LITERATURE CITED

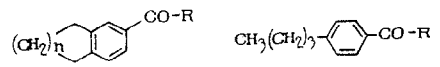
1. A. N. Vavilova and B. A. Trofimov, The Chemistry of Physiologically Active Compounds [in Russian], Moscow (1989), p. 51.
2. A. N. Gvozdevskii and A. A. Ivanov, Immunologiya, No. 5, 51-54 (1980).
3. E. V. Gubler and A. A. Genkin, Applications of Statistical Nonparametric Criteria in Medical and Biological Research [in Russian], Leningrad (1978), p. 137.
4. A. Ya. Klyats, Lab. Delo, No. 7, 422-424 (1972).
5. L. A. Mansurova, M. S. Sorokin, and N. A. Sevast'yanova, Khim.-farm. Zh., No. 9, 1088-1091 (1987).
6. L. I. Slutskii, The Biochemistry of Normal and Pathological Changes in Connective Tissue [in Russian], Leningrad (1969), p. 219.
7. B. A. Trofimov, A. N. Vavilova, S. V. Kalmykov, and V. B. Kazimirovskaya, Khim.-farm. Zh., No. 12, 1463-1465 (1989).
8. Kh. Frimel', Methods in Immunology [in Russian], Moscow (1979), p. 520.
9. R. B. Dean, Anal. Chem., 23, No. 5, 636-639 (1951).
10. N. K. Jerne and A. A. Nordin, Science, 140, No. 3565, 405-409 (1963).

SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 4-ACYL-1,2-POLYMETHYLENEBENZENES

V. K. Daukshas, P. G. Gaidyalis, L. K. Labanauskas, L. F. Gumbaragite, and G. A. Gasperavichene

UDC 615.276:547.572].012.1.07

Some acyl derivatives of coumaran, 1,3-dibenzodioxolane, and their cyclic homologs display antiinflammatory ((AI) activity, and are of low toxicity [2]. In order to examine the relationships between chemical structure and AI, and to identify novel drugs, we have synthesized and tested some carbocyclic (IIa, b, IIIa, b, and IVa-c) and alkyl (V, VI) analogs of these compounds, which are either novei, or have not been tested for AI.



Ic, IIa, b; IIIa, b; IVa-c Г, Д

I—IV: R = Me (I), Et (II, V), CH_2CH_2Ph (III, VI, $CH_2CH_2NMe_2 \times HCl$ (IV).

I—IV: n = 1(a), 2(b), 3(c).

Ketones (IIa, b), (V), and (VI) were obtained by the Friedel—Crafts acylation of indane, tetralin, or butylbenzene with 3-phenylpropionyl or propionyl chloride in the presence of anhydrous $AlCl_3$, and the aminoketone hydrochloride (IVc) by the Mannich condensation of ketone (Ic) with dimethylamine hydrochloride and paraformaldehyde.

The properties of the novel compounds are shown in Tables 1 and 2. The structures of the products were confirmed by UV, IR, and PMR spectroscopy. The UV absorptions of the carbocyclic compounds (IIIa, b) were stronger and more bathochromically shifted than those of the butyl analog (VI), the UV absorptions of the tetralin (IIIb) being strongest and most shifted. The absorption for the carbonyl group in the IR spectra of (IIIa, b), (V), and (VI) was in the same position (1688 cm^{-1}).

Compounds (Ic) [8], (IIa) [3], (IIb) [5], (IVa) [4], and (IVb) [6] have been reported previously, and the indane, tetralin, butylbenzene, and 3-phenylpropionic acid were commercial materials.

Vilnyus University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 10, pp 41-42, October, 1991. Original article submitted December 12, 1990.

