2-TRIMETHYLAMMONIUMACETOXYMETHYL-2-ARYLINDAN-1,3-DIONE CHLORIDES SUBSTITUTED IN THE PHTHALOYL RING

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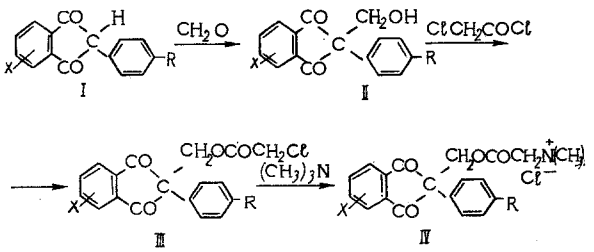
Much attention has been given recently to ganglion-blocking media of brief effect, used in controlled hypotonicity [1]. It was shown [2-4] that 2-(ω-aminoacyloxymethyl)-2-arylindan-1,3-diones, having a quaternary nitrogen atom, are ganglion blockers of brief effect. 2-Trimethylammoniumacetoxymethyl-2-phenylindan-1,3-dione (IVe) was found to be the most active. During its hydrolysis, occurring even in very weakly basic media, 2-hydroxymethyl-2-phenylindan-1,3-dione ("omephin") is formed, which easily cleaves the hydroxymethyl group with formation of 2-phenylindan-1,3-dione ("phenylin"). These materials, blood anticoagulants, produce a side effect of IVe on the coagulating system of the blood, which is not always desirable. It is known [5] that introduction of substituents into the phthaloyl ring of 2-arylindan-1,3-diones decreases or eliminates completely their anticoagulating properties. A series of 2-trimethylammonium-acetoxy-methyl-2-arylindan-1,3-dione chlorides (IVa-d), having substituents on the phthaloyl ring (CH_3O, Cl) was synthesized by the scheme presented below for the purpose of obtaining ganglion blockers of brief effect, devoid of the undesirable side effect.



a: X = 5-CH_3O, R = H;
b: X = 5-CH_3O, R = CH_3O;
c: X = 4-Cl, R = H;
d: X = 5-Cl, R = H,
e: X = H, R = H;
f: X = H, R = CH_3O.

5-Methoxy-, 4-chloro-, and 5-chloro-2-phenylindan-1,3-diones (Ia, c, d) are described in the literature [6, 7]. 2-(p-Methoxyphenyl)-5-methoxylindan-1,3-dione (Ib), which we obtained for the first time, and also Ia, were synthesized by the described method of [8]. To confirm the structure of the synthesized compounds their IR spectra were taken in the region of stretching vibrations of double bonds (Table 1). The ester-group C=O band at 1771-1760 cm^{-1} is observed in spectra of IIIa-d and IVa-d, which agrees with literature data [9] for esters having substituents with a strong negative induction effect in the α-position. In addition, a characteristic doublet of the C=O band of indan-1,3-dione [10] is observed. In spectra of IIIc, d and IVd only two C=O bands are observed instead of three. Evidently here the first band of dicarbonyl absorption (~1750 cm^{-1}) is overlapped by the ester-group band. We observed analogous effects earlier [1, 3].

The effect of IVa-d on the arterial pressure, respiration, and vegetative ganglia was studied by the generally accepted method in acute experiments on cats, narcotized with urethan (1 g/kg). Toxicity was

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TABLE 1. 2-Chloroacetoxymethyl-2-aryl-4(or 5) and 2-Trimethylammoniumacetoxymethyl-2-aryl-4(or 5) Substituted Indan-1,3-diones

