SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-AROYLMETHYLENE-SUBSTITUTED 1-METHYL(PHENYL)-PIPERAZIN-2-ONES

A. V. Milyutin,[1] N. V. Safonova,[1] R. R. Makhmudov,[2] G. N. Novoselova,[2] A. F. Goleneva,[2] and Yu. S. Andreichikov[3]

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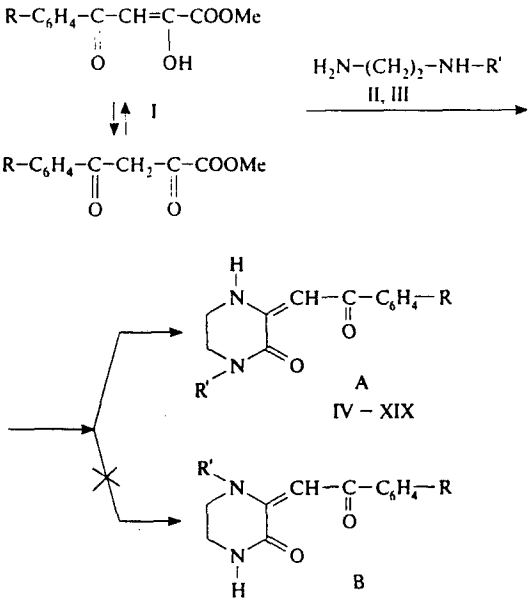
It was demonstrated that 3-aroylmethylenepiperazin-2-ones exhibit antiinflammatory, anticonvulsive, and analgetic activity on a background of rather low toxicity [1]. It was established that one of the factors determining the activity is the character of acylmethylene derivative in position 3 of the piperazinone cycle. At the same time, arylamides of aroylpyroracemic acids (noncyclic analogs of piperazinones) are known to exhibit antimicrobial effect with respect to *Staphylococcus aureus* [2].

In this connection, it was of interest to study the effect of substituents in position 1 of the piperazinone cycle on the biological activity. To this end, we have synthesized 1-methyl(phenyl)-3-aroylmethylenepiperazin-2-ones and characterized their biological activity. The target products were obtained by interaction of methyl esters of 4-aryl-2-hydroxy-4-oxo-2-butenoic acids (I) with N-methyl- and N-phenylethylenediamines (II, III). It was reported that the ester of aroylpyroracemic acid (a ketone form of I) reacts with amines at the α-ketone carbonyl [4, 5]. In the case of nonsymmetric ethylenediamines, the reaction may lead to two products (A and B, see the scheme below). Taking into account the electronic effects of the methyl group and benzene ring, we may expect that the reactions of N-methylethylenediamine and N-phenylethylenediamine would lead to compounds of the B and A type, respectively. However, the steric effect of the methyl group in N-methylethylenediamines also favors the formation of compound A. The reaction proceeds smoothly with a good yield in an alcohol medium (boiling for 1 – 1.5 h) in the presence of catalytic amounts of glacial acetic acid [2].



R′ = Me (II, IV – X). R = H (IV), *p*-Me (V), *o*, *p*-Me_2 (VI), *p*-OMe (VII), *p*-F (VIII), *p*-Cl (IX), *p*-Br (X);
R′ = Ph (III, XI – XIX), R = *p*-Me (XI), *o*, *p*-Me_2 (XII), *o*, *m*-Me_2 (XIII), *p*-OMe (XIV), *p*-OEt (XV), *p*-Cl (XVI), *p*-Br (XVII), *p*-NO_2 (XVIII), R-C_6H_5 = α-naphthyl (XIX).

The structures of the target products were established by IR and ^{1}H NMR spectroscopic data. The ^{1}H NMR spectra measured in DMSO-d_6 (with HMDS as the internal standard) contained a broad signal due to one amino group in the region of 10.88 – 11.15 ppm. The spectra of previously studied piperazinones, having no substituents at the nitrogen atoms, exhibited an additional signal at 8.50 – 8.90 ppm attributed to the proton of the amide group [2]. The signal at 10.88 – 11.15 ppm is characteristic of amino groups involved in the intramolecular hydrogen bond, which is possible only in compounds of the A type [6, 7]. The IR spectra (nujol mulls) showed an absorption band in the region of 1610 – 1595 cm^{-1}, which corresponded to a carbonyl group involved in the intra-

[1] Pharmaceutical Institute, Perm', Russia.
[2] Institute of Technical Chemistry, Ural Division, Russian Academy of Sciences, Perm', Russia.
[3] Institute of Natural Sciences, Perm' State University, Perm', Russia.

