SYNTHESIS AND ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF N-[2-(*p*-HYDROXYPHENYL)-1,1-DIALKYLETHYL]MALONAMIC ACID ESTERS AND HYDRAZIDES

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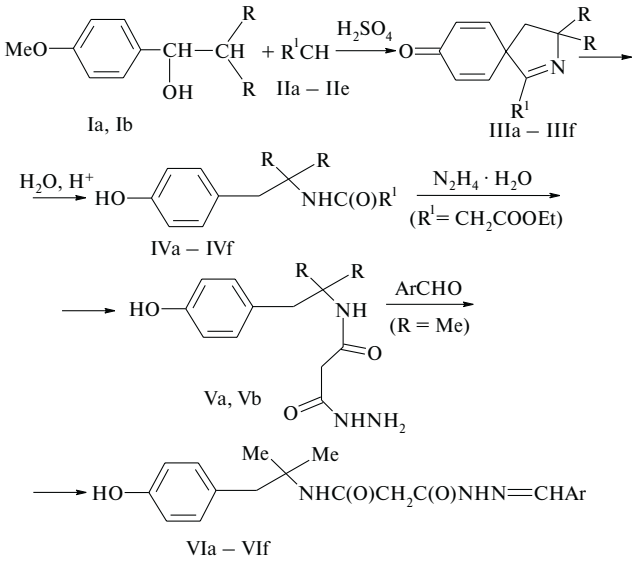
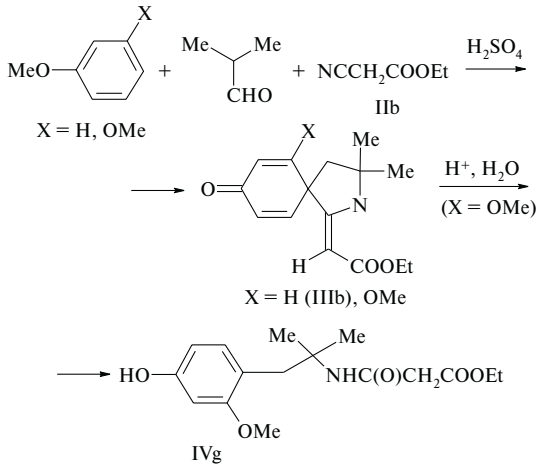
The group of malonamic acid esters, amides, and hydrazides [1] contains substances possessing anticonvulsant [2], antiinflammatory [3], and tuberculostatic [4] activity. Recently [5], we have found a new synthetic pathway to N-[2-(*p*-hydroxyphenyl)-1,1-dialkylethyl]malonamic acid ethylates via substituted spiro-(1-pyrroline-3,1′-cyclohexadienes). It was of interest to study the pharmacological properties of both the new malonamic acid derivatives and some of the intermediate spiropyrrolines (IIIa, IIIb).

At this stage, we have studied the antiinflammatory and analgesic activity of a series of spiranes (IIIa, IIIb) and amides (IVa – IVg). For comparison, we have also synthesized and characterized some N-substituted amides of benzoic (IVc, IVd), benzylthiocarboxylic (IVe), and phenylacetic (IVf) acids.





I, V: R = Me (a), 2R = $(CH_2)_5$ (b);

II: R^1 = SMe (a), CH_2COOEt (b), Ph (c), CH_2Ph (d), SCH_2Ph (e);

III: R = Me (a, b, c), R^1 = SMe (a); CH_2COOEt (b);

IV: R = Me (a, c, e), 2R = $(CH_2)_5$ (b, d, f); R^1 = CH_2COOEt (a, b), Ph (c, d), SCH_2Ph (e), CH_2Ph (f);

VI: Ar = 4-FC_6H_4 (a); 4-$MeOC_6H_4$ (b), 3,4-$(MeO)_2C_6H_3$ (c), 4-OH-3,5-(*tert*-Bu)$_2C_6H_2$ (d), 4-$NO_2C_6H_4$ (e), 2-furyl (f).

The synthesis of spiropyrroline (IIIa) and amides (IVa – IVf) was based on the interaction of carbinols (Ia, Ib) with the corresponding nitriles (IIa – IIe) in a toluene or CH_2Cl_2 medium in the presence of a 96% sulfuric acid solution (see scheme). As demonstrated in [5], the intermediate spiropyrrolines (IIIc, IIId, IIIf) cannot be isolated: these products readily undergo dienone – phenol rearrangement in acid medium when accompanied by the addition of water and form the corresponding amides (IVc, IVd, IVf). The yields of amides IVb and IVd containing pentamethylene fragments is lower as compared to the yield of dimethyl analogs because the former compounds are susceptible to the formation of stable emulsions in a water – CH_2Cl_2 system at pH > 7, which hinders isolation of the product.

