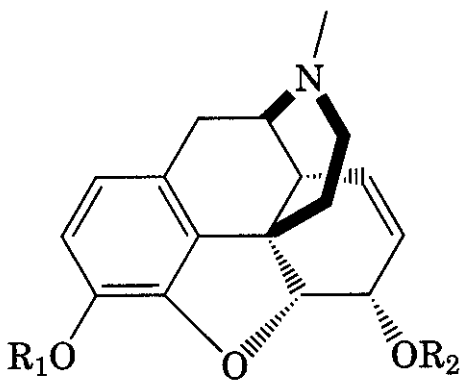
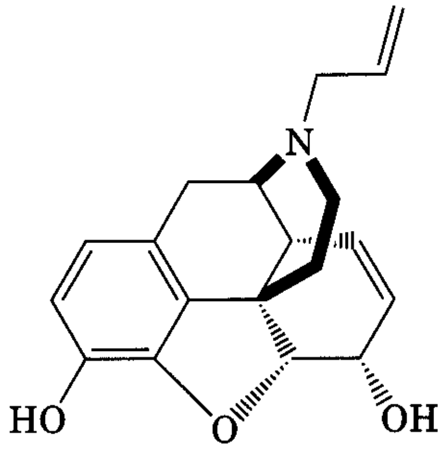


(1)morphine $R_1 = R_2 = H$
(2) codeine $R_1 = CH_3, R_2 = H$
(3) heroin $R_1 = R_2 = COCH_3$

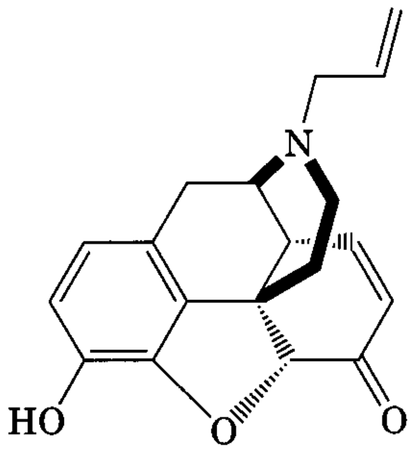
relevant. Acetylation masks the polar hydroxy groups, so that penetration into the central nervous system (**CNS**) is enhanced; hydrolysis then occurs to liberate the phenolic hydroxyl, giving an active analgesic, and ultimately regenerates morphine (5). Heroin was thus one of the first prodrugs.

Modifications to the C-ring of morphine are legion, but none of the derivatives is free from addictive liability, though many have been used clinically. N-Demethylation and realkylation yield more interesting analogs, notably N-allylnormorphine and nalorphine (**4**), which is a morphine antagonist (6). Further modification leads to naloxone (**5**), which unlike nalorphine has very little **agonist** activity (7) and has retained a place in therapy for treatment of opiate-induced respiratory depression. Naloxone will also precipitate withdrawal symptoms in opiate addicts, thereby facilitating diagnosis.

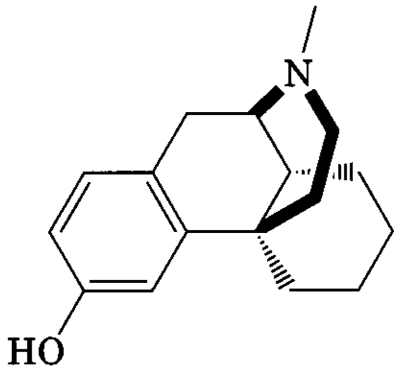


(4) nalorphine

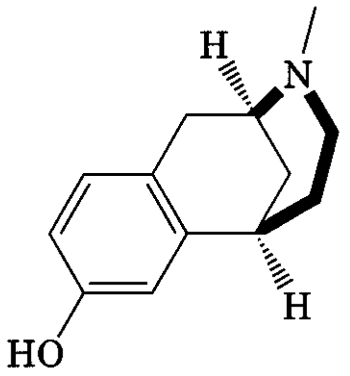
Total synthesis of morphine is difficult, but analogs lacking the dihydrofuran ring are accessible (8) from **1-benzylisoquinolines**, in analogy with the biosynthesis of morphine, to give the morphinans (6). The system may be simplified even further (9), to give the **benzomorphans** (**7**), although neither these nor the morphinans have provided the long-sought analgesic without addictive properties.



(5) naloxone



(6) morphinan



(7) benzomorphan

A semisynthetic route to morphine analogs was found (10) from thebaine (**8**) using Diels–Alder reactions in the C-ring. **Adducts** such as (9) have the distinction of enormous potency (**11**), sufficient to immobilize rhinoceroses at moderate dose levels! Unfortunately, the addictive liability runs parallel to the increase in analgesic potency, a tendency that was partly overcome (12) in the analog buprenorphine (**10**).