2-[δ-(N-ARYLPIPERAZINO)BUTYNYL]- AND 2-[δ-(N-ARYLPIPERAZINO)BUTYL]-2-PHENYLINDANE-1,3-DIONES

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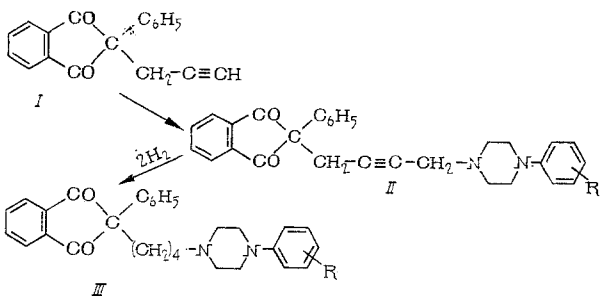
In a continuation of systematic investigations in the arylpiperazinodiketone series [1-3] a way was also studied of synthesizing 2-[δ-(N-arylpiperazino)butyl]-2-phenylindanediones, homologs of the earlier synthesized arylpiperazinoalkylindane-1,3-diones.

The usual way of synthesizing piperazinoalkyl diketones by alkylation of 1,3-diketones with alkyl halides with subsequent exchange of the halogen for an arylpiperazine residue did not give satisfactory results. It was found that a convenient method of synthesizing 2-[δ-(N-arylpiperazino)butyl]-2-phenylindane-1,3-diones [(IIIa-IIIf), Table 1] is hydrogenation of the triple bond in2-[δ-(N-arylpiperazino)butynyl]-2-phenylindane-1,3-diones in methanol in the presence of Raney nickel [4, 5]. The yield of reaction products amounts to 60-70%, since during the reaction cleavage of the molecule (2-phenylindane-1,3-dione can be isolated from the reaction mixture) and tarring occur. The 1,3-dicarbonyl group is not lost under the reaction conditions. The starting 2-[δ-(N-arylpiperazino)butynyl]-2-phenylindane-1,3-diones [(IIa-IIf), see Table 1] were obtained in good yields by aminomethylation of 2-propargyl-2-phenylindane-1,3-dione(I) with paraform and N-arylpiperazines in dioxane in the presence of monovalent copper salts [6, 7].



Compounds (II) and (III) are yellow crystalline materials, forming stable salts with inorganic and organic acids. The structure of compounds (II) and (III) was confirmed by IR-spectral data: two frequencies of carbonyl groups are observed in the interval of 1740-1705 cm^{-1}. It is interesting to note that in spectra of compounds (II) the absorption maximum in the interval of 2260-2100 cm^{-1}, characteristic for the acetylene bond, is not observed. However, the structure of (II) is completely confirmed by NMR-spectral data. The NMR spectrum of 2-[δ-N-phenylpiperazino)butynyl]-2-phenylindane-1,3-dione (IId) is deuterochloroform solution contains, in addition to signals of methylene protons of the piperazine ring at τ 7.88 and 7.06 ppm, also two triplets of methylene-group protons of the butyne system at τ 6.96 and 6.87 ppm. Signal splitting is explained by interaction of protons through the $-C\equiv C$ bond. The spectrum also contains a multiplet of aromatic protons at τ 1.9-2.45 ppm.

The study of pharmacological properties of compounds (II) and (III) was carried out in experiments on white mice upon interperitoneal introduction of the investigated materials. Acute toxicity (LD_{50}) was determined. Tranquilizing properties (rotating-rod test [8], "tube" test [9], hypothermal effect) and anal-

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TABLE 1. 2-[δ-(N-Arylpiperazino)butynyl]- and 2-[δ-(N-Arylpiperazino)butyl]-2-phenylindane-1,3-diones