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As was also demonstrated in [5], compound IIIb cannot be synthesized using a scheme employing the interaction of carbinol Ia with cyanoacetic ester. For this reason, we used a different method based on the three-component condensation of anisole, isobutyric aldehyde, and cyanoacetic ester in CH_2Cl_2 in the presence of a concentrated sulfuric acid solution (see the experimental part below). Analysis of the ^1H NMR spectrum of compound IIIb measured in DMSO-d_6 (Table 2) showed that this substance occurs entirely in the enamine form with an intramolecular hydrogen bond between carbonyl and NH group. Additional evidence is provided by the IR spectrum, where the absorption band of the ester group is shifted to 1615 cm^{-1}. An analogous condensation of 1,3-dimethoxybenzene with isobutyric aldehyde and cyanoacetic ester leads (after hydrolysis and opening of the pyrroline cycle) to amide IVg.

The hydrazinolysis of esters IVa and IVb by hydrazine hydrate in ethanol led to the corresponding hydrazides (Va and Vb, respectively); the interaction of compound Va with aromatic aldehydes yielded hydrazones VIa – VIf.

The yields and some physicochemical characteristics of the synthesized compounds are presented in Table 1; the parameters of the IR and ^1H NMR spectra are given in Table 2. The results of IR and ^1H NMR measurements confirmed the proposed structures of compounds III – VI. According to the NMR data, hydrazones VIa – VIf represent mixtures of *Z*- and *E*-isomers with the ratio varying from 1 : 1 to 1 : 3. The spectra display two sets of signals due to protons of the CH=N groups (δ = 7.85 – 7.95 and 8.10 – 8.35 ppm) and the signals from protons of the amide, hydrazide, methyl (δ = 1.15 and 1.21 ppm), and benzyl (δ = 2.82 – 2.83 and 2.85 – 2.86 ppm) groups (Table 2). At this stage of research, unambiguous assignment of the observed signals to certain structural forms is impossible.

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were recorded with an UR-20 spectrophotometer using samples prepared as nujol mulls. The ^1H NMR spectra were measured on a Bruker AM-300 spectrometer (working frequency, 300 MHz) using DMSO-d_6 as solvent and HMDS as internal standard. The mass spectra were obtained using a Finnegan MAT spectrometer (electron impact ionization energy, 70 eV). The course of reactions was monitored and the product purity was checked by TLC on Silufol UV-254 plates (Czech Republic) eluted in a toluene – ethyl acetate (1 : 1) system and developed by treating it with a chloranyl solution in toluene (the spot color after development is indicated in Table 1).

Reagents: methylene chloride (Lancaster Co., England). Ethyl acetate (reagent grade) for TLC and column chromatography was washed with water and saturated $NaHCO_3$, dried over $MgSO_4$, and distilled. Toluene (analytical grade), as well as hexane, cyanoacetic ester, benzonitrile, benzyl rhodan, and benzyl cyanide (high-purity grade) were used without additional purification.

2-Methylthio-4′-oxo-5,5-dimethylspiro-(1-pyrroline-3,1′-cyclohexadiene) (IIIa). Compound IIIa was synthesized as described in [5].

2-Carboethoxmethylidene-4′-oxo-5,5-dimethylspiro-(pyrrolidine-3,1′-cyclohexadiene) (IIIb). To 12 ml of a 96% sulfuric acid was gradually (over 20 min) added with stirring at a temperature within 10 – 12°C a mixture of 5.43 ml (5.41 g, 50 mmole) anisole, 4.54 ml (3.62 g, 50 mmole) freshly distilled isobutyric aldehyde, 5.30 ml

