The Synthesis and Antiinflammatory Activity of 1-Alkyl-Isochroman-1-yl Acetic Acids Derivatives.

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Descrevemos neste trabalho a síntese e o perfil anti-inflamatório de ácidos 1-alquil-isocromanil acéticos, obtidos a partir do safrol. O ácido 1-metil-isocromanil acético (**6**), obtido em alto rendimento global a partir do produto natural, mostrou-se o mais ativo no teste do edema induzido por carragenina na pata de rato, com efeito inibidor do edema comparável àquele da indometacina.

We describe in this paper the synthesis and AI profile of 1-alkyl-isochroman-1yl acetic acids synthesized from natural safrole. The 1-methyl-isochroman-1yl acetic acid (**6**) was obtained in high overall yield from the natural product; and showed in the carrageenam paw edema essay an AI activity comparable to indomethacin in the reduction of the edema in rats.

Key words: *isochromanyl acetic acids; antiinflammatory.*

Introduction

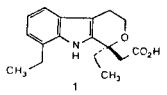
A research area in medicinal chemistry of continuos and ever-growing development is that of non-steroidal antiinflammatory agents (NSAIA)[2]. Among the acidic NSAIA the aryl- and heteroarylacetic acids represent an important pharmaceutical class of drugs with sales of US$ 1.500 millions in 1989[3]. This class of therapeutic useful agents present antiinflammatory (AI), analgesis and antipyretic properties[4].

The AI activity of these agents has been attributed to inhibition of inflammatogenic prostaglandins (PG) production arising from arachidonic acid cascade (AAC) via a cyclooxigenase dependent pathway[4]. The molecular basis of the interaction between acidic NSAI drugs and CO has been studied by several groups and proposed a topographic model for it[5].

Several different structural classes of arylcarboxylic acids have been developed based on the known structure-antiinflammatory activity relationship grounded on this topographic model, which had defined three minimum structural requirements for AI activity: an acidic side chain belonging to the acetic or propionic series; a central aryl - or heteroaryl moiety and a hydrofobic residue[5].

A common drawback of NSAIA is their ulcerogenic liability[6], for this reason the search of new agents having low incidence of gastro-intestinal (GI) side effects is an attractive goal in the development of this class of drugs. In Table 1 are illustrated some new agents introduced in 1983-1987 period[7].

Recently, a new NSAIA containing an 1-alkyldihydropyrane acetic acid moiety, was reported[8]. This derivative (**1**) was described as a clinically effective agent with safety profile with respect to GI tract[8]. It has been also described that AI activity of (**1**) is associated with the presence of the dihydropyrane system[8,9].



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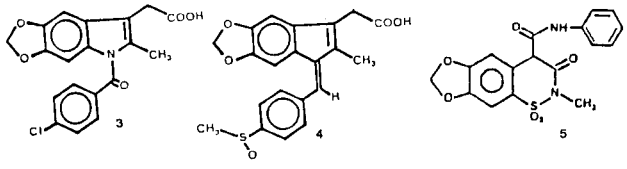
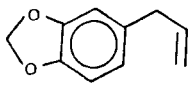
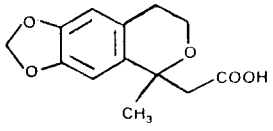


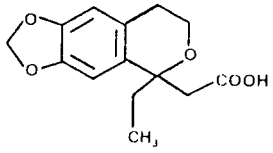
As part of a continuing research programme aiming at the synthesis of modified NSAIA using safrole (**2**) as starting material, we have described in previous works the synthesis of an indomethacin analogue (**3**)[10],a sulindac analogue (**4**) and an oxicam related derivative (**5**)[12,13]

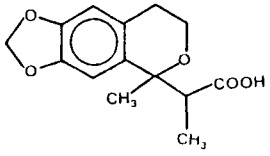
In this paper we wish to described the synthesis and the results of a preliminary pharmacological evaluation of the AI profile of the isochroman acetic acids derivatives (**6**), (**7**) and (**8**), designed as being structurally related to (**1**), where the acidic framework containing the dihydropyrane system include the methylenedioxy ring present in the starting natural product and considered as a mimic sub-unit to indole ring of (**1**).

