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Abstract

Full Text

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IODOMETHYLATION OF 2-SUBSTITUTED INDANDIONES-1,3

2-Amino-2-arylindandiones-1,3 (I) are physiologically active substances possessing narcotic, anticonvulsant, and anesthetic action (^{1}). Two of these preparations are already undergoing clinical trials (^{2}). In order to clarify the relationship between chemical structure and physiological activity of aminoindandiones, the study of 2-aminomethyl-2-arylindandiones-1,3 (II) was of interest.

(I) (II)

2-amino-2-arylindandione-1,3 structure: $NR'R''$, Ar 2-aminomethyl-2-arylindandione-1,3 structure: CH_2N

(III) ⟶ (IV)

2-hydroxymethyl-2-phenylindandione-1,3: CH_2OH, C_6H_5 2-halomethyl-2-phenylindandione-1,3: CH_2

Since β-diketones do not form Mannich bases (^{3}), and the dialkylaminomethylation method developed by Böhme (^{4}) can hardly find broader application because of the difficult accessibility of dialkylaminomethyl halides, 2-halomethyl-2-substituted indandiones-1,3 could serve as starting substances for the synthesis of 2-aminomethyl-2-arylindandiones-1,3. 2-Chloromethyl- and 2-bromomethyl-2-phenylindandiones-1,3 (IV, $X = \mathrm{Cl}, \mathrm{Br}$) were obtained by us* by the action of phosphorus pentachloride or phosphorus and bromine on 2-hydroxymethyl-2-phenylindandione-1,3 (III), which in turn is obtained by the action of formaldehyde on 2-phenylindandione-1,3 (^{5}). In view of the low mobility of the chlorine and bromine atoms in the above-mentioned compounds, we were most interested in 2-iodomethyl-2-phenylindandione-1,3 (IV, $X = \mathrm{J}$), which, however, could not be obtained by the described route. It was obtained by prolonged heating of 2-chloromethyl-, or better 2-bromomethyl-2-phenylindandione-1,3 with sodium iodide in glacial acetic acid. Thus, its preparation is a complex three-stage synthesis (starting from 2-phenylindandione-1,3).

Subsequently we studied the possibilities of direct iodomethylation of 2-phenylindandione-1,3 with methyl iodide. It turned out that, upon heating 2-phenylindandione-1,3 with an excess of methyl iodide in the presence of potassium carbonate, 2-iodomethyl-2-

phenylindandione-1,3. The method is general also for other 2-aryl-, as well as 2-aralkyl- and 2-alkylindandiones-1,3:

$$\text{2-substituted indandione-1,3} \xrightarrow[K_2CO_3]{CH_2I_2} \text{2-iodomethyl-2-substituted indandione-1,3}$$

$$R = C_6H_5,\ p\text{-}C_6H_4OCH_3,\ o\text{-}C_6H_4OCH_3,\ OCH_2O\text{-}C_6H_3,$$
$$\alpha\text{-}C_{10}H_7,\ CH_2C_6H_5,\ CH_2C_6H_4OCH_3,\ CH_3.$$

It is interesting to note that by this method 2-iodomethyl-2-α-naphthylindandione-1,3 was also obtained; Slovak chemists (6) had unsuccessfully attempted to obtain it by the action of methylene iodide on the sodium salt of 2-α-naphthylindandione-1,3 in butanol solution. The authors explain this by steric difficulties, but here, apparently, it is necessary to carry out the reaction at a higher temperature. We heated 2-α-naphthylindandione-1,3 with methylene iodide and potassium carbonate to 140–150°, but under these conditions side processes also occur, since the yield of 2-iodomethyl-2-α-naphthylindandione-1,3 is only 19.5%. By the action of methylene iodide on benzalphthalide in the presence of sodium butylate, the above-mentioned authors obtained 2-iodomethyl-2-phenylindandione-1,3 (identical with that obtained by us), but in only 45% of theory.

By heating with methylene iodide even to 180°, we were unable to obtain the iodomethyl derivatives of 2-xanthydryl- and 2-benzhydrylindandiones-1,3, probably owing to bulky substituents, nor of 2-*p*-nitrophenylindandione-1,3. In the latter case this may be explained by the equalized electronic structure of 2-*p*-nitrophenylindandione-1,3 (7).

The infrared absorption spectra of 2-iodomethyl-2-substituted indandiones-1,3 in the range 1500–1800 cm^{-1} (recorded in paraffin oil) have two maxima in the region 1708–1745 cm^{-1}, characterizing the diketone form, and a maximum at about 1595 cm^{-1}, assigned to the aromatic system (Table 1).

