Stimulation of humoral immunity in mice by undecan-2-one, undecan-2-ol and their derivatives

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Abstract

The in vivo effect of some derivatives of aliphatic 2-ketone, undecan-2-one, on humoral immunity in mice were studied. Stimulatory effect on anti-SRBC antibody production was presented by undecan-2-ol, undecan-2-olR(-) enantiomer, undecan-2-ol acetate and undecan-2-one acetics. No effect of S(+) enantiomer of undecan-2-ol was observed. Serum lysozyme level increased in mice inhaled with undecan-2-ol.

Key words: undecan-2-ol, enantiomers, humoral immunity, mice.

(Introduced by the authors)

Introduction

Undecan-2-one is a component of a few essential oils and the extracts obtained from many exotic plants. High concentrations of it are observed in the essential oils derived from plants belonging to the Rutaceae family. The oil from Ruta chalepensis L. which grows in Turkey was reported to contain undecan-2-one (66.5%) and that from R. montana up to 84.2% of this ketone [1]. Ruta graveolens which grows in China contains 67.0% of undecan-2-one [2] and that from Cuba 48.7% [3]. Siparuna guianensis (Aubl.) from the Brazilian Amazonian Region was found to possess undecan-2-one in 32.5% and 31.7% in the fruit oil and leaf oil, respectively [4]. The ketone has also been found in the oils derived from Zanthoxylum pinnatum and Cymbopogon schoenanthus (L.) Spreng (54.3 and 14.7%, respectively) [5, 6]. High contents of this ketone have also been observed in the bark oil from Glycosmis pentaphylla Cor. (58.1%) [7] and in the root oils from Pilocarpus spicatus St Hill. (20.8%) [8] and Philodendron acutatum Schott. (9.6-12.7%) [9].

The synthetic undecan-2-one is often used in the food and fragrance industry, owing to its pleasant fruit – floral odour with an orange – herbal note.

Recently, we have reported some data on the immunonotropic effects of undecan-2-one [10]. This substance, introduced to mice by inhalation increased their cellular and humoral immunity in various in vivo and ex vivo tests. The aim of the present study was to evaluate the effect of its derivative, undecan-2-ol, and various derivatives of undecan-2-one and undecan-2-ol on humoral immunity in mice.

Materials and Methods

Synthesis of ketone

Undecan-2-one was prepared by dr Marek Gliński in Faculty of Chemistry, Warsaw Technical University, by ketonization of a mixture of acetic and decanoic acids in the presence of 20wt%MnO₂/Al₂O₃ catalyst under flowing conditions. Yield of ketone 70.0%, purity 99.9% (GC), nD²⁰=1.4262. The purity of the ketone, physical properties and spectral data were determined [11].

Synthesis of alcohol

2-undecanol was prepared by reduction of 2-undecanone using sodium borohydride in a water/propan-2-ol solution. Yield of undecan-2-ol 91%, its purity 98.9% (GC)
It has a fatty with a mild fruity note odour and therefore can be used as potential starting material for the creation of perfumes and flavours for the corresponding cosmetics and food industries.

Ethylene and propylene acetals of undecan-2-one were prepared starting from undecan-2-one.

Synthesis of acetals

Acetals were prepared in the reaction between ketone and ethane-1, 2-diol or propane-1,2-diol in toluene in the presence of sulfosalicylic acid as a catalyst. All derivatives were prepared in a 2-5 g scale [13].

Synthesis of enantiomers

Enantiomerically pure undecan-2-ols and undecan-2-ol acetates were prepared by biocatalytic enantioselective synthesis. Products of these reactions were separated on the column chromatography. Column chromatography was performed on silica gel (Kieselgel 230-400 mesh) and mixture of hexan, etyl acetate. Specific rotations of enantiomers were measured in etanol with an Autopol (Rudolf) polarimeter.

The absolute configuration of enantiomers was determined by correlation with literature data [14, 15]. The purity of compounds was confirmed by GC/MS, GC (Chirasil-Dex column), IR, 1H NMR and the measurements of refractive index.

The 1H NMR spectra were recorded on a Bruker 250 DPX spectrometer, in CDCl3 using TMS as internal standard. The IR spectra were measured using Specord M 80 spectrometer (film or KBr pellet). Microanalyses were performed on a Perkin Elmer 2400 CHN elemental analyser. Melting points (uncorrected) were determined on Boetius apparatus.

Mice

The study was performed on 10-12 weeks old female Balb/c and (Balb/cxDBA2)F1 mice, weighing 25-28 g, delivered from the Polish Academy of Sciences and from the own breeding colonies.

