Nonsteroidal Antiinflammatory Agents. 14.[1] Synthesis and Pharmacological Profile of 6-Chloro-5-(cyclopentylmethyl)indan-1-carboxylic Acid

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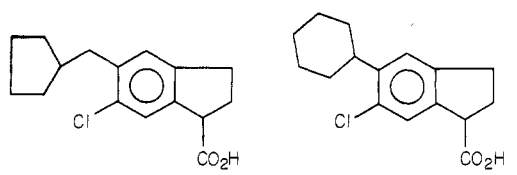
The preparation of 6-chloro-5-(cyclopentylmethyl)indan-1-carboxylic acid is described. This acid has good antiinflammatory and analgesic activities without producing irritation in the gastrointestinal tract up to the highest tested dose.

The most common side effects of acidic nonsteroidal antiinflammatory drugs in man, as well as in animals, are gastrointestinal symptoms, i.e., mucosal damage, bleeding, and ulceration.[2] Therefore, the therapeutic use of the drugs is very often limited by their gastrointestinal intolerability. One of the most important goals of research activities in this field is the development of potent antiinflammatory drugs with very low or even no gastrointestinal ulcerogenicity. In this paper we describe the synthesis and pharmacological profile of a new indancarboxylic acid, 6-chloro-5-(cyclopentylmethyl)indan-1-carboxylic acid (1), which has been shown to be antiinflammatory and surprisingly nonulcerogenic after acute and chronic treatment in rats and monkeys.

Compound 1 is an isomer of the known 6-chloro-5-



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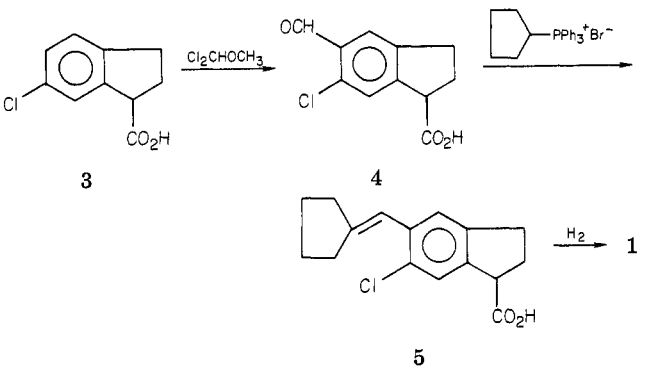
cyclohexylindan-1-carboxylic acid (2, clidanac),[3] which has been recently introduced into the market.

Chemistry. The synthesis of compound 1 is shown in Scheme I. The reaction of 6-chloroindan-1-carboxylic acid (3)[4] with dichloromethyl methyl ether in methylene chloride in the presence of aluminum chloride afforded 6-chloro-5-formylindan-1-carboxylic acid (4). Wittig reaction of the aldehyde 4 with cyclopentyltriphenylphosphonium bromide[5] in the presence of sodium hydride in dimethyl sulfoxide resulted in the olefin 5. Subsequent catalytic hydrogenation in ethanol with PtO_2 as catalyst generated the designed compound 1.

Pharmacology and Results

As indicated in Table I, compound 1 exhibits antiinflammatory activity in the carrageenan edema (acute inflammation) test, with an ED_{50} of approximately 30 mg/kg after a single oral application, and in the adjuvant arthritis

Scheme I



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(subchronic inflammation) test, with an ED_{40} of about 30 mg/kg after 4 days of oral drug treatment. Additional studies have demonstrated antinociceptive[6a] and antipyretic activity for compound 1 with effective doses between 10 and 30 mg/kg po in the rat. In determination of the pain threshold,[6b] analgesic activity was also proved in healthy subjects with a ≤200-mg/kg dose of 1.

The gastrointestinal tolerability of compound 1 has been evaluated under acute and chronic conditions (Table I). Compound 1 did not cause any mucosal damage in the rat stomach after a single oral application up to the highest tested dose (400 mg/kg), whereas clidanac (2) has been shown to be ulcerogenic in antiinflammatory active doses. Even more surprising, compound 1 did not exhibit gastrointestinal toxicity in rats and monkeys during chronic daily drug treatment up to 400 mg/kg po for 4 weeks. Neither epithelial lesions in the stomach nor gastrointestinal bleeding or lethality caused by ulcerative enteritis has been observed.

Since the characteristic pharmacological profile of the commonly used acidic nonsteroidal antiinflammatory agents (antiinflammatory, antinociceptive, antipyretic, and ulcerogenic) is related to their ability to inhibit the biosynthesis of prostaglandins (PGs) from arachidonic acid (AA) by inhibiting the enzyme cyclooxygenase,[10] we have investigated the influence of compound 1 on AA metabolism in vitro and in vivo. Compound 1 inhibited the conversion of AA to PGs in a microsomal preparation of sheep seminal vesicles,[11] with an IC_{50} of about 10^{-4} mol/L, and in zymosane-stimulated murine macrophages,[12] with