Compound	R	Yield, %	mp (deg)	Found, %				Empirical formula	Calculated, %			
				C	H	Cl	N		C	H	N	Cl
IIa	o-CH_3O	89	148	77,33	6,30	—	6,36	$C_{30}H_{28}N_2O_3$	77,56	6,07	6,03	—
IIa·2HCl		—	180—2	—	—	13,31	5,43	$C_{30}H_{28}N_2O_3 \cdot 2HCl$	—	—	5,21	13,19
IIb	m-CH_3O	71	113	77,80	6,23	—	6,17	$C_{30}H_{28}N_2O_3$	77,56	6,07	6,03	—
IIb·$C_2H_2O_4$		—	161	69,13	5,35	—	5,08	$C_{30}H_{28}N_2O_3 \cdot C_2H_2O_4$	69,30	5,45	5,05	—
IIc	p-CH_3O	88	130	77,38	6,37	—	5,85	$C_{30}H_{28}N_2O_3$	77,56	6,07	6,03	—
IIc·2HCl		—	199—201	—	—	13,54	5,36	$C_{30}H_{28}N_2O_3 \cdot 2HCl$	—	—	5,21	13,19
IId	H	86	134	80,39	5,89	—	6,61	$C_{29}H_{28}N_2O_2$	80,15	6,03	6,44	—
IId·2HCl		—	189	—	—	13,64	5,28	$C_{29}H_{26}N_2O_2 \cdot 2HCl$	—	—	5,52	13,97
IIe	m-Cl	78	104	74,53	5,49	7,86	5,91	$C_{29}H_{25}ClN_2O_2$	74,27	5,37	5,97	7,56
IIe 2HCl		—	200	—	—	19,25	5,84	$C_{29}H_{25}ClN_2O_2 \cdot 2HCl$	—	—	5,17	19,62
IIf	o-Cl	84	128	74,01	5,02	7,92	5,64	$C_{29}H_{25}ClN_2O_2$	74,27	5,37	5,97	7,56
IIf·$C_2H_2O_4$		—	144	66,45	4,69	—	5,10	$C_{29}H_{25}ClN_2O_2 \cdot C_2H_2O_4$	66,61	4,86	5,01	—
IIIa·$2H_2SO_4$	o-CH_3O	38	192—3	53,96	5,20	—	4,01	$C_{30}H_{32}N_2O_3 \cdot 2H_2SO_4$	54,20	5,45	4,21	—
IIIb·$C_2H_2O_4$	m-CH_3O	171—3	39	69,04	6,35	4,88	—	$C_{30}H_{32}N_2O_3 \cdot C_2H_2O_4$	68,80	6,13	5,01	—
IIIc	p-CH_3O	107	45	76,78	6,58	5,93	—	$C_{30}H_{32}N_2O_3$	76,89	6,88	5,97	—
IIIc·H_2SO_4		252	—	63,40	5,81	4,86	—	$C_{30}H_{32}N_2O_3 \cdot H_2SO_4$	63,59	6,04	4,94	—
IIId	H	111	43	79,34	7,00	6,29	—	$C_{29}H_{30}N_2O_2$	79,42	6,89	6,38	—
IIId·H_2SO_4		208	—	65,23	5,86	5,08	—	$C_{29}H_{30}N_2O_2 \cdot H_2SO_4$	64,90	6,01	5,22	—
IIIe·H_2SO_4	m-Cl	201	33	60,59	5,22	4,63	6,44	$C_{29}H_{29}ClN_2O_2 \cdot H_2SO_4$	60,98	5,47	4,90	6,20
IIIf	o-Cl	109	48	73,85	5,97	5,98	—	$C_{29}H_{29}ClN_2O_2$	73,63	6,17	5,92	—
IIIf·$C_2H_2O_4$	—	203—4	—	66,32	5,29	4,82	—	$C_{29}H_{29}ClN_2O_2 \cdot C_2H_2O_4$	66,13	5,54	4,95	—

TABLE 2. Pharmacological Activity of 2-[δ-(N-Arylpiperazino)-butynyl]- and 2-[δ-(N-Arylpiperazino)butyl]-2-phenylindane-1,3-diones in Experiments on White Mice upon Intraperitoneal Introduction (confidence limits at P = 0.05 given in parentheses)