Futhermore, the tricyclic pattern of these isochroman derivatives preserve all theoretical structural requirements for the AI activity and assure a real analogy in the molecular arrangement between the pharmaceutically useful compound, and these synthetic derivatives.









Results and Discussion

The retrosynthetic map (see Figure 1) for these isochroman derivatives shows that they could be prepared from the corresponding phenethyl alcohol compound (**9**) by using acid-catalysed condensation reaction with the appropriated carbonyl compound[14].

The key step in the planned synthetic route represents a variance of the well-known Friedel-Crafts reaction , wherein intramolecular regioalkylation of the 6 position of the aromatic system by an hemiketal or a derived oxonium ion intermediate, formed *in situ* from the reaction of alcohol (**9**) and the desired keto ester is essential to produce the quartenary benzylic stereogenic center (see Scheme 1).

In this step it could be used a Lewis acid as acidic catalyst for the intramolecular alkylation[16]. Indeed the presence of the methylenedioxy brigde in the alcohol (**9**) prevent the employ of these conditions[10,11]. It was gratifying therefore to find, after careful examination of experimental conditions, that treating alcohol (**9**) with a small excess of keto-ester (**10**) in toluene, at reflux, in the presence of catalic aumount of p-toluenesulfonic acid we are able to obtain, as only product, the 1-alkyl-1-substituted isochroman esters (**11**) in high yield[1b], except **11c**.

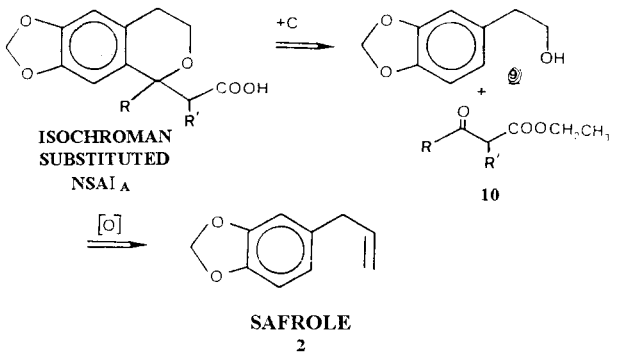


Figure 1. *Retrosynthetic Map*

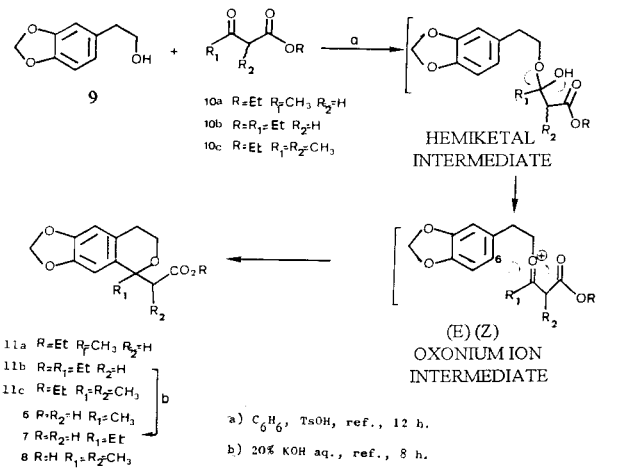
The alcohol (**9**) could be prepared from safrole (**2**) in 90 % yield by emploing previously described conditions[17,18].

In fact was found that differents keto esters derivatives react with (**9**) to afford the 1,1-disubstituted isochroman derivatives in generally good yields, exception to the keto ester (**10c**), which furnished the cyclic compound (**11c**) in modest 20% yield.

On other hand the complete regiocontrol observed in this intramolecular cyclization reaction could be rationalized by considering the suitable activation effect promoved by the methylenedioxy unit at 6-position of the phenyl ring. In fact we are never able to detect any evidence for the formation of others cyclic products in this process.

