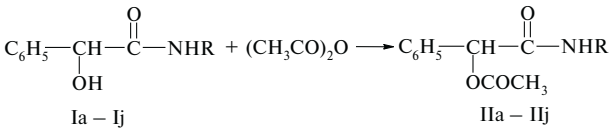
SYNTHESIS AND STUDY OF THE ANALGESIC AND ANTIINFLAMMATORY ACTIVITY OF α-ACETOXYPHENYLACETIC ACID AMIDES

I. V. Mashevskaya,[1] M. I. Vakhrin,[1] V. A. Safin,[1] I. A. D'yakova,[2] M. A. Nikiforova,[2] S. Yu. Solodnikov,[2] and L. V. Anikina[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 35, No. 4, pp. 22 – 23, April, 2001.

Original article submitted February 17, 1990.

In order to study the effect of acetylation on the biological activity of compounds, we have synthesized a series of O-acetyl derivatives of phenylhydroxyacetic acid amides according to the scheme



Ia – Ij IIa – IIj

(for R see Table 1)

The initial compounds Ia – Ij were obtained using the method described in [1]; the acetylation reaction with acetic anhydride was performed on heating in benzene. The yields and physicochemical characteristics of acetyl derivatives IIa – IIj are presented in Table 1. The target products were obtained with a yield of 50 – 67%. All compounds are readily soluble in DMSO, DMF, acetone, and ethanol; compounds IIa and IIb are moderately soluble in water.

The proposed structures of compounds IIa – IIj were confirmed by the ^{1}H NMR spectroscopic data. The spectra display singlet signals due to protons of the CH groups (δ = 6.00 – 6.20 ppm) and CH_3 groups of the acetyl component (δ = 2.00 – 2.18 ppm). In the spectra of compounds IIb, IId, and IIg, the signals from protons of the alkyl groups range within δ = 0.81 – 4.37 ppm. The spectra also contain signals due to the protons of amide groups; the spectrum of unsubstituted amide IIa displays two signals from protons of the NH group, which is evidence of hindered rotation in the amide group.

Compounds IIa – IId, IIh, and IIi were characterized with respect to their antiinflammatory and analgesic properties. The results of these tests are summarized in Table 2. It was established that only compound IIi produced a reliable analgesic action comparable with that of a reference drug (analgin). At the same time, all compounds exhibited pro-

[1] State Pharmaceutical Academy, Perm, Russia.
[2] Institute of Natural Sciences, Perm State University, Perm, Russia.

TABLE 1. Yields and Physicochemical Characteristics of Compounds IIa – IIj

Compound	R	Yield, %	M.p., °C*	Empirical formula	^{1}H NMR chemical shift: δ, ppm				
					CH	CH_3	Alkyl	Aryl	NH
IIa	H	62	110 – 112	$C_{10}H_{11}NO_3$	6.04	2.08	–	6.83 – 7.80	6.43, 6.73
IIb	CH_3	65	92 – 93	$C_{11}H_{13}NO_3$	6.07	2.14	2.76	6.93 – 8.03	6.50
IIc	*n*-C_3H_7	67	165 – 166	$C_{13}H_{17}NO_3$	6.13	2.10	2.30 – 3.30	7.00 – 7.80	7.60 – 8.30
IId	*n*-C_4H_9	62	94 – 95	$C_{14}H_{19}NO_3$	6.03	2.11	0.81 – 3.14	6.87 – 7.80	6.37
IIe	C_6H_5	60	115 – 116	$C_{16}H_{15}NO_3$	6.20	2.18	–	7.03 – 7.63	7.96
IIg	C_6H_4–CH_3-4	53	147 – 148	$C_{17}H_{17}NO_3$	6.17	2.14	2.24	6.70 – 7.63	7.96
IIh	C_6H_4–Cl-4	50	142 – 143	$C_{16}H_{14}ClNO_3$	6.00	2.00	–	7.03 – 8.06	10.06
IIi	$C_6H_5CH_2$	63	78 – 79	$C_{17}H_{17}NO_3$	6.07	2.08	4.37	6.93 – 7.56	6.63
IIj	C_5H_4N-2	57	89 – 90	$C_{15}H_{14}N_2O_3$	6.20	2.14	–	6.33 – 8.50	9.19

* Compounds IIb, IIc, IId, and IIh were recrystallized from aqueous ethanol and the other, from acetone.

