The Synthesis and Analgesic Properties of New Spiroisochromanyl Acid Derivatives Synthesized from Natural Safrole [1]

Lucio M. Cabral and Eliezer J. Barreiro*

LASSBIO-Laboratório de Avaliação e Sintese de Substâncias Bioativas, Faculdade de Farmácia and Instituto de Química, Universidade Federal do Rio de Janeiro, CP.68006, 21944-190, Rio de Janeiro, RJ, Brazil

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We describe in this paper the synthesis of a new spiro[2-carboxycyclopentane-1,1-(6,7-methylenedioxy)isochroman] and a spiro[2-carboxycyclohexane-1,1-(6,7-methylenedioxy)isochroman] acids **11** and **12**, obtained from natural safrole (**7**), isolated from Sassafras oil. These derivatives were obtained in high overall yield using a synthetic route in which was observed brevity and appreciable diastereoselectivity in the intramolecular regioalkylation of the 6-position of the aromatic system of the natural starting material, the key step of the synthetic route representing a variable in the well-known Friedel-Crafts reaction. The new acids, derivatives **11** and **12**, were obtained in *ca.* 74% and 78% overall yield. They show a good analgesic profile in the pharmacological assay, the test in mice abdominal contortion.

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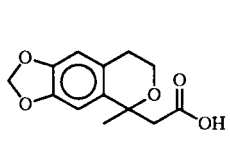
Introduction.

One of the great interests in the research area in medicinal chemistry is that of nonsteroid antiinflammatory agents (NSAIA) [2]. This class of therapeutically useful agents presents antiinflammatory (AI), antipyretic and analgesic properties, attributed to inhibition of prostaglandins bioformation, blocking the arachidonic acid cascade at cyclooxygenase level [3].

Several different structural classes of NSAIA with a carboxylic acid group have been developed based on the known structure activity relationships of this series [4]. Among several of the AI derivatives having an adequate profile with the desired analgesic properties, 1-alkyldihydropyran acetic acid derivatives were recently described [5], represented by etodolac (**1**) [6] and pemedolac (**2**) [7]. These compounds were described as clinically effective with their AI and analgesic activity associated with the presence of the dihydropyran acetic acid sub-unit. Meanwhile the AI and analgesic property ratios in these compounds seem to be affected by conformational variables in this ring, like the introduction of a benzyl unit in the dihydropyran system, producing **2** from **1**, as a powerful analgesic derivative [8].

As part of a continuing research program aiming at the synthesis of modified NSAIA using a naturally abundant product, safrole (**7**), isolated from Sassafras oil, as starting material, we have described in previous papers, the synthesis and AI properties of a sulindac analogue **3** [9], an oxican related derivative **4** [1a] and a new series of 1-alkylisochroman-1-ylacetic acid derivatives **5** and **6** [10]. These last compounds were designed as being structurally related to **1**. The acidic framework containing the dihydropyran ring, including the methylenedioxy unit present in the natural starting material, was considered as



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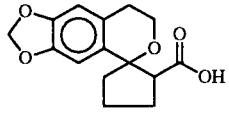

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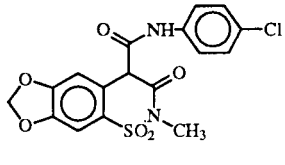

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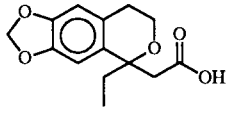

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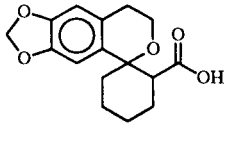

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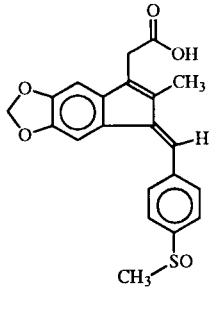

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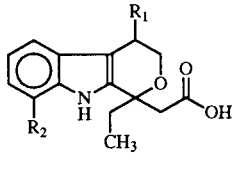


1 $R_1 = H, R_2 = Et$
2 $R_1 = C_6H_5, R_2 = Et$

a mimic sub-unit to the indole ring of **1**. The pharmacological evaluation of the AI and analgesic activity of these compounds [11] indicated that a possible strategy to improve the analgesic profile could be the introduction of an adequate degree of restriction in the conformational freedom of the dihydropyran ring by the introduction of a spiro character in the quaternary carbon atom. This fact led us to identify the new spiro derivatives **11** and **12** as attractive synthetic targets.

