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Abstract

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CHEMISTRY

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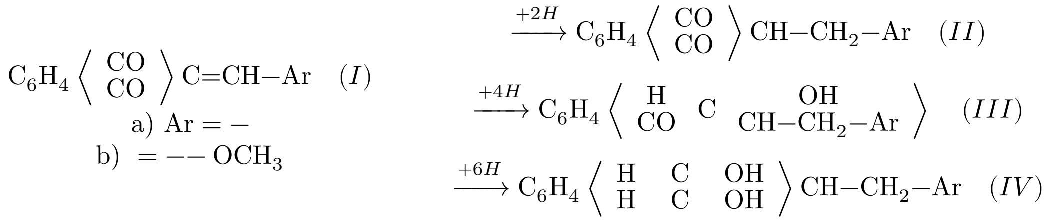
CATALYTIC HYDROGENATION OF 2-SUBSTITUTED INDANDIONES-1,3 TO THE CORRESPONDING INDANDIOLS-1,3

Since many 2-arylindandiones-1,3 are valuable anticoagulants of the blood, for example, 2-phenylindandione-1,3 (“phenylin”) ($^{1-3}$), 2-anisylindandione-1,3 (“anisylone”) (^{4}), and others, and find application in medicine, we have studied also their homologs–2-aralkylindandiones-1,3, among which substances possessing anticoagulant action were also found (^{5}). 2-Aralkylindandiones-1,3 (II) are obtained by selective hydrogenation of 2-arylideneindandiones-1,3 (I) with sodium hydrosulfite (dithionite), $Na_2S_2O_4 \cdot 2H_2O$ ($^{6-8}$), and also (and usually in better yield) by catalytic hydrogenation in the presence of skeletal nickel. In order that the carbonyl groups should not be hydrogenated simultaneously, the catalyst was partly “poisoned” by the addition of potassium iodide, as was done in the hydrogenation of other λ, β-unsaturated ketones ($^{9-13}$). Without the addition of potassium iodide, hydrogenation of 2-arylideneindandiones-1,3 (I) often proceeds to 2-aralkylindandone-1-ol-3 (III) and even to aralkylindandiols-1,3 (IV). In the present work the conditions for obtaining the latter compounds have been studied in more detail.



$$C_6H_4\left\langle \begin{matrix}CO\\CO\end{matrix}\right\rangle C{=}CH{-}Ar \quad (I) \qquad \begin{matrix}\text{a) } Ar = -\\ \text{b) } = -- OCH_3\end{matrix}$$

$$\xrightarrow{+2H} C_6H_4\left\langle \begin{matrix}CO\\CO\end{matrix}\right\rangle CH{-}CH_2{-}Ar \quad (II)$$

$$\xrightarrow{+4H} C_6H_4\left\langle \begin{matrix}H\\CO\end{matrix}\; C \;\begin{matrix}OH\\CH{-}CH_2{-}Ar\end{matrix}\right\rangle \quad (III)$$

$$\xrightarrow{+6H} C_6H_4\left\langle \begin{matrix}H & C & OH\\H & C & OH\end{matrix}\right\rangle CH{-}CH_2{-}Ar \quad (IV)$$

There is almost no information in the literature on the preparation of 2-substituted indandiols-1,3 by hydrogenation of the corresponding indandiones-1,3, with the exception of the work of Carboni (^{14}), who reduced

2-isonitrosoindandione-1,3 to 2-aminoindandiol-1,3 (an intermediate product for the synthesis of χ-nitro-2-(dichloroacetamido)-indandiol-1,3)—a cyclic analog of chloromycetin, resembling it also in biological action. Indandiols-1,3 with tertiary hydroxyl groups (of type XI) have been obtained from 2-substituted indandiones-1,3 by the action on them of an excess of Grignard reagent (15–17); their hydroxyl groups are readily exchanged for halogen, which opens a route to the synthesis of derivatives. Indandiols-1,2 are better known; they have been obtained by oxidation of the corresponding indenes (usually a mixture of stereoisomers is obtained) (18). In individual cases, indandiols have been obtained from dihalogen derivatives of indane by replacement of halogen by hydroxyl groups (19). α-, β-Indanols, as well as 1-methoxy-β-indanol and 2-acetoxy-α-indanol, have found practical application as repellents in insect control (20).

