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Abstract

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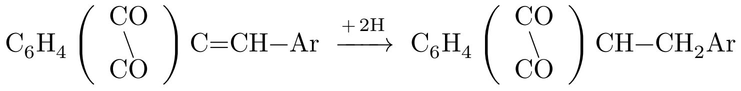
SYNTHESIS OF 2-ARALKYLINDANDIONES-1,3 BY CATALYTIC HYDROGENATION OF 2-ARALKYLIDENEINDANDIONES-1,3

Many 2-substituted indandiones-1,3 are physiologically active substances. Thus, for example, 2-phenylindandione-1,3 is an active blood anticoagulant and is used in the Soviet Union under the name “phenylin” (1–3). Some other derivatives of indandione-1,3 (4) possess the same action, among which the most active are 2-arylindandiones-1,3: 2-α-naphthylindandione-1,3 (5), 2-anisylindandione-1,3 (“anisidone”) (6), and 2-oxymethyl-2-phenylindandione-1,3 (“omephin”) (7). In this connection, such 2-substituted indandiones-1,3 are also of interest in which the aromatic radical is somewhat removed from carbon atom 2, i.e., compounds of type II. The simplest example of the latter type is 2-benzylindandione-1,3 (IIa), obtained by condensation of diethyl phthalate with the ester of hydrocinnamic acid (8). Of the derivatives of 2-benzylindandione-1,3, only 2-*p*-nitrobenzylindandione-1,3 has been described in the literature, obtained by cyclization of *p*-nitrobenzylbenzoylacetic ester (9,10). In a number of works it has been established that by analogous cyclization one cannot obtain indandione-1,3 (11), nor 2-benzylindandione-1,3 (9,10), nor 2-*p*-methoxybenzylindandione-1,3 (10).

Recently we developed a new general method for obtaining 2-aralkylindandiones-1,3 (II) by selective hydrogenation of 2-aralkylideneindandiones-1,3 (I) with sodium dithionite (hydrosulfite) ($Na_2S_2O_4 \cdot 2H_2O$) (12):



$$C_6H_4\left(\begin{array}{c}CO\\ \diagdown\\ CO\end{array}\right)C{=}CH{-}Ar \xrightarrow{+2H} C_6H_4\left(\begin{array}{c}CO\\ \diagdown\\ CO\end{array}\right)CH{-}CH_2Ar$$

(I) (II)

The initial 2-aralkylideneindandiones-1,3 (I) are readily obtained by condensation of aromatic aldehydes with indandione-1,3 (13), or with the sodium salt of the ethyl ester of indandionecarboxylic acid (14). By the above-mentioned method we successfully obtained various 2-methoxybenzylindandiones-1,3 (15), aminobenzylindandiones-1,3 (16), as well as analogues of 2-aralkylindandiones-1,3 in which aryl is replaced by a five-membered heterocyclic system (IIe,) (17). Among the compounds obtained, substances possessing anticoagulant action were found (4). Unfortunately, the yield of aralkylindandiones-1,3 upon hydrogenation with sodium hydrosulfite is small. To improve the yields and to develop a preparative method for obtaining 2-aralkylindandiones-1,3, we turned to the study of the catalytic hydrogenation of 2-aralkylideneindandiones-1,3. It was necessary to find a suitable catalyst that would make it possible selectively to hydrogenate the double C—C bond in the α, β-position to the carbonyl groups, without reducing the latter. Our attention was attracted by a report by Japanese authors that selective hydrogenation of the C—C bond of benzalacetone, mesityl oxide, and a number of other α, β-unsaturated ketones can be achieved by hydrogenating them with skeletal nickel cataly-

with addition of potassium iodide or other metal halides (18–22). It has been noted in the literature (23) that analogous selectivity in the hydrogenation of α,β-unsaturated ketones can also be achieved by partial poisoning of a nickel catalyst with methyl iodide. We applied a similar method to the catalytic hydrogenation of aralkylideneindandiones. Hydrogenation under various conditions was systematically studied using

Table 1

	Ar	Ni catalyst, g	KI, g	Solvent volume, ml	Reaction duration, h	Source	Yield of II, % upon hydrogenation with $Na_2S_2O_4$	Yield of II, % upon catalytic hydrogenation
a	phenyl	1	2.5	100	7.0	(12)	19.1	70.6
	p-methoxyphenyl	1	2.5	100	5.5	(15)	31.0	52.6
	4-hydroxy-3-methoxyphenyl	1	2.5	50	7.0	(15)	38.9	11.8
	3,4-dimethoxyphenyl	3	5.0	100	6.5	(15)	15.0	38.4
	3,4-methylenedioxyphenyl	1	2.5	100	7.0	(15)	21.0	54.4
	furyl	1	2.5	100	12.0	(17)	26.0	54.4
	thienyl	1	2.5	100	10.0	(17)	39.8	95.6
	o-methoxyphenyl	1	–	50	6	(15)	45.9	89.0

Note. Reaction temperature: a– , 60–65°; , 78°.

benzalindandione-1,3 (Ia) as an example. It was found that by hydrogenating I in an amount of 0.015 mole in alcoholic solution in the presence of skeletal nickel (grade W-2) with addition of potassium iodide at a temperature of 60–65° and ordinary pressure, 2-benzylindandione-1,3 (IIa) can be obtained in 70.6% yield (whereas in hydrogenation with sodium dithionite (12) the yield is only 19.1%). In an analogous manner (and also usually in better yield), other 2-aralkylindandiones-1,3 (II –), as well as their analogs with heterocyclic radicals (II ,), were obtained. The reaction conditions and yields are shown in Table 1. The products of catalytic hydrogenation proved to be identical with 2-aralkylindandiones-1,3 (and their heterocyclic analogs) obtained by hydrogenation with sodium dithionite (12, 15, 17).

