SYNTHESIS AND CARDIOVASCULAR ACTIVITY OF 3-SUBSTITUTED 1-CARBOXYMETHYLHYDANTOINS

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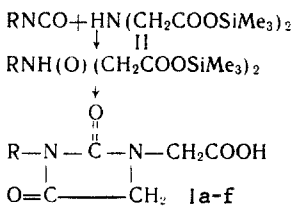
Various hydantoins have found use as anti-arrhythmic materials [5].

In our earlier work we reported on the synthesis of a new representative of a series of carbo-functional hydantoins (Ia-f) and their activity on the cardiovascular system of experimental animals compared to 2-hydroxyethylurea [1].

1-Carboxymethyl-3-organohydantoins are easily prepared by the reaction of isocyanates with silylated iminodiacetic acids (II) followed by intramolecular spontaneous or thermal cyclocondensation of the resulting urea [2, 3]. The general scheme for the synthesis of new compounds is the same in these publications.



R = Me_3C(Ia), 3-MeC_6H_4(Ib), 1,3,5-MeC_6H_2(Ic), 2-BrC_6H_4(Id), 2-ClC_6H_4(Ie), 4-$BrC_6H_4SO_2$(If)

Control of the isocyanate addition to the amine was accomplished by IR spectroscopy judging by the disappearance of absorption band of the isocyanate group in the 2280 cm^{-1} region. The reaction was practically finished in 1 hour and it was not necessary to isolate the formed N-organo-N'-bis(trimethylsiloxycarbonylmethyl)ureas, because they spontaneously or upon heating were quantitatively transformed into the desilylated hydantoins Ia-d. Their composition and structure were verified by IR spectroscopy, displaying the absorption bands of the cyclic carbonyl group (1770, 1730 cm^{-1}) and the carboxyl group (1695 cm^{-1}), and also by potentiometric analysis of the acidic protons and by elemental analysis (Table 1).

EXPERIMENTAL (CHEMICAL)

Operations with easily hydrolyzable materials were carried out under an atmosphere of dry nitrogen. IR spectra were recorded on a VR20 instrument (GRD) in KBr tablets. The elemental analysis data corresponded with the calculated values.

1-Carboxymethyl-3-(t-butyl)hydantoin (Ia). (a) To 11.5 g (0.041 moles) of II was added with cooling and stirring 4.1 g (0.041 mole) of t-butylisocyanate in 30 ml of dry acetone and the mixture was kept for 1 h at 20°C. The solution was then added to 100 ml of water and after 1 day the colorless rhombic crystals were filtered off and dried under vacuum at 100°C to give 6.8 g of Ia. (b) A mixture of 3.5 g (0.013 mole) of II and 1.3 g (0.013 mole) of t-butylisocyanate in a test tube with a reflux condenser was heated at 140°C for 30 min. Cooling gave two layers; the upper was hexamethyldisiloxane, 2 g, n_D^{20} 1.3870. Recrystallization of the solidified lower layer from water and drying gave 2.4 g (87.7%) of hydantoin Ia.

1-Carboxymethyl-(3-methylphenyl)hydantoin (Ib). To a solution of 17.0 g (0.062 mole) of II in 50 ml of dioxane over a period of 30 min was added with cooling and stirring 8.2 g (0.062 mole) of 3-methylphenylisocyanate in 10 ml of dioxane. After standing for 1 h, the solution was added to 100 ml of water and the resulting precipitate was filtered the next

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TABLE 1. Characteristics of 1-Carboxymethyl-3-organohydantoins

Compound	Yield, %	mp, °C	Empirical formula
Ia*	76,5	117—108	$C_9H_{14}N_2O_4$
Ib**	78,3	134—137	$C_{12}H_{12}N_2O_4$
Ic	87,7	above 40	$C_{14}H_{18}N_2O_5 \cdot H_2O$
Id	86,7	123—126	$C_{11}H_9BrN_2O_4$
Ie	82,1	155—159	$C_{11}H_9ClN_2O_4$
If	79,6	150—156	$C_{11}H_9BrN_2O_6$

*M(cryoscopic in Dioxane) = 209.8. Calculated = 214.2.
**M = 260.0. Calculated = 248.2.

