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SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 3,4-POLYMETHYLENEDIOXY-1-(3-PHENYLPROPIONYL)BENZENES

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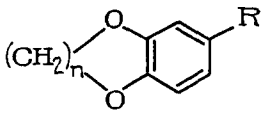
3,4-Methylenedioxy-1-(3-phenylpropionyl)benzene exhibits anti-inflammatory activity and has low toxicity [1]. Therefore, in order to study the relationship between chemical structure and pharmacological properties and to investigate novel pharmaceuticals, we have synthesized and studied some new structural analogs (IIa-d) of this ketone.

3,4-Polymethylenedioxy-1-(3-phenylpropionyl)benzenes IIa-d were synthesized by a Friedel–Crafts reaction involving acylation of the corresponding 1,2-polymethylenedioxybenzene (Ia-d) [2, 3] with 3-phenylpropionyl chloride in the presence of anhydrous aluminum chloride.



I a-d, *II* a-d

R = H (Ia - d). $COCH_2CH_2Ph$ (IIa - r): n = 2 (a), 3 (b), 4 (c), 5 (d).

The structures of compounds IIa-d synthesized were confirmed by the UV, IR, and PMR spectroscopic data (Tables 1 and 2), and the experimental data of elemental analysis corresponded to the calculated values.

In the UV spectra of compounds IIa-d the absorption bands are shifted to shorter wavelength and become less intense when the number of methylene groups (n) is increased in their heterocyclic ring, suggesting that the alkoxy substituents undergo a more significant disruption of conjugation with the aromatic ring by turning about the $C_{AR}-O$ bond [4]. In the IR spectra of ketones IIa-d the band due to stretching vibrations of the carbonyl group conjugated with the aromatic ring occurs in the region of 1660-1680 cm^{-1}.

EXPERIMENTAL (CHEMICAL)

The UV spectra were recorded on a Specord UV-VIS instrument (Germany) in ethanol, the IR spectra were recorded on a UR-20 instrument (Germany) in vaseline oil, and the PMR spectra were recorded on a Tesla BS 487C instrument (Czech Republic, 80 MHz) in CCl_4, with TMS as internal standard.

3,4-Polymethylenedioxy-1-(3-phenylpropionyl)benzenes (IIa-d). Anhydrous $AlCl_3$ (7.3 g, 55 mmole) was added at 0-5°C to a solution of 50 mmole of the respective compound Ia-d and 9.3 g (55 mmole) of 3-phenylpropionyl chloride in 60 ml of anhydrous CH_2Cl_2. The mixture was agitated for 3 h at 15-20°C, poured on to ice, acidified with HCl, and extracted with CH_2Cl_2. The extract was washed with water, dried, and concentrated.

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds IIa-d were administered perorally as a suspension in a 1% solution of carboxymethylcellulose with Tween 80 added. Male BALBc mice of weight 18-22 g and male Wistar rats of weight 150-220 g were used.

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TABLE 1. Properties of Synthesized Compounds IIa-d

Compound	Yield, %	bp, °C/1 mm	mp, °C (ethanol)	UV spectrum		IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
				λ_{max}, nm	lgε		
IIa	78	—	48-9	232	4,25	1660	$C_{17}H_{16}O_3$
				276	4,05		
				310	3,81		
IIb	65	—	64-5	226	4,22	1675	$C_{18}H_{18}O_3$
				272	4,05		
				301	3,76		
IIc	75	210-2	—	226	4,13	1680*	$C_{19}H_{20}O_3$
				275	4,03		
				296	Shld		
IId	72	216-8	—	223	»	1670*	$C_{20}H_{22}O_3$
				271	4,04		
				292	Shld		

*in pure form.

TABLE 2. PMR Spectroscopic Data (δ, ppm) for Compounds IIa-d

Compound	$(CH_2)_{n-2}$	$COCH_2CH_2$	OCH_2	5-H	6-H	2-H	C_6H_5
IIa	—	2,88 t[a]	4,25 s	6,68 d[b]	7,23-7,38 m		7,00 s
		3,01 t[a]					
IIb	2,18 q[a]	3,00 t[a]	4,18 t[a]	6,80 d[b]	7,30-7,48 m		7,10 s
		3,03 t[a]	4,26 t[a]				
IIc	1,58-2,10 m	2,92 t[a]	4,13 t[a]	6,76 d[b]	7,43 dd[b,c]	7,43 d[c]	7,13 s
		2,95 t[a]	4,41 t[a]				
IId	1,60-1,93 m	2,72 t[a]	3,98-4,15 m	6,80 d[b]	7,42 dd[b,c]	7,48 d[c]	7,10 s
		2,75 t[a]	4,23-4,43 m				

[a]J 5-6 Hz.
[b]J 8-9 Hz.
[c]J 2-3 Hz.

TABLE 3. Acute Toxicity and Anti-inflammatory Activity of Compounds IIa, c, d

Compound	LD_{50}, mg/kg	Suppression of inflammation compared to control, ED_{50}, mg/kg	
		carrageenin	bentonite
IIa	1430 (1150-1680)	137 (109-146)	118 (109-133)
IIc	2522 (2241-2736)	88 (72-103)	68 (53-81)
IId	-*	163 (151-176)	-**
ASA	1650 (1320-2060)	280 (239-321)	236 (204-268)
ibuprofen	796 (585-1126)	35 (30-40)	30 (26-35)

Note: The value ranges when $p < 0.05$ are shown in brackets. One asterisk indicates the toxicity was not determined because of its weak anti-inflammatory activity; two asterisks indicate the compound had low activity.

The acute toxicity for the mice was determined by a modification of the method of Litchfield and Wilcoxson [5]. The anti-inflammatory activity was studied using experimental models of carrageenin and bentonite edema of rat paw, which were recorded 1, 2, 3, and 5 h after administration of the compound under study. The graphically calculated ED_{50} values — the doses producing a 50% reduction in edema of the paw relative to the control — are given in Table 3. Five doses each of the compounds under study were administered to groups of 10 animals.

It was established that ketone IIc was less toxic than ketone IIa, acetylsalicylic acid (ASA), and ibuprofen, while the anti-inflammatory activity of IIc was superior to that of its previously known structural analog — the methylenedioxy derivative [1] — and ASA but inferior to that of ibuprofen. Ketones IIa and IId were less active than IIc, while ketone IIb was virtually devoid of any anti-inflammatory activity.

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