Compound	Yield, %	mp	Found, %		Empirical formula	Calc., %		IR spectra* (cm^{-1})		
			Cl	N		Cl	N	$\nu_{C=O}$ of ester	$\nu_{C=O}$ of indan-1,3-dione	
IIIa	82	110—1	9,68	—	$C_{19}H_{15}ClO_5$	9,88	—	1768 (55)	1746 (38),	1710 (68)
IIIb	59	145—6	9,16	—	$C_{20}H_{17}ClO_6$	9,12	—	1769 (70)	1738 (55),	1702 (76)
IIIc	62	86—7	19,72	—	$C_{18}H_{22}Cl_2O_4$	19,52	—	1752 (48)	1752 (48),	1718 (53)
IIId	74	101—2	19,60	—	$C_{18}H_{22}Cl_2O_4$	19,52	—	1755 (59)	1755 (59),	1713 (63)
IVa	83	199—200†	8,75	3,25	$C_{22}H_{24}ClNO_5$	8,94	3,35	1766 (54)	1741 (45),	1711 (62)
IVb	82	200—1†	8,01	3,50	$C_{23}H_{26}ClNO_6$	8,13	3,21	1762 (62)	1748 (47 sh.),	1712 (68)
IVc	37	205—6†	16,65	3,24	$C_{21}H_{21}Cl_2NO_4$	16,79	3,12	1771 (50)	1750 (38),	1715 (58)
IVd	71	221—2†	16,60	2,95	$C_{21}H_{21}Cl_2NO_4$	16,79	3,12	1766 (44)	1766 (44),	1720 (74)

* Taken in mineral oil on an IKS-14 instrument (NaCl prism) in the interval of 1800-1480 cm^{-1}. Percent absorption is in parentheses. Two or three vibration bands of aromatic rings at around 1600 and 1500 cm^{-1}, which are not indicated in the table, are observed in all cases.

† Melts with decomposition.

TABLE 2. Pharmacological Acitvity of 2-Trimethylammoniumacetoxymethyl-2-arylindan-1,3-dione Chlorides*

Compound	Hypotensive activity (ED_{30} in mg/kg)	Ganglion-blocking activity (ED_{50} in mg/kg)		Intravenous toxicity (LD_{50} in mg/kg)	Prothrombinic time up to and 12 h after introduction of preparations (sec)	
		on intracardiac ganglion of the vagus nerve	on the upper jugular sympathetic ganglion		control	experiment
IVa	1,1(0,98÷1,24)	0,74† (0,49÷0,99)	1,4 (0,2÷2,6)	7,8 (7,12÷8,54)	13,4 (12,7÷14,1)	13,4 (11,9÷14,1)
IVb	1,1(0,4÷1,8)	0,76† (0,53÷0,99)	1,2 (0,7÷1,7)	8,0 (7,3÷8,7)	14,0 (13,7÷14,3)	13,4 (12,9÷13,9)
IVc	1,3	0,54† (0,40÷0,68)	1,5 (1,15÷1,95)	5,0 (4,13÷6,05)	13,7 (13,3÷14,1)	15,1 (14,8÷15,4)
IVd	0,66(0,36÷0,96)	0,65† (0,56÷0,74)	1,6 (0,7÷2,5)	5,2 (4,48÷6,03)	13,8 (13,4÷14,2)	14,9 (14,4÷15,4)
IVe	1,39(0,29÷2,49)	0,39 (0,33÷0,45)	0,66 (0,52÷0,80)	8,6 (7,8÷9,3)	13,8 (13,5÷14,1)	16,0 (15,5÷16,5)
IVf	0,77(0,54÷1,00)	0,44 (0,35÷0,53)	0,76 (0,51÷1,01)	9,9 (9,0÷10,9)	—	—

* Confidential boundaries were determined at P = 0.05.

† The difference is statistically significant.

determined in experiments on white mice. The obtained results are presented in Table 2. Data of the pharmacological investigation of the earlier synthesized [1] compounds (IVe, f), not having substituents in the phthaloyl ring, are presented for comparison.

As follows from Table 2, IVa-f in doses of 0.66-1.39 mg/kg caused a decrease in arterial pressure. The executed analysis showed that the hypotensive effect is associated with the ganglion-blocking properties of compounds IVa-f. Compounds IVa-d were found to be less active in relation to intracardiac ganglia of the bagus nerve than their analogs (IVe, f). In relation to the upper jugular sympathetic ganglion the studied compounds did not differ statistically significantly from one another. Duration of ganglion blockage amounted to 3-5 min.

It was found during the study of acute toxicity that IVa-f show a relatively high toxicity, while the toxicity increases upon introducing a halogen atom into the phthaloyl ring.