TABLE 1. Yields and Physicochemical Characteristics of Compounds III – VI

Compound	Yield, %	M.p., °C (solvent)	Empirical formula	R_f (spot color)
IIIa	52	95 – 97 (ethanol – water)	$C_{12}H_{15}NOS$	0.80 (blue)
IIIb	30	195 – 197 (ethanol)	$C_{15}H_{19}NO_3$	0.68 (violet)
IVa	64	100 – 102 (toluene – hexane)	$C_{15}H_{21}NO_4$	0.38 (light red)
IVb	15	119 – 121 (toluene)	$C_{18}H_{25}NO_4$	0.51 (light red)
IVc	58	141 – 142 (dichloroethane)	$C_{17}H_{19}NO_2$	0.67 (cherry red)
IVd	38	148 – 150 (ethanol – water)	$C_{20}H_{23}NO_2$	0.72 (cherry red)
IVe	81	131 – 132 (ethanol – water)	$C_{18}H_{21}NO_2S$	0.84 (red-orange)
IVf	29	158 – 160 (toluene)	$C_{21}H_{25}NO_2$	0.69 (dark red)
IVg	45	103 – 106 (acetone – water)	$C_{16}H_{23}NO_5$	0.35 (cacao)
Va	64	182 – 183 (ethanol – water)	$C_{13}H_{19}N_3O_3$	0 (cherry red)
Vb	84	101 – 102 (ethanol – water)	$C_{16}H_{23}N_3O_2$	0 (cherry red)
VIa	72	221 – 222 (ethanol)	$C_{20}H_{22}FN_3O_3$	0.11 (pink)
VIb	74	217 – 218 (ethanol)	$C_{21}H_{25}N_3O_4$	0.14 (pink)
VIc	87	221 – 222 (ethanol)	$C_{22}H_{27}N_3O_5$	0.06 (pink)
VId	98	231 – 232 (ethanol)	$C_{28}H_{39}N_3O_4$	0.20 (pink)
VIe	65	218 – 219 (acetonitrile)	$C_{20}H_{22}N_4O_5$	0.13 (pink)
VIf	71	189 – 190 (ethanol – water)	$C_{18}H_{21}N_3O_4$	0.17 (pink)

(5.65 g, 50 mmole) cyanoacetic ester, and 30 ml CH_2Cl_2. The reaction mass was stirred for 40 min and poured onto a mixture of 150 g crushed ice and 40 ml of 25% NH_4OH (pH ~ 8). Finally, the product was extracted with methylene chloride, the extract was dried over $MgSO_4$, the solvent was distilled off, and The residue was crystallized from 40 ml of ethanol to obtain 3.92 g (30%) of compound IIIb.

N-[(1-*p*-Hydroxyphenyl-2-methyl)-2-propyl]malonamic acid ethyl ester (IVa). To 30 ml of a 96% sulfuric acid was added dropwise with stirring a mixture of 18.0 g (0.1 mole) carbinol Ia, 10.7 ml (11.3 g, 0.1 mole) cyanoacetic ester IIb, and 70 ml toluene. The reaction mass was stirred for 1 h and poured into 300 ml of water. The precipitated resin was dissolved in 50 ml of chloroform, carefully (so as to

