ORIPAVINE

Laboratory and Scientific Section, Division for Policy Analysis and Public Affairs, UNODC, 20 January 2006

Response to INCB on the subject: Ease of convertibility of oripavine into narcotic drugs other than thebaine (in general, and in illicit settings)

The chemistry of converting oripavine into synthetic opiates is comparable to that of converting thebaine. Individual synthesis steps use common chemical reactions. Immediate (direct) end-products are, for example, oxymorphone from oripavine, and oxycodone from thebaine. Via additional steps, the same end-products can be synthesized from either thebaine or oripavine.

Syntheses starting from oripavine typically require an additional step to protect the free 3-hydroxy group (which is the only structural difference between oripavine and thebaine). The chemistry of this step is basic, and also removal of that protection group is easily accomplished.

In addition to oxymorphone, available literature also mentions the direct manufacture (i.e., not via thebaine) of buprenorphine and etorphine from oripavine. Other opioids and uncontrolled nal-compounds (such as naloxone and naltrexone) can also be synthesized from oripavine. A comprehensive review of those is currently beyond the resources of LSS, and it is important to note that we do not have detailed information on those specific syntheses (including yields), nor do we have information from legitimate manufacturers on the actual synthesis routes used industrially.

Oripavine is also easily convertible into thebaine, thus opening up all syntheses starting from thebaine.

While individual steps of all these syntheses do not use very complex chemistry (this applies to syntheses starting from both thebaine and oripavine), syntheses are typically lengthy (several steps) and require knowledge of organic chemistry and a laboratory of a certain level of sophistication. Syntheses could be carried out in certain illicit settings, and there is some information on the Internet on related conversions starting from thebaine or codeine, or converting one synthetic opioid into another (http://heroinhelper.com/curious/chemistry/rhodium.shtml). However, there is no specific literature on illicit manufacture, or yields, of synthetic opioids from oripavine. (It should also be noted that even on that Internet site, relevant conversions are grouped as requiring advanced knowledge of chemistry.)

While the above might be interpreted as not meeting the criteria for “ease of conversion”, there is an interesting aspect of the thebaine-oripavine analogy, which might also be considered in the overall assessment. This relates to the justification for the inclusion of thebaine into Schedule I of the 1961 Convention (and it may be more a legal than a technical issue), which appears to have been based on its convertibility “into such drugs as hydrocodone, oxycodone and thebacon (listed in Schedule I), and codeine and dihydrocodeine (listed in Schedule II)” [Commentary to 1961 Convention, p.24, footnote 10]. Therefore, if the conversions of thebaine into Schedule I drugs were considered to meet the criteria of the “convertibility rule”,...
then, the chemistry of oripavine conversions suggests that the same should apply to oripavine as well.

Nevertheless, in addition to assessing the ease of conversion, and as pointed out in INCB’s proposal for the 33rd ECDD, a scheduling decision should also take the similarity of oripavine to controlled opiates into account. The following references are relevant, e.g.:


  The dependence potential of thebaine is at least partially attributed to oripavine which is one of the principal metabolites of thebaine. The analgesic potency of oripavine in mice is found to be much higher than that of thebaine and comparable to morphine. The reinforcing effect of this substance also appears to be more potent than thebaine. In rats the physical dependence potential of oripavine at a dose of 4 mg/kg is almost comparable to that of morphine at 0.5 mg/kg. Studies carried out on monkeys show that oripavine possesses weak morphine-antagonist properties. Further pharmacological studies of other metabolites of thebaine are recommended.


  Oripavine and… appear to have analgesic potency of the same order as morphine in these species [mouse and rat] but have lower therapeutic indexes because of severe toxicity.

  …, oripavine did show some cross tolerance with morphine, …