Riga Technical University
Faculty of Material Science and Applied Chemistry

ABSTRACTS

of the
52nd International Scientific Conference
of Riga Technical University

Section:
Material Science and Applied Chemistry
October 13–15, 2011, Riga, Latvia

RTU Publishing House
Riga 2011

Practical Synthesis of Drotaverine Impurity Standard

Viktors Kumpins, Daina Zicane, Maris Turks, *Riga Technical University*

Drotaverine hydrochloride (**2**) is used as antispasmodic drug arising from papaverine (**1**) class of biologically active compounds. It is marketed also under name of NO-SPA.[1,2] Drug Master File of drotaverine documents a list of potential impurities that may arise during both, the chemical synthesis and partial degradation. One of those regulated compounds is 6,7-diethoxy-1-(4-ethoxy-3-hydroxybenzyl)-3,4-dihydroisoquinolinium chloride (**3**). The latter is an imine tautomer of drotaverine and additionally differs from the parent structure with free 3-hydroxy group in the benzylic substituent. We report here for the first time the full synthesis of the above mentioned standard impurity. The developed synthetic route (Fig.1) allows one to obtain several grams of the required product. The synthesis consists of 11 steps with the key-process being Bischler-Napieralski cyclisation[3] of isoquinoline cycle (process **4**→**3**). In turn, the linear precursor was obtained from commercially available 2-(3,4-diethoxyphenyl)ethylamine (**5**) and (3-benzyloxy-4-ethoxyphenyl)acetic acid (**6**). The latter was obtained in 6 steps from commercial 3,4-dihydroxybenzaldehyde (**7**). Synthetic sequence towards this carboxylic acid started with an orthogonal protection[4] of both hydroxyl groups at C(3) and C(4) and was followed by reduction of aldehyde. Then the transformation of the resulting benzyl alcohol lead to benzyl chloride and its nucleophilic substitution with KCN provided benzyl cyanide which hydrolysis gave the above mentioned carboxylic acid required for the amide coupling.

1. Chinoin Gyogyszer es Vegyeszet Termekek Gyara RT. Belgian Patent BE621917; *Chem. Abstr.* 1963, vol. 59, 8713g.
2. Bolaji, O. O.; Onyeji, C. O.; Ogundaini, A. O.; Olugbade, T. A.; Ogunbona, F. A. *Eur. J. Drug Metab. Pharmacokinetics* **1996**, *21*, 217.
3. Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.
4. Kametani, T.; Iida, H.; Kibayashi, C. A. *Heterocycles*, **1970**, *7*, 339.

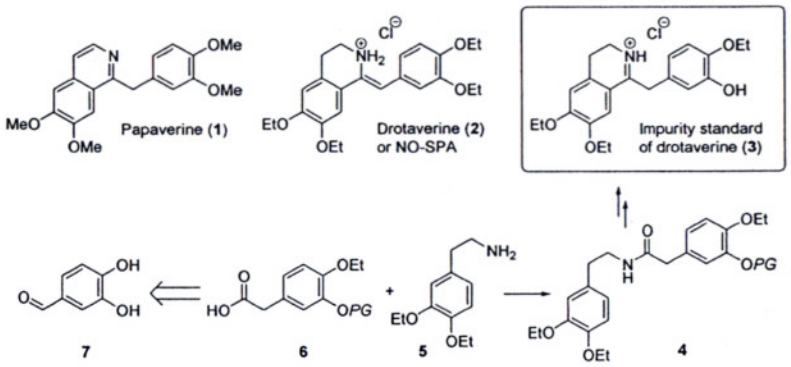

Fig.1 Synthetic scheme towards **3** and its comparison with papaverine and drotaverine