TABLE 2. Antiinflammatory (I) and Analgesic (II) Activity of Compounds II

Compound	II	I		
	Edema volume growth, % of initial foot volume	Latent period of defensive reflex (sec) after		
		30 min	60 min	120 min
IIa	10.0 ± 4.3 $p < 0.001$	9.4 ± 1.8 $p < 0.5$	9.9 ± 1.9 $p > 0.5$	10.8 ± 1.7 $p > 0.5$
IIb	33.5 ± 5.9 $p < 0.001$	12.4 ± 2.6 $p < 0.1$	10.1 ± 1.6 $p < 0.5$	10.2 ± 1.5 $p < 0.5$
IIc	37.3 ± 9.9 $p < 0.002$	5.8 ± 0.6 $p < 0.1$	5.7 ± 0.4 $p < 0.02$	9.2 ± 1.5 $p < 0.5$
IId	35.6 ± 5.6 $p < 0.001$	7.0 ± 0.9 $p < 0.5$	6.8 ± 1.4 $p < 0.25$	9.3 ± 0.8 $p > 0.5$
IIh	43.9 ± 6.9 $p < 0.01$	8.9 ± 0.6 $p > 0.5$	8.7 ± 1.2 $p > 0.5$	8.6 ± 0.5 $p < 0.5$
IIi	18.8 ± 1.8 $p < 0.001$	11.5 ± 0.7 $p < 0.05$	9.3 ± 1.4 $p > 0.5$	17.1 ± 1.4 $p < 0.05$
Ortophen	27.9 ± 5.2 $p < 0.001$	–	–	–
Analgin	–	13.1 ± 0.9 $p < 0.01$	12.8 ± 1.9 $p < 0.05$	16.3 ± 3.0 $p < 0.1$
Control (2% starch jelly)	72.6 ± 8.9	8.5 ± 0.9	8.9 ± 0.8	10.8 ± 1.6

nounced antiinflammatory properties. The most active compounds IIa and IIi were even more effective than ortophen.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured at 25°C on an RS-60 spectrometer (working frequency, 60 MHz) using deuterated DMSO as the solvent and HMDS as the internal standard. The data of elemental analyses for nitrogen agree with the results of calculations based on the empirical formulas.

α-Acetoxyphenylacetic acid methylamide (IIb). To a solution of 1.65 g (0.01 mole) of α-acetoxyphenylacetic acid methylamide Ib in 10 ml of benzene was added with stirring 2ml (0.02 mole) of acetic anhydride. The mixture was boiled for 5 – 6 h, after which the solvent (benzene) was distilled off. The residual mass was diluted with 5 ml of water and neutralized. The precipitate was filtered, dried, and recrystallized from aqueous ethanol. Yield of compound IIb, 1.34 g (65%); m.p., 92 – 93°C.

Compounds IIa and IIc – IIj were synthesized using analogous procedures.

EXPERIMENTAL PHARMACOLOGICAL PART

The analgesic activity was studied on a group of both male and female white mongrel mice weighing 18 – 22 g subjected to a hot plate test. The compounds were injected 1 h before test in a dose of 50 mg/kg (i.p.) with a 2% starch jelly (0.1 ml per 100 g body weight) [2]. The reference drug was analgin administered in a dose of ED_{50} = 93 mg/kg. The drug activity was evaluated 30, 60, and 120 min after introduction by measuring the increase in the latent time of the defensive response (hind paw licking).

The antiinflammatory activity was studied on a group of both male and female rats weighing 180 – 220 g using a carrageenan-induced edema model [2]. An increase in the foot edema volume was determined oncometrically before and 4 h after carrageenan injection. The reference drug was ortophen (10 mg/kg).

REFERENCES

1. M. S. Mashevskaya, V. S. Zalesov, and L. B. Falaleeva, USSR Inventor's Certificate No. 803358 (08.10.80).
2. B. A. Prozorovskii, *Farmakol. Toksikol.*, No. 4, 497 – 502 (1978).
3. F. P. Trikus, N. L. Makhorod, and B. N. Kolebanov, *Nonstandard Antiinflammatory Agents* [in Russian], Zdorov'e, Kiev (1975).