THE CHEMISTRY OF OPIOIDS

PART 1:

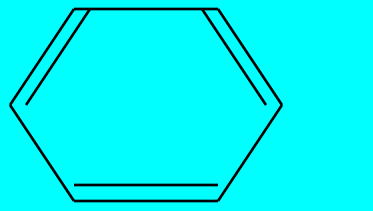
THE REVISION OF BASIC ORGANIC CHEMISTRY

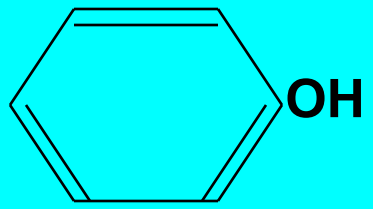
Name these molecules and radicles.

CH_4

CH_3CH_3

$CH_3CH_2CH_3$



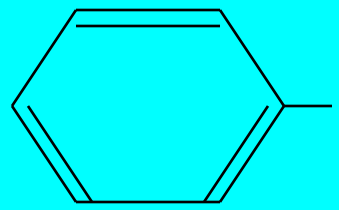


CH_3-

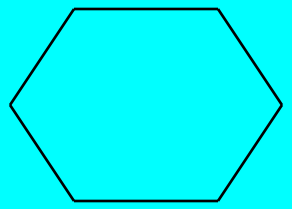
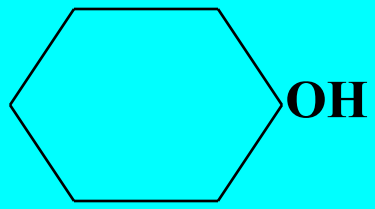
CH_3CH_2-

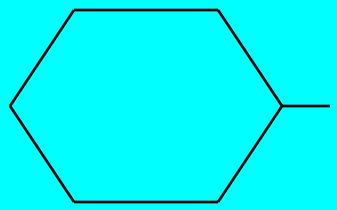
$CH_3CH_2CH_2-$

NH_2-



Name these molecules and radicles.

CH_4	methane
CH_3CH_3	ethane
$CH_3CH_2CH_3$	propane
	benzene
	phenol

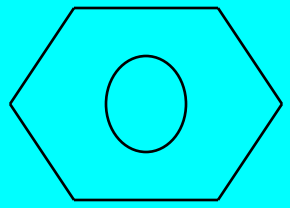
CH_3-	methyl
CH_3CH_2-	ethyl
$CH_3CH_2CH_2-$	propyl
NH_2-	amine
	benzyl
	phenyl

Name these molecules and radicles.

CH_3COOH

CH_3COO-

$CH_3CH_2CH_2NH_2$



$CH_3CH_2CH_2NH_2$

Name these molecules and radicles.

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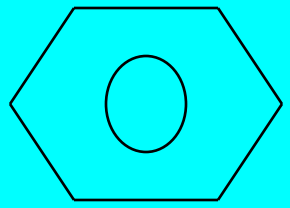


