PROBLEM 33

[SUPPL Problem 33 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

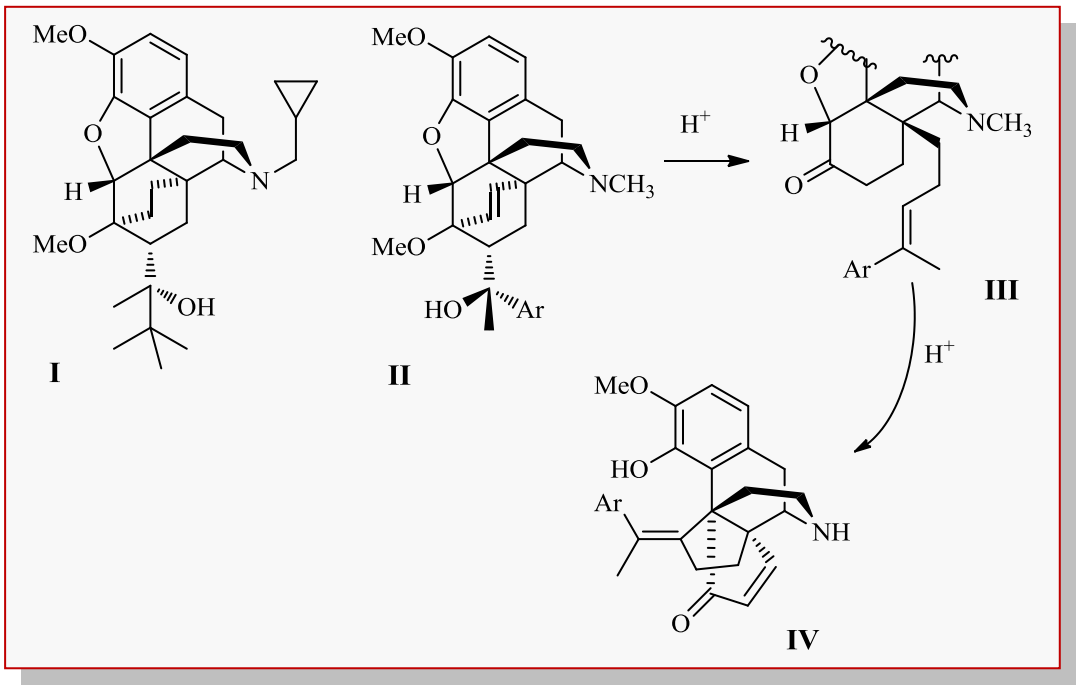
Humanity has craved for the control of pain almost from its beginnings. From Salix bark salicylates, camphor, acetanilide of coal tar and plant opiates known to Sumerians 5000 years ago, to acetaminophen, steroids and ibuprofen, a dearth of organic chemicals have found their way into our bathroom cabinets and sophisticated clinicians' recipes to kill pain.

Among the strongest analgesics, morphine and related opiates continue to attract the attention of synthetic chemists [1] and clinicians who continue to use morfine itself and equivalents [2]. Some are so potent that can cause severe respiratory depression, e.g. buprenorphine **I** (a prescription drug). This compound resists antagonist treatment because of its strong affinity for a particular opiate receptor in nerve cells and lipophilicity.

In the course of attempting to diminish the lipophilic character of the natural alkaloid oripavine scaffold conferred by the ethylene bridge of the [2,2,2]bicyclic portion of **1** to obtain **2**, prof. Hiroshi Nagase and coworkers at Kitasato University in Tokyo ran into an unexpected observation: the transmogrification of the starting material into the novel skeleton of **4** in good yield.

Although the synthesis of the desired compound with the vinyl terminus had been reported years before [3,4] (acid exposure of **II** to **III**, itself transformed further by mineral acid to **IV**, Scheme SP33.1.1), Nagase's odd product expanded the potential of opiates frameworks to better modulate agonist or antagonist activities on analgesic

receptors besides adding an intriguing process for reaction mechanism fans like yourself.



SCHEME SP33.1

REFERENCES AND NOTES.

[1] Brownstein MJ. Proc. Natl. Acad. Sci. USA 1993;90:5391-5393.

[2] WHO (World Health Organization) recognizes six opioids to treat moderate to severe pain: Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone, and Pethidine. Although effects are similar, chemical structures differ from morphine. Consumption of opioids per capita since 1980 has skyrocketed. See: http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/wproME.pdf

[3] Bentley KW, Hardy DG, Meek B. J. Amer. Chem. Soc. 1967;89:3293-3303.

[4] Bentley KW, Hardy DG, Howell CF, Fulmor W, Lancaster JE, Brown JJ, Morton GO, Hardy Jr RA. J. Amer. Chem. Soc. 1967;89: 3303-3311.