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Abstract

Full Text

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2-β-HYDROXYETHYL-2-PHENYLINDANDIONE-1,3

Some 2-substituted indandiones-1,3 are good blood anticoagulants. Thus, for example, 2-phenylindandione-1,3 (I), under the name "phenylin," has already entered medical practice and has been recognized as a better blood anticoagulant than dicoumarin, which has been used until now in the USSR ([1–3]). Active blood anticoagulants are also 2-anisylindandione-1,3 ([4]), 2-naphthylindandione-1,3 ([5,6]), and especially 2-diphenylacetylindandione-1,3 ("diphenacin") ([7,8]). The opinion has been expressed ([9]) that the anticoagulant action of preparations of the oxycoumarin and indandione-1,3 series is connected with their ability to enolize. However, one of us, together with M. N. Koptelova ([10]), was able to show that replacement of the active hydrogen in phenylindandione by chlorine, bromine, a nitro group, and an oxymethyl group does not substantially reduce its anticoagulant activity. Of these derivatives, 2-oxymethyl-2-phenylindandione-1,3, under the name "omefin," has been proposed for clinical practice ([11]). It was therefore of interest to prepare the next homolog—2-β-hydroxyethyl-2-phenylindandione-1,3 (II).

Alkylation of 2-phenylindandione-1,3 in position 2 is usually carried out by the action of a halide on a salt of 2-phenylindandione-1,3 ([12,13]). We carried out oxyethylation of 2-phenylindandione-1,3 without preparing its salt, simply by prolonged heating of 2-phenylindandione-1,3 with an excess of ethylene chlorohydrin in the presence of potash at 140°. Replacement of the excess ethylene chlorohydrin by alcohols did not give satisfactory results.

$$\text{(I)} \xrightarrow[K_2CO_3]{ClCH_2CH_2OH} \text{(II)} \xrightarrow{HNO_3} \text{(III)}$$

IV

The 2-β-hydroxyethyl-2-phenylindandione-1,3 (II) obtained is a white crystalline substance with m.p. 154°. Its oxidation with nitric acid gave the corresponding acid: 2-carboxymethyl-2-phenylindandione-1,3, or 2-phenylindandionyl-(2)-acetic acid (III). Through the acid chloride of this acid, its ethyl ester (IV) was prepared. Both this ester and the acid itself have already been described in the literature, although obtained by another route.

On boiling with acetic anhydride, 2-β-hydroxyethyl-2-phenylindandione-1,3 gives the corresponding acetate (V), m.p. 77°. Analogously, with *p*-nitrobenzoyl chloride, the *p*-nitrobenzoate (VI) was obtained. Its reduction gave the *p*-aminobenzoate (VII). This is an analogue of anesthesin in which the β-hydrogen of the ethyl group is replaced by a phenylindandione residue. The substance is rather unstable; under the action of mineral acids it becomes brown, apparently as a result of an easily occurring polycondensation between aromatic

amino group and the carbonyl group, which has also been observed for other analogous derivatives [14].

(V) (VI)

VII

According to preliminary results, 2-β-hydroxyethyl-2-phenylindandione-1,3, in contrast to 2-β-hydroxymethyl-2-phenylindandione-1,3, does not possess anticoagulant properties.

Experimental Part

2-β-Hydroxyethyl-2-phenylindandione-1,3. 50 g (0.225 mole) of 2-phenylindandione-1,3, 47 g (0.350 mole) of potassium carbonate, and 62 ml (0.923 mole) of ethylene chlorohydrin are heated on an oil bath at 140° (bath temperature). The resulting red solution is poured into water; the precipitated solid is separated, washed with soda solution, and crystallized from 120 ml of alcohol. Yield 42 g (70%) of 2-β-hydroxyethyl-2-phenylindandione-1,3. White crystals, m.p. 154°. Readily soluble in benzene, alcohol, ethyl acetate, dichloroethane, chloroform, and ether. In concentrated sulfuric acid it dissolves with a violet coloration.

Found, %:	C 77.00; H 5.30
$C_{17}H_{14}O_3$. Calculated, %:	C 76.68; H 5.26

By acidifying the red aqueous filtrate, after separation of 2-β-hydroxyethyl-2-phenylindandione-1,3, with hydrochloric acid, 2.5 g of unreacted 2-phenylindandione-1,3 (m.p. 146°) was recovered; thus the total yield of 2-β-hydroxyethyl-2-phenylindandione-1,3, calculated on the indandione-1,3 that entered into the reaction, is 73.5% of theory.