$CH_3CH_2CH_2NH_2$

acetic acid

acetate

propylamine

phenyl propylamine

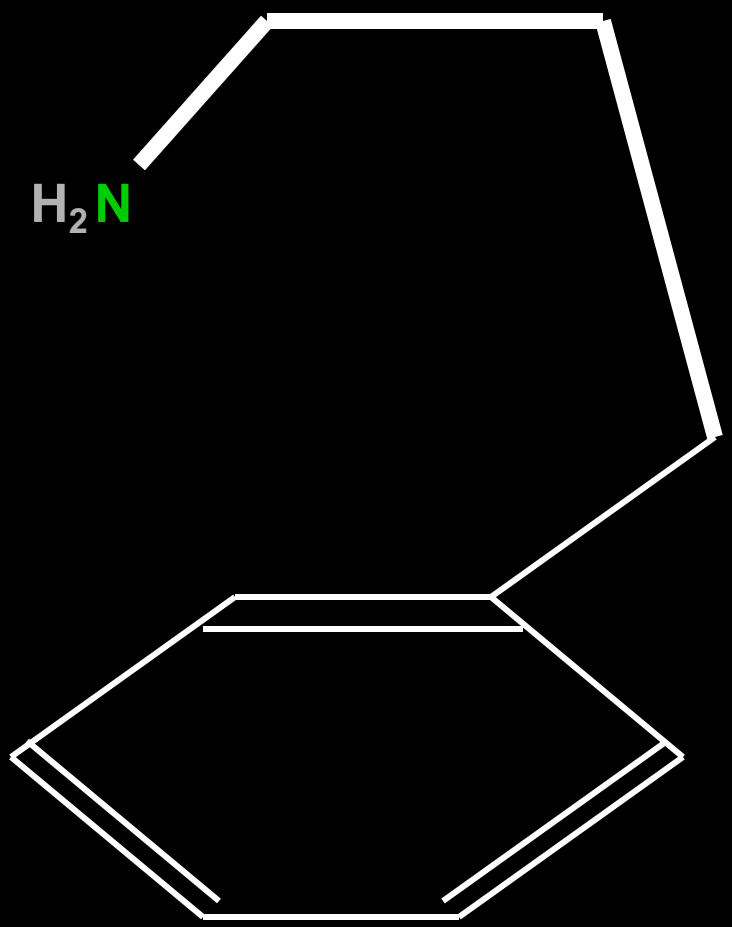
PART 2:

AN ORIENTATION TOWARDS THE CHEMISTRY OF OPIOIDS

Having revised the basic vocabulary of organic chemistry, come to appreciate the following molecules, which have been drawn in three dimensions, in preparation for some revelations.

Look at the following molecule, and see what you see about its structure.