 0091-150X/91/2510-0716$12.50

TABLE 1. Properties of (IIIa, b), (IVc), (V), and (VI)

Compound	Yield, %	Bp, °C/mm; n_D^{20}	Mp, °C	UV spectrum		IR spectrum $\nu_{C=O}$, cm^{-1}	Empirical formula
				λ_{max}, nm	lg ε		
IIIa	70	198—200/1	51—2	209 257 288	4,39 4,08 shoulder	1688	$C_{18}H_{18}O$
IIIb	75	207—9/1	63—4	212 258 288	4,46 4,19 shoulder	1688	$C_{19}H_{20}O$
IVc	66	—	158—9	211 216 261 288	4,23 shoulder 4,10 shoulder	1672	$C_{16}H_{23}NO \cdot HCl$
V	82	286—8/750 1,5158	—	252	4,17	1688	$C_{13}H_{18}O$
VI	46	180—2/1 1,5570	—	208 253	4,38 4,06	1688	$C_{19}H_{22}O$

TABLE 2. PMR Spectral Data (δ, ppm) for (IIIa, b), (IVc), (V), and (VI)

Compound	CH_3CH_2N	$(CH_2)_4$	CH_2Ar	CH_2Ph	CH_2CO, NCH_2CH_2CO	ArH		
						C₅H	6-H	3-H, 5-H
IIIa	—	2,05 q[a]	2,52 t[a]	3,05 t[b]	3,05 t[b]	6,92—7,25 m		7,55—7,75 m
IIIb		1,58—1,90 m	2,55—2,90 m	2,98 t[b]	3,02 t[b]	7,08 s	7,45 d[c]	7,48—7,58 m
IVc[d]	2,88 s	1,42—1,92 m	2,58—3,02 m	—	3,55 s	—	7,15 d[c]	7,63—7,87 m
V	0,91 t[a] 1,12 t[a]	1,20—1,81 m	2,58 t[a]	—	2,82 q[a]	—	7,13 d[c]	(2H), 7,73 d[c] (3H)
VI	0,91 t[a]	1,08—1,72 m	2,45 t[a]	2,95 t[b]	3,01 t[b]	7,08 s	6,95 d[c]	(2-H), 7,71 d[c] (3-H)

[a] J=7 Hz.
[b] J=4—5 Hz.
[c] J=9 Hz.
[d] Dissolved in deuteromethanol.

EXPERIMENTAL (CHEMISTRY)

UV spectra were obtained on a Specord M 40 (Germany) in ethanol, and IR spectra on a Specord M 80 (Germany) in Vaseline mull. PMR spectra were recorded on a Tesla BS-487C (Czech SSR) (80 MHz) in CCl_4, internal standard TMS.

The yields of the novel compounds are shown in Tables 1 and 2. Their elemental analyses were in agreement with the calculated values.

1,2-Polymethylene-4-(3-phenylpropyl)benzenes (IIIa, b) and 1-butyl-4-propionylbenzene (V). To a mixture of 50 ml of dry dichloromethane, 50 mmole of indane, tetralin, or butylbenzene, and 60 mmole of propionyl chloride or 3-phenylpropionyl chloride was added at 5°C over 0.5 h 8.0 g (60 mmole) of anhydrous $AlCl_3$, and the mixture stirred for 3 h at 20°C. It was then poured on to ice, acidified with HCl, extracted with dichloromethane, the extract washed with water and sodium carbonate solution, dried, the solvent removed, and the residue distilled in vacuo and recrystallized from ethanol.

4-(3-Dimethylaminopropionyl)-1,2-pentamethylenebenzene Hydrochloride (IVc). A mixture of 20 ml of ethanol, 9.4 g (50 mmole) of the ketone (Ic), 4.5 g (55 mmole) of dimethylamine hydrochloride, 4.5 g (150 mmole) of paraformaldehyde, and two drops of conc. HCl was boiled for 8 h. The ethanol was then removed under reduced pressure, and the residue recrystallized from a 1:1 mixture of acetone and 2-propanol.