TABLE 2. Spectroscopic Characteristics of Compounds III – VI

Compound	IR spectrum: ν, cm^{-1}	^{1}H NMR spectrum: δ, ppm						
		R	CH_2 (s, 2H)	2.6-H	3.5-H	other H arom	NH	other protons
IIIa	1700 (C=O), 1660 (C=C), 1620 (C=N)	1.43 (s, 6H)	2.23	6.75 (d, 2H)	6.22 (d, 2H)	–	–	2.38 (s, 3H, SMe)
IIIb	3325 (NH), 1660 (C=O), 1615 (O–C=O), 1600 (C=C)	1.40 (s, 6H)	2.11	6.77 (d, 2H)	6.13 (d, 2H)	–	7.85 (s, 1H)	1.16 (t, 3H, CH_3) 3.98 (q, 2H, OCH_2) 4.23 (s, 1H, –CH=)
IVg	3405 (NH), 3150 (broad, OH + NH),1725 (OC=O), 1640 (C=O), 1605, 1590 (C=C)	1.36 (s, 6H)	2.65	6.25 (d, 1H) 6.35 (s, 1H)	6.78 (d, 1H)	–	9.05 (s, 1H)	1.24 (t, 3H, CH_3), 3.14 (s, 2H, CH_2CO), 3.72 (s, 3H, OMe), 4.10 (q, 2H, OCH_2), 7.33 (s, 1H, OH phenol)
Va	3425, 3305, 3250 (NH + OH), 1660 (C=O), 1605, 1590 (C=C)	1.12 (s, 6H)	2.82	6.63 (d, 2H)	6.89 (d, 2H)	–	4.13 (bs, 2H) 8.85 (s, 1H) 9.03 (s, 1H)	2.94 (s, 2H, CH_2CO) 7.20 (s, 1H, OH phenol)
Vb	3585 (OH), 3335 (broad, NH), 1640 (C=O), 1585, 1560, 1515	1.05 – 1.58 (m, 8H); 1.96 (d, 2H)	2.80	6.62 (d, 2H)	6.87 (d, 2H)	–	4.25 (bs, 2H) 8.90 (s, 1H) 9.05 (s, 1H)	2.98 (s, 2H, CH_2CO), 7.08 (s, 1H, OH phenol)
VIa	3360 (NH),3400 (broad, NH + OH), 1660 (C=O), 1610 (C=N), 1550, 1510	1.15, 1.20 (2s, 6H)	2.83, 2.86	6.64 (m, 2H)	6.90 (m, 2H)	7.20 (m, 2H, 3′,5′-H), 7.74 (m, 2H, 2′,6′-H)	7.30, 7.39 (2s, 1H), 11.36, 11.43 (2s, 1H)	3.12, 3.48 (2s, 2H, CH_2CO), 7.95, 8.23 (2s, 1H, CH=N), 8.94 (s, 1H, OH phenol)
VIb	3350 (NH), 3160 (broad, NH + OH), 1670 (C=O), 1655 (C=O), 1610 (C=N), 1595 (C=C), 1550, 1520	1.15, 1.20 (2s, 6H)	2.82, 2.86	6.63 (d, 2H)	6.90 (d, 2H)	6.95 (m, 2H, 3′,5′-H), 7.62 (m, 2H, 2′,6′-H)	7.28, 7.38 (2s, 1H), 11.10, 11.19 (2s, 1H)	3.10, 3.47 (2s, 2H, CH_2CO), 3.80 (s, 3H, OMe), 7.90, 8.15 (2s, 1H, CH=N), 8.93 (s, 1H, OH phenol)
VIc	3375 (NH), 3200 (broad, NH + OH), 1660 (C=O), 1610 (C=N), 1590 (C=C), 1525	1.15, 1.20 (2s, 6H)	2.82, 2.85	6.63 (m, 2H)	6.91 (m, 2H)	6.95 (dd, 1H, 5′-H), 7.16 (dd, 1H, 6′-H), 7.30 (d, 1H, 2′-H)	7.25, 7.38 (2s, 1H), 11.13, 11.20 (2s, 1H)	3.11, 3.48 (2s, 2H, CH_2CO), 3.80 (d, 6H, 2 OMe), 7.87, 8.13 (2s, 1H, CH=N), 8.93 (s, 1H, OH phenol)
VId	3570 (OH), 3285, 3200, 3100 (broad, NH + OH), 1660 (C=O), 1590 (C=C), 1560, 1515	1.15, 1.21 (2s, 6H)	2.83, 2.86	6.62 (m, 2H)	6.91 (m, 2H)	7.38 (s, 2H)	7.28, 7.45 (2s, 1H), 11.08, 11.10 (2s, 1H)	1.42 (d, 18 H, *t*-Bu), 3.10, 3.48 (2s, 2H, CH_2CO), 7.87, 8.10 (2s, 1H, CH=N), 7.12, 7.16 (2s, 1H, OH phenol), 8.93 (s, 1H, OH phenol)
VIe	3360 (NH), 3260 (broad), 3070 (C–H arom), 1670 (C=O), 1660 (C=O), 1610 (C=N), 1580 (C=C), 1540, 1525	1.15, 1.21 (2s, 6H)	2.82, 2.86	6.62 (m, 2H)	6.91 (m, 2H)	7.95 (dd, 2H, 2′,6′-H) 8.25 (dd, 2H, 3′,5′-H)	7.38, 7.42 (2s, 1H), 11.10, 11.15 (2s, 1H)	3.17, 3.50 (2s, 2H, CH_2CO), 8.05, 8.35 (2s, 1H, CH=N), 8.95 (s, 1H, OH phenol)
VIf	3355 (NH), 3225 (broad) 3070 (C–H arom), 1670 (C=O), 1620 (C=N), 1570, 1550 (shoulder), 1515	1.15, 1.20 (2s, 6H)	2.82, 2.86	6.62 (d, 2H)	6.91 (d, 2H)	6.56 (dd, 1H, 4′-H), 6.80 (d, 1H, 3′-H), 7.73 (d, 1H, 5′-H)	7.24, 7.37 (2s, 1H), 11.20, 11.25 (2s, 1H)	3.10, 3.45 (2s, 2H, CH_2CO), 7.85, 8.15 (2s, 1H, CH=N), 8.92 (s, 1H, OH phenol)

