SEARCH FOR NEW DRUGS

2-[γ-(N-ARYLPIPERAZINO)PROPYL]-2-ARYLINDANDIONES-1,3 AND -INDANDIOLS-1,3

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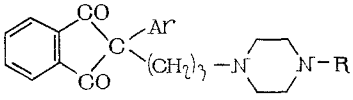
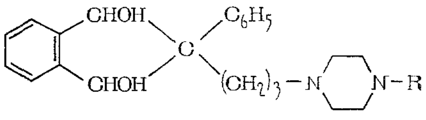
During our studies in the series of arylpiperazino diketones [1, 2] in the search for neuro- and psychotrophic agents the methods for synthesizing 2-[γ-(N-arylpiperazino)propyl]-2-arylindandiones-1,3 and the corresponding indandiols-1,3, homologs of the previously synthesized arylpiperazinodiones-1,3 and diols-1,3, were investigated. The starting compounds, 2-(γ-halogenopropyl)-2-arylindandiones-1,3, and the tosylate of 2-(γ-hydroxypropyl)-2-phenylindandione-1,3, were prepared by previously developed methods [3, 4]. Alkylation of 2-arylindandiones-1,3 with dibromopropane or with 1-bromo-3-chloropropane yielded, in addition to the expected 2-γ-halogenopropyl derivatives, a mixture of different difficult-to-separate byproducts. The mixture was separated by preparative column chromatography or by vacuum distillation.

p-Toluenesulfonic acid esters (tosylates) were successfully used for alkylating amines [4]. However the tosylate of 2-(γ-hydroxypropyl)-2-phenylindandione-1,3 was also difficult to prepare in pure form. On using it as the starting compound, the yield of 2-(γ-piperazinopropyl)indandiones-1,3 was not increased; therefore it was advisable to use the γ-bromo derivative.

2-[γ-(N-Arylpiperazino)propyl]-2-arylindandiones-1,3 (Ia–Im; Table 1) were synthesized by the action of double quantities of N-arylpiperazines on 2-(γ-halogenopropyl)-2-arylindandiones-1,3. The arylpiperazino derivatives were also prepared from the tosylate of 2-(γ-hydroxypropyl)-2-phenylindandione-1,3. Reduction of Ia–If with sodium borohydride in ethanol medium [1, 5] yielded the corresponding 2-[γ-(N-arylpiperazino)propyl]-2-phenylindandiols (IIa–IIf; Table 2):



I



II

Compounds I are yellowish crystalline compounds which form stable salts with hydrogen chloride. Compounds II are colorless crystalline compounds which form stable salts with oxalic acid. The structure of compounds I and II was confirmed by IR spectral data. For I two frequencies of carbonyl groups are observed in the range 1700-1730 cm^{-1}, in the spectra of compounds II the carbonyl absorption is absent but at about 3300 cm^{-1} there was observed absorption bands of the valence vibrations of the hydroxyl groups.

Study of the pharmacological properties of compounds I and II was carried out on white mice with intraperitoneal administration of the compounds being investigated. The results were statistically analyzed

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TABLE 1. 2-[γ-(N-Arylpiperazino)propyl]-2-arylindandiones-1,3

