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Abstract

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Preparation of 2,2-Disubstituted 1-Aminoindanones-3

A large number of indane derivatives are known that contain an amino group in the five-membered ring. Some of these compounds belong to the class of 2-aminoindandiones-1,3, studied in detail by many authors, for example ([1–4]). Also known are 1-aminoindanes ([5–9]), 1,3-diaminoindanes ([10]), 1-aminoindanols-2 ([11]), and 2-aminoindanols-1 ([12]). Most of these compounds possess definite physiological activity. It was therefore of interest to obtain 1-aminoindanones-3 (I), substances belonging to the β-aminoketones of the indane series. No data on the synthesis of these compounds could be found in the literature. Only certain *N*-benzoyl derivatives of 1-aminoindanones-3 (II) have been obtained ([13,14]).

(I) (II) (III)

For (II) and (III): a) $R_1 = H$; $R_2 = C_6H_5$. b) $R_1 = C_6H_5$; $R_2 = C_6H_5$. c) $R_1 = C_6H_5$; $R_2 = CH_3$. It is no longer possible to obtain the free 1-aminoindanones-3 from them. Compounds II very readily undergo hydramine cleavage, forming the corresponding 2,3-disubstituted indones III or products of their further transformation.

For the same reasons, the reduction of 3-aminoindones IV has likewise so far not achieved the goal, since the expected products (I, $R_2 = H$) should be unstable. It seemed probable that only 2,2-disubstituted 1-aminoindanones-3 (I) would be stable, since they do not contain an easily eliminated hydrogen atom in position 2 of the five-membered ring.

In this connection we found that reduction of 2,2-disubstituted 1-iminoindanones-3 (V) ([13,15]) gives the expected 1-aminoindanones-3 (VIII), though in low yields. The reduction is carried out with hydrochlorides of 1-iminoindanones-3 (VI), since they are readily obtained from the corresponding 3-aminoindones (IV) and in the reaction mixture form the starting β-iminoketones (V)

$$\text{(IV)} \quad \text{(V)} \xrightarrow[CH_3COOH]{Zn} \quad \text{(VIII)}$$

For (V)–(VII) a) $R = CH_3$; b) $R = C_6H_5$.

Preliminary experiments show that 1-aminoindanones-3 are also formed upon reduction of other 2,2-disubstituted 1-iminoindanones-3.

2,2-Disubstituted 1-aminoindanones-3 are colorless substances, readily soluble in ordinary organic solvents, and give all the characteristic reactions of a primary amino group. They have been characterized as acetyl or phthalyl derivatives, and also as salts. The carbonyl group was demonstrated spectroscopically (see Table 1).

Table 1

IR absorption spectra of the 1-aminoindanones-3 obtained

Compound	Benzene absorption	$\nu_{C=O}$	$\delta_{NH_3^+}$?	ν_{NH_2} or $\nu_{NH_3^+}$
VIIa	1492 (44)1607 (68)	1700 (95)	–	3292 (61)3350 (64)
VIIb	1494 (40)1604 (49)	1704 (88)	–	3337 (40)3400 (40)
Amine hydrochloride VIIb	1494 (60)1604 (73)	1717 (90)	1530 (67)1633 (53)	3443 (75)3475 (70) p

According to literature data, indanone-1 in the solid state has a carbonyl band at 1698 cm^{-1} ([16]); in the medium of various solvents these values are noticeably increased (indanone-1 1710 cm^{-1} ([17]), 1721 cm^{-1} ([18]), 1708 cm^{-1} ([19]), 2-ethylindanone-1 1715 cm^{-1} ([17])). For amine hydrochloride (VIIb), the appearance of two new bands, 1530 and 1633 cm^{-1}, is of interest. On the one hand, these could be the frequencies of deformation vibrations of the N–H bond of the ammonium group; on the other hand, the vibrations $\nu_{NH_3^{\oplus}}$ occur no higher than at 3200 cm^{-1} ([20]). In the present case, we are as yet unable to assign these frequencies definitively.

The succinic acid salt of amine VIIa, as was to be expected, has a noticeable anticonvulsant effect with low toxicity of the preparation, and also a weak analgesic effect.