The structure of 2-benzylindandione-1,3 (IIa) and 2-*p*-methoxybenzylindandione-1,3 (II) was also confirmed by recording their IR absorption spectra (in the solid state). From the literature (24) it is known that the diketo form of indandione-1,3 derivatives is characterized by a split peak in the region 1705–1770 cm^{-1} and by a frequency of 1580–1600 cm^{-1}. The first region characterizes two carbonyl groups, and the second the aromatic system.

In the IR spectrum of solid 2-benzylindandione-1,3, two carbonyl bands are observed at 1710 cm^{-1} (94.3) and 1743 cm^{-1} (76.8), as well as bands at 1592 cm^{-1} (49.3) and 1602 cm^{-1} (48), assigned to the aromatic ring. In the IR spectrum of solid 2-*p*-methoxybenzylindandione-1,3 there are also two carbonyl bands at 1706 cm^{-1} (79) and 1736 cm^{-1} (63) and corresponding

bands belonging to the aromatic ring: 1512 cm^{-1} (63.5); 1588 cm^{-1} (41.5) and 1614 cm^{-1} (47).

Using 2-benzylindandione-1,3 (IIa) as an example, it was found that the maximum yield of the latter is obtained if, for 0.015 mole of the starting arylideneindandione in 100 ml of alcohol, 1 g of skeletal nickel and 2.5 g of potassium iodide are taken.

A decrease in the amount of potassium iodide leads to resinification of the products. If the hydrogenation is carried out without potassium iodide, then the carbonyl groups also are reduced and, depending on the reaction conditions, 2-benzylindanon-1-ol-3 or 2-benzylindandiol-1,3 can be obtained; this will be the subject of a separate communication. An analogous phenomenon is also observed in the hydrogenation of other 2-ylideneindandiones-1,3. The only exception is the hydrogenation of 2-*o*-methoxybenzalindandione-1,3 (I3). In its hydrogenation under conditions analogous to the preceding ones, only insignificant absorption of hydrogen is observed and the yield of the corresponding 2-*o*-methoxybenzylindandione-1,3 (II3) is negligible. It proved that in this case the corresponding aralkylindandione (II3) can be obtained in good yield only under more vigorous reaction conditions: hydrogenation at the boiling temperature (78°); moreover, in this case a more active catalyst is necessary —skeletal nickel without addition of potassium iodide. Here, evidently, the steric influence of the methoxy group in the *o*-position is manifested, since *n*-methoxybenzalindandione-1,3 (I6) is hydrogenated very readily.

With a skeletal nickel catalyst with addition of potassium iodide, under analogous conditions, 2-*n*-diethylaminobenzalindandione-1,3 is not hydrogenated; it is hydrogenated in very good yield with sodium hydrosulfite (16). 2-*o*-oxybenzalindandione-1,3 and 2-α-pyrrolalindandione-1,3 also are not hydrogenated (the latter is not hydrogenated with sodium hydrosulfite either (17)).

In the experimental part, as examples, the hydrogenation of 2-benzalindandione-1,3 and 2-*o*-methoxybenzalindandione-1,3 is described in detail.

Experimental Part

2-Benzylindandione-1,3 (IIa). Into a hydrogenation flask (volume 300 ml) are placed 3.51 g (0.015 mole) of 2-benzalindandione-1,3, 100 ml of alcohol, 2.5 g of potassium iodide, and approximately 1 g of skeletal nickel (grade W-2) (25), suspended in abs. 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 gasometer containing hydrogen. 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. By means of a shaker the reaction vessel is shaken and heated with an infrared lamp. After 7 hours of shaking at 60–65°, about 300 ml of hydrogen has been absorbed. On the next day the flask is disconnected, the catalyst and unreacted starting product are removed by filtration, the filtrate is diluted with 400 ml of water, 10 ml of conc. hydrochloric acid is added, and after 3 hours the precipitated solid is separated. Yield 2.5 g (70.6%) of 2-benzylindandione-1,3, m.p. 94–96°; crystallization from diluted methanol (1 : 1) does not change the melting point; with an authentic sample it gives no depression of the melting point.

Analogously, IIb–d were obtained; in isolating IIe–zh from the reaction mixture, hydrochloric acid is not used.

2-*o*-Methoxybenzylindandione-1,3 (II3). 3.96 g (0.015 mole) of 2-*o*-methoxybenzalindandione-1,3 in 100 ml of alcohol in the presence of 1 g of skeletal nickel without additions of potassium iodide are hydrogenated in the aforementioned apparatus at the boiling temperature of the solvent (78°) for 6 hours. Analogous

In this way 3.55 g of 2-*o*-methoxybenzylindandione-1,3 is isolated (yield 89%); after crystallization from a methanol–water mixture (2:1), m.p. 86–88°. With an authentic 2-*o*-methoxybenzylindandione-1,3 (^{15}) it gives no depression of the melting point.

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