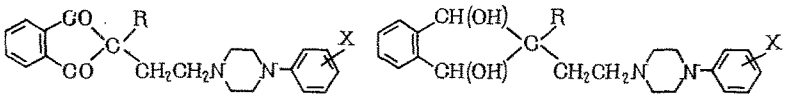
2-β-(N-ARYLPIPERAZINO)ETHYL INDANDIONES-1,3 AND INDANDIOLS-1,3

I. A. Berzinya, S. K. Germane,
Ya. Ya. Dregeris, and A. K. Aren

UDC 615.21:547.665

2-Arylpiperazino-2-substituted indandiones-1,3 and the corresponding indandiols have marked neurotropic properties [1]. In the course of systematic investigations into the field of aminodiones and aminodiols by reaction of N-arylpiperazines with the tosylates of 2-β-hydroxyethyl-2-phenyl-[2] and 2-β-hydroxyethyl-2-methyl indandiones-1,3 [3] the corresponding 2-(N-arylpiperazino)ethyl-2-phenyl-(Ia-Ig) and 2-(N-arylpiperazino) ethyl-2-methyl indandiones-1,3 (Ih-Ii) were synthesized. By reduction of Ia-Ii with sodium borane according to a method developed previously [1, 4] the corresponding 2-(N-arylpiperazino) ethyl-2-substituted indandiols IIa-IIi were obtained. The arylpiperazinodiones-1,3 (Ia-Ii) are yellowish crystalline substances forming stable salts with hydrogen chloride (Table 1). The 2-β-(N-arylpiperazino) ethyl indandiols-1,3 (IIa-IIi) are colorless crystalline substances forming likewise stable dihydrochlorides (Table 2):



I a-i *II* a-i

R=CH_3, C_6H_5, X=H, OCH_3, Cl

The structures of the compounds I and II were confirmed by the data of the IR spectra. For I two frequencies of carbonyl groups were observed (~1705, 1740 cm^{-1}), in the spectrum of II the frequencies of the carbonyl absorption are absent, but in the 3300 cm^{-1} region absorption bands of the oscillations of hydroxyl groups were detected.

The disturbance of the motor coordination by the compounds I and II was studied by the "rotating bar" test, the "tube" test, and the "attraction" test. The hypothermic effect was determined with an electrothermometer. For the evaluation of the analgesic action the method of the thermal pain stimulus was applied. Further investigations concerned the degree of potentiation of hexenal narcosis by the compounds I and II, the general effect on the behavior of animals and the acute toxicity. The experimental material was subjected to statistical processing and in all cases the mean effective doses (ED_{50}) and the mean lethal doses (LD_{50}) were calculated, see Table 1.

The tests were carried out on white mice. The substances studied were administered intraperitoneally 30 min before the test. The experimental data are presented in Table 3 from which it is evident that all 2-β-(N-arylpiperazino)ethyl-2-substituted indandiones-1,3 (Ia-Ii) have an extremely low toxicity as compared to the corresponding indandiols (IIa-IIi) the toxicity of which is many times higher. The same regularity was also observed in the case of 2-arylpiperazino-2-substituted indandiones-1,3 and indandiols-1,3 [1]. An exception were 2-(N-arylpiperazino)ethyl-2-methyl indandione (Ii) and the corresponding diol (IIi); for the latter the toxicity was 3.5 times lower than for the corresponding dione. The p-OCH_3 and p-Cl-substituted indandiol derivatives (IIa and IId) had the highest toxicity.

All compounds synthesized show a tranquilizing effect, i.e., they cause hypothermia, disturb the coordination of movements, potentiate hexenal narcosis, and manifest analgesic properties characteristic of depressors of the central nervous system. The analgesic effect and the capability to potentiate hexenal narcosis are more marked in piperazine derivatives of indandiones (I) than in the corresponding derivatives of indandiol (II), but the reverse is true for the tranquilizing properties. As to activity the compound

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 10, pp. 25-29, October, 1968. Original article submitted May 5, 1968.