The esters (**11a**), (**11b**) and (**11c**) were hydrolized under usual conditions to give the desired isochroman acetic acids. (**6**), (**7**) and (**8**), respectively (see Scheme 1).

These compounds were tested by oral administration in the rats using carrageenam paw edema essay[10]. The first compound examined in this serie, the derivative (**6**), had shown a good AI activity (34%) comparable to indomethacin (40%) in edema reduction at dose of 25 mg/kg. In contrast, the corresponding methyl ester (**12a**) at dose of 50 mg/kg p.o., was almost devoid of activity in this test. The homologue



SCHEME 1

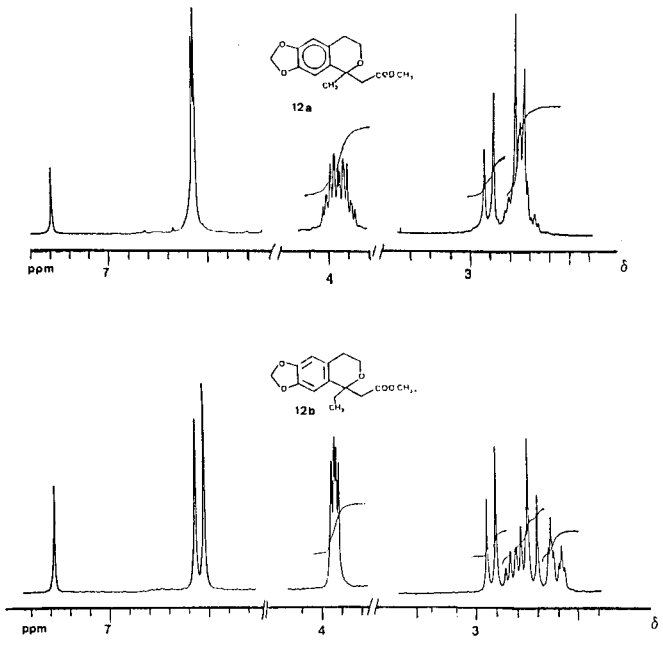


Figure 2. *^{1}H NMR spectra at 200 MHz of methyl esters 12a and 12b.*

Table 1. *New NSAIA Introduced In 1983-7 Period*[a].

Year[b]	Unan Name (Common Name)	Country
	Alminoprofen (Minalfen)	France
	Isoxican (Pacyl)	USA
1983	Oxaprozin (Duraprox)	USA
(50)	Suprofen (Maldocyl)	Belgium
	Fisalamine (Salofalk)	UK
	Indobufen (Ibustrim)	Italy
	Isoferolac (Sofenac)	France
1984	Picetoprofen (Calmatex)	Spain
(41)	Pimaprofen (Basicum)	Japan
	Etodolac (Lodine)	USA
1985	Nabumetone (Relifex)	UK
(40)	Nimesulide (Mesulide)	USA
	Amfenac (Fenazox)	USA
1986	Felbinac (Napageln)	USA
(49)	Loxoprofen (Loxonin)	Japan
1987	Flunoxaprofen (Priaxin)	Italy (61)
(61)	Tenoxican (Tilcodil)	Switzerland

[a] *Ref. 7;*
[b] *In parenthesis the total of new drugs introduced in the year.*

acid (**7**) shown a reduced AI activity and the α-methyl acid (**8**) gave a poor activity[20]. These preliminar results seems indicate that, in this serie, the AI activity could be abolished by modification of the 1-alkyl substituent, being the 1-methyl substituted isochroman acetic acid (**6**) the most active[21].