Compound	Ar	R	mp (°C)	Yield, (in%)	Found (in %)				Empirical formula	Calculated (in %)			
					C	H	N	Cl		C	H	N	Cl
Ia	C_6H_5	o-$CH_3OC_6H_4$	184	60	76,70	6,80	6,25	—	$C_{29}H_{30}N_2O_3$	76,75	6,65	6,15	—
Ia·2HCl			206—7	—	—	—	5,60	13,08	$C_{29}H_{30}N_2O_3 \cdot 2HCl$	—	—	5,31	13,44
Ib	C_6H_5	m-$CH_3OC_6H_4$	102	45	76,72	6,38	6,05	—	$C_{29}H_{30}N_2O_3$	76,65	6,65	6,15	—
Ib·2HCl			207—8		—	—	5,58	13,27	$C_{29}H_{30}N_2O_3 . 2HCl$	—	—	5,31	13,44
Ic	C_6H_5	p-$CH_3OC_6H_4$	135	55	76,74	6,96	6,41	—	$C_{29}H_{30}N_2O_3$	76,65	6,65	6,15	—
Ic·2HCl			193—4		—	—	5,49	13,69	$C_{29}H_{30}N_2O_3 \cdot 2HCl$	—	—	5,31	13,44
Id	C_6H_5	C_6H_5	136	53	78,84	6,69	6,96	—	$C_{28}H_{28}N_2O_2$	79,21	6,64	6,59	—
Id·2HCl			198—200		—	—	5,78	14,44	$C_{28}H_{28}N_2O_2 . 2HCl$	—	—	5,63	14,25
Ie	C_6H_5	o-ClC_6H_4	110	52	72,83	5,89	5,94	8,05	$C_{28}H_{27}ClN_2O_2$	73,27	5,93	6,10	7,72
Ie·HCl			254—5		—	—	5,54	14,17	$C_{28}H_{27}ClN_2O_2$	—	—	5,65	14,31
If	C_6H_5	m-ClC_6H_4	130	36	73,47	5,98	5,91	7,62	$C_{28}H_{27}ClN_2O_2$	73,27	5,93	6,10	7,62
If·2HCl			221—2		—	—	5,63	20,17	$C_{28}H_{27}ClN_2O_2 \cdot 2HCl$	—	—	5,25	19,98
Ig·2HCl	p-$CH_3OC_6H_4$	o-$CH_3OC_6H_4$	220—1	23	64,89	6,44	4,88	12,55	$C_{30}H_{32}N_2O_4 \cdot 2HCl$	64,63	6,10	5,03	12,75
Ih·HCl	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	200—1	15	64,91	5,88	5,28	13,01	$C_{30}H_{32}N_2O_4 \cdot 2HCl$	64,63	6,10	5,03	12,75
Ii·2HCl	p-$CH_3OC_6H_4$	CH_2CH_2OH	238—40	20	60,94	6,60	5,64	13,80	$C_{25}H_{30}N_2O_4 \cdot 2HCl$	60,10	6,47	5,66	14,34
Ij	p-$CH_3OC_6H_4$	m-ClC_6H_4	125—6	—	70,90	5,99	5,97	—	$C_{29}H_{29}ClN_2O_3$	71,25	5,94	5,73	—
Ij·HCl			208—10	36	66,34	5,72	5,69	13,77	$C_{29}H_{29}ClN_2O_3 \cdot HCl$	66,28	5,71	5,38	13,52
Ik	p-$CH_3OC_6H_4$	C_6H_5	142	25	76,78	6,76	6,30	—	$C_{29}H_{30}N_2O_3$	76,65	6,61	6,17	—
Ik·HCl·H_2O			204—5	20	68,20	6,82	—	7,50	$C_{29}H_{30}N_2O_3 \cdot HCl \cdot H_2O$	68,44	6,49	—	6,98
Il·HCl.H_2O	p-ClC_6H_4	o-$CH_3OC_6H_4$	241—2	18	64,07	5,90	5,38	13,00	$C_{29}H_{29}ClN_2O_3 . HCl \cdot H_2O$	64,09	5,89	5,16	13,08