TABLE 1. 2-β-(N-Arylpiperazino)ethyl-2-phenyl- and 2-β-(N-Arylpiperazino)ethyl-2-methyl Indandiones-1,3

Compound	Melting point (degrees)	Yield, %	Found, %				Gross molecular formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
Ia	142	78	76,54	6,26	6,50	—	$C_{28}H_{28}O_3N_2$	76,34	6,40	6,40	—
Ia·2HCl	218—20	—	—	—	5,41	14,03	$C_{28}H_{28}O_3N_2 \cdot 2HCl$	—	—	5,45	13,80
Ib	126	70	76,15	6,35	6,21	—	$C_{28}H_{28}O_3N_2$	76,34	6,40	6,40	—
Ib·HCl	258—60	—	—	—	6,04	7,83	$C_{28}H_{28}O_3N_2 \cdot HCl$	—	—	5,87	7,43
Ic	102	58	76,06	6,27	6,17	—	$C_{28}H_{28}O_3N_2$	76,34	6,40	6,40	—
Ic·HCl	224—6	—	—	—	5,61	7,21	$C_{28}H_{28}O_3N_2 \cdot HCl$	—	—	5,87	7,43
Id	160	75	73,13	5,89	6,31	8,05	$C_{27}H_{25}O_2N_2Cl$	72,88	5,66	6,29	7,96
Id·HCl	160—2	—	—	—	5,50	14,98	$C_{27}H_{25}O_2N_2Cl \cdot HCl$	—	—	5,81	14,72
Ie	151	72	72,78	5,49	6,64	7,81	$C_{27}H_{25}O_2N_2Cl$	72,88	5,66	6,29	7,96
Ie·HCl	234—6	—	—	—	6,21	15,03	$C_{27}H_{25}O_2N_2Cl \cdot HCl$	—	—	5,81	14,72
If	86	68	72,94	5,81	6,21	7,60	$C_{27}H_{25}O_2N_2Cl$	72,88	5,66	6,29	7,96
If·HCl	203—5	—	—	—	6,11	14,50	$C_{27}H_{25}O_2N_2Cl \cdot HCl$	—	—	5,81	14,72
Ig	114	65	78,69	6,07	6,44	—	$C_{27}H_{26}O_2N_2$	78,99	6,38	6,82	—
Ig·2HCl	195—7	—	—	—	5,42	14,86	$C_{27}H_{26}O_2N_2 \cdot HCl$	—	—	5,78	14,66
Ih	148	61	73,33	7,06	7,41	—	$C_{23}H_{26}O_3N_2$	72,99	6,92	7,39	—
Ih·2HCl	215—8	—	—	—	6,03	15,46	$C_{23}H_{26}O_3N_2 \cdot 2HCl$	—	—	6,25	15,70
Ii	132	53	68,76	6,15	7,55	9,60	$C_{22}H_{23}O_2N_2Cl$	69,01	6,05	7,31	9,25
Ii·2HCl	245—8	—	—	—	6,50	—	$C_{22}H_{23}O_2N_2Cl \cdot 2HCl$	—	—	6,14	—

TABLE 2. 2-β-(N-Arylpiperazino)ethyl-2-phenyl- and 2-β-(N-Arylpiperazino)ethyl-2-methyl Indandiols-1,3

