($1,15*10^{-4}$ 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°C, 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-menthyl isovalerate were obtained. Bp 123°C / 6 mm Hg, n_D^{20} 1,4480.

Isovaleric acid α-monoglyceride

A steel autoclave of 100 ml capacity was charged with 0,035 g ($1,15*10^{-4}$ mol) of Pd $(Acac)_2$, 0,212 g ($8,085*10^{-4}$ mol) of PPh_3, 0,263 g ($1,386*10^{-3}$ mol) of TsOH, and 5,975 g ($6,35*10^{-2}$ mol) of glycerin. The autoclave was sealed, purged twice with CO to remove air from the system, and then filled with CO to a pressure of 1,0-1,1 MPa. After that 7,125 g ($12,7*10^{-2}$ mol) of isobutylene was introduced into the autoclave, and the carbon monoxide pressure was increased to 2,0 MPa. Stirring and heating were switched on. The reaction mixture was stirred within 4 h at a temperature of 100°C and a pressure of 2,0 MPa. Then the autoclave was allowed to cool down to a room temperature and left for a night. The next day, after the pressure was released to atmospheric, the reaction mixture was fractionated in a vacuum. The desired products were separated from the obtained mixture of products with unreacted glycerin by means of column adsorption chromatography on silica gel (0,005-0,04 mm). Chloroform and chloroform: methanol blend (9:1 by volume) were used as eluents. 1,81 g (30,8% of the initial quantity) of unreacted glycerin, 0,91 g (16,2%) (or 23,2 % on converted glicerin) of isovaleric acid α-monoglyceride and 1,08 (13,1 %) (or 18,7 % on converted glicerine) of isovaleric acid α,α'-diglyceride were obtained. Isovaleric acid α-monoglyceride, Bp 187°C / 30 mm Hg, n_D^{20} 1,4440. Isovaleric acid α,α'-diglyceride, Bp 198°C / 24 mm Hg, n_D^{20} 1,4390.

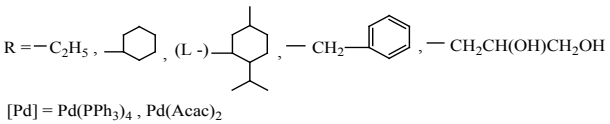
Results and Discussion

Hydroalkoxycarbonylation reaction of isobutulene with carbon monoxide and monohydric 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 [8]: temperature 100°C; CO pressure 2,0 MPa; reaction time 4 h; reactants and catalyst components ratio [alcohol]:[isobutylene]:[Pd(P $Ph_3)_4$]:[PPh_3]:[TsoH]=435:550:1:3:12. The yields of the products were 71-95% (on converted alcohols).

Synthesis of isovaleric acid α-monoglyceride carried out at optimal conditions of hydroalkoxycarbonylation of isobutylene with carbon monoxide and glycerin in the presence of Pd$(Acac)_2$-PPh_3-TsOH system [9]: temperature 100°C; CO pressure 2,0 MPa; reaction time 3 h; reactants and catalyst components ratio [glycerin]:[isobutylene]:[Pd(A $cac)_2$]:[PPh_3]:[TsoH]= 550:1100:1:7:12. The yield of the isovaleric acid α-monoglyceride was 18,7% (on converted glicerin).

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. Evidence for this proposal comes from the

$$(CH_3)_2C=CH_2 + CO + ROH \xrightarrow{[Pd]-PPh_3-TsOH} (CH_3)_2CHCH_2C(O)OR$$



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.

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. 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 α-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.