Table I—Plasma Nalbuphine Levels in Dogs after Subcutaneous Administration of 1 mg/kg

Hours	Plasma Nalbuphine Level, ng/ml	
	Dog 1	Dog 2
0.083	99	14
0.17	123	48
0.33	72	50
0.5	65	42
0.75	42	38
1.0	38	40
1.25	33	27
1.5	57	32
2.0	46	28
2.5	36	33
3.0	49	28
5.0	25	21

tated on a mixer for 5–10 sec, followed by incubation in a heating block[8] at 60° for 10 min. The incubated reaction mixture was then evaporated to dryness for 2 hr[9].

The dried product was dissolved in 25 μl of hexane, and 2–4-μl aliquots were injected into the gas chromatograph[10] equipped with a 2-mCi ^{63}Ni-electron-capture detector. The column was 3.8% methyl vinyl silicone gum rubber[11] (1.2 m long and 4 mm i.d.). Helium carrier gas, 75 ml/min, and 10% methane in argon (purge gas), 88 ml/min, were used. The oven, detector, and injection port temperatures were 235, 250, and 250°, respectively. The pulse interval setting was 50.

The peak heights of nalbuphine and naloxone heptafluorobutyrates were measured, and the ratio was calculated.

Dog Study—Nalbuphine hydrochloride in normal saline solution (5 mg/ml) was administered subcutaneously to two 10-kg beagle dogs, one male and one female, at a dose of 1 mg/kg. Blood was collected from the cephalic vein[12] in heparinized tubes at specified times after dosing. Plasma obtained after centrifugation was extracted and analyzed for nalbuphine by the described electron-capture GLC method.

[8] Temp-Blok, Lab-Line Instruments, Melrose Park, Ill.

[9] The Buchler Evapo-Mix was attached to a vacuum pump for this procedure. The derivatization procedure requires dry conditions and works well only when the relative humidity is 50% or less.

[10] F & M 402, Hewlett-Packard.

[11] UCC-W-982 on High Performance Chromosorb W, Hewlett-Packard.

[12] Butterfly-19 (Abbott) with a siliconized needle was placed in the vein.

RESULTS

The retention times of the heptafluorobutyryl derivatives of nalbuphine and naloxone were 3.7 and 2.2 min, respectively. Figure 1 is a typical chromatogram of nalbuphine extracted from dog plasma. Extracts of human plasma gave identical results. Human and dog plasma blanks extracted and treated with heptafluorobutyric acid showed no interfering peaks at the retention times of nalbuphine or naloxone heptafluorobutyryl derivatives.

The reproducibility of peak height ratios for quadruplicate samples of plasma made 10.0 and 1.0 ng/ml in nalbuphine hydrochloride was 5 and 14% (percent standard deviation), respectively. The recovery of nalbuphine added to plasma was 70% after correcting for aliquot losses during extraction. There was a linear relationship between the peak height ratio and the plasma concentration of naltrexone. The lower limit of sensitivity was approximately 0.5 ng/ml, and the upper limit of the linear dynamic range was greater than 50 ng/ml.

Table I presents the concentrations of nalbuphine found in the plasma of two dogs after subcutaneous administration of 1 mg of nalbuphine hydrochloride/kg. The peak concentrations were 123 and 50 ng/ml in Dogs 1 and 2, respectively. The peak times in the two dogs were 10 and 20 min (0.17 and 0.33 hr), respectively. Nalbuphine was still detectable in plasma 5 hr after administration.

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Anti-Inflammatory 1-Substituted 2-Imidazolidinones

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Received February 7, 1977, from the *Research and Development Department, Norwich-Eaton Pharmaceuticals Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication June 22, 1977.

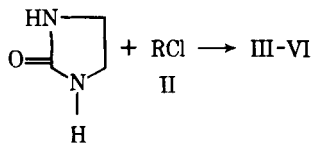
Abstract □ The synthesis and anti-inflammatory activity of a series of 1-substituted 2-imidazolidinones are reported. These compounds exerted marked anti-inflammatory activity in the carrageenan-induced hindpaw edema assay in the rat in doses that failed to elicit side effects. Their ED_{50} values were near the value of aspirin but markedly higher than the value of indomethacin.

Keyphrases □ 2-Imidazolidinones, 1-substituted—synthesized, anti-inflammatory activity evaluated □ Anti-inflammatory activity—various 1-substituted 2-imidazolidinones evaluated □ Structure-activity relationships—various 1-substituted 2-imidazolidinones evaluated for anti-inflammatory activity

A series of 1-(arylmethyl)-2-imidazolidinones was evaluated as anti-inflammatory agents. The target compounds, III–VI (Table I), were prepared by reaction of 2-imidazolidinone (I) with the appropriate arylmethyl chloride (II) (Scheme I).