In this paper we wish to describe the synthesis and analgesic evaluation of these new spiro isochroman acid derivatives **11** and **12** obtained from safrole (**7**) in *ca.* 74% and 78% overall yield, respectively.

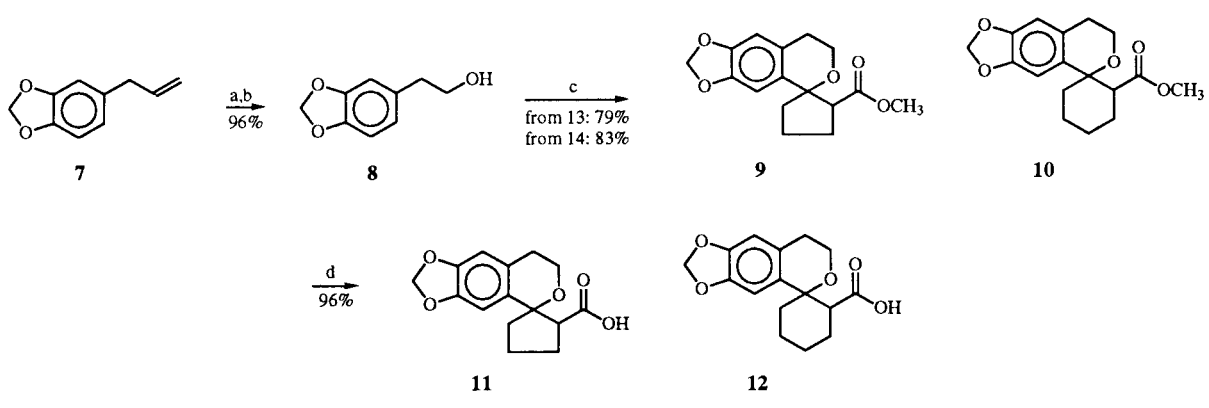
Chemistry.

Our synthetic approach to the new derivatives **11** and **12** indicated the methylenedioxyphenylacetic alcohol derivative **8** as an important intermediate, which can be submitted to a modified Friedel-Crafts reaction, using acid-catalysis condensation conditions with the appropriate cyclic carbonyl compounds [12] to promote an intramolecular regioalkylation of the 6 position of the ring of phenylethyl alcohol **8**, producing in a single synthetic operation the benzylic spiro center of the desired dihydropyran system. The alcohol derivative **8** could be easily prepared from natural product **7** using a previously described procedure [13,14] involving ozonolyzis of the terminal double bond, followed by a reductive work-up. In fact, the key step in the planned synthetic route could be carried out after a careful examination of the experimental conditions. This step was executed differently than that anticipated because we are not able to promote the desired intramolecular acylation process using any Bronsted acid (*e.g. p*-toluenesulfonic acid) as catalyst as previously accomplished in the synthesis of derivatives **5** and **6** [10]. Fortunately, it was gratifying therefore to find that treatment of the alcohol **8** with an equimolecular amount of the appropriate β-ketoester-2-carbomethoxycyclopenten-1-one (**13**) and 2-carbomethoxycyclohexen-1-one (**14**), in tetrahydrofuran, employing an ethereal solution of boron trifluoride as Lewis acid catalyst [15] produced as the only product the new 4-spiro-substituted isochroman esters **9** and **10** in 79% and 83% yield respectively, as a diastereomeric mixture (Scheme 1).

