CATALYTIC SYNTHESIS OF N-ALKYLOCTAHYDROISOINDOLES

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Catalytic hydroamination of 1,2-bis-(hydroxymethyl)cyclohexane by aliphatic nitriles over a nickel catalyst yielded a series of N-alkyl-substituted octahydroisoindoles. Conditions for their synthesis were selected. The IR, PMR, and mass spectra and the probable mechanism of formation of these compounds are discussed.

No information has been published on the synthesis, chemical properties, or biological activity of the octahydroisoindoles.

In the present work we describe a practical synthesis of N-alkyloctahydroisoindoles. The starting materials are products of multiton manufacture, viz., diethyl phthalate and aliphatic nitriles; thanks to the oxidative ammonolysis of hydrocarbons that has been developed, the latter are readily available.

The basic scheme for the synthesis of N-alkyloctahydroisoindoles is:
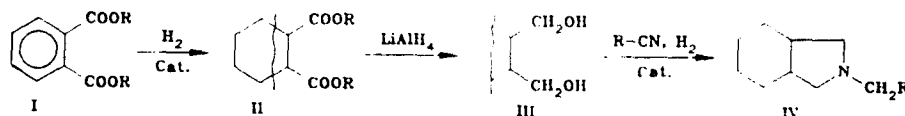
To obtain diethyl hexahydrophthalate (II) we developed a catalytic hydrogenation of diethyl phthalate (I) in a flow unit. We used three kinds of nickel catalysts: nickel on aluminum oxide (Ni/Al$_2$O$_3$); nickel on magnesium oxide (Ni/MgO); and nickel on silica gel (Ni/SiO$_2$). Ni/Al$_2$O$_3$ is the most widely used heterogeneous catalyst for the hydrogenation of aromatic compounds. Benzene is hydrogenated to cyclohexane, and phenol to cyclohexanol, over it in high yield. But when diethyl phthalate is hydrogenated, along with hydrogenation of the aromatic ring there is reduction of the ester group, so that 1,2-dimethylcyclohexane is formed. One of the reasons this product is formed is apparently the acidity of the γ-Al$_2$O$_3$ support, which appreciably promotes the dehydration and decarboxylation of the ester groups. Ni/MgO has much milder hydrogenating activity, and can hydrogenate the aromatic ring of diethyl phthalate while retaining the functional groups. But after some hours the activity of this catalyst falls off sharply. Probably on a weakly basic support such as magnesium oxide, hydrolysis of ester groups is insignificant, but the acid thus formed poisons the catalyst.

The most efficient catalyst for hydrogenation of diethyl phthalate is nickel on silica gel. It is quite resistant to poisoning by phthalic acid, and, thanks to the weakly acid properties of the support, it does not hydrolyze the ester groups.

The second step in the synthesis of N-alkyloctahydroisoindoles is the synthesis of the diol 1,2-bis(hydroxymethyl)cyclohexane (III), which consists of the reduction of ester (II) by lithium aluminum hydride by a known method [1].

This diol is subjected to hydroamination by an aliphatic nitrile. It is known that the necessary condition for this reaction is the reduction of the nitrile to a primary amine [2]; the latter can then react with carbonyl compounds or alcohol on the catalyst surface in the presence of hydrogen.

Diol (III) has two reaction centers that can take part in hydroamination. Therefore, depending on the alcohol–nitrile ratio, we can expect either individual aminoalcohol or diamine, or a mixture of the two. But, as studies have shown, the reaction can take another path. According to published data, hydroamination of alcohols and carbonyl compounds proceeds by an imine mechanism [3]. In the hydroamination of (III) one of the alcohols is dehydrogenated to form aldehyde (V), which reacts further with amine to form azomethyne (VI). At the same time, the second alcohol group is dehydrogenated to carbonyl. The azomethyne is hydrogenated on the catalyst to the respective secondary amine (VII), which then undergoes intramolecular cyclization to give octahydroisoindole. The overall mechanism is as follows:
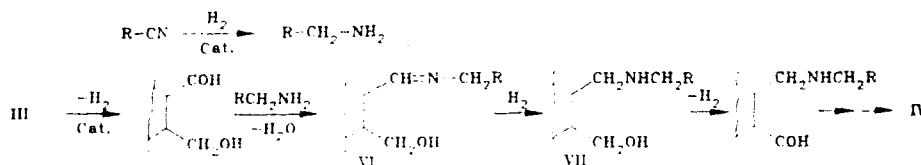
Besides the octahydroisoindole the reaction products contain nearly 20% of octahydroisobenzofurane (VIII), due to the intramolecular condensation of (III).
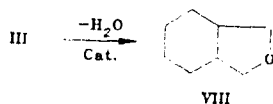
The idea that octahydroisoindole is formed by amination of octahydroisobenzofurane has not been confirmed because, under the reaction conditions, the latter compound is practically unchanged.