Hydrogenation of 2-benzylideneindandione-1,3 (Ia) in alcoholic solution in the presence of skeletal nickel (grade W-2) (21) at 60–65° and ordinary pressure gave 2-benzylindandiol-1,3 (IVa) in 75.6% yield. The presence in it of two hydroxyl groups was proved by obtaining the di-*p*-nitrobenzoate of 2-benzylindandiol-1,3 (V).

structural formula of the di-*p*-nitrobenzoate of 2-benzylindandiol-1,3 (V)

structural formula of the corresponding di-phenylurethane (VI)

2-Anisalindandione-1,3 (Ib), in the presence of skeletal nickel (grade W-2), under similar conditions is hydrogenated to the 1,3-diol already at room temperature, with formation of 2-*p*-methoxybenzylindandiol-1,3 (IVb) in 75.8% yield. The indandiols-1,3 obtained (IVa, b), in contrast to 2-aralkylindandiones-1,3 (II) and 2-aralkylindanon-1-ols-3 (III), do not react with hydroxylamine. The structure of 2-*p*-methoxybenzylindandiol-1,3 was proved by obtaining the corresponding di-phenylurethane VI.

In order to be certain that both carbonyl groups had been hydrogenated, IR spectra of compounds IVa and IVb were taken in the region of double bonds (in the solid state). Indeed, in these spectra (in contrast to the IR spectra of 2-benzylindandione-1,3 (IIa), 2-benzylindanon-1-ol-3 (IIIa), and, respectively, IIb and IIIb) no maxima are observed in the region of the carbonyl groups. Having obtained good results in the hydrogenation of 2-arylideneindandiones-1,3 (I), we considered it advisable to test the possibility of selective hydrogenation of 2-arylindandiones-1,3 using 2-phenylindandione-1,3 (VII) as an example.

$$\begin{array}{cccc} & & \text{2-phenylindanon-1-ol-3} & \text{di-}p\text{-nitrobenzoate derivative} \\ \text{2-phenylindandione-1,3} & \xrightarrow{+2H} & (VIII) & (X) \\ (VII) & \xrightarrow{+4H} & \text{2-phenylindandiol-1,3} & \text{general indandiol structure} \\ & & (IX) & (XI) \end{array}$$

In fact, in the hydrogenation of 2-phenylindandione-1,3, depending on the reaction conditions, we were able to add to molecule VII either 2 atoms of hydrogen and obtain 2-phenylindanon-1-ol-3 (VIII), or 4 atoms of hydrogen with formation of 2-phenylindandiol-1,3 (IX). The latter compound was obtained by hydrogenation of 2-phenylindandione-1,3 in the presence of skeletal nickel (grade W-2) at 60–65° for 7 h. After separation of the catalyst and dilution of the filtrate with water, an oil separates from the reaction mixture, which is extracted with ether. After removal of the ether, a thick syrup-like product was obtained, which could not be crystallized. The analytical data for the latter correspond to 2-phenylindandiol-1,3 (IX). In contrast to the starting 2-phenylindandione-1,3, the product obtained does not dissolve in sodium carbonate. The presence in it of two hydroxyl groups was proved by obtaining the di-*p*-nitrobenzoate of 2-phenylindandiol-1,3 (X); this is a solid crystalline substance.

In the hydrogenation of substituted indanones-1 to the corresponding indanols-1, according to the literature, a mixture of stereoisomers is formed ([22,23]). Upon their crystallization, one—the less soluble isomer—is isolated, while the other remains in solution ([18,24]). We have not yet investigated the stereochemical structure of the 2-substituted indandiols-1,3 that we obtained.

Experimental Part

2-Benzylindandiol-1,3 (IVa). In a hydrogenation flask (volume 100 ml) are placed 3.51 g (0.015 mole) of 2-benzalindandione-1,3, 60 ml of alcohol, and ~1 g of skeletal nickel (grade W-2) suspended in absolute alcohol. By means of a rubber tube the flask is connected to the lower end of a reflux condenser, the upper end of which is connected to a hydrogen gasometer. A stream of hydrogen is used to displace air from the system through the side arm of the flask, after which the side arm is tightly closed with a stopper through which a thermometer has been inserted. With the aid of a shaker the reaction vessel is shaken and heated with an infrared lamp for 8 hours at 60–65°. On the following day the flask is disconnected. The catalyst is removed by filtration; the filtrate is diluted with 400 ml of water and 50 ml of saturated sodium chloride solution (to accelerate coagulation). After 3 hours the precipitate that has separated is collected. Yield: 2.72 g (75.6%) of 2-benzylindandiol-1,3; it is crystallized from a methanol–water mixture (1 : 1), and then from benzene, m.p. IVa 131–133°.

