SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 6-ARYLPIPERAZINO-2-AROYL-CYCLOHEXANONES-1

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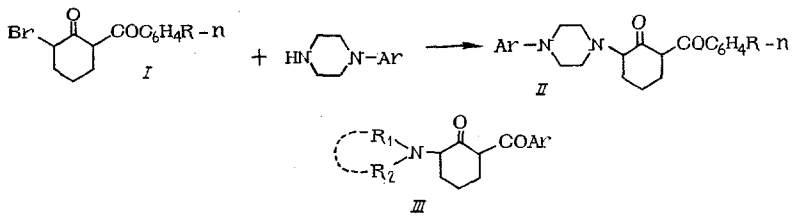
The reaction of 6-bromo-2-aroylcyclohexanones-1 (I) with N-arylpiperazines in benzene solution at room temperature was studied. A series of 6-arylpiperazino-2-aroylcyclohexanones-1 (II) was obtained as a result. The obtained compounds, white crystalline materials, form stable salts with hydrogen chloride.



The structure of compounds (II) was confirmed by IR spectra. Two absorption maxima of aromatic double bonds appear around 1580-1600 cm^{-1} in all compounds in the solid state, the carbonyl maximum of the aroyl group appears at 1680-1690 cm^{-1}, and the maximum of the cyclohexanone C=O is found in the range of 1705-1715 cm^{-1}.

The pharmacological properties of the synthesized compounds (II) and 6-amino-derivatives of 2-aroylcyclohexanones-1 (III) were studied. We investigated the effect on the central nervous system of certain arylpiperazino, piperidino, and morpholino-derivatives of 2-aroylcyclohexanones-1. Experiments were carried out on white mice, into which 30 min before the experiment aqueous solutions of hydrochlorides of the studied materials were introduced intraperitoneally. Various methods were used to evaluate the depressing properties of the synthesized materials: disruption of movement coordination and the effect on the tonicity of skeletal muscle was studied by the test of rotating rods [1] and the tube test [2]. Average effective doses, producing a hypothermal effect of 3° and below, were determined to characterize the hypothermal effect of the studies materials. The analgesic effect of the materials was studied using "hot plates" [3]. The effectiveness of the obtained compounds as media, able to intensify the effect of narcotic materials, was studied on white mice, into which the studied compound was introduced interperitoneally 30 min before intravenous introduction of hexenal in a dose of 70 mg/kg, and the index (I) of intensification of hexenal narcosis (ratio of duration of narcosis in test animals to the duration of narcosis in control mice) was determined for each compound. To compare the tranquilizing properties of derivatives (III) the experimental material was subjected to statistical treatment, and the average effective doses (ED_{50}) and average lethal doses (LD_{50}) [4] were calculated in all cases. The results of the pharmacological study are presented in Tables 1 and 2. It follows from the obtained data that compounds (III) possess a definite physiological activity. Results of this investigation make it possible to conclude (see Table 1) that compounds (III) show tranquilizing properties, depending on both the aroyl group and the amine group.

Compounds (II) also show tranquilizing properties, i.e., they produce hypothermia, disrupt movement coordination, intensify hexenal narcosis, and display analgesic properties, characteristic for depressants of the central nervous system. The tranquilizing properties of (II) clearly correlate with the arylpiperazine residue. The tranquilizing activity of the studied compounds increases significantly upon intro-

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TABLE 1. Pharmacological Activity of Amino Derivatives of 2-Aroylcyclohexanones (III)*

