CHEMIJA. 2005. T. 16. Nr. 1. P. 61–64

Synthesis of 1-(2-methyl-2,3-dihydrobenzo [*b*]furan-5-yl)-3-phenyl-2-propen-1-one derivatives and analogues

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A series of new 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-one derivatives (**2b-k**) were synthesized by the condensation of 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-1-ethanone with aromatic aldehydes. Analogously 1-(5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-3-phenyl-2-propen-1-one (**6**) was obtained from 1-(5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-1-ethanone (**5**). The synthesized compounds were tested for anti-inflammatory activity.

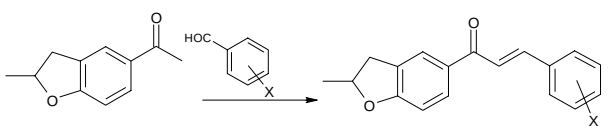
Key words: 2,3-dihydrobenzo[*b*]furane derivatives, 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-ones, 1-(5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-3-phenyl-2-propen-1-one, Claisen rearrangement, anti-inflammatory activity

INTRODUCTION

Cyclic alkoxy- and dialkoxychalkone derivatives [1–3] and their steric analogues [4] are well known for their anti-inflammatory activity and low toxicity. Previously we have also found that their anti-inflammatory activity varies depending on the nature of substituents or on both aromatic rings of chalkones [2, 3]. The presence of methyl group in the 2nd position of 2,3-dihydrobenzo[*b*]furane usually enhances the anti-inflammatory activity of chalkones [1]. For this reason and as an extension of our interest in studies of the structure–activity relationship of alkoxy- and dialkoxychalkones a series of 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-one (**2a**, known for anti-inflammatory activity) derivatives (**2b-k**, **6**) and the compound of related structure **10**, were synthesized and investigated for their anti-inflammatory activity.

RESULTS AND DISCUSSION

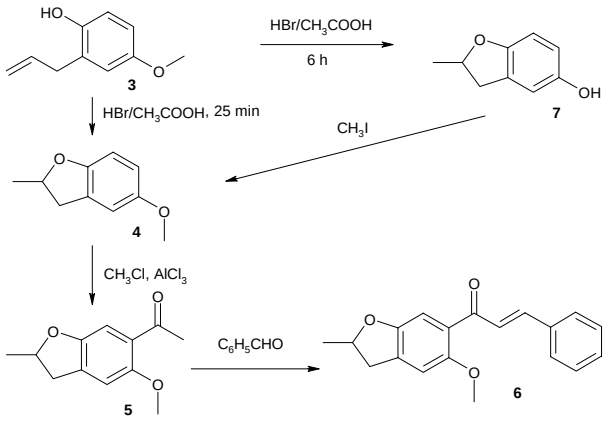
1-(Methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-ones (**2b-k**) were synthesized by the base-catalysed condensation of 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-1-ethanone (**1**) with aromatic aldehydes in methanol:



1 **2a-k**

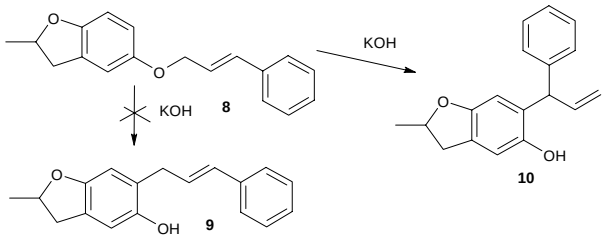
X = H(a), 2-F(b), 4-F(c), 2-Cl(d), 4-Cl(e), 4-Br(f), 4-CH_3(g), 4-OH(h), 4-OCH_3(i), 3,4-$(OCH_3)_2$(j), 2-furyl(k).

The yield of compounds 2b-k was higher when aldehydes containing the electron withdrawing group were used. Analoguously 1-(5-methoxy-2methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-3-phenyl-2-propen-1-one (**6**) was synthesized by the condensation of 1-(5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-1-ethanone (**5**) with benzaldehyde. Compound **5** was synthesized by the acylation of 5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan (**4**) with acethyl chloride in the presence of anhydrous aluminium chloride. Compound **4** was synthesized by the methylation of hydroxyderivative **7** [6]. Later it has been found that **4** can be synthesized directly and with a better yield (60% instead of 36%) from allylderivative **3** treating it with a diluted solution of aqueous hydrogen bromide in acetic acid for a short time. 5-Hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan (**7**) was obtained from compound **3** by known methods [7].