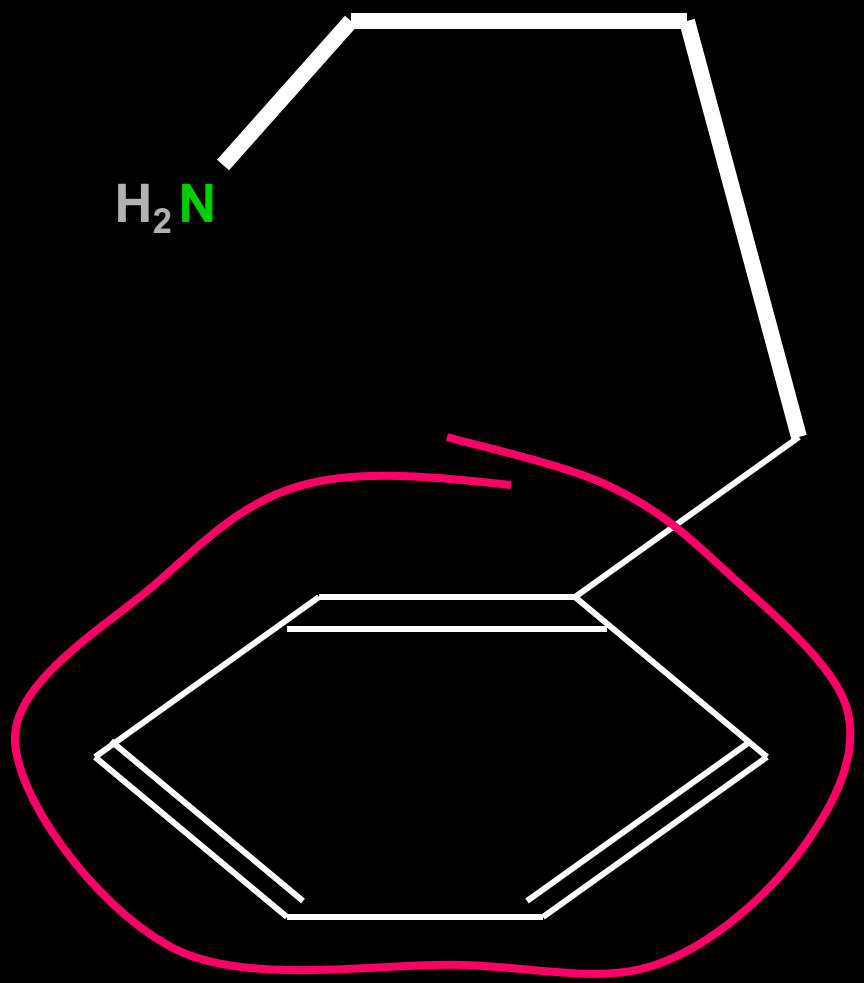
phenylpropylamine

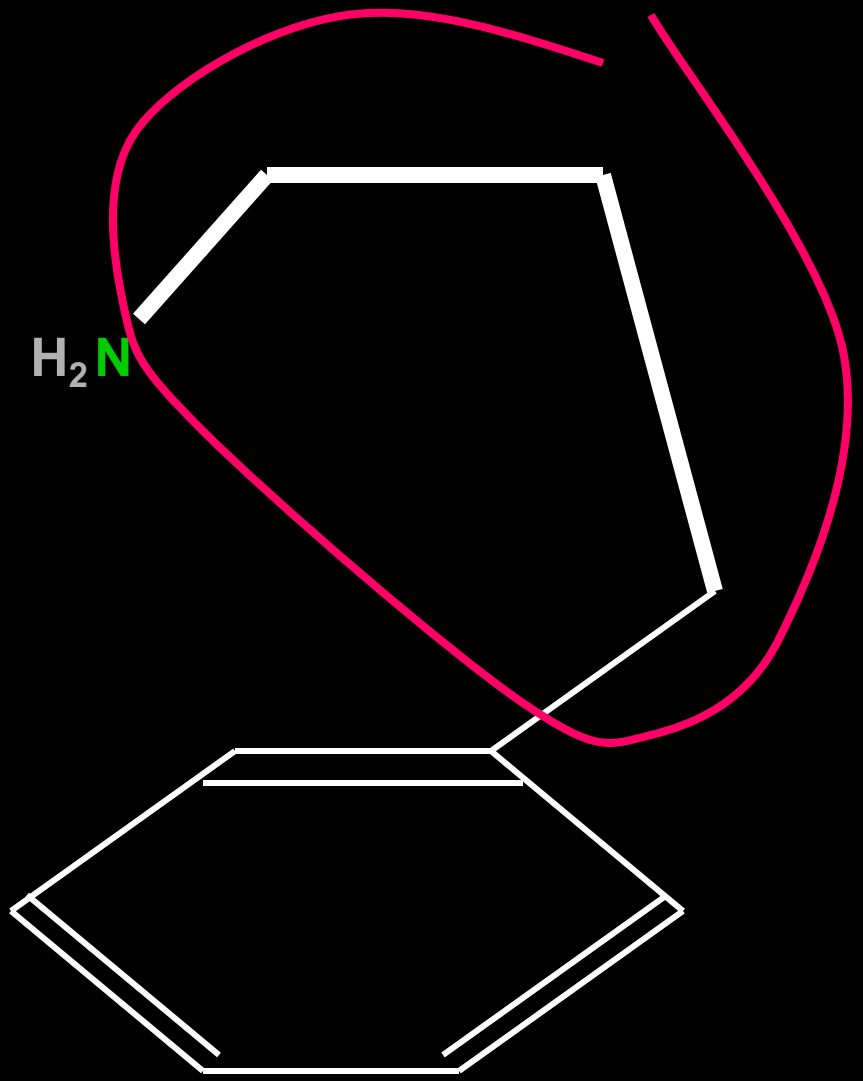


Notice how phenylpropylamine consists of a footplate, formed by the phenyl ring, from which rises the propyl chain, like the neck of a swan or the tail of a scorpion, at the tip of which hangs the amine with its nitrogen atom.