TABLE 2. 2-[γ-(N-Arylpiperazino)propyl]-2-phenylindandiols-1,3

Compound	R	mp (°C)	Yield (in%)	Found (in %)				Empirical formula	Calculated (in %)			
				C	H	N	Cl		C	H	N	Cl
IIa	o-$CH_4OC_6H_4$	194—5		76,28	7,60	6,08	—	$C_{29}H_{34}N_2O_3$	75,95	7,47	6,15	—
IIa·$2C_2H_2O_4$		183—5	62	—	—	4,64	—	$C_{29}H_{34}N_2O_3 \cdot 2C_2H_2O_4$	—	—	4,38	—
IIb	m-$CH_3OC_6H_4$	96—97		75,90	7,51	5,98	—	$C_{29}H_{34}N_2O_3$	75,95	7,47	6,15	—
IIb·$C_2H_2O_4$		148—50	66	—	—	5,42	—	$C_{29}H_{34}N_2O_3 \cdot C_2H_2O_4$	—	—	5,10	—
IIc	p-$CH_3OC_6H_4$	78—79		75,61	7,25	6,00	—	$C_{29}H_{34}N_2O_3$	75,95	7,47	6,15	—
IIc·$C_2H_2O_4$		192—3	70	—	—	5,14	—	$C_{29}H_{34}N_2O_3 \cdot C_2H_2O_4$	—	—	5,10	—
IId	C_6H_5	160—16		78,12	7,48	6,73	—	$C_{28}H_{32}N_2O_2$	78,45	7,52	6,53	—
IId·$2C_2H_2O_4$		187—8	69	—	—	4,52	—	$C_{28}H_{32}N_2O_2 \cdot 2C_2H_2O_4$	—	—	4,60	—
IIf	m-ClC_6H_4	166—7		72,30	6,68	6,39	7,95	$C_{28}H_{31}ClN_2O_2$	72,63	6,74	6,04	7,65
IIf·$2C_2H_2O_4$		183—4	72	—	—	4,14	—	$C_{28}H_{31}ClN_2O_2 \cdot 2C_2H_2O_4$	—	—	4,36	—

TABLE 3. Pharmacological Activity of 2-[γ-(Arylpiperazino)propyl]-2-phenylindandiones-1,3 and- phenylindandiols-1,3 in Experiments on White Mice with Intraperitoneal Administration (the confidence limits for P = 0.05 are given in parentheses)

Compound	LD_{50} (in mg/kg)	ED_{50} (in mg/kg)				Index of potentiation of hexenal narcosis
		rotating rod [7]	"tube" test [8]	hypothermia at 3°C and below	analgesic activity*	
Ia	780 (634–859)	55 (42–71)	50 (38–66)	25 (18–45)	4,4 (3,5–5,6)	4,4
Ib	940 (854–1 034)	6 (4–8)	26 (20–34)	50 (35–72)	30 (16–57)	1,2
Ic	900 (833–972)	42 (29–60)	42 (29–60)	56 (43–128)	80 (53–120)	1,5
Id	850 (819–1 037)	38 (27–53)	38 (27–53)	40 (23–70)	240 (171–336)	0,9
Ie	1 200 (1 140–1 368)	49 (40–58)	49 (40–58)	70 (54–91)	84 (76–93)	6,9
If	1 550 (1 069–3 247)	12 (8–17)	12 (8–17)	17 (15–19)	80 (57–112)	2,9
Ig	800 (640–10 000)	27 (22–32)	28 (24–32)	25 (17–37)	9 (7–10)	5,5
Il	520 (382–707)	35 (25–48)	30 (22–40)	13 (10–17)	27 (18–42)	7,3
IIa	127 (114–141)	32 (22–46)	32 (22–46)	7 (5,4–9,1)	42 (32–55)	3,7
IIb	265 (240–294)	54 (34–86)	33 (22–49)	26 (15–44)	62 (43–90)	2,3
IIc	190 (161–224)	33 (22–49)	33 (22–49)	26 (15–44)	42 (28–63)	4,0
IId	183 (165–202)	31 (22–43)	31 (22–43)	32 (22–46)	42 (32–55)	3,7
IIf	140 (111–176)	42 (32–55)	42 (32–55)	14 (11–18)	70 (54–91)	2,8

*By the "hot plate" method.

and the mean effective doses (ED_{50}) and also the mean lethal doses (LD_{50}) were calculated by the previously described method [6]. Various methods were used to estimate the tranquilizing properties [7-9].

It is clear from the data in Table 3 that all the compounds synthesized show tranquilizing properties which are more pronounced in the case of compounds Ib and If, that is, in the m-substituted arylpiperazino derivatives. It was shown that all the indandiol-1,3 derivatives (IIa–IIf) display a relative high acute toxicity by comparison with the corresponding indandione-1,3 derivatives (Ia–If) which is characteristic also of the series of 2-[N-arylpiperazino]- and 2-[β-(N-arylpiperazino)ethyl]-2-phenylindandione-1,3 [1, 2]. The toxicity increases also with an increase in the number of methylene groups between the diketone grouping and the remainder of the N-arylpiperazine, that is, in the order: 2-piperazino-, 2-(β-piperazinoethyl)-, 2-(γ-piperazinopropyl)-2-phenylindandiones-1,3.