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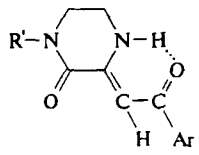
TABLE 1. Physico-Chemical Characteristics of Compounds IV – XIX

Compound	Yield, %	M.p., °C	Empirical formula	IR spectrum ν, cm^{-1}		^1H NMR spectrum, δ, ppm				
				CONH	CO	$-CH_3$	$-CH_2CH_2-$	–CH=	Ar	NH
IV	60	120 – 121	$C_{13}H_{14}N_2O_2$	1670	1595	3.08	3.63	6.74	7.95	10.98
V	70	165 – 167	$C_{14}H_{16}N_2O_2$	1665	1595	3.08	3.64	6.74	7.73	10.98
VI	82	149 – 151	$C_{15}H_{18}N_2O_2$	1665	1595	3.08	3.64	6.38	7.39	11.02
VII	80	154 – 156	$C_{14}H_{16}N_2O_3$	1670	1595	3.08	3.57	6.74	7.60	10.88
VIII	90	159 – 161	$C_{13}H_{13}N_2O_2F$	1675	1608	3.08	3.64	6.74	7.88	11.05
IX	89	183 – 185	$C_{13}H_{13}N_2O_2Cl$	1675	1610	3.08	3.64	6.74	7.90	11.05
X	90	189 – 191	$C_{13}H_{13}N_2O_2Br$	1680	1610	3.08	3.64	6.74	8.02	11.11
XI	87	156 – 158	$C_{19}H_{18}N_2O_2$	1666	1604		3.88	6.74	7.80	11.08
XII	93	158 – 159	$C_{20}H_{20}N_2O_2$	1665	1602		3.91	6.36	7.53	10.91
XIII	92	155 – 156	$C_{20}H_{20}N_2O_2$	1665	1604		3.88	6.33	7.53	10.95
XIV	78	139 – 141	$C_{19}H_{18}N_2O_3$	1665	1608		3.91	6.87	7.70	11.15
XV	87	161 – 162	$C_{20}H_{20}N_2O_3$	1670	1610		3.95	6.43	7.46	11.11
XVI	75	174 – 176	$C_{18}H_{15}N_2O_2Cl$	1680	1610		3.84	6.95	7.67	11.05
XVII	95	193 – 194	$C_{18}H_{15}N_2O_2Br$	1680	1608		3.86	6.95	7.66	11.11
XVIII	76	263 – 265	$C_{18}H_{15}N_3O_4$	1680	1608		3.84	6.95	7.67	11.05
XIX	78	156 – 157	$C_{22}H_{18}N_2O_2$	1680	1610		3.50	5.97	7.64	11.12

molecular hydrogen bond [6 – 8]. In addition, the IR spectra contained absorption bands at 1665 – 1680 cm^{-1} (amide carbonyl) and a broad band at 3220 – 3190 cm^{-1} (bound NH group). All these data suggest that, irrespective of the character of the substituent at the nitrogen atom, the reaction leads only to the formation of compounds of the A type.



A

Homogeneity of the reaction products was confirmed by thin-layer chromatography on Silufol UW-254 plates in the benzene – ethyl ether – acetone (1 : 1 : 1) solvent system. The chromatograms were developed in iodine and examined under UV illumination.

All compounds are crystalline substances having a light-yellow color, moderately soluble in ethanol and benzene, poorly soluble in water, and soluble in DMFA and DMSO. In the presence of sulfate (Cu^{2+}), the alcohol solutions acquire a green color.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds were measured on a Specord M-80 spectrophotometer (Carl Zeiss, Germany) using samples prepared as nujol mulls. The ^1H NMR spectra were recorded on a RYa-2310 (60 MHz) spectrometer (Russia) using DMSO-d_6 as solvent. The characteristics of compounds IV – XIX are given in Table 1. The data of elemental analyses agree with the results of analytical calculations.