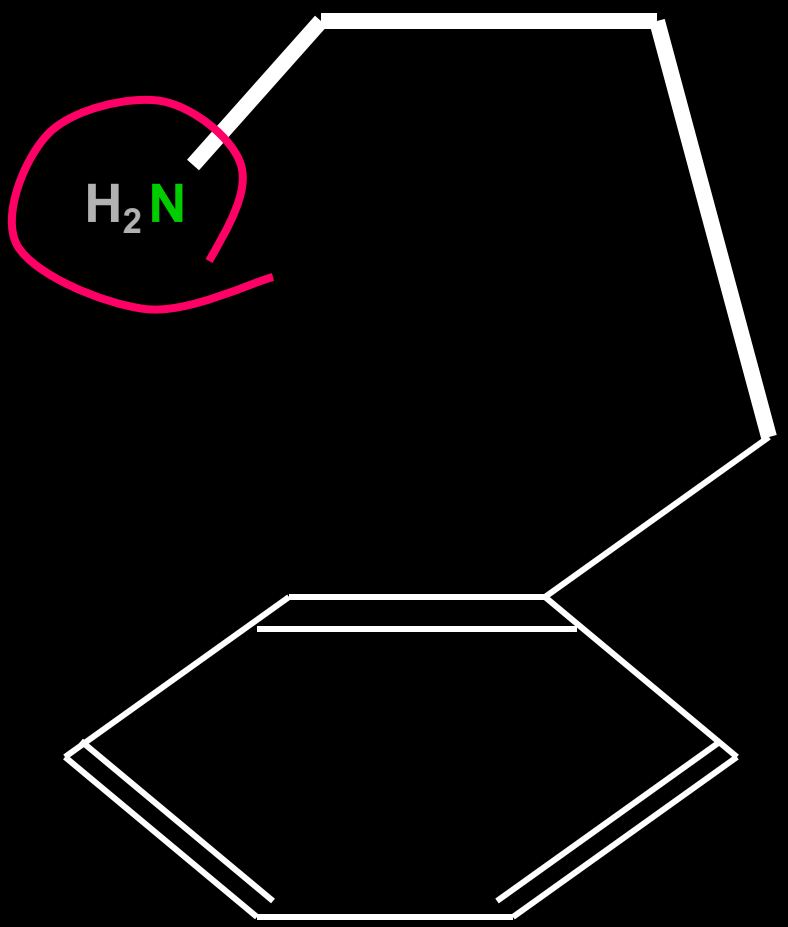
The phenyl ring sits on a flat plane. The propyl neck rises upwards off that plane and away from you, producing a gap or a mouth between it and the phenyl plate.