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Table I. Antiinflammatory Activity and Gastrointestinal Tolerability of 1 in Comparison to Marketed Nonsteroidal Antiinflammatroy Drugs

compd	antiinflammatory act. (rat) carrageenan edema:[a] ED_{50}, mg/kg	antiinflammatory act. (rat) adjuvant arthritis:[b] ED_{40}, mg/kg	gastrointestinal tolerability (rat) acute UD,[c] mg/kg	chronic UD,[d] mg/kg	blood loss,[e] mg/kg	lethality,[f] mg/kg
1	30	30	>400	>100	>100	>100
				>400[g]	nt[h]	>400[g]
clidanac	4	4	⩽3	nt[h]	nt[h]	nt[h]
ibuprofen	50-100	>150	30	30-100	200	400
indometacin	4	2	4	4	4	8
diclofenac	2	2	20	20	20	20
naproxen	15	10	5	5-10	>30	>30
benoxaprofen	15-30	10	>200	⩽30	<50	<50

[a] See ref 7. [b] See ref 8. [c] See ref 9. [d] Ten times the po UD (day 10): ⩾4 ulcers/stomach. [e] Days 3, 7, and 10: ⩾3 times the control. [f] By perforating ulcerative enteritis during the 10-day treatment. [g] Results from a 4-week toxicity study. [h] Not tested.

an IC_{50} of about 10^{-6} mol/L. For studying the influence of compound 1 on AA metabolism in vivo, we used two different models, AA-induced mortality in mice[13] and the prolongation of pregnancy time in rats.[14] We found a significant protective effect against AA-induced mortality in mice with a single oral dose of 30 mg/kg, which reflects a systemic PG-synthesis inhibition, but the pregnancy time in rats was not influenced by the same antiinflammatory active dose of compound 1.

From the results reported here, we conclude that compound 1, in the same manner as clidanac and other acidic nonsteroidal antiinflammatory agents, exhibits its antiinflammatory, antinociceptive, and antipyretic activities by inhibiting PG synthesis in vivo. However, since compound 1 is nonulcerogenic in rats and monkeys up to 400 mg/kg, we propose, that compound 1 might inhibit PG synthesis with a certain cell or tissue specificity in vivo.

Experimental Section

Chemistry. Melting points were taken on a Büchi melting point apparatus and are uncorrected. All compounds gave spectral data consistent with the proposed structure. Where analyses are indicated only by the symbols of the elements, analytical results for the elements were within 0.4% of the theoretical values.

6-Chloro-5-formylindan-1-carboxylic Acid (4). To a suspension of 6-chloroindan-1-carboxylic acid (100 g, 508.64 mmol) in CH_2Cl_2 (500 mL) at −10 °C was added $AlCl_3$ (166 g, 1.25 mol) and then cooled at −30 °C. After 10 min, Cl_2CHOCH_3 (94 mL, 1.06 mol) was added dropwise over 45 min with vigorous stirring. After the addition, stirring was continued for 45 min at −30 °C. The reaction mixture was allowed to come to 0 °C and then poured onto ice (600 g) and concentrated HCl (100 mL). After evaporation of CH_2Cl_2 in vacuo, the deposited solid was collected, washed (H_2O), and recrystallized (toluol) to give 4 (71.2 g, 62%), mp 144–145 °C. Anal. ($C_{11}H_9ClO_3$) C, H, Cl.

6-Chloro-5-(cyclopentylidenemethyl)indan-1-carboxylic Acid (5). A solution of methylsulfinyl carbanion [prepared from NaH (80% pure, 9.6 g, 320 mmol) and Me_2SO (256 mL)] was added to a stirred mixture of cyclopentyltriphenylphosphonium bromide (88 g, 214 mmol) in Me_2SO (384 mL) under argon atmosphere at room temperature. To the red ylide solution was added dropwise a solution of 4 (16 g, 71 mmol) in Me_2SO (64 mL) while the temperature was kept below 20 °C. After the complete addition, stirring was continued for 30 min at ambient temperature. The mixture was poured onto ice (1.32 kg), and 1 N HCl (1.3 L) was added to give a white paste, which was extracted (Et_2O). The ether layer was washed, dried (Na_2SO_4), and filtered over silica gel (250 g) with Et_2O/pentane/HOAc (500:500:3.5) to give a solid (11.8 g, 60%), which was hydrogenolyzed without further purification: ^1H NMR ($CDCl_3$) δ 1.60 (4 H, m), 2.40 (6 H, m), 2.90 (2 H, m), 4.00 (1 H, t, J = 3.5 Hz), 6.55 (1 H, t, J = 1 Hz), 7.25 (1 H, s), 7.35 (1 H, s), 10.40 (1 H, broad).

6-Chloro-5-(cyclopentylmethyl)indan-1-carboxylic Acid (1). Crude olefin 5 (11.8 g) was dissolved in EtOH (80 ml) and hydrogenated in the presence of 1.2 g of PtO_2. Hydrogen uptake after 40 min was 1150 mL. The solution was filtered, the solvent was evaporated, and the residue was recrystallized from EtOH/H_2O to give 1 (9.65 g, 81%), mp 130–131 °C. Anal. ($C_{16}H_{19}ClO_2$) C, H, Cl.

Pharmacology. Antipyretic Testing. Male rats of the Wistar strain (eight in each group) weighing 110–130 g received 20 mg/kg of carrageenin in physiological saline by intravenous injection. Two hours later the substance (1–100 mg/kg) was administered orally, and the rectal temperature was recorded hourly using an Ellab thermocouple. Aminophenazone (100 mg/kg po) was used as the reference drug. The significance of the results was determined by the Student's t test.

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Registry No. 1, 68266-57-9; 3, 52651-15-7; 4, 68266-63-7; 5, 70780-14-2; cyclopentyltriphenylphosphonium bromide, 7333-52-0.

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