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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 2-METHYL-5-[ω-PHENYLACYL]COUMARANS

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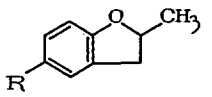
2-Methyl-5-propionylcoumaran has antiinflammatory activity and low toxicity [1]. In order to study the relationship between the chemical structure and antiinflammatory activity, and to find new therapeutic agents, we have synthesized and investigated a series of previously unknown structural analogs of these compounds, containing phenyl substituents in the acyl group (compounds II-IV).



I-IV

I—IV: R = H (I), $COCH_2Ph$ (II), $CO(CH_2)_2Ph$ (III), $CO(CH_2)_3Ph$ (IV).

Ketones II-IV were synthesized by the Friedel–Crafts reaction by acylation of 2-methylcoumaran (compound I) with the chloranhydrides of ω-phenylalkane acids in the presence of anhydrous aluminum chloride. The structures of the newly synthesized compounds II-IV were confirmed by UV, IR, and PMR spectral data; the starting compound, I, has been described previously [2]. Increases in the number of methylene groups separating the phenyl and carbonyl groups in the acyl substituent of compound II shifted the long-wave absorption band in the UV spectrum to shorter wavelengths, and increased the frequency of valent vibrations of the carbonyl group in the IR spectrum (compounds II-IV).

EXPERIMENTAL (CHEMICAL)

UV spectra were recorded on a Specord UV-VIS apparatus (Germany) in ethanol. IR spectra were recorded on a UR-20 (Germany) apparatus in Vaseline, and PMR spectra were recorded on a Tesla BS-487C (Czech Republic, 89 MHz) in CCl_4, using TMS as the internal standard.

Experimentally determined elemental analyses agreed with calculated values. The properties and yields of the newly synthesized compounds are shown in Tables 1 and 2.

3-Methyl-5-(ω-phenylacyl)coumarans (II-IV). Anhydrous $AlCl_3$ (12.0 g, 90 mmoles) was added to a mixture of 40 ml of anhydrous CH_2Cl_2, 83 mmoles of the chloranhydride of the appropriate acids, and 10.1 g (75 mmoles) of compound I at a temperature of −10°C for 15 min, and the reactions were mixed for 30 min at 20°C, poured onto ice, acidified with hydrochloric acid, and extracted with CH_2Cl_2; extracts were washed with water, dried, and evaporated.

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TABLE 1. Properties of Newly Synthesized Compounds II-IV

Compound	Yield, %	Boiling temperature, °C (1 mm Hg); melting temperature, °C (solvent)	UV spectrum λ_{max}, nm	UV spectrum lg ε	IR spectrum, $\nu_{C=O}$, cm^{-1}	Elemental formula
II	86	197—8 78—9 (ethanol)	228 294	4,11 4,16	1655	$C_{17}H_{16}O_2$
III	84	204—5 50—1 (hexane)	228 290	4,29 4,34	1670	$C_{18}H_{18}O_2$
IV	80	208—10 35—6 (hexane)	228 288	4,05 4,10	1675	$C_{19}H_{20}O_2$

TABLE 2. PMR Spectral Data (δ, ppm) for Compounds II-IV

Compound	CH_3 CH_2	CH_2CO CH_2Ph	CHAr	CH—O	7-H	C_6H_5	4-H 6-H
II	1,21 d[a]	3,95 s	2,45 dd[b,c] 2,95 dd[b,c]	4,55—4,85 m	6,51 d[b]	7,05 s	7,55—7,75 m
III	1,35 d[a]	2,35—3,25 m		4,55—4,97 m	6,56 d[b]	7,06 s	7,50—7,70 m
IV	1,34 d[a] 1,90 c[a]	2,56 t[a] 2,69 t[a]	2,58 dd[b,c] 3,13 dd[b,c]	4,55—4,98 m	6,51 d[b]	7,03 s	7,45—7,62 m

[a]J = 6 Hz.
[b]J = 8-9 Hz.
[c]J = 16 Hz.

TABLE 3. Antiinflammatory Activity and Acute Toxicity of Compound III after Oral Dosage

Compound	Dose, mg/kg	Mean percentage reduction in inflammation (compared to controls) I	Mean percentage reduction in inflammation (compared to controls) II	LD_{50}, mg/kg
III	50	55,3	47,6	2850 (2720—3120)
Acetylsalicylic acid	100	16,5	37,3	1650 (1320—2060)
Ibuprofen	80	30,8	22,0	800 (647—936)
Voltaren	25	50,1	48,8	340 (232—510)
Indomethacin	5	26,7	37,1	56,4 (28,3—89,1)

Notes. Numbers in brackets are the limits of variation at $p < 0.05$. (I) Carragheenin; (II) bentonite edema of the rat footpad.

EXPERIMENTAL (PHARMACOLOGICAL)

The compounds of interest were given orally as suspensions in 0.5% carboxymethylcellulose. Studies were carried out using male BALB/c mice weighing 18-22 g and male Wistar rats weighing 180-220 g.

Acute toxicity for mice was determined by the method of Litchfield and Wilcoxon, as modified by Rot [3]. Antiinflammatory activity was studied using experimental carragheenin [4] and betonite [5] edema in the rat footpad. Table 3 shows arithmetic mean values for percentage reduction of edema (in comparison with controls), measured 1, 2, 3, and 5 h after dosage with the study compounds.

Compound III was found to have high antiinflammatory activity and low toxicity. This compound was less active than voltaren and indomethacin, but was significantly more active than acetylsalicyclic acid and ibuprofen, and was significantly less toxic than all control therapeutic agents tested (see Table 3). Decreases and increases in the number of methylene groups separating the phenyl and carbonyl groups in the acyl substituent of compound III produced compounds II and IV, respectively, which had almost no antiinflammatory activity. Removal of the phenyl group from the acyl substituent of compound III produced the less active and more toxic propionyl analog [1].

These studies show the value of seeking new therapeutic agents among the type of ketones considered here.

REFERENCES

1. V. K. Daukshas, P. G. Gaidyalis, O. Yu. Pyatrauskas, et al., Khim.-farm. Zh., No. 5, 569-573 (1987).
2. J. Entel, C. H. Ruof, and H. C. Howard, J. Am. Chem. Soc., **73**, 2365 (1951).
3. M. L. Belen'skii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Leningrad (1963), 2nd edn., pp. 18-106.
4. C. A. Winter, E. A. Richley, and G. W. Muss, Proc. Soc. Exp. Biol. (N.Y.), No. 3, 544-547 (1962).
5. J. Marek, Pharmazie, **36**, 46-49 (1981).