DISCUSSION

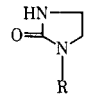
The compounds were tested for anti-inflammatory activity according to a reported method (1). Each compound was suspended in 0.5% methylcellulose, and 300 mg/kg po was administered to three male Wistar

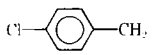
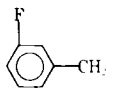
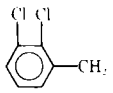


I

Scheme I

Table I—Physical and Analytical Data for 1-(Arylmethyl)-2-imidazolidinones (III-VI)



Compound	R	Melting Point	Yield, %	Recrystallization Solvent	Formula	Analyses, % Calc.	Analyses, % Found
III		164-166°	19	Acetonitrile	$C_{10}H_{11}ClN_2O$	C 57.01 H 5.26 N 13.30	56.73 5.25 13.22
IV		103-105°	28	Ether[a]	$C_{10}H_{11}FN_2O$	C 61.84 H 5.71 N 14.43	61.98 5.72 14.62
V		110-113°	12	Benzene	$C_{10}H_{10}Cl_2N_2O$	C 49.00 H 4.11 N 11.43	49.08 4.24 11.54
VI		153-155°	23	Methanol	$C_{14}H_{14}N_2O$	C 74.31 H 6.24 N 12.38	74.32 6.25 12.15

[a] Trituration of the crude product with ether gave analytically pure IV.

Table II—Anti-Inflammatory Evaluation

Compound	Dose, mg/kg po	Number of Rats	Percent Inhibition of Edema Formation[a] 4 hr	6 hr	ED_{50}[b], mg/kg
III	300	3	59.4	56.1	190
IV	300	3	55.9	76.6	155
V	300	3	68.9	69.2	103
VI	300	3	52.4	31.9	180
Aspirin	300	3	58.5	57.6	167
Indomethacin	10	10	63.0	49.0	10

[a] Compared to control (untreated) hindpaw 4 and 6 hr after carrageenan administration. [b] Calculated by the Litchfield and Wilcoxon method [J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949)] and based on inhibition of edema formation at the 4-hr interval.

rats, 1 hr prior to subplantar injection of 0.05 ml of a 1% solution of carrageenan[1] into the left hindfoot. The percentage reduction of edema formation (as compared to a nondrug-treated control) in the rat hindpaw was recorded 4 and 6 hr after carrageenan administration. For comparison, the reference anti-inflammatory drugs aspirin and indomethacin were tested (Table II). The ED_{50} value of each compound was also obtained by conducting antiedema studies in the presence of three to four lower doses of drug.

Compounds III–VI exhibited marked anti-inflammatory activity 4 hr after carrageenan injection. Compound V appeared to have a somewhat stronger antiedema effect than the other three compounds at 4 hr. The anti-inflammatory activity of three of the four compounds was maintained for 6 hr after carrageenan injection, the antiedema action of IV becoming even greater. A decrease in action was observed at 6 hr with VI. The activities of the four compounds compared favorably with the activity of aspirin but were less than the activity of indomethacin.

No side effects were noted with any compound based on this limited evaluation. When ED_{50} values of these compounds were obtained, V appeared to have the lowest value. Its effectiveness was greater than that of aspirin but less than that of indomethacin. Compounds III, IV, and VI appeared to be either slightly less or slightly more effective than aspirin.

EXPERIMENTAL[2]

The general procedure for the preparation of 1-(arylmethyl)-2-imidazolidinones (III–VI) (Table I) is as follows.

A mixture of 21.5 g (0.25 mole) of 2-imidazolidinone (I), 34.5 g (0.25 mole) of potassium carbonate, 10 g (0.06 mole) of potassium iodide, and 0.25 mole of the arylmethyl chloride (II) in 300 ml of dimethyl sulfoxide was stirred and heated at 100–105° for 3 hr; it was then cooled and poured into 1.3 liters of cold water. The mixture was extracted with 1.3 liters of chloroform, and the chloroform solution was washed with 150 ml of water, dried (magnesium sulfate), and concentrated to dryness *in vacuo* to give the crude product. Recrystallization from the appropriate solvent (Table I) gave the analytical sample.

The IR spectrum for 1-(4-chlorophenylmethyl)-2-imidazolidinone (III) showed 3.10 (NH) and 5.91 (C=O) μm. The NMR spectrum for III (dimethyl sulfoxide-d_6) showed δ 3.25 (s, 4H, imidazole 4-CH_2 and 5-CH_2), 4.22 (s, 2H, $C_6H_5CH_2$), 6.38 (t, 1H, exchangeable, NH), 7.26, and 7.43 (2 d, 4H, J = 9 Hz, phenyl CH) ppm.

The IR and NMR spectra of IV–VI were consistent with the assigned structures, and the physical and analytical data for III–VI are included in Table I.

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[1] Viscarin, Algin Corporation of America.

[2] Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. NMR spectra were obtained on a Varian A-60A instrument and were compared with tetramethylsilane as an internal standard.