The studied compound in dilutions of 10^{-6} showed a N-cholinolytic activity in experiments on the isolated direct muscle of the rabbit stomach. In experiments on the isolated intestine of the guinea pig (IVa-f) in dilutions of 10^{-5} possessed spasmolytic activity.

The anticoagulation activity was studied in experiments on rabbits upon intravenous introduction of compounds calculating 10 ml/kg (the maximally endurable dose). We chose the most frequently used method of Kvik, the determination of antithrombinic time, for the quantitative characterization of anticoagulation activity. It was established that introduction of a methoxy group into the phthaloyl ring IVa, b suppresses the anticoagulation activity, while introduction of a chlorine atom (IVc, d) only decreases this activity in comparison with IVe. Results of these experiments are presented in Table 2. It should be mentioned that the anticoagulation effect of compounds IVc, d, e, observed after 12 h, is not observed after 18 h.

EXPERIMENTAL

2-(p-Methoxyphenyl)-5-methoxyindan-1,3-dione (Ib). A mixture of 14.8 g of 6-methoxyphthalide, 10.9 ml of p-methoxybenzaldehyde, and 70 ml of ethyl acetate was heated on a water bath. To the obtained solution slowly with intense stirring was added a solution of sodium methoxide, prepared from 7 g of metallic sodium and 100 ml of methanol. The reaction mixture was heated with stirring on a water bath for 4 h, diluted with 3 liters of warm (~40°) water, activated carbon was added, and the mixture was filtered and acidified with hydrochloric acid to pH 1.0. The precipitate was separated and washed with water. Yield of (Ib) was 12.1 g (46.8%), mp 166-167° C (from acetic acid). Found, %: C 69.56; H 5.46. $C_{17}H_{14}O_4$. Calculated, %: C 69.22; H 5.16. The Ir spectrum in mineral oil contains $\nu_{C=O}$ at 1735 cm^{-1} (36% absorption) and 1695 cm^{-1} (75% absorption).

2-Hydroxymethyl-2-aryl-5-methoxyindan-1,3-diones (IIa, b). To 5 g of (Ia) or (Ib) was added 10 ml of technical formalin and the mixture was left at room temperature. After 24 h the precipitate was separated. Yield of (IIa) was 95%; yield of (IIb) was 97%. The compounds were recrystallized from an ethanol-formalin mixture (10:1). Compound (IIa) had mp 134-135° C. Found, %: C 72.63; H 5.09. $C_{17}H_{14}O_4$. Calculated, %: C 72.33; H 5.00. The IR spectrum in mineral oil contains $\nu_{C=O}$ at 1736 cm^{-1} (45%) and 1696 cm^{-1} (71%).

Compound (IIb) has mp 139-140° C. Found, %: C 69.56; H 5.46. $C_{18}H_{16}O_5$. Calculated, %: C 69.22; H 5.16. $\nu_{C=O}$ at 1730 cm^{-1} (33% absorption), 1696 cm^{-1} (55% absorption).

2-Chloroacetoxymethyl-2-aryl-4a(or 5)-substituted Indan-1,3-diones (IIIa-d, see Table 1). A solution of 0.02 mole of (IIa-d)* and 1.8 ml of chloroacetyl chloride in 10 ml of anhydrous dioxane was heated with a reflux condenser for 10 h. The solution was cooled and diluted with 200 ml of water. After 24 h the precipitate was separated, dried (in the case of precipitation of an oil it was dissolved in ether, dried with anhydrous sodium sulfate, after which the ether was removed in vacuum), and recrystallized from methanol (IIa, d) or a mixture of benzene and n-hexane (IIb, c).

2-Trimethylammoniumacetoxymethyl-2-aryl-4(or 5)-substituted Indan-1,3-dione Chlorides (IVa-d, see Table 1). Of (IIIald) 0.002 mole was dissolved in 5 ml of dioxane saturated with trimethylamine (~0.006 mole) and the mixture was left at room temperature. After a day the residue was separated and recrystallized from a mixture of anhydrous ethanol and ether.

*For synthesis of (IIc, d) see [6].

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