Eurasian Chemico-Technological Journal 16 (2014) 299-302

# Biological Active Esters of the Isovaleric Acid

Kh.A. Suerbaev[1*], G.Zh. Zhaksylykova[1], N.O. Appazov[2]

[1]Al-Farabi Kazakh National University, al-Farabi av. 71, Almaty, Kazakhstan
[2]Korkyt Ata Kyzylorda State University, 29A Aiteke bie str., Kyzylorda, Kazakhstan

## Abstract

Hydroalkoxycarbonylation of olefins with carbon monoxide and alcohols under condition of homogeneous – catalysis with transition metal complexes allows facile one-step synthesis of practically useful carbon acid esters. Many of them have biological activity and are constituents of drugs or valuable intermediate products in drug synthesis. Hydroalkoxycarbonylation of isobutylene with carbon monoxide and alcohols in the presence of catalytic system $Pd(PPh_3)_4$-$PPh_3$-TsOH was applied for preparing of biological active isovaleric acid esters: *l*-menthylisovalerate (main active component of the spasmolytic medicine "Validolum"), ethylisovalerate (intermediate product for obtaining sedative and spasmolytic medicines "Ethyl ester of $\alpha$-bromisovaleric acid" and "Corvalolum"), cyclohexylisovalerate (bactericide activity) and benzylisovalerate (bactericide and antifungus activity). Hydroalkoxycarbonylation reaction of isobutylene with carbon monoxide and alcohols (ethanol, cyclohexanol, *l*-menthol, benzyl alcohol) in the presence $Pd(PPh_3)_4$-$PPh_3$-TsOH system carried out at conditions: temperature 100 ºC; CO pressure 2.0 MPa; reaction time 4 h; reactants and catalyst components ratio [alcohol]:[isobutylene]:[$Pd(PPh_3)_4$]:[$PPh_3$]:[TsOH] = 435:550:1:3:12. The yields of the products were 71-95% (on converted alcohols). The selectivity in linear reaction products was 100%. Such a high regioselectivity is apparently provided both by the structure of the starting alkene (isobutylene) and by the reaction mechanism. The most probable is a hydride mechanism. Due to the more advanced technology of production the Medicines will have better qualitative characteristics. The cost of production of the Medicines with the use of new technologies is 2-3 times lower as compared to the medicines produced by existing at the present traditional technologies.

## Introduction

Isobutylene carbonylation with carbon monoxide and alcohols under conditions of homogeneous catalysis with transition metal complexes allows facile one-step synthesis of practically useful isovaleric acid esters [1-3]. Many of them have biological activity and are components of pharmaceuticals (Validolum, Corvalolum, etc) or valuable intermediates for their synthesis [4]. Some isovalerate esters possess a characteristic odor and are used as fragrance compounds in the manufacture of perfumes, cosmetics and food essences [5].

We applied hydroalkoxycarbonylation of isobutylene with carbon monoxide and suitable alcohols in the presence of catalytic system $Pd(PPh_3)_4$-$PPh_3$-TsOH to prepare of biological active isovaleric acid esters: *l*-menthylisovalerate (possesses spasmolytic properties; it used as main active component of the spasmolytic medicine Validolum), ethylisovalerate (possesses aromatic (fruit) odor; intermediate product for obtaining sedative and spasmolytic medicines Ethyl ester of $\alpha$-bromisovaleric acid and Corvalolum), cyclohexylisovalerate (bactericide activity (against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa); antifungal activity (against Candida albicans)) and benzylisovalerate (bactericide activity (against Escherichia coli, Staphylococcus aureus)).

New efficient technologies for preparation of drugs are based on isovaleric acid esters – Validolum, Ethyl ester of $\alpha$-bromisovaleric acid (EEBIA) and Corvalolum – were worked out. Validolum – is a spasmolytic (sedative) medicine [4]. It has a sedative effect on the nervous system and a moderate reflex vaso-dilating effect. EEBIA possesses sedative and spasmolytic properties. It is included in Corvalolum composition and may be used for producing other medicines. Corvalolum is a combined medicine and consists of EEBIA, phenobarbital, so-

* Corresponding author. E-mail: khsuerbaev@mail.ru

dium hydroxide, peppermint oil, ethyl alcohol and water. Corvalolum possesses anetic and spasmolytic properties [4].