TABLE 2. Change in AAP and FHC (in % of the original) as a Function of Time after Intravenous Introduction of the Compounds

Compound	AAP			FHC		
	30	60	120	30	60	120
	min					
Ia	0	0	—	0	0	—
Ib	−15±7	−25±2	−22±6	−15±7	−18±4	−22±5
Ic	Respiration stopped 5 min after injection					
Id	−8±3	−26±4	−22±4	0	0	0
IIa	−19±4	−26±6	−20±6	0	0	0
IIb	0	0	0	0	0	0
IIIa	−15±7	−10±3	—	0	0	—
IIIb	−20±4	−40±6	—	0	−15±4	—
IIIc	0	0	—	0	0	—
IIId	0	0	—	0	0	—
IVa	−15±3	−40±7	—	−15±4	−9±3	—
IVb	0	0	—	0	0	—
IVc	0	0	—	0	0	—
IVd	−25±2	−12±2	—	−15±4	−8±2	—

day to give, after drying under vacuum and grinding, 11.9 g of Ib in the form of a yellow powder. The material was soluble in ethanol and water upon heating.

1-Carboxymethyl-3-(1,3,5-trimethylphenyl)hydantoin hydrate (Ic). To a solution of 18.4 g (0.066 mole) of II in 20 ml of dioxane was added a solution of 10.7 g (0.066 mole) of 1,3,5-trimethylphenylisocyanate in 50 ml of dioxane. After 1 h the mixture was added to 150 ml of water and after partial evaporation on the water bath two layers formed. The lower layer was removed and, after evaporating on the water bath to constant weight, gave 17.1 g of hydrated Ic in the form of a yellow amorphous mass. The material is soluble in water and alcohol upon heating.

1-Carboxymethyl-3-(2-bromophenyl)hydantoin (Id). To a solution of 15.4 g (0.056 mole) of II in 50 ml of o-xylene was added 11.0 g (0.056 mole) of 2-bromophenylisocyanate and the mixture was heated to boiling, cooled, and treated with 40 ml of i-PrOH. The solvents were removed under vacuum and the residue was heated three times with 50 ml of water. The decanted water was cooled to give colorless crystals of Id weighing 15.2 g after filtration and drying under vacuum. The substance was soluble in ethanol and dimethyl sulfoxide.

1-Carboxymethyl-3-(2-chlorophenyl)hydantoin (Ie). Compound II (9.1 g, 0.033 mole) and 5.1 g (0.033 mole) of 2-chlorophenylisocyanate were mixed with cooling. The resulting N-(2-chlorophenyl)-N'-bis-(trimethylsiloxycarboxymethyl)urea, $n_D^{20} = 1.5010$, was dissolved in 20 ml of dioxane, and over a period of 1 h, poured into 75 ml of water. The reaction mixture was concentrated to constant composition and the residue was filtered and dried under vacuum to give 7.3 g of Ie as a white powder. The synthesis of the 3-chlorophenyl- and 4-chlorophenyl-analogs of hydantoin Ie are described in [3].

1-Carboxymethyl-3-(4-bromophenylsulfonyl)hydantoin (If). To a solution of 9.8 g (0.037 mole) of 4-bromophenylsulfonylisocyanate in 30 ml of dioxane was added 10.4 g (0.037 mole) of II, and during 2 h, 60 ml of water was added to the mixture. Half of the mixture was evaporated on the water bath, and the precipitate resulting on cooling was filtered off and dried under vacuum to give 11.3 g of If in the form of a white powder.

EXPERIMENTAL (BIOLOGICAL)

The influence of the new hydantoin and urea derivatives on the arterial pressure and the frequency of cardiac contractions was studied in acute and chronic experiments with rats. Experimental studies were carried out on narcotized and nonnarcotized Wistar rats weighing 250 g (using 5-6 rats for each material).