1-Butyl-4-(3-phenylpropionyl)benzene (VI). In a mixture of 50 ml of dry dichloromethane, 48.3 g (360 mmole) of butylbenzene, and 4.8 g (36 mmole) of anhydrous $AlCl_3$ was added at 10°C over 0.5 h 6.1 g (36 mmole) of 3-phenylpropionyl chloride. The mixture was stirred for 4 h at 20°C, and the ketone (VI) isolated as for (V).

TABLE 3. Acute Toxication of AI of (IVa-c) and (V) by the Subcutaneous Route

Compound	LD_{50}, mg/kg	Dose, mg/kg	Mean percentage suppression of inflammation (compared to control)	
			carrageenin	bentonite
IVa	519 (415—727)	50	51,5	65,9
IVb	210 (171—273)	50	43,5	14,3
IVc	...*	50	30,1	0
V**	...*	50	18,4	0
Lysine acetylsalicylate	1000 (890—1130)	50	18,4	8,6
		150	37,4	9,8
Acetylsalicyclic acid**	1000 (743—1382)	200	28,1	6,5
Ibuprofen**	800 (647—936)	80	30,8	22,0

Notes. One asterisk denotes no measurement in view of low AI, while two asterisks denote oral administration. Confidence limits for $p \leq 0.05$ given in brackets.

EXPERIMENTAL (PHARMACOLOGICAL)

Ketones (IIa, b), (IIIa, b), (V), and (VI), being insoluble in water, were given orally as suspensions in 1% carboxymethylcellulose solution with the addition of Tween-80, while the aminoketone hydrochlorides (IVa-c) were administered subcutaneously as the 1% aqueous solutions. Mongrel white mice weighing 18-25 g and white rats weighing 150-230 g of both sexes were used.

The acute toxicities in mice were determined by a modification of the method of Lichfield and Wilcoxon [1]. AI was evaluated using carrageenin and bentonite model edemas of the rat paw. Table 3 shows the mean arithmetical values for the percentage reduction in edema as compared with the controls, measured 1, 2, 3, and 5 h following introduction of the test compound.

The aminoketone hydrochloride (IVa) was found to possess high AI, being as active in this respect as its heterocyclic analogs (the corresponding coumaran and 1,3-benzoidoxolanes), while being less toxic [2]. Increasing the number of methylene groups in the ring in aminoketone (IVa) reduced its AI (aminoketones IVb, c), while replacement of the dimethylamino-group in aminoketones (IVa, b) by hydrogen or the phenyl group gave (IIa, b) and (IIIa, b), which were devoid of AI. The acylic analogs of these ketones were either of low activity (V), or inactive (VI).

LITERATURE CITED

1. M. L. Belen'kii, Fundamentals of the Quantitative Measurement of Pharmacological Activity, 2nd edn. [in Russian], Leningrad (1963), pp. 81-106.
2. V. K. Daukshas, P. G. Gaidyalis, O. Yu. Pyatrauskas, et al., Khim.-farm. Zh., 21, No. 5, 369-473 (1987).
3. R. T. Arnold and R. A. Barns, J. Am. Chem. Soc., 66, 960-964 (1944).
4. B. Brunova, V. Musil, Z. Horakova, and O. Nemcek, Česk. Farm., 18, 28-32 (1969); Chem. Abstr., 71, 112852b (1969).
5. H. Kölbel, Brennstoff-Chem., 30, 73-70 (1949); Chem. Abstr., 44, P2217c (1950).
6. C. Mannich and D. Lammering, Ber. Chem. Ges., 55, 3510-3526 (1922).
7. J. Marek, Pharmazie, 36, 46-49 (1981).
8. Z. J. Veidelek, J. Nemec, and M. Protiva, Coll. Czech. Chem. Commun., 38, 2768-2777 (1975).
9. C. A. Winter, E. A. Richley, and G. W. Nuss, Proc. Soc. Exp. Biol. (New York), Vol. III, pp. 544-547 (1962).