3 **7** **4** **5** **6**

In our previous experience [8–10], carbonyl group is necessary for anti-inflammatory activity of chalkone derivatives. The reduction of carbonyl group led to inactive alkohols. However, the source [4] has reported about strong anti-inflammatory activity of 6-[3-phenyl-2-propenyl]-2,3-dihydrobenzo[*b*]furan-5-ol. For this reason it was interesting to synthesize the analogue of the mentioned compound, alkohol **9**, and to investigate the reasons of its activity. According to source [4], compound **9** should result from C-alkylation of compound **7** with 3-phenyl-2-propenyl chloride analoguously like 3-(2,3-dihydrobenzo[*b*]furan-5-yloxy)-1-phenyl-1-propene. However, compound **9** underwent a spontaneous Claisen type rearrangement to give compound **10**.



Both compounds **2b-k** and **6** possess no or slight (1/4 to 1/2 of that shown by compound **2a**) anti-inflammatory activity. Compound **10** was inactive as well.

Due to the low activity of compounds **2b-k**, **6** and **10** their acute toxicity was not investigated.

The postulated structures of the newly synthesized compounds **2b-k**, **5**, **6**, **8** and **10** are in agreement with their IR and ^{1}H NMR spectral and elemental analysis (Table) data. 1-(2-Methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-1-ethanone (**1**) was obtained by known methods [5].

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) in nujol and ^{1}H-NMR spectra –- on a BS-587A (80 MHz, Tesla, Brno, Czech Republic) with TMS as internal standart. Chemical shifts (δ) are reported in ppm.

1-(2-Methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-ones (**2b-k**): The mixture of 2 g (11.3 mmol) 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-1-ethanone, 11.3 mmol aromatic aldehyde, solution of 0.4 g (10 mmol) sodium hydroxide in 4 ml water and 20 ml methanol was refluxed for 4 h (**2b-f**, **i**, **j**), or 20 h (**2h**), or kept at room temperature for 3 days (**2k**). Then the reaction mixture was acidified with 2 ml of acetic acid, poured into 150 ml of water, extracted with benzene. After drying and evaporating of benzene *in vacuo* the obtained product was crystallized from 2-propanol or distilled *in vacuo*.

2b: Yield 1.5 g (46%), b. p. /1 mm 225–230 °C. IR ν (cm^{-1}): 1660 (C=O). ^{1}H NMR ($CDCl_3$): 1.43 (3H, d, CH_3), 2.67–3.52 (2H, m, CH_2), 5.01 (1H, st, CH), 6.77 (1H, s, 7-H), 6.98–7.90 (8H, m, CH=CH and ArH);

2c: Yield 2.2 g (68%), m.p. 104–105 °C. IR ν (cm^{-1}): 1656 (C=O). ^{1}H NMR ($CDCl_3$): 1.48 (3H, d, CH_3), 2.67–3.52 (2H, m, CH_2), 4.98 (1H, st, CH), 6.78 (1H, s, 7-H), 6.95–7.69 (8H, m, CH=CH and ArH);

2d: Yield 2.1 g (62%), b. p. /1 mm 190–193 °C, m.p. 67–69 °C. IR ν (cm^{-1}): 1656 (C=O). ^{1}H NMR ($CDCl_3$): 1.47 (3H, d, CH_3), 2.67–3.53 (2H, m, CH_2), 5.00 (1H, st, CH), 6.78 (1H, s, 7-H), 7.20–8.22 (9H, m, CH=CH and ArH);

2e: Yield 3.5 g (90%), m. p. 135–136 °C. IR ν (cm^{-1}): 1656 (CO). ^{1}H NMR ($CDCl_3$): 1.48 (3H, d, CH_3), 2.67–3.52 (2H, m, CH_2), 5.02 (1H, st, CH), 6.80 (1H, s, 7-H), 7.29–7.90 (8H, m, CH=CH and ArH);

2f: Yield 3.1 g (82%), m. p. 136–137 °C. IR ν (cm^{-1}): 1654 (C=O). ^{1}H NMR ($CDCl_3$): 1.47 (3H, d, CH_3), 2.67–3.53 (2H, m, CH_2), 4.98 (1H, st, CH), 6.77 (1H, s, 7-H), 7.47–7.61 (8H, m, CH=CH and ArH);