Due to the more advanced technology of production the Medicines will have better qualitative characteristics. The cost of production of the Medicines with the use of new technologies is 2-3 times lower as compared to the medicines produced by existing at the present traditional technologies.

## Experimental

The complex $Pd(PPh_3)_4$ was obtained according to the known procedure [6]. *p*-Toluenesulfonic acid was recrystallized from 96% ethanol and dried until the composition $TsOH*H_2O$. Triphenylphosphine was recrystallized from an ether-ethanol mixture to a constant melting point. Absolute ethanol, isobutylene of 99.5% purity, carbon monoxide of 99.8% purity, *l*-menthol of 99.7% purity, cyclohexanol of 99.5% purity and benzyl alcohol of 99.2% purity were used. The experiments were carried out in the solvent-free mode in a laboratory stainless steel autoclave unit (100 ml). A reactor was charged with components of a catalyst system and an corresponding alcohol, hermetically sealed, and purged twice with carbon monoxide to remove air. Then, isobutylene was fed, carbon monoxide was admitted to a required pressure, and heating and stirring were switched on. The progress of the reaction was monitored by following the pressure drop in the autoclave and by sampling. After completion of the reaction, the reactor was cooled to room temperature, and the excess gas was allowed to bleed. The reaction mixture was subjected to fractional distillation to isolate the pure products. The determination of the purity and the analysis of the products were carried out by means of a GLC technique, IR-spectroscopy and $^1H$ NMR techniques. Gas chromatography was performed on a Hewlett-Packard 3890-II-Plus chromatograph with a flameionization detector; HP-Innowax cross-linked PEG capillary column (30000*0.25mm), film thickness 0.25 μm. Injector temperature 200 ºC, detector temperature 200 ºC, carrier gas nitrogen (25 ml/min). The oven temperature was programmed from 75 to 175 ºC at a rate of 10 ºC/min. The $^1H$ NMR spectra were measured on a Varian Mercury-300 instrument (300 MHz) against internal TMS.

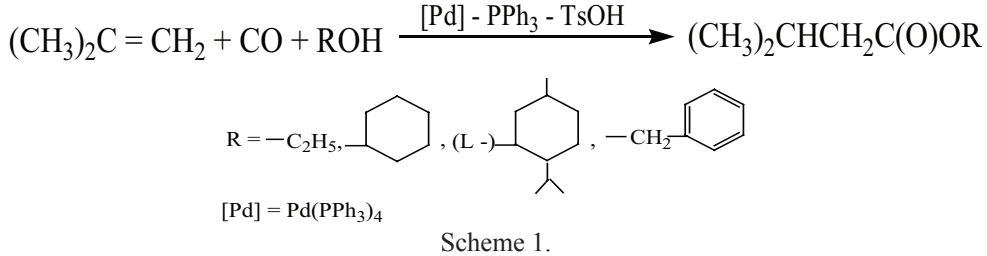
### *L-Menthylisovalerate*

The 100 ml autoclave equipped with a stirrer and a carbon monoxide and isobutylene feeding device was charged with 0.133 g ($1.15*10^{-4}$ mol) of $Pd(PPh_3)_4$, 0.263 g ($1.38*10^{-3}$ mol) of TsOH, and 7.854 g ($5.02*10^{-2}$ mol) of *l*-menthol. The autoclave was sealed, purged with CO to remove air, and filled with CO to a pressure of 1.0-1.1 MPa. Then 3.562 g ($6.35*10^{-2}$ mol) of isobutylene was introduced and stirring and heating were switched on. The carbon monoxide pressure was brought to 2.0 MPa, the temperature was elevated within 1 h to 100 ºC, and the reaction mixture was agitated under these conditions for 4 h. On completion, the autoclave was cooled to room temperature and the reaction mixture was fractionated in a vacuum. 3.58 g (45.6% of the initial quantity) of unreacted *l*-menthol and 6.24 g (51.6%) (or 94.9% on converted *l*-menthol) of *l*-mentylisovalerate were obtained. Bp 123 ºC/6 mm Hg, $n_D^{20}$ 1.4480.