Table 1

2,2-Disubstituted indandione-1,3	$\nu_{C=O}$, cm^{-1}	ν_{arom}, cm^{-1}
2-Methyl-2-phenyl- (8)	1710(91); 1747(58)	1596(68)
2-Iodomethyl-2-phenyl-	1712(90); 1743(74)	1598(68)

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2,2-Disubstituted indandione-1,3	$\nu_{C=O}$, cm^{-1}	ν_{arom}, cm^{-1}
2-Iodomethyl-2-α-naphthyl-	1709(75); 1743(55)	1594(53)
2-Iodomethyl-2-benzyl-	1708(75); 1745(60)	1597(55)
2-Iodomethyl-2-methyl-	1710(91); 1740(82)	1595(72)

Note. In parentheses—the percent absorption.

Experimental Part

2-Iodomethyl-2-phenylindandione-1,3. 11.1 g (0.05 mole) of 2-phenylindandione-1,3, ground in a mortar with 6.9 g (0.05 mole) of potassium carbonate and 12.1 ml (0.15 mole) of methylene iodide, is heated with a reflux condenser on an oil bath for 1.5 hours at a bath temperature of 180–190°. The end of the reaction is readily determined by the change in the color of the reaction mass: at first it is red; upon completion of the reaction it is yellow or light orange. To the mixture cooled to ~50° about 30 ml of ether is added, and on the second day the precipitate is separated, washed with a small amount of ether, then with warm water, and finally with a small amount of methanol. The yield of 2-iodome-

tyl-2-phenylindandione-1,3: 14.9 g (82.4% of theory). Yellowish crystals with m.p. 189–193°. After recrystallization from acetone or acetic acid, white or light-yellow crystals with m.p. 193–194°.

Found, %: I 35.28, 35.28. $C_{16}H_{11}O_2I$. Calculated, %: I 35.03.

2-Iodomethyl derivatives of 2-anisyl-, 2-veratryl-, 2-piperonyl-, 2-benzyl-, and 2-*p*-methoxybenzylindandiones-1,3 were obtained analogously. The reaction conditions and constants of the compounds obtained are given in Table 2. In the case—

Table 2

general structure: 2-iodomethyl-2-*R*-indandione-1,3

R	Oil-bath temperature, °C	Yield, %	Solvent for crystallization	M.p., °C	Product color	Empirical formula	I found	I calculated
anisyl	150–160	76.5	Ethanol	130–134	Light-yellow	$C_{17}H_{13}O_3I$	32.20	32.37
veratryl	160–170	68.4	Acetic acid	203–205	Yellow	$C_{18}H_{15}O_4I$	29.97	30.07
piperonyl	160–170	76.0	Acetic acid	171–173	Yellow	$C_{17}H_{11}O_4I$	31.34	31.25
α-naphthyl	140–150	19.5	Acetone	200–202	White	$C_{20}H_{13}O_2I$	30.63; 30.71	30.80
benzyl	140–150	66.6	Ethanol	168–170	White	$C_{17}H_{13}O_2I$	33.62; 33.66	33.75
p-methoxybenzyl	140–150	52.7	Ethanol	125–127	White	$C_{18}H_{15}O_3I$	31.26; 31.33	31.26

of 2-*p*-methoxybenzylindandione-1,3, it is expedient to evaporate the ether filtrate in vacuo, after which an additional amount of 2-iodomethyl-2-*p*-methoxybenzylindandione-1,3 is isolated.

2-Iodomethyl-2-methylindandione-1,3. 6.4 g (0.04 mole) of 2-methylindandione-1,3, dissolved with 5.6 g (0.04 mole) of potassium carbonate and 6.6 ml (0.08 mole) of methylene iodide, are heated for 1.5 h at an oil-bath temperature of 140–150°. To the warm mixture about 50 ml of ether is added, it is thoroughly stirred and immediately filtered. After distilling off the ether in vacuo and cooling the residue in a refrigerator, yellowish crystals of 2-iodomethyl-2-methylindandione-1,3 separate. They are separated and washed with a small amount of ether. Yield 5 g (41.6% of theory). M.p. 95–103°. After recrystallization from a methanol–water mixture (2:1), white crystals with m.p. 102–104° are obtained.

Found, %: I 42.22; 41.91. $C_{11}H_9O_2I$. Calculated, %: I 42.30.

2-Iodomethyl-2-α-naphthylindandione-1,3 was obtained analogously (see Table 2).

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

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