Compound	LD_{50}, mg/kg	ED_{50} (mg/kg)				Potency index of hexenal narcosis
		rotating rod	"tube" test	hypothermia by 3° and less	analgesic activity	
IIa	9400 (8392÷10528)	530 (294÷954)	80 (52÷124)	100 (55÷180)	37 (22÷161)	1,9
IIb	>4000	43 (26÷70)	55 (31÷95)	75 (47÷120)	95 (68÷133)	1,2
IIc	3650 (3109÷4270)	200 (154÷260)	120 (97÷147)	150 (80÷255)	135 (90÷202)	2,1
IId	450 (410÷495)	>300	>300	35 (25÷49)	390 (285÷531)	3,0
IIe	9000 (7438÷10890)	17 (13÷22)	40 (31÷52)	28 (20÷40)	620 (443÷878)	1,5
IIf	>2000	150 (107÷210)	150 (107÷210)	90 (50÷144)	700 (538÷910)	0,9
IIIa	420 (366÷479)	62 (43÷90)	62 (43÷90)	39 (31÷48)	52 (30÷88)	1,1
IIIb	350 (260÷460)	66 (51÷79)	66 (51÷79)	35 (26÷46)	>100	0,9
IIIc	450 (388÷522)	115 (82÷161)	115 (82÷161)	105 (50÷220)	>200	1,3
IIId	>1000	120 (108÷133)	76 (65÷87)	140 (108÷182)	260 (80÷440)	3,4
IIIe	>1000	500	76 (65÷37)	140 (108÷182)	>500	2,4
IIIf	430 (367÷490)	78 (66÷92)	70 (56÷87)	58 (45÷75)	95 (68÷133)	1,2

gesic activity (hot plate method [10]) were evaluated from the ED_{50} value. The potency index of hexenal narcosis was also determined for all compounds.

It is seen from data presented in Table 2 that tranquilizing properties are expressed most in compounds (IIe) and (IIb), i.e., in m-substituted arylpiperazinobutynyl derivatives. The corresponding saturated derivatives (IIIe) and (IIIb) possess less expressed activity. Hypothermal activity is displayed to the greatest degree by compounds (IId) and (IIe), and by (IIIa,b,e) in the series of piperazinobutyl derivatives. An analgesic effect was noted in compounds containing the o-methoxyphenyl radical (IIIa and IIa); this effect was expressed weakly in the remaining compounds. Compounds containing an unsubstituted phenyl radical (IId and IIId) are most active in ability to intensify hexenal narcosis. Acute toxicity of arylpiperazinobutyl derivatives is significantly lower than of the corresponding butyl derivatives.

Results of the executed investigation, and also of preceding research [1-3], make it possible to conclude that with an increasing number of methylene groups between the diketone grouping and the N-arylpiperazine residue, i.e., in the 2-piperazino-, 2-(β-piperazinoethyl)-, 2-(γ-piperazinopropyl)-, 2-(δ-piperazinobutyl)-2-phenylindane-1,3-diones, toxicity increases, while their neurotropic properties change to an insignificant degree.

EXPERIMENTAL

2-Propargyl-2-phenylindane-1,3-dione (I). The compound was obtained by a modified method of [6]. In 200 ml of n-propanol was dissolved 2.3 g of sodium; 22.2 g of 2-phenylindane-1,3-dione, 14.9 g of sodium iodide, and 8.5 ml of propargyl chloride were added; and the mixture was boiled to decolorization (~1-2 h). The cooled solution was poured into water, and the precipitate was separated and crystallized from alcohol. Yield was 23 g (89%), mp 137°.

2-[δ-(N-Arylpiperazino)butynyl]-2-phenylindane-1,3-diones (II). We dissolved 0.01 mole of (I) in 100 ml of dry dioxane, added 0.015 mole of the corresponding N-arylpiperazine, dissolved in 30 ml of dioxane, 0.03 mole of paraform, and 0.2 g of monovalent copper acetate, and boiled the mixture for 0.5-1 h. The cooled solution was poured into water and the precipitated oily residue was crystallized from alcohol.

Hydrochloride salts of (II) were obtained by saturation of benzene or ether solutions of bases with dry hydrogen chloride and were crystallized from isopropanol.

2-[δ-(N-Arylpiperazino)butyl]-2-phenylindane-1,3-diones (III). To a suspension of 0.01 mole of (II) in 100 ml of methanol was added an equimolar amount of Raney nickel, and the mixture was hydrogenated at room temperature until absorption of hydrogen ceased. The catalyst was separated, and the red solution was poured into water. The precipitate was separated, dissolved in ether, and dried with anhydrous magnesium sulfate. The ether solution was saturated with dry hydrogen chloride. The precipitate was filtered, suspended in water, and the yellow oily base was precipitated with ammonia and crystallized from alcohol.

Salts of (III) were obtained by addition to an ether solution of base of calculated amounts of a saturated solution of oxalic or sulfuric acid in ether. The precipitate was filtered and crystallized from isopropanol.

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