Synthesis, analgesic and anti-inflammatory activity of (1Z,3Z)-4-aryl-4-hydroxy-1-(3,3-dialkyl-3,4-dihydroisoquinoline-1(2H)-ylidene)-but-3-en-4-ones

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SYNTHESIS, ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF (1Z,3Z)-4-ARYL-4-HYDROXY-1-(3,3-DIALKYL-3,4-DIHYDROISOQUINOLINE-1(2H)-YLIDENE)-BUT-3-EN-4-ONES

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It is established that 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones react with 3,3-dialkyl-1-methyl-3,4-dihydroisoquinolines with the formation of (1*Z*,3*Z*)-4-aryl-4-hydroxy-1-(3,3-dialkyl-3,4-dihydroisoquinoline-1(2*H*)-ylidene)-but-3-en-4-ones. The synthesized compounds were tested for anti-inflammatory and analgesic properties.

Key words: dioxinones, 1-methyl-3,4-dihydroisoquinolines, analgesic activity, anti-inflammatory activity.

Acylation of 1-methyl-3,4-dihydroisoquinolines by 5-arylfuran-2,3-diones produced aroylpyruvyl-substituted 1-methyl-3,4-dihydroisoquinolines, (2*Z*,5*Z*)-1-aryl-3-hydroxy-5-(3,3-dialkyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-pent-2-en-1,4-diones [1], the analgesic and anti-inflammatory activity of which was studied. We reacted 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin–ones (**Ia** and **Ib**) with 3,3-dialkyl- 1-methyl-3,4-dihydroisoquinolines (**IIa** – **c**) in a 1:1 ratio with heating in anhydrous toluene for 60 – 90 min (TLC monitoring) to produce (1*Z*,3*Z*)-4-aryl-4-hydroxy-1-(3,3-dialkyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-but-3-en-2-ones (**IIIa** – **d**) in order to study the analgesic and anti-inflammatory activity of aroylacetyl-substituted 1-methyl-3,4-dihydroisoquinolines.

Compounds **IIIa** – **d** were prepared in high yields (Table 1) and were yellow crystalline compounds or oils that were difficultly soluble in common organic solvents and insoluble in water and alkanes.

The structures of **IIIa** – **d** were confirmed using IR and PMR spectroscopy. Thus, IR spectra of **IIIa** – **d** contained bands for stretching vibrations of the enol OH and the NH groups that were involved in forming intramolecular H-bonds (IHB) as a broad band at 3384 – 3417 cm^{-1} and for the 2-carbonyl involved in forming an IHB as a broad band at 1582 – 1591 cm^{-1}.

PMR spectra of solutions of **IIIa** – **d** in DMSO-d_6 showed resonances for protons and other groups bonded to the aromatic rings, a singlet for the six protons of the two isoquinoline 3-methyls at 1.27 – 1.28 ppm (**IIIb** – **d**), a singlet for the three methyl protons at 1.27 and a group of resonances for the nine 3-butyl protons on the isoquinoline ring at 0.96 – 1.21 ppm (**IIIa**), a singlet for the two isoquinoline 4-CH_2 protons at 2.82 – 2.84, a singlet for the C^1H proton at 5.67 – 5.74, a singlet for the C^3H proton at 6.18 – 6.23, a singlet for the NH proton at 10.42 – 10.51, and a singlet for the enol OH proton at 16.04 – 16.06 for the ketoenol form B (**IIIa** – **d**). Furthermore, PMR spectra (**IIIa** – **d**) showed minor sets of resonances for diketone form C that included resonances for protons and other groups bonded to the aromatic rings, a singlet for six protons of the two isoquinoline 3-methyls at 1.19 – 1.20 (**IIIb** – **d**), a singlet for the three methyl protons at 1.24 and a group of resonances for the nine 3-butyl protons on the isoquinoline ring at 0.90 – 1.25 (**IIIa**), a singlet for the two protons of the isoquinoline 4-CH_2 at 2.76 – 2.79, a singlet for the two C^3H_2 protons at 4.00 – 4.07, a singlet for the C^1H proton at 5.76 – 5.82, and a singlet for the NH proton at 10.95 – 11.07. The spectral properties of **IIIa** – **d** were consistent with their existence in DMSO-d_6 solution as a mixture of ketoenol form B and diketone form C in a ratio of ~9:1.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded as mineral-oil mulls on an FSM-1201 spectrophotometer. PMR spectra were recorded in DMSO-d_6 on a Bruker AM-400 spectrometer (operating frequency 400 MHz) with TMS internal standard. The purity