The action of the above materials on rats narcotized with 40 mg/kg urethane was evaluated by the change in the average arterial pressure (AAP) and the frequency of heart contraction (FHC) after a single introduction into the jugular vein of 0.2 ml of the experimental substance, previously dissolved in 10% ethanol, at the rate of 5 mg/kg.

The AAP was measured electromanometrically in the carotid by the use of transformed pressure (Ugo Basile Model 800, Italy) and amplified pressure (Elema, Sweden). The FHC was measured with a cardiotachometer, disregarding pulse wave pressure. AAP and FHC were registered on a polarograph (Watanabe, Model MC 6601, Japan). Readings were carried out during

the introduction of the materials and for 120 min thereafter. As controls for the AAP and FHC readings, animals treated with 0.2 ml of 10% ethanol instead of the test materials were measured. In the case of the discovery of an influence of the test materials on AAP and FHC with narcotized animals, these materials were studied on animals behaving freely.

With nonnarcotized animals, the studied materials were introduced in the form of suspensions into the stomach (doses of 50 mg/kg) by means of a probe, using a modification of the method of Laksa. During the introduction and for 3 hours thereafter, the AAP for the animals was registered in the peritoneal aorta through a siliconated polyethylene catheter, introduced into the peritoneal aorta one day before the experiment. The AAP and FHC were registered simultaneously for 5 animals using a microprocessor, allowing statistical processing of the AAP and FHC data at any moment of the experiment.

For testing the influence of the experimental materials, the AAP and FHC were calculated as percent of the initial, assumed to be 100. The results were statistically worked up by the method of Fischer–Student. Differences were calculated to be significant at the 95% confidence level ($P \leq 0.05$).

The results are presented in Table 2.

The compounds Ia-d and the earlier-prepared [4] 4,4'-bis-(1-carboxymethyl-3-hydantoyl)diphenyl oxide hydrate (IIa), 1-methyl-[2,4-bis-(10carboxymethyl-3-hydantoyl)]benzene (IIb), 1,3-bis-(1-carboxymethyl-3-hydantoyl)xylene (IIc), and 1,4-bis-(1-carboxymethyl-3-hydantoyl)butane (IId) were studied.

The hydantoin derivatives Ia-d and IIa-d upon introduction into the stomach of stimulated animals in doses of 50 mg/kg did not change the AAP and FHC. The results upon introduction intravenously in doses of 5 mg/kg are shown in Table 2. As indicated, under these conditions compounds Ia and IIb were completely inert. These are similar to compounds IIc-d, not included in the Table.

Compounds Ib, Id, and IIa showed hypotensive activity and decreased the AAP by 15-20% over a period of 30 min after introduction. Notably, these materials continued their hypotensive effects over more than 2 h. A change in FHC was noted only for Ib, which reduced the heart contraction rhythm.

Introductory screening for influence on the cardiovascular system also was carried out on the monofunctional ureas $RNHC(O)NHCH_2CH_2OH$, where R = cyclohexyl (IIIa), $Cl(CH_2)_6$ (IIIb), 1,3,5-MeC_6H_2 (IIIc), 3-ClC_6H_4 (IIId), and the ureas $RNHC(O)N(CH_2CH_2OH)_2$ (IVa-d) where the radicals R have the same structure.

Upon peroral introduction into the animals in doses of 50 mg/kg, compounds IIIc and IVa did not influence the AAP and FHC. As Table 2 shows, compounds IIIa, IIIb, IVa, and IVd showed hypotensive activity; IIIb and IVa decreased the AAP by 40% 60 min after introduction, but the effect was not prolonged. A reduction in heart contraction rhythm also was noted in the first 30 min after introduction of compounds IVd and IVa.

These results show that the 1-carboxymethyl-3-organohydantoin and the N-organo-N'-(2-hydroxyethyl)urea series contain compounds capable of affecting arterial pressure and the frequency of heart contractions.

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