Chemistry

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1960

SovietRxiv

Abstract

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A New Method for the Synthesis of 3-Aryl-1,4,5,6-tetrahydropyridazines

p-Diphenylylcyclobutane

(Presented by Academician A. N. Nesmeyanov, 23 VI 1960)

The only acceptable method known for the synthesis of 3-aryl-1,4,5,6-tetrahydropyridazines (II) is the hydrolysis of adducts (I) of 1-arylbutadienes and azodicarboxylic ester (1–5):

$$\text{Ar—butadiene+NCOOC}_2\text{H}_5\text{=NCOOC}_2\text{H}_5 \longrightarrow \text{adduct } (I) \xrightarrow[-2CO_2]{\substack{\text{KOH, alcohol}\\ -2C_2H_5OH}} \text{3-aryl-1,4,5,6-tetrahydropyridazine } (II)$$

A drawback of this method is the difficult accessibility of the starting arylbutadienes.

In the present work a new route to the synthesis of tetrahydropyridazines II is proposed, consisting in the reduction with lithium aluminum hydride of 6-aryl-4,5-dihydropyridazin-3-ones (III), which are readily obtained by the interaction of β-aroylpropionic acids with hydrazine (7,8,10):

$$\text{ArH+succinic anhydride} \xrightarrow{\text{AlCl}_3} \text{ArCOCH}_2\text{CH}_2\text{COOH} \xrightarrow{\text{NH}_2\text{NH}_2} (III) \xrightarrow{\text{LiAlH}_4} (II)$$

It was shown that the reduction of dihydropyridazinones proceeds analogously to the reduction of acid amides (6) (the carbonyl group is converted into a methylene group) and that the nitrogen-carbon bond in the ring is not affected.

The structure of the tetrahydropyridazines II obtained by reduction of dihydropyridazines III was confirmed in two examples. Thus, 3-phenyl- and 3-*p*-anisyl-tetrahydropyridazines ($II,\ Ar = C_6H_5$ and $p\text{-}CH_3OC_6H_4$), synthesized by this route, proved (as was shown by their reaction with phenyl isothiocyanate) to be identical with preparations obtained by hydrolysis of the corresponding adducts I:

$$(III) \xrightarrow{\text{LiAlH}_4} (II) \xrightarrow{\text{C}_6\text{H}_5\text{NCS}} \text{phenylthiourea derivative}$$

$$(I) \xrightarrow[\text{alcohol}]{\text{KOH}} (II) \xrightarrow[\text{alcohol}]{\mathrm{C_6H_5NCS}} \text{phenylthiourea derivative}$$

$$\text{Ar} = C_6H_5 \text{ and } p\text{-}CH_3OC_6H_4$$

Having proved the structure of the products of reduction of dihydropyridazinones III as aryltetrahydropyridazines (II), we also synthesized by this route

the previously undescribed 3-*n*-diphenylyltetrahydropyridazine

$$\mathrm{C_6H_5{-}C_6H_5} \xrightarrow[\text{2) } \mathrm{NH_2NH_2}]{\text{1) } {\mathrm{CO} \atop \mathrm{CO}}\text{, } \mathrm{AlCl_3}} \text{3-}n\text{-diphenylyl tetrahydropyridazinone} \xrightarrow{\mathrm{LiAlH_4}} \text{3-}n\text{-diphenylyltetrahydropyridazin}$$

and studied its behavior in the reaction of catalytic decomposition developed by us earlier, which is a method for the synthesis of arylcyclobutanes ([3]-[5]).

It turned out that, in the decomposition of *n*-diphenylyltetrahydropyridazine, proceeding by the usual route with formation of *n*-diphenylylcyclobutane and *n*-diphenylylethylene, the molar ratio of the amounts of arylcyclobutane and arylethylene formed is equal to 9, which is the maximum ratio of all those observed previously ([5]):

$$\text{3-}n\text{-diphenylyltetrahydropyridazine} \xrightarrow[-\mathrm{N_2}]{\text{Pt/KOH, 250–300°}} \text{[diradical]} \longrightarrow \mathrm{C_6H_5C_6H_4}\text{–cyclobutane and } \mathrm{C_6H_5C_6H_4}$$

The obtained *n*-diphenylylcyclobutane was characterized by its UV absorption spectrum.

On the absorption curve of this hydrocarbon there are a characteristic minimum (λ_{min} 224; $\lg \varepsilon_{\text{min}}$ 3.42) and maximum (λ_{max} 250; $\lg \varepsilon_{\text{max}}$ 4.26). It should be noted that the arylcyclobutanes studied earlier had a characteristic minimum in the region 230-240 mμ and a characteristic maximum in the region 260-270 mμ. This difference, as well as a certain smoothing of the absorption curve, is apparently a consequence of the presence in the diphenylylcyclobutane molecule of a system of two phenyl nuclei.