Found, %:	C 80.34; H 6.62
$C_{16}H_{16}O_2$. Calculated, %:	C 80.00; H 6.67

Di-*p*-nitrobenzoate (V). 0.8 g (0.0033 mole) of 2-benzylindandiol-1,3, 1.3 g (0.007 mole) of *p*-nitrobenzoyl chloride, and 10 ml of anhydrous pyridine are boiled under reflux for 3 min. The reaction mixture is cooled and poured, with vigorous stirring, into 50 ml of water. The resinous product that separates solidifies upon cooling; on the following day it is filtered off and washed on the filter with a 5% soda solution (to remove *p*-nitrobenzoic acid), and then with water. The resulting V is crystallized from *n*-butanol, m.p. 197–199°.

Found, %:	N 5.04
$C_{30}H_{22}O_8N_2$. Calculated, %:	N 5.20

2-*p*-Methoxybenzylindandiol-1,3 (IVb). 3.96 g (0.015 mole) of 2-anisalindandione-1,3 in 60 ml of alcohol with ~1 g of skeletal nickel (grade W-2) are hydrogenated in the apparatus described above at room temperature for 7 hours. On the following day the flask containing the reaction solution is disconnected, and, analogously to IVa, 3.07 g (75.8%) of 2-*p*-methoxybenzylindandiol-1,3 (IVb) is isolated; after two crystallizations from benzene, m.p. 142–143°.

Found, %:	C 75.56; H 6.56
$C_{17}H_{18}O_3$. Calculated, %:	C 75.56; H 6.67

Di-phenylurethane (VI). 0.5 g of 2-*p*-methoxybenzylindandiol-1,3 and 0.5 ml of phenyl isocyanate are heated on a boiling water bath for 10 min. The mixture is then cooled, and 30 ml of petroleum ether is added to the reaction mixture. The precipitate that separates is collected and washed on the filter with petroleum ether until the odor of phenyl isocyanate disappears. The product obtained

crystallized from *n*-heptane, m.p. VI 91–94°.

$C_{31}H_{28}O_5N_2$.	Found, %: N 5.79
	Calculated, %: N 5.51

2-Phenylindandiol-1,3 (IX). 3.33 g (0.015 mole) of 2-phenylindandione-1,3 in 50 ml of alcohol with ~ 1 g of skeletal nickel (grade W-2) is hydrogenated in the apparatus mentioned above at 60–65° for 7 hr. On the following day the flask with the reaction solution is disconnected, and the catalyst is separated by filtration. The filtrate is diluted with 400 ml of water and 50 ml of saturated sodium chloride solution. The reaction product separates in the form of an oil, which is extracted from the water with ether (3 times with 100 ml). The ether extracts are dried over anhydrous sodium sulfate, and the ether is distilled off on a boiling water bath. 1.57 g of a thick syrupy oil is obtained, which is dried in a vacuum desiccator over phosphorus pentoxide. The oil could not be crystallized; yield of IX 46.3%.

$C_{15}H_{14}O_2$. Found, %: C 79.80; H 5.84
Calculated, %: C 79.65; H 6.19

Di-*p*-nitrobenzoate (X). 1.0 g (~ 0.0044 mole) of 2-phenylindandiol is dissolved in 15 ml of anhydrous pyridine, 2.2 g (~ 0.012 mole) of *p*-nitrobenzoyl chloride is added, and the mixture is boiled for 30 min. After cooling, it is poured into 200 ml of water, and the product separates as a resin. The contents are then cooled in a refrigerator, and the resinous precipitate, after separation, is washed with 5% soda solution and then with water. After two crystallizations from *n*-butanol, the m.p. of the di-*p*-nitrobenzoate (X) is 190–193°.

$C_{29}H_{20}O_8N_2$. Found, %: N 5.17
Calculated, %: N 5.34

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