Compound	Melting point (degrees)	Yield, %	Found, %				Gross molecular formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
IIa	193	73,2	75,73	7,35	6,40		$C_{28}H_{32}O_3N_2$	75,64	7,25	6,30	—
IIa·2HCl	240—2	—	—	—	5,36	13,25	$C_{28}H_{32}O_3N_2 \cdot 2HCl$			5,41	13,70
IIb	210	75	76,00	7,36	6,20	—	$C_{28}H_{32}O_3N_2$	75,64	7,25	6,30	—
IIb·2HCl	214—6	—	—	—	5,79	13,97	$C_{28}H_{32}O_3N_2 \cdot 2HCl$	—	—	5,41	13,70
IIc	178	71	75,56	7,56	6,15	—	$C_{28}H_{32}O_3N_2$	75,64	7,25	6,30	—
IIc·2HCl	197—8	—	—	—	5,80	13,54	$C_{28}H_{32}O_3N_2 \cdot 2HCl$			5,41	13,70
IId	205	70	71,95	6,45	6,03	7,56	$C_{27}H_{29}O_3N_2Cl$	72,25	6,50	6,26	7,89
IId·HCl	196—9	—	—	—	5,46	14,03	$C_{27}H_{29}O_3N_2Cl \cdot HCl$	—	—	5,76	14,56
IIe	226	79	72,40	6,25	6,38	7,98	$C_{27}H_{29}O_3N_2Cl$	72,25	6,50	6,26	7,89
IIe·HCl	232—4	—	—	—	5,66	14,26	$C_{27}H_{29}O_3N_2Cl \cdot HCl$	—	—	5,76	14,56
IIf	215	72	72,14	6,56	6,48	7,68	$C_{27}H_{29}O_2N_2Cl$	72,25	6,50	6,26	7,89
IIg	210	75	78,29	7,49	7,03	—	$C_{27}H_{30}O_2N_2$	78,22	7,29	6,75	—
IIg·HCl	215—9		—	—	6,34	7,51	$C_{27}H_{30}O_2N_2 \cdot HCl$	—	—	6,20	7,86
IIh	170	78	72,40	7,69	7,22	—	$C_{23}H_{30}O_3N_2$	72,22	7,91	7,32	—
IIh·HCl	192—4		—	—	6,48	8,31	$C_{23}H_{30}O_3N_2 \cdot HCl$			6,68	8,47
IIi	158	77	68,43	7,16	7,35	9,62	$C_{22}H_{27}O_2N_2Cl$	68,29	7,03	7,24	9,16
IIi·HCl	205—7		—	—	7,03	16,37	$C_{22}H_{27}O_2N_2Cl \cdot HCl$	—	—	6,61	16,74

TABLE 3. Pharmacological Activity of 2-β-(N-Arylpiperazino) ethyl-2-substituted Indandiones-1,3 and Indandiols-1,3 (in parentheses the fiducial limits for P = 0.05)

Compound	R	X	LD_{50} (mg/kg)	"Rotating bar" test	"Tube" test	"Attraction" test	Lowering of the body temperature	Analgesic activity	Index of potentiation of hexenal narcosis
				ED_{50} (mg/kg)					
Ia	C_6H_5	p-OCH_3—	2 200 (1 618—2 992)	160 (123—208)	160 (123—208)	>500	60 (45—80)	550 (423—715)	4,2
Ib	C_6H_5	o-OCH_3—	1 600 (1 143—3 240)	300 (227—792)	300 (227—792)	>800	120 (83—174)	800	2,4
Ic	C_6H_5	m-OCH_3—	2 000 (1 587—2 520)	290 (98—420)	190 (142—255)	>500	290 (98—420)	29 10—42	1,9
Id	C_6H_5	p-C	900 (744—1 089)	1 300 (93—182)	120 (70—216)	130 (93—182)	130 (90—188)	39 (27—57)	6,7
Ie	C_6H_5	o-Cl	1 800 (1 513—2 142)	440 (355—546)	250 (206—302)	>500	290 (98—420)	35 (27—45)	5,8
If	C_6H_5	m-Cl	3400 (2 671—4 218)	17 (12—24)	74 (47—127)	>500	62 (46—83)	38 (23—63)	6,0
Ig	C_6H_5	H	2 600 (1 940—3 424)	240 (205—281)	240 (205—281)	>600	300 (166—540)	40 (30—53)	2,0
Ih	CH_3	o-CH_3	1 100 (932—1 298)	60 (33—108)	66 (46—96)	>500	56 (43—73)	28 (21—36)	6,5
Ii	CH_3	o-Cl	2 050 (1 864—2 255)	110 (88—136)	100 (81—124)	>50	200 (125—320)	30 (25—36)	4,2
IIa	C_6H_5	p-OCH_3	42 (36—49)	11 (7—18)	13 (9—18)	>20	8 (4—16)	—	6,5
IIb	C_6H_5	o-OCH_3	48 (40—58)	37 (26—52)	31 (23—40)	40 (32—50)	29 (22—38)	17 (12—24)	5,8
IIc	C_6H_5	m-OCH_3	430 (380—436)	2,0 (1,2—3,2)	6,2 (4,7—8,1)	>20	14 (11—18)	50 (37—68)	5,0
IId	C_6H_5	p-Cl	35 (30—41)	11 (8—15)	14 (7—27)	>20	6 (4—8)	24 (20—30)	3,6
IIe	C_6H_5	o-Cl	690 (603—788)	42 (30—58)	42 (30—58)	>50	27 (18—39)	56 (45—70)	3,4
IIf	C_6H_5	m-Cl	250 (192—325)	15 (11—19)	18 (13—25)	>20	18 (13—25)	37 (22—61)	2,4
IIg	C_6H_5	H	56 (45—70)	17 (12—24)	17 (12—24)	>20	14 (11—17)	22 (18—28)	2,7
IIh	CH_3	o-OCH_3	145 (112—188)	24 (19—30)	25 (19—33)	30 (23—39)	28 (21—36)	20 (15—27)	4,2
IIi	CH_3	o-Cl	7 100 (5 444—9 230)	15 (11—19)	15 (11—19)	15 (11—19)	18 (13—25)	110 (75—159)	4,0

