was evaluated in the rat after intraperitoneal administration; for I it was found to be comparable with that of an equivalent dose of 4-isobutylphenyl-2-propionic acid, and for II and III it was found somewhat lower.

Conclusions

The results obtained apparently demonstrate that the new oligomeric derivatives of 4-isobutylphenyl-2-propionic acid described in this paper show a considerable pharmacological interest. In fact, all the derivatives proved to be sustained-release products, with both a prolonged antiinflammatory activity and a higher plasma half-life, with regard to equivalent doses of free drug. In addition, the oligomeric derivative with the lowest molecular weight has shown a remarkably increased initial bioavailability.

Experimental Section

IR and NMR were in agreement with the assigned structures. NMR spectra were recorded with a Varian 60-MHz spectrometer (Me_4Si): the amount of 4-isobutylphenyl-2-propionic acid residues was determined by comparing the value of a "4-isobutylphenyl-2-propionic acid single hydrogen" (obtained by working out the average among the values derived from signals of aromatic α-methyl and p-isobutyl hydrogens) with that of a "poly(oxyethylene) single hydrogen". TLC's were performed on Merck Kieselgel 60 glass plates, eluting with a $MeOH/CHCl_3/AcOH$ (70:35:4) mixture; the spots were detected with iodine. Owing to the very narrow molecular weight distribution of the starting poly(oxyethylenes), all compounds gave a single spot after purification. Titration experiments were performed by dissolving the samples in a 1:1 $H_2O/MeOH$ (I and II) mixture or in H_2O (III), adding a measured excess of aqueous 0.1 N NaOH, and keeping the reaction mixtures at 70 °C for 1 h. Solutions were then titrated with standard acid, and the alkali consumption gave an indication of the amount of linked 4-isobutylphenyl-2-propionic acid (see Table I).

4-Isobutylphenyl-2-propionic Acid Imidazolide. The imidazolide was prepared by dissolving 4-isobutylphenyl-2-propionic acid (10 g, 0.048 mol) in dry (CaH_2) alcohol-free chloroform (100 mL), adding portionwise N,N'-carbonyldiimidazole (CDI; 10 g, 0.06 mol), and stirring for 1 h at room temperature, until effervescence ceased. Imidazolide was not isolated, but the resulting solution was used directly in the subsequent step.

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Monoester of Tetraethylene Glycol (I). This product was prepared by adding to the above solution Fluka tetraethylene glycol (31 g, 0.16 mol). The reaction mixture was left at 60 °C for 48 h in a thermostatic bath, then it was washed with water (2 × 50 mL), aqueous 0.1 N HCl (2 × 50 mL), water (2 × 50 mL), aqueous 0.1 N NaOH (2 × 50 mL), and water (2 × 50 mL), dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness in vacuo. The product was then purified by extracting the residue with *n*-heptane (~250 mL) and drying to constant weight at 30 °C (0.1 mmHg): yield 14.8 g (80%). The product failed to crystallize. It could be distilled with some decomposition at 180–185 °C (0.01 mm).

Diesters of Poly(oxyethylene) of Molecular Weight 1000 and 2000 (II and III). Product II was prepared by adding to the above imidazolide solution Fluka poly(oxyethylene), M_r 1000 (19.2 g, 0.019 mol), and by following the same procedure as in the case of I: yield 19.8 g (75%). The product failed to crystallize. Product III was similarly prepared with Fluka poly(oxyethylene), M_r 2000 (38.4 g, 0.019 mol). The product was finally purified by dissolving in a small amount of chloroform and diluting with 5 volumes of a *n*-heptane/ether (2:1) mixture. The precipitate was filtered and dried to constant weight at 20 °C (0.1 mmHg): yield 40.10 g (88%); mp 25–30 °C.

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Azaprostaglandin Analogues. Synthesis and Biological Properties of 11-Azaprostaglandin Derivatives

Achille Barco,* Simonetta Benetti, Gian Piero Pollini,

Istituto Chimico, Via Borsari 46, Ferrara, Italy

Pier Giovanni Baraldi, Mario Guarneri,

Istituto di Chimica Farmaceutica, Via Scandiana 21, Ferrara, Italy

Carmelo Gandolfi,

Ricerca e Sviluppo Chimico, Farmitalia Carlo Erba, Via C. Imbonati 24, Milano, Italy

Roberto Ceserani,* and Daniela Longiave

Ricerca e Sviluppo Biologico, Farmitalia Carlo Erba, Via C. Imbonati 24, Milano, Italy. *Received May 19, 1980*

New nitrogen analogues of prostaglandins (**11**, **11a**, **12**, and **12a**) have been synthesized starting from a 4,5-disubstituted 2-pyrrolidinone nucleus (**5** and **5a**) containing one side chain and a suitable functionality for elaborating the second one. These analogues had no better activity than natural prostaglandins in vitro [guinea pig ileum and trachea, rat stomach fundus strip, uterus and portal vein, ADP-induced guinea pig platelet-rich plasma (PRP) aggregation]. They similarly lacked any interesting activity in vivo [anesthetized rat blood pressure, stress, and acetylsalycilic acid (ASA) induced gastric lesions in rat].

In the last few years, in the light of experience in the steroid field,[1] a multitude of prostaglandin analogues in which carbon atoms of the cyclopentane ring are substituted for hetero atoms have been synthesized, in the hope of obtaining interesting biological properties. Several laboratories have directed their attention toward the synthesis of γ-lactam analogues, and 8-aza, 9-aza, 10-aza, 11-aza, 12-aza, and 8,12-diaza analogues of the 11-deoxy-PGE_1 and PGE_2 series have been reported.[2]

As part of our continuing interest[3-5] in nitrogen analogues of prostaglandins, this paper reports the synthesis and biological behavior of new 11-azaprostaglandin analogues (**11**, **12**, **11a**, and **12a**).

Chemistry. The synthetic approach to the title compounds involves construction of a 4,5-disubstituted 2-pyrrolidinone nucleus containing an intact α-C_7 side chain and a suitable function for elaborating the second one. The key intermediate, **5**, was secured by two alternative pathways starting from the readily available diester **1**.[6] The ethoxide-ion catalyzed Michael addition of **1** with diethyl acetamidomalonate[7] proceeded with concomitant cyclization, giving a good yield of the disubstituted pyrrolidinone **2**. Stereoselective one-step decarboethoxylation of the geminal diester **2** was accomplished by heating in wet Me_2SO containing NaCl[8] to give **3** as sole product. The assigned trans disposition of the two side chains was based on the chemical shift of the C_{12} H and the vicinal coupling constant $J_{8,12}$ which is 5 Hz in full accord with the literature.[9] Compound **3b** was prepared starting from **1**, through the alternative sequence shown in Scheme I. Treatment of **3** and **3b** with an aqueous–methanolic potassium carbonate solution proceeded with hydrolysis of the more hindered ester with the probable assistance of the lactam moiety, as recently suggested for similar compounds,[10] affording the acid **5** which was reduced, by the mixed carboxylic–carbonic anhydride method,[11] with

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