The results related to this homologue serie can be racionalized by some structural effects different than that caused by the modification of the partition coefficients which must be similar in the homologue serie. In fact, a possible effect that could be responsable by the severe modification of the observed biological profile, is a possible different conformational behavior of the dihydropyrane ring, as function of the different 1-alkyl-substituent. In fact, the careful analysis of the PMR spectra of the corresponding methyl esters (**12**a) and (**12**b), at the dihydropyrane protons region, shown a significative difference in the shape of the signals. In the spectrum of the 1-ethyl derivative (**12**b) the signal *at ca.* γ. 2.50-3.00 ppm, attributed to the benzylic protons,occurs as a broad multiplet signal perturbed by an AB-pattern signalof the acetic ester methylene (-CH_2-CO_2-Me). It is notewhorty that the signal due to the methylene protons at C-3(-CH_2-O) occurs as a sharp multiplet at *ca.* δ 3.90 ppm. In the spectrum of the 1-methyl derivative (**12**a) the first signal appearing at ca. 2.7-2.9 ppm due to the benzylic protons occurs as a more resolved multiplet also perturbed by an AB-pattern. In contrast, the signal due to C-3 protons, in the spectra of this compound appears as a broad multiplet at *ca.*δ 3.90-4.10 ppm (see Figure 2).These nicely differences in the PMR spectrum of these derivatives, represents a distinct conformational arrangement, indicating an effect due the nature of the 1-alkyl substituent. Then, we can especulate that the difference observed in the AI properties of these both derivatives ie (**6**) and (**7**), can be originated by the distinct conformational arrangement adopted by the heterocyclic-oxygenated ring.

Conclusion

In conclusion, the synthetic route described here represents an useful apprach to different 1-alkyl-1-substituted isochroman acetic acids using the natural safrole (**2**) as starting meterial. The AI activity observed to derivative (**6**) prompt us to follow in this study introducing other appropriated structural modifications in order to improve the AI activity.

Experimental

Nuclear magnetic resonance (^{1}H-NMR) spectra, unless otherwise stated, were determined in deuterochloroform containing *ca.* 1% TMS as an internal standard with a Bruker HP 80 SY at 80 MHz or with a Varian T-60 at 60 MHz spectrometer. Splitting patterns are as follows: s, singlet; d, doublet; t, triplet: q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained with a Perkin-Elmer 397 spectrophotometer by using sodium chloride plates for neat liquids and potassium bromide plates for solids. Ultraviolet (UV) spectra were determined in ethanol solution on a Beckman DV-6 or Varian UV-vis 634-S spectrophotometer. The mass spectra were obtaines with a Varian MAT-SS-100 MS computer system.

The progress of all reactions was monitored by TLC which was performed on 2.0 cm x 6.0 cm aluminium sheets pre-coated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under an ultraviolet light, sprayed with concentred slfuric acid for spot visualisation. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4A molecular sieves. Reactions were generally stirred under a dry nitrogen atmosphere. The usual work-up means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous magnesium or sodium sulfate and filtered.

General Procedure for the Preparation of the Ethyl Ester of 1-alkyl substituted 6,7-methylene-dioxy-isochroman-1-yl Acetic Acids (**11**a), (**11**b) *and* (**11**c). The appropriate keto ester (1.4 m mol) was placed in a 25-ml flask equipped with a Dean-Stark trap, containing 15 ml of dry benzene and a catalic ammount of p-toluenesulfonic acid (0.026g; 0.14 mmol). The alcohol (**9**) (0.2g; 1.22 m moles) was added to the reaction mixture and stirred at reflux for 12 h. The cooled mixture was worked-up by usual manner to give an oily residue, which was dissolued by toluene (*ca.* 25 ml) and washed with a 5% aqueous sodium bicarbonate solution (2x10ml). The organic layer (negative $FeCl_3$ test) was dried, evaporated and next chromatographed on silica gel column (ethyl acetate: n-hexane, 1:9) to give the ethyl esters (**11**a) (80%), (**11**b) (92%) and (**11**c) (20%).

The ester (**11**a): IR (film): γ 2920, 1730, 1480, 1240, 1040 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.45(s,1H); 6.35 (s,1H); 5.90 (s,2H); 4.25-3.75 (m,4H); 2.80 (br m, 2H), 2.30 (s,2H), 1.35 (s,3H), 1.05 (t, 3H) ppm.