Ar	LD_{50} (mg/kg)	Rotating-rod test	Tube test ED_{50} (mg/kg)	Analgesic activity	Decrease in body temperature by 3° and below	Index of intensification of hexenal narcosis (I)
C_6H_5	76 (63÷91)	50 (40÷63)	33 (27÷39)	32 (23÷43)	23 (18÷28)	8,0
$C_6H_4OCH_3$-p	650 (585÷715)	43 (34÷55)	43 (34÷55)	230 (176÷325)	32 (22÷46)	3,7
C_6H_4Cl-p	700 (555÷882)	32 (23÷43)	32 (28÷43)	150 (88÷255)	50 (34÷72)	3,6
$C_6H_2(OCH_3)_3$	540 (450÷650)	62 (43÷90)	70 (54÷91)	200 (143÷286)	60 (42÷95)	2,6
C_6H_5	74 (63÷87)	26 (22÷31)	27 (22÷32)	32 (22÷46)	23 (18÷29)	7,6
$C_6H_4OCH_3$-p	180 (162÷200)	45 (63÷56)	45 (36÷56)	70 (54÷91)	25 (16÷37)	2,4
C_6H_4Cl-*n*	63 (45÷88)	35 (25÷47)	35 (25÷47)	56 (38÷81)	45 (33÷61)	2,8
$C_6H_2(OCH_3)_3$	86 (78÷96)	50 (39÷64)	60 (49÷73)	58 (45÷75)	54 (45÷65)	2,3

*Here and in Table 2 confidence intervals are presented in parentheses at P = 0.05.

Note. For the first four compounds $R_1 + R_2 = -(CH_2)_2-O-(CH_2)_2-$; for the remaining compounds $R_1 + R_2 = -(CH_2)_5-$.

TABLE 2. Pharmacological Activity of Certain Arylpiperazino Derivatives of 2-Aroylcyclohexanones (II)

Ar	R	LD_{50} (mg/kg)	Rotating-rod test	Tube test	Analgesic activity	Decrease in temperature by 3° and below	Index of intensification of hexanal narcosis (I)
				ED_{50} (mg/kg)			
C_6H_5	H	445 (408÷485)	80 (55÷116)	80 (55÷116)	240 (171÷336)	80 (55÷116)	0,5
C_6H_5	OCH_3	640 (551÷742)	80 (55÷116)	80 (55÷116)	160 (114÷224)	30 (19÷48)	0,8
C_6H_5	Cl	740 (638÷880)	180 (130÷250)	180 (130÷250)	48 (30÷77)	200 (111÷360)	1,1
$C_6H_4OCH_3$-p	H	560 (408÷762)	50 (31÷80)	50 (31÷80)	>300	70 (54÷91)	2,2
$C_6H_4OCH_3$-p	OCH_3	765 (695÷841)	180 (129÷252)	180 (129÷252)	280 (200÷392)	60 (41÷95)	1,1
$C_6H_4OCH_3$-p	Cl	1000 (813÷1230)	30 (21÷42)	30 (21÷42)	>600	64 (46÷90)	1,2
$C_6H_4OCH_3$-*o*	H	380 (336÷429)	20 (13÷31)	20 (13÷31)	56 (37÷84)	14 (7÷27)	1,9
$C_6H_4OCH_3$-o	OCH_3	370 (272÷503)	11 (8÷15)	11 (8÷15)	31 (23÷40)	13 (9÷19)	1,8
$C_6H_4OCH_3$-*o*	Cl	770 (631÷939)	19 (13÷27)	19 (13÷27)	90 (60÷122)	3 (1,5÷4,5)	2,2

TABLE 3. Arylpiperazino Derivatives of 2-Aroylcyclohexanones-1 (II)