2g: Yield 1.8 g (58%), m. p. 128–130 °C. IR ν (cm^{-1}): 1652 (C=O). ^{1}H NMR (Acetone-D_6): 1.44 (3H, d, CH_3), 2.35 (3H, s, CH_3), 2.87–3.72 (2H, m, CH_2), 5.01 (1H, st, CH), 6.80 (1H, s, 7-H), 7.22–7.73 (8H, m, CH=CH and ArH);

2h: Yield 0.7 g (18%), m. p. 178–180 °C. IR ν (cm^{-1}): 1680 (C=O). ^{1}H NMR (Acetone-D_6): 1.39 (3H, d, CH_3), 2.77 (1H, s, OH), 2.67–3.52 (2H, m, CH_2), 5.02 (1H, st, CH), 6.87 (1H, s, 7-H), 7.32–7.90 (8H, m, CH=CH and ArH);

2i: Yield 1.2 g (36%), m. p. 116–118 °C. IR ν (cm^{-1}): 1659 (C=O). ^{1}H NMR ($CDCl_3$): 1.46 (3H, d, CH_3), 2.67–3.53 (2H, m, CH_2), 3.82 (3H, s, OCH_3), 5.01 (1H, st, CH), 6.78 (1H, s, 7-H), 6.95–7.67 (8H, m, CH=CH and ArH);

2j: Yield 0.8 g (22%), b. p. / 1 mm 280-285 °C. IR ν (cm^{-1}): 1679 (C=O). ^{1}H NMR (Acetone-D_6): 1.51 (3H, d, CH_3), 2.83–3.75 (2H, m, CH_2), 4.08 (6H, s, OCH_3), 5.32 (1H, st, CH), 7.15 (1H, s, 7-H), 7.41–8.47 (7H, m, CH=CH and ArH);

2k: Yield 1.0 g (36%), m. p. 57–60 °C. IR ν (cm^{-1}): 1652 (C=O). ^{1}H NMR (Acetone-D_6): 1.49 (3H, d, CH_3), 2.70–3.55 (2H, m, CH_2), 5.00 (1H, st, CH), 6.55–7.97 (8H, m, CH=CH and ArH).

1-(5-Methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-1-ethanone (**5**): To a stirred and cooled to –10 °C solution of 6.7 g (40 mmol) 5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan (**4**) and 4 g (50 mmol) acetyl chloride in 50 ml of dichloromethane 7 g (50 mmol) of anhydrous aluminium chloride was added portionwise below –8 °C. Then the reaction mixture was kept at 0–5 °C and poured into ice water. Dichloromethane solution was washed with sodium car-

bonate solution, dried and evaporated. The obtained oil was distilled in vacuo. **2 g**: Yield 4.8 g (58%), b. p. 146–149 °C. IR ν (cm^{-1}): 1664 (C=O). ^{1}H NMR (Acetone-D_6): 1.46 (3H, d, CH_3), 2.50 (3H, s, $COCH_3$), 2.65–3.50 (2H, m, CH_2), 3.73 (3H, s, OCH_3), 5.02 (1H, st, CH), 6.97 and 7.03 (2H, s, ArH).

1-(5-Methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-3-phenyl-2-propen-1-one (**6**): The mixture of 1.6 g (7.8 mmol) 1-(5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-1-ethanone (**5**), 0.9 g (8.5 mmol) benzaldehyde, 20 ml methanol and solution of 0.4 g (10 mmol) sodium hydroxide in 3 ml water was refluxed for 4 h, cooled to room temperature, poured into 150 ml of water, acidified with 2 ml of acetic acid and extracted with benzene. Benzene solution was dried and evaporated, the obtained product was distilled *in vacuo*. Yield 1.8 g (78%), b. p. /1 mm 250–255 °C. IR ν (cm^{-1}): 1648 (C=O). ^{1}H NMR (Acetone-D_6): 1.49 (3H, d, CH_3), 2.52–3.37 (2H, m, CH_2), 3.75 (3H, s, OCH_3), 5.07 (1H, st, CH), 6.97–7.88 (9H, m, CH=CH and ArH).