In order to verify the possible regiocontrol of this process, a careful analysis of the pmr spectra of esters **9** and **10** was performed. The pmr spectra of the ester **9** showed as the principal characteristic, two signals occurring at 6.51 and 6.61 ppm as two singlets indicating a typical *para*-aromatic hydrogen pattern. Another representative signal in this spectrum occurs at 5.89 ppm and was attributed to the methylenedioxy group in both spectra of these two esters **9** and **10** with the presence of the major isomer in a 9:1 ratio. It was observed by the relative integration of the signals of the dihydropyran hydrogens. In fact, the analysis of the pmr spectrum of **10** showed two sets of multiplet signals at 3.87 and 3.66 ppm, 4.21 and 5.31 ppm (J = 5.0 Hz) attributed to the isochromanyl ring hydrogens, suggesting a global diastereoselective process. Curiously, in the spectra of both esters was observed just a single signal due to the methylenedioxy hydrogens at 5.86 and 5.89 ppm, respectively. Despite several attempts to separate the major isomer using chromatographic methods (*e.g.* tlc and column) we were not able to obtain it in a high degree of purity. In order to obtain an indication of the diastereomeric nature of this isomer a preliminary conformational analysis of ester **9** was performed using the force field molecular mechanics method (MM2) [16] that shows an energy barrier of 0.7 kcal/mole between the two diastereoisomers, favoring the *SR/RS* compound (Figure 1).

On the other hand, the complete regiocontrol observed

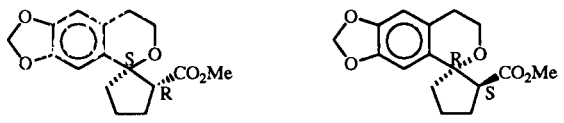
Scheme 1



7 8 9 10

11 12

a) O_3, AcOH, Zn; b) $NaBH_4$, MeOH, O°C; c) BF_3•EtOEt, THF, 2-Carbomethoxycyclopentan-1-one (13) or Carbomethoxycyclohexan-1-one (14); d) KOH, MeOH/HOH, ref.



SR/RS
Diastereoisomer

Figure 1

in this reaction is probably due to a suitable activation effect promoted by the methylenedioxy group at the C-6 position of the phenyl ring in alcohol **8**. The diastereoselectivity observed in this process can be attributed to the nature of the probable oxonium ion intermediate, which must suffer nucleophilic attack of the regioactivated C-6 position of the aromatic ring by the less hindered side, *i.e.* by the face opposite to the ester group.

Finally, the esters **9** and **10** were hydrolyzed under classical conditions [1a] to produce the desired spiroisochroman acetic acids **11** and **12**. These compounds were submitted to pharmacological evaluation first using the carrageenan induced rat paw edema test [17], showing weak antiinflammatory activity as anticipated. Fortunately, when these compounds were submitted to the analgesic test, using the writhing test, using i.p. injection of a 2% acetic acid solution as the constrictor agent [17], there was observed, after oral administration of the test compounds in mice, a very powerful analgesic activity to the acid **11**. It was possible to osberve the reduction of the number of constrictions induced by the acetic acid solution. Comparing the analgesic effect observed with the acid **12**, the spirocyclopentane acid **11** was two-fold more active showing a comparable analgesic profile to that observed for dipirone used as a standard at the same molar concentration. These results seem to indicate that conformational constraints favoring the analgesic profile induced by the spirocyclopentane ring is more effective than that caused by the spiro-6 membered ring.

EXPERIMENTAL

Proton magnetic resonance (pmr) was determined in deuteriochloroform containing *ca.* 1% tetramethylsilane as internal standard with VXR Varian at 300 MHz. Infrared (ir) spectra were obtained in a Perkin-Elmer 781 spectrophotometer. Mass spectra were measured on a CG/MS Micromass 12 apparatus.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm x 6.0 cm aluminium sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light. 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. 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.