Experimental Part

Succinic acid salt of 1-amino-2-methyl-2-benzylindanone-3. To a suspension of 7.4 g of 1-imino-2-methyl-2-benzylindanone hydrochloride (VIa) ([13]) in 30 ml of glacial acetic acid, 3.5 g of zinc dust is added. The mixture is shaken well and boiled for 20 min, after which a second 3.5 g portion of zinc is added and boiling is continued for another 20–25 min. The light solution is decanted from the unreacted zinc into 200 ml of water, 5 ml of concentrated hydrochloric acid is added, and the mixture is shaken several times with ether. The aqueous layer

is made alkaline, extracted with ether, and the ethereal extracts are dried over anhydrous sodium sulfate and evaporated to dryness. The residue is dissolved in a hot solution of 3 g of succinic acid in 15 ml of methanol, cooled, and 100 ml of ether is added. After one day, 2.34 g of the succinic acid salt of the amine is separated (29%) (from the filtrate, a small amount of a by-product can be isolated—also a salt of a primary amine—which could not be identified exactly). Colorless crystals, m.p. 164-165° (from water), readily soluble in alcohol and acetic acid.

Found, %: N 3.95. $C_{21}H_{23}O_5N$. Calculated, %: N 3.79.

1-Amino-2-methyl-2-benzylindanone-3 (VIIa). A suspension of the succinic acid salt in water is made alkaline and the amine is separated. Colorless needles (from an ether—petroleum ether mixture), m.p. 75-76° (sinters at 65°). Readily soluble in most organic solvents.

Salts of strong acids of amine (VIIa) are difficult to isolate in pure form, since they are excellently soluble in water and are hygroscopic.

Found, %: N 5.91. $C_{17}H_{17}ON$. Calculated, %: N 5.58

Acetyl derivative of amine (VIIa). 1 g of the succinic-acid salt of amine (VIIa) is boiled with 3.5 ml of acetic anhydride and 2.5 ml of acetic acid for 2 hours. Several milliliters of alcohol are added, the mixture is boiled for several more minutes, and the solution is poured into water. White powder, 0.63 g (79%). M.p. 154-155° (from diluted alcohol*).

Found, %: N 4.65. $C_{19}H_{19}O_2N$. Calculated, %: N 4.78

Hydrochloride of 1-amino-2-phenyl-2-benzylindanone-3 (VIIb). To a suspension of 2.94 g of VIIb in 10 ml of acetic acid, 1.3 g of zinc dust is added, the mixture is shaken well and boiled for half an hour. A second 1.3 g of zinc is added and the mixture is boiled for another half hour. The solution is decanted from the unreacted zinc into 50 ml of water and 30 ml of conc. hydrochloric acid is added. The mixture is shaken twice with 40 ml of ether. The ether extracts and the aqueous layer, on standing, separate the amine hydrochloride. In all, 0.96 g (32%) is obtained. Colorless crystals, m.p. 164.5-165.5° (from diluted alcohol). The compound differs somewhat from its 2-methyl analog: in water it is partially hydrolyzed, liberating the free base (see below). It is sparingly soluble in water.

Found, %: N 4.04. $C_{22}H_{20}ONCl$. Calculated, %: N 4.01

1-Amino-2-phenyl-2-benzylindanone-3 (VIIb). 0.2 g of amine hydrochloride (VIIb) is dissolved in diluted alcohol and made alkaline. The separated oil crystallizes when rubbed with a glass rod, after which water is added to the mixture until the amine is completely precipitated. After several days, 0.155 g of colorless crystals is separated (86%), m.p. 150.5-151.5° (from alcohol).

Found, %: N 4.50. $C_{22}H_{19}ON$. Calculated, %: N 4.47

1-Phthalimido-2-phenyl-2-benzylindanone-3. 0.3 g of amine hydrochloride is boiled in 5 ml of glacial acetic acid with 0.3 g of phthalic anhydride for 2.5 hours. The mixture is poured into 50 ml of water, heated to boiling, and the water is decanted from the resinified product (this procedure is repeated twice more). The phthalimido derivative is crystallized from alcohol. Colorless crystals, m.p. 206–207°.

Found, %: N 3.28. $C_{30}H_{21}O_3N$. Calculated, %: N 3.16

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* Throughout, the alcohol : water ratio = 1 : 1.

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