avoid emulsification) washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Finally, the solvent was distilled off and the residue was crystallized from toluene with hexane additive to obtain 10.2 g of compound IVa. The aqueous layer was washed with 30 ml toluene. The combined toluene fractions were washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, evaporated to half volume, and allowed to stand in the cold. The precipitate was crystallized from toluene with hexane additive to obtain additionally 7.7 g of compound IVa; total yield, 17.9 g (64%).

N-[(2-*p*-Hydroxyphenyl-1,1-pentamethylene)ethyl]-malonamic acid ethyl ester (IVb). Compound IVb was obtained by a method analogous to that used for the synthesis of IVa, proceeding from carbinol Ib [6] and cyanoacetic ester IIb.

Benzoic acid N-[(1-*p*-hydroxyphenyl-2-methyl)-2-propyl]amide (IVc). To 50 ml of a 96% sulfuric acid was added dropwise with stirring at a temperature within 20 – 50°C (cooling on a water bath) a solution of 18.0 g (0.1 mole) of carbinol Ia and 10.3 g (0.1 mole) of benzonitrile in 100 ml of toluene. When all the toluene solution was added, the reaction mass was stirred for 1 h and poured into 300 ml of cold water. The precipitated resin was separated, dissolved in 50 ml of CH_2Cl_2, and allowed to stand, during which crystals of compound IVc precipitate. The second por-

TABLE 3. Antiinflammatory and Analgesic Activity of Compounds III, IV and VI

Compound	LD_{50}, mg/kg	Antiinflammatory activity		Analgesic activity		
		percentage edema volume growth relative to initial foot volume	percentage inhibition of edema growth relative to control	time to defensive reflex (sec) for drug introduced after		
				30 min	60 min	120 min
IIIa	890 (560 ÷ 1291)	73.2 ± 6.6 $p > 0.5$	– 2.1	13.5 ± 1.9 $p < 1.02$	13.3 ± 1.4 $p < 0.02$	13.4 ± 1.5 $p < 0.5$
IIIb	> 2000	69.5 ± 7.4 $p > 0.5$	3.1	11.4 ± 1.1 $p < 0.1$	17.5 ± 2.4 $p < 0.001$	19.5 ± 2.0 $p < 0.01$
IVa	> 2000	89.1 ± 5.3 $p < 0.05$	– 24.3	18.0 ± 1.6 $p < 0.001$	12.6 ± 3.4 $p < 0.25$	23.9 ± 4.7 $p < 0.01$
IVb		59.1 ± 9.5 $p < 0.25$	17.6	10.8 ± 0.7 $p < 0.1$	15.0 ± 0.7 $p < 0.001$	16.0 ± 1.6 $p < 0.02$
IVc		77.5 ± 5.5 $p < 0.5$	– 8.1	11.9 ± 1.2 $p < 0.05$	12.2 ± 2.1 $p < 0.25$	15.8 ± 3.9 $p < 0.25$
IVd		77.2 ± 5.3 $p < 0.5$	– 7.7	12.0 ± 0.9 $p < 0.02$	12.2 ± 0.9 $p < 0.02$	9.6 ± 1.0 $p < 0.5$
IVe	> 2000	37.3 ± 1.5 $p < 0.001$	48.0	8.9 ± 0.7 $p > 0.5$	9.8 ± 0.9 $p < 0.5$	13.4 ± 1.0 $p < 0.5$
IVf	> 2000	44.1 ± 10.0 $p < 0.01$	38.5	15.2 ± 2.1 $p < 0.01$	9.23 ± 1.9 $p < 0.5$	16.1 ± 3.6 $p < 0.25$
IVg		73.9 ± 9.3 $p > 0.5$	–3.1	14.4 ± 2.1 $p < 0.01$	19.7 ± 2.9 $p < 0.001$	11.1 ± 2.0 $p < 0.5$
VIa		46.4 ± 6.0 $p < 0.02$	35.3	9.6 ± 2.1 $p > 0.5$	8.6 ± 0.2 $p > 0.5$	9.7 ± 1.4 $p > 0.5$
VIb		43.1 ± 3.2 $p < 0.002$	39.9	12.0 ± 1.5 $p < 0.05$	14.1 ± 2.6 $p < 0.05$	13.2 ± 1.9 $p < 0.25$
VIc		59.6 ± 4.4 $p < 0.25$	16.9	10.3 ± 0.4 $p < 0.25$	11.5 ± 1.3 $p < 0.1$	10.8 ± 0.8 $p > 0.5$
VId		65.9 ± 7.3 $p > 0.5$	8.1	9.7 ± 0.6 $p < 0.5$	9.8 ± 1.2 $p > 0.5$	12.7 ± 1.1 $p < 0.5$
VIe	> 2000	35.3 ± 3.6 $p < 0.01$	50.6	11.5 ± 3.0 $p < 0.5$	11.9 ± 1.5 $p < 0.1$	12.0 ± 1.8 $p < 0.5$
VIf	> 2000	35.5 ± 2.2 $p < 0.001$	50.5	11.3 ± 1.8 $p < 0.25$	12.6 ± 1.6 $p < 0.05$	16.3 ± 3.9 $p < 0.25$
Ortophen		27.9 ± 5.2 $p < 0.001$	61.1	–	–	–
Analgin		–	–	13.1 ± 0.9 $p < 0.01$	12.8 ± 1.9 $p < 0.05$	16.3 ± 3.0 $p < 0.1$
Control		71.7 ± 4.8	–	8.5 ± 0.9	9.0 ± 0.8	10.8 ± 1.6