Study of antibody production

Mice were immunized with 10% SRBC (0.1 ml intra-peritoneally), and subjected to inhalations for 3 consecutive days, according to the following scheme: 5 mice in one cage, 5 drops of tested compound for 60 minutes, the cage covered by linen during inhalation. The cages with control mice were accordingly covered by linen for 60 minutes.

Mice were bled in anaesthesia (3.6% chloral hydrate), from retroorbital plexus, 7 days after immunization. The antibody level was evaluated with haemagglutination assay in inactivated (56°C, 30 min) sera. After performing a series of sera dilutions, 0.5 % SRBC were added and the mixture was incubated for 60 min at room temperature, then centrifuged (10’, 150 g) and shaken. The hemagglutination titer was evaluated in a light microscope – as the last dilution in which at least 3 cell conglomerates were present in at least 3 consecutive fields at objective magnification 20×. Stimulation indices were calculated as a ratio of log titer of each experimental serum to the mean log titer of simultaneously performed control.

Lysosome level was determined according to the method described [10]. Statistical analysis was performed by Student t-test. Experiments were approved by the Local Ethical Committee.

Results

Lysosome concentration in the sera of mice inhaled for 3 days with undecan-2-ol was significantly higher than in the sera of control ones (9.80±0.40 mg/L versus 7.85±0.45 mg/L, P<0.01).

The effect of undecan-2-one, undecan-2-ol and their derivatives on antibody production is presented on the Table 1.

<table>
<thead>
<tr>
<th>Compound used for inhalation</th>
<th>Number of mice</th>
<th>Mean stimulation index of antibody titer ±SE</th>
<th>Significance of difference from the control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (non-inhaled)</td>
<td>40</td>
<td>1±0.04</td>
<td>–</td>
</tr>
<tr>
<td>Undecan-2-one 10%</td>
<td>5</td>
<td>1.38±0.02</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Undecan-2-ol 1%</td>
<td>5</td>
<td>1.37±0.03</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Undecan-2-ol 10%</td>
<td>5</td>
<td>1.29±0.02</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>S(+) undecan-2-ol (E-1) 1%</td>
<td>10</td>
<td>1.04±0.13</td>
<td>n.s.</td>
</tr>
<tr>
<td>R(–) undecan-2-ol (E-2) 1%</td>
<td>10</td>
<td>1.36±0.06</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>S(+) undecan-2-ol acetate(E-3) 1%</td>
<td>10</td>
<td>1.31±0.05</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>R(–) uncecan-2-ol acetate(E-4) 1%</td>
<td>10</td>
<td>1.34±0.11</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Undecan-2-one ethylene acetal 1%</td>
<td>10</td>
<td>1.64±0.06</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Undecan-2-one propylene acetal 1%</td>
<td>10</td>
<td>1.72±0.07</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
Except S(+) which was one of the two enantiomers of undecan-2-ol, all other tested substances highly significantly stimulated this parameter of immunity.

Discussion

In this paper we present for the first time the evidence of immunostimulatory activity of racemic undecan-2-ol and its component, pure R(−) enantiomer, as well as of some other derivatives (acetate and acetals). Similarly to undecan-2-one, undecan-2-ol has been found in nature too. It exists in many plants, as one of the major components of essential oils from *Ruta graveolens* L. [3] and *Philodendron acutatum* Schott. [9] and from *Eucalyptus risdoni*, from *Curcuma aeruginosa* Roxb. and *Curcuma heyneana* Val. [16].

R(−) – undecan-2-ol was detected in the essential oil from *Listea odorifera*, S(+) undecan-2-ol has been found in cacao butter [17]. *Ruta graveolens* is also a natural, rich source of undec-2-y1 acetate [2].

Ethylene acetal of undecan-2-one and propylene acetal of undecan-2-one are newly prepared compounds. Furthermore, besides undecan-2-one is present in many plants, ethylene and propylene acetals of undecan-2-one have not been found in nature. They have characteristic pleasant odours and therefore can be used as potential starting materials for the creation of perfumes and flavours for the corresponding cosmetics and food industries. Ethylene acetal has an intensive, herbageous-spicy odour, propylene acetal has a nettle-like with a pitch note odour [13].

Immunostimulatory fragrances and food additives may be beneficial for improving immune system function in immunocompromised subjects, and for additional, immunostimulatory treatment of patients suffering from various infections. However, abuse of foods and fragrances with immunomodulatory properties may not be recommended for healthy persons everyday use [18].

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References