Fig. 1

Experimental Part

β-Aroylpropionic acids were obtained by the usual Friedel-Crafts procedure from succinic anhydride and the corresponding aromatic compound (benzene, anisole, and diphenyl).

β-Benzoylpropionic acid; yield 75%, m.p. 111-112° (from alcohol).
β-Anisoylpropionic acid; yield 50%, m.p. 139-140° (from alcohol).
β-*n*-Phenylbenzoylpropionic acid, yield 85%, m.p. 181-182° (from a mixture of acetone with ligroin). Literature data, respectively: m.p. 111-113° ([7]), 140-141° ([8]), 183° ([9]).

6-Aryl-4,5-dihydropyridazinones-3. 6-Phenyl-4,5-dihydropyridazinone-3. A solution of 28.5 g (0.160 mole) of benzoylpropionic acid in 160 ml of 1 *N* potassium hydroxide solution was mixed with a solution of 21 g

(0.161 mole) of hydrazine sulfate in 160 ml of a 1 N KOH solution and heated for 1 hour on a water bath. The crystals that separated on cooling were filtered off and recrystallized from alcohol. Yield 25.0-26.5 g (90-95%); m.p. 149-150°. Literature data (7): m.p. 149-150°.

6-Anisyl-4,5-dihydropyridazon-3 was obtained by mixing equimolar amounts of anisoylpropionic acid and hydrazine hydrate in methyl alcohol. The reaction mixture was heated for 6 hours on a water bath; the crystals that separated on cooling were filtered off and recrystallized from alcohol. Yield 90%; m.p. 146-147°. Literature data (8): m.p. 147-148°.

6-*p*-Diphenylyl-4,5-dihydropyridazon-3 was synthesized by the same procedure; yield 74%; m.p. 248° (from alcohol). Literature data (10): m.p. 248°.

Synthesis of 3-aryl-1,4,5,6-tetrahydropyridazines. An equimolecular amount of dihydropyridazone was added to a solution of freshly prepared lithium aluminum hydride in abs. ether, and the mixture was heated for 24 hours, after which, on cooling, the complex formed was decomposed with the theoretical amount of water; the precipitate was filtered off, and the ether was distilled off from the filtrate in vacuo (under nitrogen). To separate it from unreacted dihydropyridazone, the residue was dissolved in ligroin, the solution was decanted and dried with magnesium sulfate; after removal of the ligroin, the remaining tetrahydropyridazine was recrystallized from alcohol.

3-Phenyl-1,4,5,6-tetrahydropyridazine, yield 47%, b.p. 165-166° (10 mm). Literature data (3): b.p. 160° (8 mm). The addition product with phenyl isothiocyanate had m.p. 107-108°. A mixed melting-point test with an authentic specimen* melted without depression.

3-Anisyl-1,4,5,6-tetrahydropyridazine, yield 81%, b.p. 210-211° (18 mm); m.p. 78-80° (from ligroin). Literature data (5): b.p. 205-206° (16 mm); m.p. 78-80°. Addition product with phenyl isothiocyanate: m.p. 116-117° (from ligroin).

Found, %: C 66.63; 66.71; H 5.66; 5.69
$C_{18}H_{19}N_3OS$. Calculated, %: C 66.43; H 5.89

A mixed melting-point test with an authentic specimen* melted without depression.

3-*p*-Diphenylyl-1,4,5,6-tetrahydropyridazine, yield 62%, m.p. 154-155° (from alcohol). Addition product with phenyl isothiocyanate—m.p. 175-176° (from a mixture of ligroin with acetone).

Found, %: N 11.12; 11.15
$C_{23}H_{23}N_3S$. Calculated, %: N 11.25

Catalytic decomposition of 3-*p*-diphenylyl-1,4,5,6-tetrahydropyridazine. The decomposition of tetrahydropyridazine and the isolation and purification of the products of this reaction were carried out according to the previously described procedure (5).

***p*-Diphenylylcyclobutane**, yield 41%, b.p. 153-154°/10 mm; m.p. 25-26°.

Found, %: C 92.26; 92.06; H 7.75; 7.60
$C_{16}H_{16}$. Calculated, %: C 92.26; H 7.74

The evolved gas contained 91% nitrogen and 9% ethylene (identified as the dibromide: b.p. 130-131° at 760 mm, n_D^{20} 1.5370. Literature data (11): b.p. 129-130° at 755 mm, n_D^{20} 1.5379).

* Synthesized from 3-aryl-1,4,5,6-tetrahydropyridazine obtained by hydrolysis of the adduct (I) of azodicarboxylic ester and the corresponding 1-arylbutadiene-1,3.

Along with *n*-diphenylylcyclobutane, *n*-diphenylylethylene was isolated. Yield 4.5%; b.p. 145-147° (10 mm); m.p. 117-118° (from alcohol). Literature data [12]: b.p. 136-138° (6 mm); m.p. 119°.

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Received
22 VI 1960

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