Note: *p* is the level of confidence relative to control.

tion of crystals precipitated from the toluene layer washed with 200 ml of water and allowed to stand for 1 – 2 h. The third portion was obtained from the aqueous layer washed with 40 ml of toluene and alkalized with dry $NaHCO_3$ to pH ~ 7. The three portions were combined, dried, and recrystallized from dichloroethane to obtain 15.6 g (58%) of compound IVc; m.p., 141 – 142°C.

A similar procedure was used to obtain amide IVd proceeding from carbinol Ib and benzonitrile; the final product was recrystallized from aqueous ethanol (Table 1).

N-[(1-*p*-Hydroxyphenyl-2-methyl)-2-propyl]carbamic acid thiobenzyl ester (IVe). To 15 ml of a 96% sulfuric acid was added dropwise with stirring at a temperature within 10 – 20°C (cooling on a water bath) a solution of 9.0 g (50 mmole) of carbinol Ia and 5.96 g (40 mmole) of benzyl rhodan in 110 ml of toluene. When all the solution was added, the reaction mass was stirred for 0.5 h and the thickening mass was poured into 300 ml of cold water. The aqueous layer was washed with toluene (2 × 40 ml) and neutralized with dry $NaHCO_3$ to pH ~ 8. The precipitate was separated by filtration and dried. The toluene layer was allowed to stand in the cold and the precipitate product was also separated and dried. Finally, the combined precipitates were recrystallized from aqueous ethanol to obtain 9.2 g (81%) of compound IVe.

A similar procedure was used to obtain amide IVf proceeding from carbinol Ib and benzyl cyanide.

N-[(1-*p*-Hydroxy-*m*-methoxyphenyl-2-methyl)-2-propyl]malonamic acid ethyl ester (IVg). To 60 ml of a 96% sulfuric acid was added dropwise with stirring a mixture of 13.1 ml (13.8 g, 0.1 mole) 1,3-dimethoxybenzene, 9.1 ml (7.2 g, 0.1 mole) of freshly distilled isobutyric aldehyde, and 10.6 ml (11.3 g, 0.1 mole) of cyanoacetic ester, and 30 ml toluene. The reaction mass was stirred for 1 h and poured into 300 ml of water. The aqueous layer was separated, washed with 30 ml of toluene, and neutralized with dry $NaHCO_3$ to pH ~ 7. The product was extracted with CH_2Cl_2 (2 × 70 ml), the extract was dried over $MgSO_4$, and the solvent was distilled off. This yielded 19.3 g of a viscous gummy product. After chromatography of a 1-g portion on 70 g of silica gel eluted with a hexane – ethyl acetate (2 : 1) mixture, the fraction with R_f = 0.35 was collected, the solvent was distilled off, and the residue was crystallized from acetone (with water added on cooling to –20°C). This yielded 0.44 g of compound IVg with m.p. = 103 – 106°C; total yield, 45% (calculated for the initial charge of reagents).