## Results and Discussion

Hydroalkoxycarbonylation reaction of isobutulene with carbon monoxide and alcohols (ethanol, cyclohexanol, *l*-menthol, benzyl alcohol) in the presence $Pd(PPh_3)_4$-$PPh_3$-TsOH system carried out at optimal conditions of isobutylene hydromenthoxycarbonylation [7]: temperature 100 ºC; CO pressure 2.0 MPa; reaction time 4 h; reactants and catalyst components ratio [alcohol]:[isobutylene]:[$Pd(PPh_3)_4$]:[$PPh_3$]:[TsOH] = 435:550:1:3:12 (Scheme 1).

The yields of the products were 71-95% (on converted alcohols). The selectivity in linear reaction products was 100%. Such a high regioselectivity is apparently provided both by the structure of the starting alkene (isobutylene) and by the reaction mechanism. The most probable is a hydride mechanism [2, 8]. Evidence for this proposal comes from the observation of an exceptionally strong effect of the TsOH addition, which being a proton donor, facilitates formation of the primary active hydride complexes of the catalytic cycle.




Scheme 1.

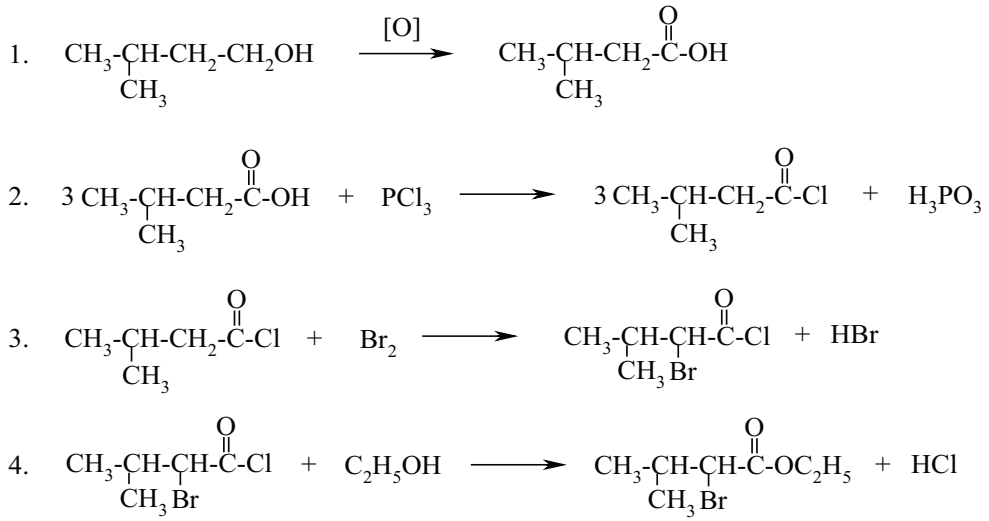
*l*-Menthylisovalerate is a main active ingredient of the drug Validolum. Validolum has a sedative effect on the nervous system and a moderate reflex vaso-dilating effect. It is used at light attacks of stenokardia, neurosis, hysteria. It is also used as anantienetic at sea air sickness.

The existing industrial production of Validolum is based on the two stage scheme of the synthesis of *l*-menthylisovalerate: 1) oxidation reaction of isoamil alcohol to isovaleric acid; 2) esterification reaction of isovaleric acid by *l*-menthol. Such a technology of obtaining *1*-menthylisovalerate is characterized by low technical-economic (duration of the esterification process is 48 h, yield of the target product no more than 75%) and low ecological characteristics (large amounts of waste waters at the stages of neutralization and washing) and low quality of products because of the presence of impurities. Validolum obtained by traditional technology contains 11 admixtures, the content of which reaches 8%.