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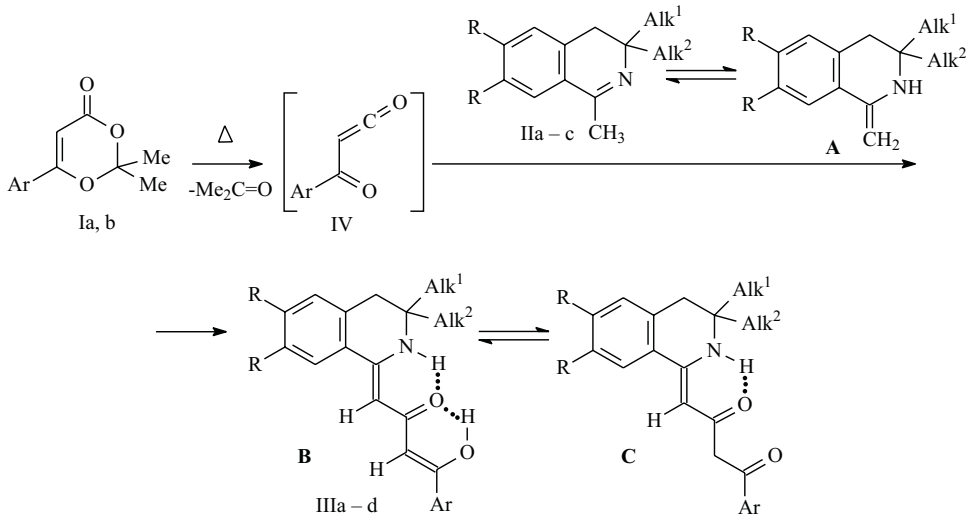

I: Ar = Ph (a), C_6H_4Me-*n* (b); II: R = H, Alk^1 = Me, Alk^2 = Bu (a), R = OMe, Alk^1 = Alk^2 = Me (b), R = OEt, Alk^1 = Alk^2 = Me (c); III: R = H, Alk^1 = Me, Alk^2 = Bu, Ar = C_6H_4OMe-*n* (a), R = OMe, Alk^1 = Alk^2 = Me, Ar = Ph (a), Ar = C_6H_4Me-*n* (c), R = OEt, Alk^1 = Alk^2 = Me, Ar = Ph (d)

TABLE 1. Properties and Yields of **IIIa** – **d**

Compound	Yield, %	mp, °C	Empirical formula
IIIa	85	164 – 166	$C_{25}H_{29}NO_2$
IIIb	87	142 – 143	$C_{23}H_{25}NO_4$
IIIc	88	139 – 141	$C_{24}H_{27}NO_4$
IIId	89	133 – 135	$C_{25}H_{29}NO_4$

of the products was confirmed by TLC on Silufol plates with elution by EtOAc:C_6H_6 (1:5) and EtOAc with detection by iodine vapor.

(1*Z*,3*Z*)-4-Hydroxy-1-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-4-(4-tolyl)-but-3-en-2-one (IIIa). A solution of 2,2-dimethyl-6-(4-tolyl)-4*H*-1,3-dioxin-4-one (**Ib**, 2.0 mmol) and isoquinoline (**IIa**, 2.0 mmol) in anhydrous toluene (20 mL) was refluxed for 60 min and cooled. The resulting precipitate (**IIIa**) was filtered off, yield 0.60 g (85%), mp 164 – 166ºC (dec., petroleum ether).

Compounds **IIIb** – **d** were synthesized analogously.

EXPERIMENTAL BIOLOGICAL PART

Analgesic activity was studied using mongrel mice (18 – 22 g) and the hot-plate method [2]. The tested compounds were injected i.p. at a dose of 50 mg/kg as suspensions in starch paste solution (2%) 30 min before placing the animals on a metallic plate heated to 53.5°C. The index of analgesic activity was the increase of residence time of an animal on the hot plate before the onset of a defensive reflex, licking of the hind paws. The effect was evaluated 2.5 h after injection of the compounds. We used animals with an initial onset time of the defensive reflex of less than 15 sec. Each compound was tested in six animals. The reference drug was analgin.

TABLE 2. Analgesic Activity of **IIIa** – **d**

Compound	Dose, mg/kg, i.p.	Defensive reflex time, s
IIIa	50	21.7 ± 3.12 *
IIIb	50	18.3 ± 2.10 *
IIIc	50	14.0 ± 1.41 *
IIId	50	16.3 ± 3.0 *
Analgin	93 (ED_{50})	16.30 ± 3.0
Control (2% starch paste solution)	–	10.6 ± 1.21

* $p < 0.05$ compared with control.

TABLE 3. Anti-inflammatory Activity of **IIIa** and **IIIc**

Compound	Dose, mg/kg, i.p.	Edema increase w.r.t. initial size 4 h after carrageenan injection, %	Edema inhibition w.r.t. control after 4 h, %
IIIa	50	35.48 ± 2.18	49.53 *
IIIc	50	46.42 ± 5.99	36.24 *
Orthophen	10 (ED_{50})	27.88 ± 5.22	61.20 *
Control	–	85.60 ± 3.20	–

* $p \le 0.05$ compared with control.

Anti-inflammatory activity was studied in mongrel white rats of both sexes (180 – 220 g) using the acute inflammatory paw edema model induced by subplantar injection of carrageenan solution (1%, 0.1 mL). Compounds were injected at a dose of 50 mg/kg in starch paste solution (2%) 4 h before inflammation modeling. Each compound was tested in six animals. The anti-inflammatory effect was estimated from the degree of inhibition of the inflammatory reaction as % of the control [3]. The reference drug was orthophen.

Results were processed using the Student criterion. An effect was considered significant for $p \leq 0.05$ [4].

It was found that all studied compounds exhibited analgesic activity (Table 2). The most active compound was **IIIa**, which was stronger than analgin and also exhibited anti-inflammatory activity (Table 3).

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