IIc is not different from the tranquilizers described in the literature (derivatives of the phenothiazine series and butyrophenol).

EXPERIMENTAL

2-β-(N-Arylpiperazino)ethyl-2-phenyl- and 2-β-(N-arylpiperazino)ethyl-2-methyl Indandiones-1,3 (Ia-Ii). 0.01 mole 2-β-hydroxyethyl-2-phenyl- or 2-β-hydroxyethyl-2-methyl indandione-1,3 tosylate is dissolved in 100 ml dioxane, 0.02 mole of the corresponding N-arylpiperazine dissolved in 10 ml dioxane is added and the mixture is heated in a boiling water bath for 2 h. The solution is cooled, poured into 500 ml water, filtered and the precipitate is crystallized from ethyl alcohol. Ia-Ii are obtained (see Table 1).

Hydrochlorides of Ia-Ii. They are obtained by saturation of a benzene or ether solution of the bases with dry hydrogen chloride and subsequent recrystallization from absolute ethyl alcohol.

2-β-(N-Arylpiperazino)ethyl-2-phenyl and 2-β-(N-arylpiperazino)ethyl-2-methyl indandiols-1,3 (IIa-IIi) are obtained in the same way as 2-N-arylpiperazino-2-methyl indandiols-1,3 and 2-N-arylpiperazino-2-phenyl indandiols-1,3 [1] (see Table 2).

The hydrochlorides of IIa- IIi are obtained as mentioned above.

CONCLUSION

By the action of N-arylpiperazines on the tosylates of 2-β-hydroxyethyl-2-phenyl and 2-methyl-substituted indandiones-1,3 one obtains 2-β-(N-arylpiperazino)ethyl derivatives of 2-substituted indandiones-1,3 which are reduced by sodium borane to the corresponding indandiol-1,3 derivatives. The arylpiperazino derivatives of 2-substituted indandiones-1,3 and indandiols-1,3 have neurotropic properties. A certain association between structure, toxicity, and pharmacological action of these compounds was noted.

LITERATURE CITED

1. A. K. Aren, Ya. Ya. Ozol, I. A. Abolinya, et al., Khim.-Farmats. Zh., No. 6, 9 (1967).

2. Ya. Ya. Dregeris and G. Ya. Vanag, Izv. Akad. Nauk Latvian SSR, Ser. Khim., No. 3, 336 (1966).
3. G. Ya. Vanag, Ya. Ya. Dregeris and Ya. Ya. Ozol, ibid., No. 4, 480 (1966).
4. A. K. Aren and G. Ya. Vanag, Synthesis of Natural Compounds and Their Analogs and Fragments [in Russian], Moscow-Leningrad (1965), p. 280.