1-Methyl-3-phenacylidenepiperazin-2-one (IV). To 2.06 g (10 mmole) of methyl ester of 4-aryl-2-hydroxy-4-oxo-2-butenoic acid (I) in 30 ml of ethanol is added 0.74 g (10 mmole) of N-methylethylenediamine in 7 ml AcOH and the mixture is boiled for 80 – 90 min. Then the reaction mixture is poured into an evaporator and the solvent is evaporated. Alternatively, the reaction mixture is diluted with water and the precipitate is filtered. The product is recrystallized from ethanol. Yield, 1.38 g (60%) of compound IV; m.p. 120

TABLE 2. Biological Activity of Compounds V – VIII, X – XVI, XVIII, and XIX.

Compound	Dose, mg / kg	Antiinflammatory activity: edema inhibition, % of control	Analgesic activity: licking reflex, sec
V	50	31	20
VI	50	3	17
VII	50	16	23
VIII	–	–	–
X	50	28	21
XI	50	0	18
XII	–	–	–
XIII	50	35	–
XIV	50	–	24
XV	50	–	27
XVI	50	–	18
XVIII	–	–	17
XIX	50	40	17
2% Starch mucilage	–	–	11.9
Ortophen	10	53	–

– 121°C; IR spectrum, ν, cm^{-1} (nujol mull): 1670 (CONH), 1595 (CO, chelate); ^1H NMR spectrum, δ, ppm (DMSO-d_6): 3.08 (s, 3H, CH_3), 3.63 (m, 4H, $2CH_2$), 6.74 (s, 1H, CH), 7.95 (m, 5H, C_6H_5), 10.98 (bs, 1H, NH). Compounds V – XIX are obtained by similar procedures.

EXPERIMENTAL BIOLOGICAL PART

We have studied the antiinflammatory, analgetic, and antimicrobial activities and the acute toxicity of compounds V – VIII, X – XVI, XVIII, and XIX.

The acute toxicity was evaluated on 18 – 22 g mongrel mice upon peroral administration by the Pershin method [9]. The toxicity was characterized by the average lethal dose (LD_{50}) leading to the loss of 50% of animals by the end of experiment.

The antiinflammatory activity was studied on white Wistar rats weighing 170 – 200 g using a model of an acute inflammatory edema initiated by subplantar injection of 0.1 ml 1% carrageenan solution into the hind legs of the animals. The antiinflammatory activity was judged by the degree of edema inhibition (as determined by oncometric techniques and expressed in percent with respect to the control animals) upon the introduction of test compounds at a dose of 50 mg / kg as suspensions in 2% starch mucilage [10].

The analgetic activity of the synthesized compounds was studied on 18 – 22 g mongrel mice using the 'hot plate' technique [11]. The test compounds were introduced (at a dose of 50 mg / kg) 0.5 h before placing the animals onto a metal plate heated to 53.5°C. The change in the algesic reaction was evaluated by the time (measured in sec) of staying on the hot plate prior to licking the hind legs.

The antimicrobial activity of the compounds synthesized was determined with respect to the *E. coli* M_{17} and *St. aureus* P-209 standard strains by the method of consecutive double dilutions in a meat-infusion broth [9] upon loading 250 thousand microbe units per ml solution. The active dose was determined as the minimum inhibiting concentration (MIC) of the compound (maximum dilution) leading to complete suppression of the growth of test microbe.

It was established that the acute toxicity of the synthesized compounds is low, with the LD_{50} values exceeding 1000 mg / kg.

Compounds XIII and XIX (with pronounced steric effect of substituents at position 3 of the piperazinone cycle) exhibited a significant antiinflammatory action. The effect is observed only with 1-phenyldpiperazin-2-ones, while 1-methylpiperazin-2-ones with *ortho*-substituents in position 3 of the aromatic ring produce no antiinflammatory action.

The maximum analgesic activity in the series of N-methyl- and N-phenyl-substituted piperazin-2-ones was observed in compounds V, VII, XIV, and XV containing electron-donor substituents in the benzene ring of the side chain. Note that the analgesic activity is somewhat decreased upon the introduction of substituents with pronounced steric effects (compound VI).

The synthesized compounds showed no antimicrobial activity.

Thus, the data obtained in our experiments indicate that the antiinflammatory and analgesic activity in the series of 3-phenacylidenepiperazin-2-ones is determined by electronic and steric factors. The introduction of methyl and phenyl substituents in position 1 of the piperazinone cycle increases the analgesic activity. 1-N-phenyl-substituted piperazin-2-ones exhibit a higher antiinflammatory effect as compared to the nonsubstituted analogs [2].

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