N-[(1-*p*-Hydroxyphenyl-2-methyl)-2-propyl]malonamic acid hydrazide (Va). A solution of 1.0 g (3.57 mmole) of ester IVa and 0.5 ml (8.5 mmole) of 85% hydrazine hydrate in 10 ml of ethanol was boiled for 2 h, poured into 10 ml of water, and allowed to stand for 12 h. The precipitate was separated by filtration and recrystallized to obtain 0.32 g (64%) of compound Va. A similar procedure was used to obtain hydrazide Vb proceeding from ester IVb.

N-[(1-*p*-Hydroxyphenyl-2-methyl)-2-propyl]malonamic acid *p*-fluorobenzylidenehydrazide (VIa). A mixture of 0.5 g (1.79 mmole) of hydrazide Va and 0.24 g (1.97 mmole) of *p*-fluorobenzaldehyde in 5 ml of ethanol was boiled for 5 min. The precipitate was separated by filtration, washed with hot ethanol, and recrystallized to obtain 0.4 g (72%) of compound VIa. Similar procedures were used to obtain hydrazides VIb – VIe.

N-[(1-*p*-Hydroxyphenyl-2-methyl)-2-propyl]malonamic acid furfurylidenehydrazide (VIf). A mixture of 0.5 g (1.79 mmole) of hydrazide Va and 0.19 mg (1.79 mmole) of freshly distilled furfural in 3 ml of ethanol was boiled for 0.5 h. Then 1 ml of water was added and the mixture was allowed to stand for 12 h. The precipitate was separated by filtration and recrystallized from aqueous ethanol to obtain 0.39 g (71%) of hydrazide VIf.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity was studied on a group of both male and female rats weighing 180 – 220 g. A model edema was induced by subplantar injections of 0.1 ml of a 1% aqueous carrageenan solution [7]. The test compounds were intraperitoneally injected (1 h before carrageenan) with a 2% starch jelly in a dose of 50 mg/kg. The reference drug was ortophen (10 mg/kg). The increase in the foot edema volume was determined oncometrically before test and 4 h after carrageenan injection. The antiinflammatory effect was evaluated by the percentage inhibition of the model edema growth relative to that in the control group (injected with a pure 2% starch jelly).

The analgesic activity was studied on a group of both male and female white mongrel mice weighing 18 – 20 g subjected to a hot plate test [8]. The compounds were injected 1 h before test in a dose of 50 mg/kg (i.p.) with a 2% starch jelly The reference drug was analgin administered in a dose of ED_{50} = 93 mg/kg [9]. The drug activity was evaluated by determining the onset time of the defensive response (hind paw licking).

Each compound was tested in a group of six animals; the control groups contained ten animals. The acute toxicity was determined by intraperitoneal injection to white mice and evaluated by LD_{50} [10]. The experimental data were statistically processed in terms of the Student *t*-criterion [11]. The effects were considered as reliable for $p \le 0.05$.

It was established that intermediate spiropyrrolines (IIIa, IIIb) do not exhibit antiinflammatory action, although compound IIIb produced an analgesic effect [(Table 3). N-[2-(*p*-Hydroxyphenyl)-1,1-dialkylethyl]malonamic acid ethyl esters IVa, IVb, and IVg also produced a reliable analgesic effect, this activity being weakly pronounced in substituted N-(*p*-hydroxyphenylethyl)amides of benzoic (IVc, IVd), benzylthiocarboxylic (IVe), and phenylacetic (IVf) acids. In view of the similar structure of these compounds, we may suggest that the analgesic activity of the former es-

ters (IVa, IVb, and IVg) is due to carboethoxy groups present in their structures. At the same time, compounds IVa, IVb, and IVg possess no antiinflammatory properties.

In the series of N-[2-(*p*-hydroxyphenyl)-2-methylpropyl]malonamic acid arylhydrazones (VIa – VIf), the antiinflammatory activity was observed for compounds containing both nitro (VIf) and fluorine (VIa) substituents, as well as methoxy groups (VIb) in the *para* position of the aryl ring. As the lipophilicity was increased (in hydrazones VIc and VId), the antiinflammatory effect disappeared, while introduction of the furfuryl residue (in compound (VIf) increased this activity.

On the whole, the groups of esters IVa, IVb, IVg and hydrazones VIa – VIf are promising objects for the further investigation of analgesic and antiinflammatory activity.

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