R	Ar	Yield (%)	Mp (°C)	Found (%)			Empirical formula	Calculated (%)			
				C	H	Cl	N	C	H	Cl	N
Cl	C_6H_5	34,5	158	—	—	8,74	7,08	$C_{23}H_{25}ClN_2O_2$	—	—	8,93	7,06
Cl	C_6H_5	—	161—2	—	—	22,42	6,31	$C_{23}H_{25}ClN_2O_2 \cdot 2HCl$	—	—	22,65	5,96
H	$C_6H_4OCH_3$-p	41,8	148	—	—	—	7,18	$C_{24}H_{28}N_2O_3$	—	—	—	7,14
H	$C_6H_4OCH_3$-p	—	172—4	—	—	14,92	6,22	$C_{24}H_{28}N_2O_3 \cdot 2HCl$	—	—	15,24	6,02
Cl	$C_6H_4OCH_3$-p	44,3	155	—	—	8,71	6,80	$C_{24}H_{27}ClN_2O_3$	—	—	8,31	6,56
Cl	$C_6H_4OCH_3$-p	—	201—3	61,90	5,97	14,57	6,36	$C_{24}H_{27}ClN_2O_3Cl \cdot HCl$	62,19	6,09	15,30	6,05
H	$C_6H_4OCH_3$-o	52,8	121	—	—	—	7,06	$C_{24}H_{28}N_2O_3$	—	—	—	7,14
H	$C_6H_4OCH_3$-o	—	179—80	61,02	6,94	15,58	6,57	$C_{24}H_{28}N_2O_3 \cdot 2HCl$	61,90	6,50	15,24	6,02
Cl	$C_6H_4CH_3$-o	42,9	142	—	—	8,20	6,66	$C_{24}H_{27}N_2O_3 \cdot 2HCl$	—	—	8,31	6,56
Cl	$C_6H_4OCH_3$-o	—	181—3	56,93	5,94	19,93	5,13	$C_{24}H_{27}ClN_2O_3Cl \cdot 2HCl$	57,63	5,85	21,26	5,60
OCH_3	C_6H_5	31,3	166	—	—	—	7,04	$C_{24}H_{28}N_2O_3 \cdot HCl$	—	—	—	7,14
OCH_3	C_6H_5	—	204—6	67,63	6,87	8,55	6,54	$C_{24}H_{28}N_2O_3 \cdot HCl$	67,20	6,82	8,26	6,53
OCH_3	$C_6H_4OCH_3$-o	40,4	119	—	—	—	6,69	$C_{25}H_{30}N_2O_4$	—	—	—	6,63
OCH_3	$C_6H_4OCH_3$-o	—	157—9	59,98	6,76	13,71	5,44	$C_{25}H_{30}N_2O_4 \cdot 2HCl$	60,59	6,51	14,31	5,65
OCH_3	$C_6H_4OCH_3$-p	39,5	169	—	—	—	6,68	$C_{25}H_{30}N_2O_4$	—	—	—	6,63
OCH_3	$C_6H_4OCH_3$-p	—	135—7	—	—	13,39	5,94	$C_{25}H_{30}N_2O_4 \cdot 2HCl$	—	—	14,31	5,65

Note. Bases were crystallized from ethanol or dimethylformamide; hydrochlorides were crystallized from absolute ethanol with addition of ether.

ducing a methoxy group into the ortho or para positions of the phenyl group of the arylpiperazine. This regularity is expressed particularly in relation to the derivative, containing the o-methoxyphenylpiperazine residue. The hypothermal effect is most expressed in compounds containing the o-methoxyphenylpiperazine residue, particularly in the derivative having the p-chlorobenzoyl group as the aroyl substituent. Compounds (II) are of low activity in relation to analgesic effect. The toxicity of the studied compounds is average and changes as a function of the aroyl group.

It is seen from the presented data that compounds containing the o-methoxyphenylpiperazine group have a definite value in investigating tranquilizers; they differ favorably from compounds having a p-methoxyphenylpiperazine or phenylpiperazine group.

EXPERIMENTAL

6-N-Phenylpiperazino-2-benzoylcyclohexanone-1 (II, Ar = C_6H_5, R = H). To a solution of 5.62 g of 6-bromo-2-benzoylcyclohexanone-1 (I, R = H) in 50 ml of benzene was added a solution of 6.48 g of N-phenylpiperazine in 30 ml of benzene at room temperature. Phenylpiperazine hydrobromide was separated after 2-3 days, about 50 ml of ether was added to the filtrate, and the salt was precipitated by passing in hydrogen chloride. The residue was filtered and dissolved in a water–ethanol mixture and the base was precipitated with aqueous ammonia, mp 150° (from ethanol or dimethylformamide). Yield 3.1 g (42.8%). Found, %: N 7.87. $C_{23}H_{26}N_2O_2$. Calculated, %: N 7.73.

Hydrochloride Salt. White crystalline material decomposing at 182-184° (from absolute ethanol with addition of ether). Found, %: Cl 16.29; N 5.27. $C_{23}H_{26}N_2O_2 \cdot 2HCl$. Calculated, %: Cl 16.29; N 6.43.

Data on the preparation of the remaining N-arylpiperazino derivatives of 2-aroylcyclohexanones-1 are presented in Table 3.

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