The new technology developed by us makes possible to make the synthesis of *l*-menthylisovalerate in one stage by reaction of hydromenthoxycarbonylation of isobutylene by carbon monoxide and *l*-menthol in the presence of metalcomplex catalyst. The use of the more available raw materials and also the high effectiveness of the technology (duration of the process is 5 h, yield of the target product 95%) makes this process of obtaining *l*-menthylisovalerate highly profitable. The product obtained with the new technology has higher quality and contains only 3-4 admixtures, the contents of all of which is not higher than 1-1.5%.

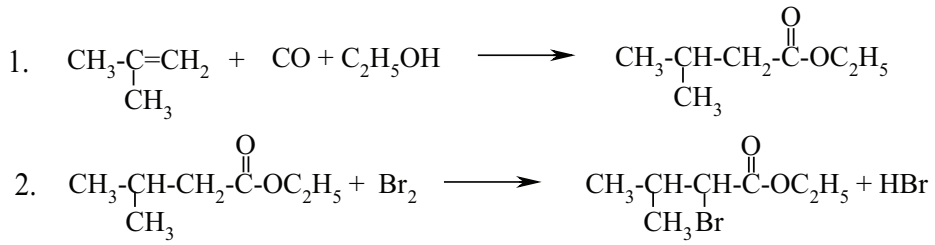
EEBIA possesses sedative and spasmolytic properties and in larger doses provides light soporific action. It is included in composition of the drug Corvalolum and may be used for producing other medicines. Corvalolium possesses anetic and spasmolytic properties. It is used for neurosis with increased irritability, for soft spasms of coronary vessels, tachycardia, anhypnosis, early stages of hypertension and bowel spasms.

The existing technology of EEBIA production is based on the four stage scheme of the synthesis (Scheme 2). The first stage is obtaining of isovaleric acid by oxidation of isoamyl alcohol. Then follows the two staged bromination of isovaleric acid with bromine in the presence of $PCl_3$. The obtained $\alpha$-bromisovaleric acid is transferred into chloranhydride, which is subjected to esterification with ethanol. This method of EEBIA obtaining is characterized with complexity and is highly labor consuming process, has low technical, economic and ecological characteristics (use of expensive and rare raw materials, use and formation of aggressive starting products and secondary by-products: $PCl_3$, HCl, $H_3PO_4$) and the low quality of the product due to the admixtures.



Scheme 2.

The proposed by us new technology of obtaining EEBIA (and Corvalolum production on its basis) is based on the new effective method of obtaining EEBIA from isobutylene, carbon monoxide, ethanol and bromine (Scheme 3). The synthesis of ethylisovalerate is carried out by hydroethoxycarbonilation reaction of isobutylene with carbon monoxide and ethanol. On the second stage the product (EEBIA) is synthesized by bromination of ethylisovalerate in the presence of the red phosphor. Quality of EEBIA obtained by the new technology is higher (contains less admixtures), the production cost is 2-3 times lower than the production cost of the existing four stage method of obtaining EEBIA.



Scheme 3.

Thus, the feasibility of synthesis of the biological active esters of isovaleric acid by isobutylene hydroalkoxycarbonylation in the presence of the catalytic system $Pd(PPh_3)_4$-$PPh_3$-TsOH was established. The reaction proceeds regioselectively at the terminal atom of isobutylene. The proposed methods are highly economical and may be used for commercial production of the biological active esters of the isovaleric acid. Optimal technological parameters for carrying out the processes were tested at the pilot plant. Technologically, organization of the productions being proposed does not present any great difficulties. Standard equipment may be used. It should be noted that all the proposed productions are based on the similar technology using one and the same equipment.

## Conclusion

1. Biological active isovaleric acid esters were synthesized by isobutylene hydroalkoxycarbonylation in the presence of the catalytic system $Pd(PPh_3)_4$-$PPh_3$-TsOH.

2. New efficient technologies for preparation of drugs are based on the isovaleric acid esters – validolum, ethyl ester of $\alpha$-bromisovaleric acid and corvalolum – were worked out.

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*Received 4 May 2014*