Spiro-[2-carbomethoxycyclopentane-1,1-(6,7-methylenedioxy)-isochroman] (**9**).

To a solution of 0.8 g (4.85 mmoles) of the alcohol **8** dissolved in 30 ml of dry tetrahydrofuran was added 0.62 g (4.90 mmoles) of 2-carbomethoxycyclopentan-1-one (**13**) dissolved in 5 ml of dry tetrahydrofuran and the mixture was stirred for 5 minutes. After this time was next added 0.6 ml of a 1*M* ethereal solution of boron trifluoride. The reaction mixture was stirred overnight at room temperature and then treated by careful addition of cold water (20 ml) and extracted with ethyl ether (3 x 25 ml). The ether layer was separated, treated with brine (15 ml) and dried. The solvent was evaporated to yield an oil which was next purified by flash chromatography using a mixture of *n*-hexanes/ethyl acetate (10:1) as eluting to afford 1.12 g (79%) of the ester **9** as a pale yellow oil; ir (film): CO 1720, CO_2 1200 cm^{-1}; pmr: 5.90 (s, OCH_2O), 3.87 (m, $COCH_2$), 3.66 (CH_2), 3.51 ppm (s, OCH_3); ms: (m/z) 290 (M+, 4%), 232 (24%), 203 (100%), 135 (49%).

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.21. Found: C, 66.31; H, 6.20.

Spiro[2-carbomethoxycyclohexene-1,1-(6,7-methylenedioxy)-isochroman] (**10**).

Using the same experimental procedure described above, 0.8 g (4.85 mmoles) of alcohol **8**, 0.76 g (4.90 mmoles) of 2-carbomethoxycyclohexan-1-one (**14**) was treated with 0.6 ml of an 1*M* ethereal solution of boron trifluoride to afford, after the same work-up, and chromatographic purification, 1.23 g (83%) of the ester **10** as a clear oil; ir: CO 1725, CO_2 1260 cm^{-1}; pmr: 6.64 (2 s, Ar), 5.86 (s, OCH_2O), 4.23 (m, OCH_2), 3.49 (s, OCH_3); ms: (m/z) 304 (M+, 6%), 220 (21%), 205 (56%), 149 (73%), 135 (100%).

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.10; H, 6.58. Found: C, 67.36; H, 6.93.

Spiro[2-carboxycyclopentane-1,1-(6,7-methylenedioxy)isochroman] (**11**).

To a mixture of 1.66 g (5.76 mmoles) of the methyl ester **9** dissolved in a mixture of 50 ml of methanol/water (1:1) was added 0.33 g (5.90 mmoles) of potassium hydroxide and the reaction mixture was stirred for 6 hours at 90°. After this time the reaction mixture was cooled and acidified to *p*H 3.0 with a 10% hydrochloric acid solution. After the usual work-up a white solid as product was obtained. Recrystallization from ethanol:water gave 1.51 g (96%) of the acid **11**, mp 150°; ir: OH 2960, CO 1710 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}O_5$: C, 65.33; H, 5.63. Found: C, 65.40; H, 5.68.

Spiro[2-carboxycyclohexane-1,1-(6,7-methylenedioxy)isochroman] (**12**).

Using the same experimental procedure described above 1.75 g (5.76 mmoles) of the methyl ester **10** was hydrolized to furnish 1.55 g (93%) of the acid **12**, mp 210°; ir: OH 2975, CO 1705 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}O_5$: C, 66.44; H, 5.88. Found: C, 66.45; H, 5.85.

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REFERENCES AND NOTES

[1a] This work is part **13** in the series: Synthesis of Bioactive Compounds from Abundant Natural Product, for part **12**, see: C. A. M. Fraga and E. J. Barreiro, *J. Heterocyclic Chem.*, **29**, 1667 (1992). This paper represents the contribution 03 from LASSBio, UFRJ; [b] Taken in part from M.Sc. Thesis of L. M. C., Universidade Federal do Rio de Janiro, R.J., Brazil, 1993.

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