Synthesis of transdermal permeation enhancers on basis of piperidine carboxylic acids derivatives II.

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Transdermal permeation enhancers are substances facilitating penetration of drugs through the skin. They temporarily influence stratum corneum, the outermost protective layer of epidermis. Highly effective transkarbam 12 served as a model substance. The aim of my work was to find out the effect of cyclization on its enhancing activity.

The following derivatives of piperidine-4-carboxylic acid esters were synthesized:

- 4-(decyloxycarbonyl)piperidinium bromide
- 4-(dodecyloxycarbonyl)piperidinium bromide
- 1-acetylpiperidine-4-carboxylic acid decyl ester
- 1-acetylpiperidine-4-carboxylic acid dodecyl ester
- 4-(decyloxycarbonyl)piperidinium 4-(decyloxycarbonyl)piperidine-1-carbamate
- 4-(dodecyloxycarbonyl)piperidinium 4-(dodecyloxycarbonyl)piperidine-1-carbamate

These unknown substances were characterized by spectral methods.

The biological activity of the prepared compounds was evaluated *in vitro* on porcine skin in modified Franz diffusion cell with theophylline as a model permeant. The amount of theophylline was measured by HPLC method with UV detection.

The results showed a significant permeation-enhancing activity of both the carbamic acid salts and *N*-acetyl derivatives of piperidin-4-carboxylates. Their activity was comparable to transkarbam 12. The decyl esters of the prepared compounds were more effective than dodecyl esters. The essential role of the carbamate anion for the interaction of these enhancers with the stratum corneum lipids was confirmed. However, the high activity of the *N*-acetyl derivatives demonstrated the importance of the basic structural features of amphiphilic enhancer such as an appropriate linking chain of polar head between the nitrogen and carbonyl, ester bond, and a suitable hydrophobic chain length.

The study presented that the rigid analogues of the effective flexible transdermal permeation enhancers do not lose their activity.