2-Carboxymethyl-2-phenylindandione-1,3 (III). 5.32 g of 2-β-hydroxyethyl-2-phenylindandione-1,3 are boiled with 50 ml of nitric acid ($d = 1.35$) until the evolution of nitrogen oxides ceases, and diluted with water. The precipitate is crystallized several times from benzene. Yield 1.68 g (30%) of 2-carboxymethyl-2-phenylindandione-1,3, or 2-phenylindandionyl(2)-acetic

acid. White crystals, m.p. 214–215°; according to the literature [13], 214–215°. Readily soluble in alcohol, dioxane, glacial acetic acid, and sodium bicarbonate.

Found, %:	C 72.91; H 4.48
$C_{17}H_{12}O_4$. Calculated, %:	C 72.85; H 4.32

Ammonium salt. 2.8 g of acid III are dissolved in 10 ml of ammonia, evaporated to dryness, and the residue is crystallized from alcohol with addition of ether. Yield 2.1 g (75%) of the ammonium salt. White crystals, m.p. 175° (decomp.). The salt is readily soluble in water; on acidification of the solution, acid III is regenerated.

Found, %:	N 4.57
$C_{17}H_{15}O_4N$. Calculated, %:	N 4.71

Ethyl ester. 2.8 g of acid III and 11.9 g of thionyl chloride are boiled for 30 min and, after cooling, poured into 10 ml of alcohol. The resulting solution is diluted with 50 ml of water, and the precipitate that separates is recrystallized from alcohol. Yield 2.34 g (76%) of the ethyl ester of acid III. M.p. 105–106°, which corresponds to the literature data (104°) (12). Readily soluble in alcohol, benzene, and dioxane.

Acetate of 2-β-hydroxyethyl-2-phenylindandione-1,3 (V). 2.66 g of 2-β-hydroxyethyl-2-phenylindandione-1,3 and 20 ml of acetic anhydride are boiled for 30 min. The cooled solution is poured into water. After decomposition of the acetic anhydride, the precipitate is crystallized twice from alcohol. Yield 2.93 g (77%) of the acetate of 2-β-hydroxyethyl-2-phenylindandione-1,3. White crystals, m.p. 77°. Readily soluble in benzene, methanol, ethanol, and glacial acetic acid.

$C_{19}H_{16}O_4$.	Found, %:	C 74.47; H 5.09
	Calculated, %:	C 74.01; H 5.23

p-Nitrobenzoate of 2-β-hydroxyethyl-2-phenylindandione-1,3 (VI). 2.66 g (0.01 mole) of 2-β-hydroxyethyl-2-phenylindandione-1,3 and 2.04 g (0.011 mole) of *p*-nitrobenzoyl chloride in 20 ml of dry benzene are boiled for 5 h. The crystals that separate are recrystallized from a mixture of alcohol with dioxane. Yield 2.49 g (50%) of the *p*-nitrobenzoate of 2-β-hydroxyethyl-2-phenylindandione-1,3. White crystals, m.p. 156°. Readily soluble in glacial acetic acid and dioxane, poorly soluble in methanol, ethanol, and benzene.

$C_{24}H_{17}O_6N$.	Found, %:	N 3.58
	Calculated, %:	N 3.37

p-Aminobenzoate of 2-β-hydroxyethyl-2-phenylindandione-1,3 (VII). To a solution of 4.154 g of the *p*-nitrobenzoate of 2-β-hydroxyethyl-2-phenylindandione-1,3 in 40 ml of glacial acetic acid, zinc dust is added and the mixture is boiled, from time to time adding new portions of zinc dust, a total of 6.4 g. The solution first becomes yellow-brown, then decolorizes. After completion of the reaction, the filtrate is diluted with water; the white precipitate is separated and thoroughly washed with water. Yield 3.81 g (98%) of the *p*-aminobenzoate of 2-β-hydroxyethyl-2-phenylindandione-1,3, m.p. 97-100° (decomp.). Readily soluble in methanol and ethanol; insoluble in dichloroethane and carbon tetrachloride. At elevated temperature, and also under the influence of mineral acids, it changes readily and darkens. Recrystallization was unsuccessful.

$C_{24}H_{19}O_4N$.	Found, %:	N 3.73
	Calculated, %:	N 3.64

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Note: Figure translations are in progress. See original paper for figures.