As hydroamination catalyst we used industrial copper–magnesium catalyst. Copper was used because its hydrogenation activity is milder than that of nickel, so that the formation of hydrogenolysis byproducts is significantly reduced. Furthermore, copper is a good catalyst for alcohol dehydrogenation; this increases the possibility that the reaction will proceed by the imine mechanism, and is responsible to a significant extent for the high catalyst activity. This activity is further intensified in hydroamination by the low dehydrogenation capability of magnesium oxide. Here a quite widely used catalyst – copper on aluminum oxide – was ineffective because of the high dehydrogenation and condensation activity of aluminum oxide; this favors the formation of a furane compound by the Yur'ev reaction.

With hydroamination of (III) by acetonitrile as an example, optimum conditions were determined for the synthesis of N-alkyloctahydroisoindoles: 240°C, 1.5 MPa hydrogen pressure, space velocity 0.5 h⁻¹.

The structures of the newly synthesized compounds (Table 1) were confirmed by elemental analysis and IR, PMR, and mass spectroscopy.

The IR spectra of the N-alkyloctahydroisoindoles lack the bands at 1500-1600 and 3500 cm⁻¹ that are typical of the stretching vibrations of the aromatic nucleus. The bands in the 2000-3000 cm⁻¹ region are typical of those vibrations. The bands in that region are evidence for the stretching vibrations of aliphatic protons.

In the PMR spectrum of N-ethyloctahydroisoindole the relative intensities of the signals of the magnetically nonequivalent methylene protons of the pyrrolidine ring determined the isomer ratio to be 1:1.5. The spectrum of the cis-isomer shows two doublets of doublets near 2.38 ($J = 7.2$; 9.6 Hz) and 2.50 ppm ($J = 9.6$; 10.6 Hz); the trans isomer's spectrum shows a doublet of doublets at 2.90 ($J = 9.6$; 6.6 Hz) and a triplet at 2.43 ppm ($J = 9.6$; 10.6 Hz).

The mass spectra of all the compounds show a molecular ion peak M⁺ (for N-ethyl- and N-propyloctahydroisoindoles, of average intensity). The main direction of fragmentation of the molecular ion is detachment of an R radical to form an (M − R)⁺ peak. All the spectra are characterized by a peak with m/z 95 that apparently corresponds to a norcaranyl cation that is formed by α- and β-scission of bonds.

EXPERIMENTAL

IR spectra were obtained with a UR-20 instrument; PMR spectra were recorded with a Bruker-360 instrument with CDCl₃, and HMDS internal standard. Mass spectra were obtained with a Varian MAT-311 mass spectrometer (50 eV electron energy). The reaction was monitored with a LKhM-8MD chromatograph, with katharometer detector, column length 2 m, filled with 15% PEG-2000 and 5% KOH on Chromosorb W (60-80 mesh). Column temperature was programmed from 50 to 220°C at 12°C/min. Flow rate of helium carrier gas, 40 ml/min.

TABLE 1. Properties of N-Alkyloctahydroisoindoles

Compound	Bp, °C	n_D^{20}	d_4^{20}	Yield, %
N-Ethyloctahydroisoindole	47...50	1.4731	0.9004	67
N-Propyloctahydroisoindole	54...56	1.4724	0.8920	65
N-Isobutyloctahydroisoindole	65...67	1.4688	0.8793	67
N-Butyloctahydroisoindole	61...62	1.4718	0.8830	66
N-Pentyloctahydroisoindole	69...70	1.4711	0.8802	62
N-Isopentyloctahydroisoindole	73...74	1.4662	0.8701	62

*Pressure 1 mm Hg.

Catalysts: 36% Cu/MgO (industrial catalyst) and 15% Ni/MgO, 15% Ni/SiO$_2$, and 15% Ni/Al$_2$O$_3$ were prepared by impregnation.

Diethyl hexahydrophthalate (II) was prepared by hydrogenation of diethyl phthalate over 15% Ni/SO$_2$ in a flow unit under hydrogen pressure. Diethyl phthalate, 150 g (0.67 mole) was passed over reduced catalyst at 230-240°C and 3.5-4.0 MPa pressure of hydrogen. Feed rate was 0.25 h^{-1} space velocity.

1,2-Bis(hydroxymethyl)cyclohexane (III) was prepared by reduction of diethyl hexahydrophthalate with lithium aluminum hydride by the procedure of [1].

N-Alkyloctahydroisoindole (IV). Compound (III) was reacted with aliphatic nitriles in a flow unit under hydrogen pressure over an industrial copper–magnesium catalyst. A 1:1 alcohol–nitrile mixture was passed over catalyst at 230-240°C, 1.5 MPa hydrogen pressure, and 0.5 h^{-1} space velocity.

LITERATURE CITED

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