EXPERIMENTAL

2-(γ-Halogenopropyl)-2-arylindandiones-1,3. A. To a solution of 2.3 g of sodium in 200 ml of n-propanol was added 22.5 g of 2-phenylindandione-1,3, 24 g of 1,3-dibromopropane, and 14.9 g of sodium iodide; then the mixture was boiled until the solution was colorless (~ 8-10 h). The solution was cooled and poured into water, and the red oil which separated was dissolved in benzene. The benzene solution was washed twice with soda solution, then with water, and was dried with anhydrous magnesium sulfate. The benzene was evaporated off in vacuo; the red oil which was obtained (~ 20-25 g) could be used immediately for the synthesis of compound I. The pure compound was obtained by preparative chromatography on an aluminum oxide column using 1 : 4 ethyl acetate–hexane as solvent and subsequent crystallization from hexane or petroleum ether. Yield of 2-(γ-bromopropyl)-2-phenylindandione-1,3 was 10 g (29%) in the form of pale yellow crystals with mp 88°C. Found %: C 63.02; H 4.30; Br 23.78. $C_{18}H_{15}BrO_2$. Calculated %: C 63.17; H 4.41; Br 23.35.

B. 2-(γ-Chloropropyl)-2-(p-methoxyphenyl)indandione-1,3 was prepared analogously from the sodium salt of 2-(p-methoxyphenyl)indandione-1,3 and 1-bromo-3-chloropropane. After vacuum distillation there was obtained an orange oil with bp 160-170°C ($1 \cdot 10^{-2}$ mm). Yield was 75%. Found %: C 69.50; H 5.19; Cl 10.20. $C_{19}H_{17}ClO_3$. Calculated %: C 69.39; H 5.17; Cl 10.80.

2-(γ-Hydroxypropyl)-2-phenylindandione-1,3 was prepared from 2-phenylindandione-1,3 and 3-chloropropanol in the presence of sodium iodide [3] as white needle-like crystals with mp 78°C (from hexane). Found %: C 77.30; H 5.97. $C_{18}H_{16}O_3$. Calculated %: C 77.12; H 5.75.

Tosylate of 2-(γ-Hydroxypropyl-2-phenylindandione-1,3 was prepared by the previously described method [4]. The product was isolated as a thick yellowish oil which was used immediately for the synthesis of compound I. The product was not isolated in the pure form.

2-[γ-(N-Arylpiperazino)propyl]-2-arylindandiones-1,3 (I). A. To a solution of 0.01 moles of 2-(γ-halogenopropyl)-2-arylindandione-1,3 in 100 ml of benzene was added 0.02 moles of the appropriate N-arylpiperazino dissolved in 30 ml of benzene, and the mixture was boiled for 30-60 min. The mixture was cooled, the precipitated hydrohalide of the starting piperazino was filtered off, and the filtrate was saturated with dry hydrogen chloride. The white precipitate obtained was filtered off, then suspended in water; the yellowish oily base was precipitated with aqueous ammonia and it was crystallized from alcohol.

B. To a solution of 0.01 mole of the tosylate of 2-(γ-hydroxypropyl)-2-phenylindandione-1,3 in 50 ml of dioxane was added 0.02 mole of N-arylpiperazinoe, and the mixture was boiled for 1 h. The solution was cooled and poured into 200 ml of water, the precipitate was dissolved in ether or benzene and the solution was dried with anhydrous magnesium sulfate. Further treatment was the same as in the case of A.

The Hydrochloride Salts of I were prepared by saturating benzene or ether solutions of the bases with dry hydrogen chloride and crystallizing them from absolute ethanol.

2-[γ-(N-Arylpiperazino)propyl]-2-phenylindandiones-1,3 (II) were prepared by the described method [1, 2] and were purified by multiple crystallizations from carbon tetrachloride or from dichloroethane with added hexane.

Oxalates of II were prepared by the addition to ether solutions of the bases of calculated quantities of a saturated solution of oxalic acid in absolute alcohol. The precipitate obtained was filtered off and crystallized from a 3 : 1 mixture of carbon tetrachloride and absolute ethanol.

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