3-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yloxy)-1-phenyl-1-propene (**8**): To a solution of 4.6 g (30 mmol) of 5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan (**7**) and 4.6 g (40 mmol) 3-phenyl-2-propenyl chloride in a mixture of 25 ml acetone and 25 ml DMSO 2.5 g (38 mmol) sodium hydroxide was added. The reaction mixture was refluxed for 7 h, cooled, poured into 500 ml of water and extracted with ether. The obtained oil was distilled *in vacuo* after evaporation of ether. Yield 5.0 g (60%), b. p. /3 mm 207–210 °C. ^{1}H NMR ($CDCl_3$): 1.28 (3H, d, CH_3), 2.67–3.35 (2H, m, CH_2), 4.77 (1H, st, CH), 4.84–5.23 (1H, m, $CH=CHCH_2$), 6.25–6.54 (4H, m, $CH=CHCH_2$, ArH), 7.17 (5H, s, C_6H_5).

2-Methyl-6-(1-phenylallyl)-2,3-dihydrobenzo[*b*]furan-5-ol (**10**): 5 g of 3-(2-Methyl-2,3-dihydrobenzo[*b*]furan-5-yloxy)-1-phenyl-1-propene (**8**) was kept for 7 days at room temperature; the obtained compound was isolated chromatografically using silica gel as a solid phase and a mixture of hexane and ether 3:1 as an eluent and recrystallized from a mixture of hexane and benzene 4:1. Yield 2.4 g (48%), m. p. 96–98 °C. ^{1}H NMR ($CDCl_3$): 1.32 (3H, d, CH_3), 2.50–3.35 (2H, m, CH_2), 4.72 (1H, st, CH), 4.70–5.00 (2H, m, $CH_2=$), 6.10–6.40 (1H, m, CH), 6.43 and 6.67 (2H, s, ArH), 7.19 (5H, s, C_6H_5), 7.64 (1H, s, OH).

PHARMACOLOGICAL EXPERIMENTS

Adult male Wistar strain rats weighing 180–220 g and male BALB/C strain mices weighing 18–22 g were used. The animals were allowed food and water *ad libitum*. They were housed in rooms at 18–20 °C with a 12-h light/dark cycle and relative humidity of 55–60%. The animals were randomly allocated into groups at the beginning of all experiments. All test compounds and the reference drugs were administered orally suspended in 0.5% solution of carboxymethylcellulose. Carrageenin-induced hind paw oedema in rats was produced by the method of Winter et al. [7]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the right hind paw 1 h after administration of the test compound. Control animals received only 0.5% carboxymethylcellulose solution. Right hind paw volume was measured with an electronic oncograph immediately before and 1, 2, 3, and 5 h after carrageenin injection. The increase of the results was matched with that in control rats. Each experiment was made with 5 groups of rats, 10 animals each (the 1st one was control). Analogously was produced and studied right hind paw oedema induced with 0.1 ml 5% bentonite suspension [8]. The data were evaluated statistically using Student's t test. A level of $p < 0.05$ was adopted for the test of significance.

CONCLUSIONS

A series of new 1-(2-methyl-2,3-dihydrobenzo[*b*]furan-5-yl)-3-phenyl-2-propen-1-one derivatives and analogues were synthesized. The convenient method for the synthesis of 5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan was elaborated. All tested compounds showed a slight or no anti-inflammatory activity.

ACKNOWLEDGEMENT

Author is grateful to Dr. E. Udrënaitë (Faculty of Medicine, Vilnius University, M. K. Èiurlionio 21, LT-03104 Vilnius, Lithuania) for testing the compounds for anti-inflammatory activity.

Received 16 December 2004
Accepted 22 December 2004

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1-(2-METIL-2,3-DIHIDROBENZO[*B*]FURAN-5-IL)-3-FENIL-2-PROPEN-1-ONO DARINIØ IR ANALOGØ SINTEZË

S a n t r a u k a

Susintetinti nauji 1-(2-metil-2,3-dihidrobenzo[*b*]furan-5-il)-3-fenil-2-propen-1-ono dariniai (**2b-k**), **6** ir struktûriðkai panaðus 2-metil-6-(1-fenilalil)-2,3-dihidrobenzo[*b*]furan-5-olis **10**. Nustatyta, kad ðiø junginiø prieðuþdegiminis aktyvumas silpnas arba jie visiðkai neaktyvûs.