The ester (**11**b): IR (film): 2915, 1730, 1450, 1240 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ 6.59 (s, 1H); 6.38 (s, 1H); 5.90 (s,2H); 4.30-3.70 (m, 4H), 2.75 (m, 2H); 1.80 (t, 2H), 1.25 (t, 6H) ppm. The ester (11c): IR (film): 2916, 1725, 1455, 1240 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): 6.40 (s,1H); 6.32 (s,1H); 5.72 (s, 2H), 4.10 - 3.85 (br.m, 4H); 2.65 (m, 3H); 1.42 (s, 3H), 1.15-1.02 (br, 6H) ppm.

The corresponding methyl esters (**12**a), (**12**b) and (**12**c) were prepared by treatment of an ethereal solution of the corresponding acids with diazomethane obtained by Diazald^R method: the methyl ester (**12**a): ^1H NMR (200 MHz, $CDCl_3$): δ 6.57 (s,1 H), 6.55 (s, 1H), 5.93 (s, 2H), 3.99-3.90 (m, 2H), 3.67 (s, 3H), 2.93 (d,J=9.2 Hz, 1H) 2.77-2.73 (m, 3H), 1.62 (s, 3H) ppm; MS (90 eV) 265 (M + 1; 100%), 249, 191, 149 m/z.

The methyl ester (**12**b): ^1H NMR (200 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.52 (s, 1H), 5.93 (s, 2H), 3.95-3.91 (m, 2H), 3.65 (s, 3H), 2.92(d,J= 9.02 HZ, 0.79 (t, 3H) ppm; MS (90 eV): 278 (M), 249 (100%) 205, 175, 147 m/z.

The methyl ester (**12**c): ^1H HMR (200 MHZ, $CDCl_3$): δ 6.59 (s, 1H), 6.58 (s, 1H), 5.93 (s, 2H), 4.10-3.92 (m, 2H), 3.62 (s, 3H), 2.92 (d, J= 9.1 Hz, 1H), 2.79-2.74 (m, 2H), 1.63 (s, 3H), 1.02 (d, J= 6.5 Hz, 3H) ppm; MS (90 eV): 279 (M + 1, 100%) m/z.

General Procedure for the Preparation of the Isochroman Acetic Acids (**6**), (**7**) *and* (**8**). An ethanolic solution (5ml) of the ethyl ester (*ca.* 0.72 mmoles) in an aqueous 20% potassium hydroxide solution (*ca.* 2ml) was refluxed for 8h and then concentrated to a cloudy aqueous solution. After cooling this solution was acidified to pH 1-2 with 10% hydrochloric acid solution, and next extracted with ethyl acetate (2x25ml) and the combined organic extracts were dried, filtered and evaporated to give an off-white foam. This material was recrystallized from benzene to afford the acids (6) (90%), (7) (88%) and (8) (85%).

The acid (**6**) mp (122-124) °C; IR (KBr): γ 3070, 1715, 1230 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.75 (br, 1H, exchangeable with deuterium oxide), 6.70 (s, 1H), 6.65 (s, 1H), 5.85 (s, 2H), 3.92 (m, 2H), 2.86 (m, 4H), 1.62 (s, 3H), ppm.

The acid (**7**): mp (118-120) °C; IR (KBr): γ 3050, 2933, 1717, 1235 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 6.48 (s, 1H); 6.42 (s, 1H), 5.85 (s, 2H), 3.96 (m, 2H), 2.87-2.69 (m, 2H), 1,92 (t, 2H), 0.99 (t, 3H) ppm.

The acid (**8**): mp (78-80) °C; IR (KBr): γ 3025 2918, 1715, 1241 cm^{-1}; ^1H NMR (200 MHz, COH_3): δ 6.59 (s, 1H), 6.55 (s, 1H), 5.94 (s, 2H), 4.08-4.00 (m, 2H); 2.95-2.56 (m, 3H), 1.64 (s, 3H), 1.02 (d, 3H) ppm.

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