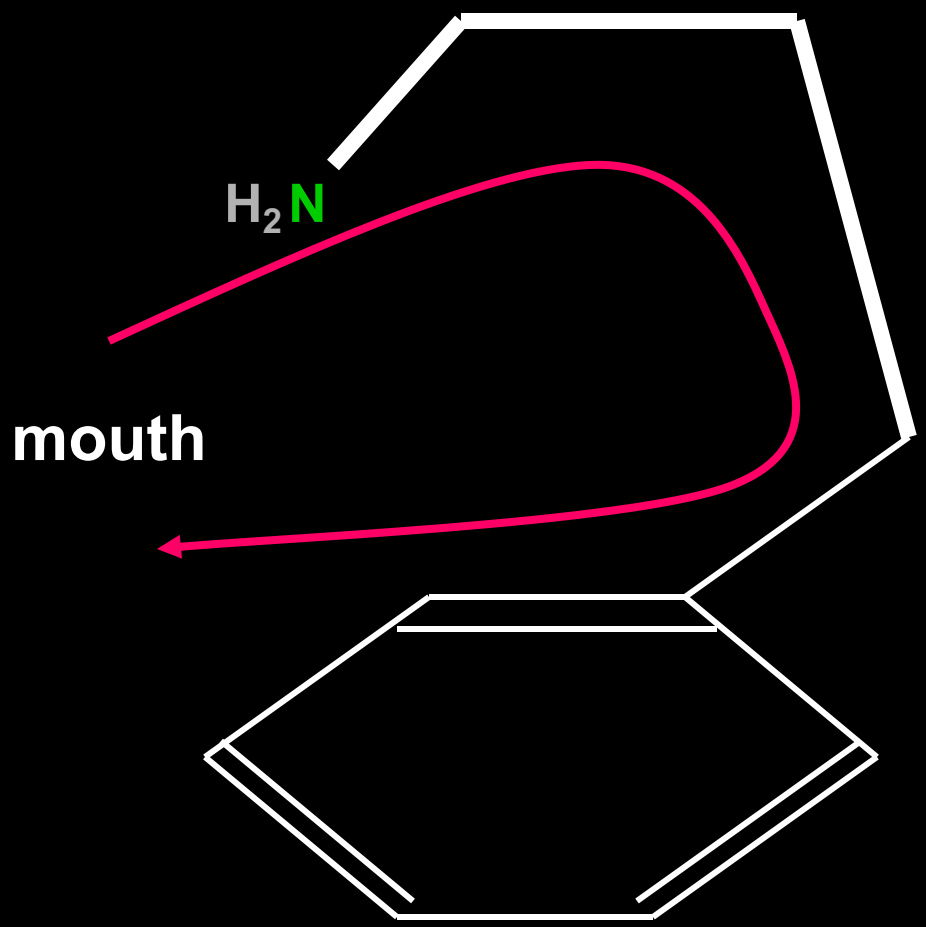
This is emphasized in the next five figures.


H_2N
footplate

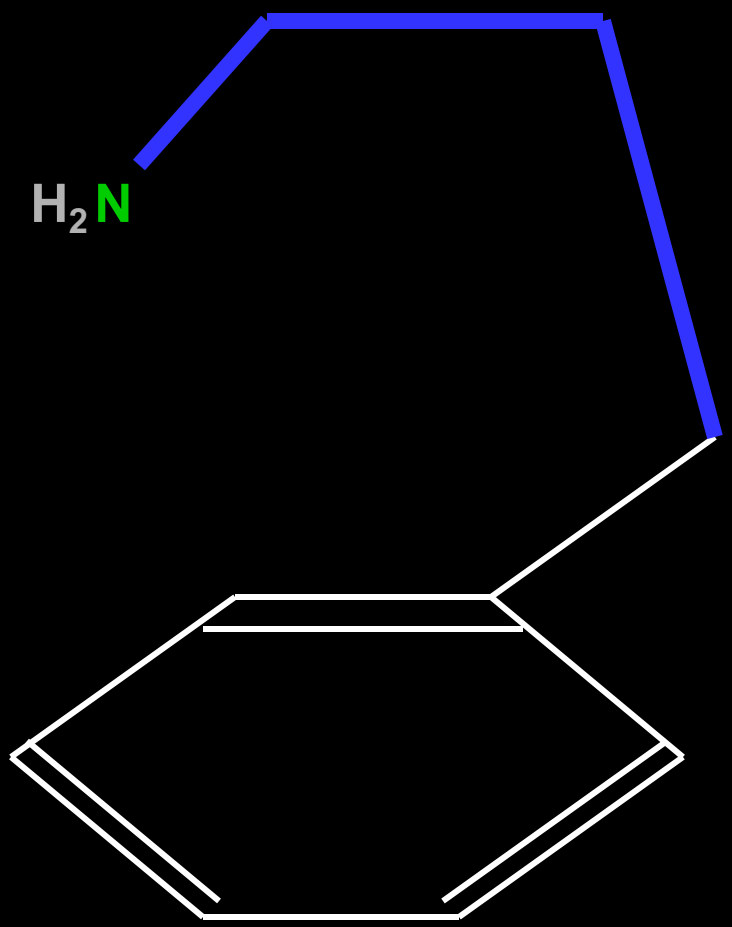

neck
H2N

head




H_2N
mouth

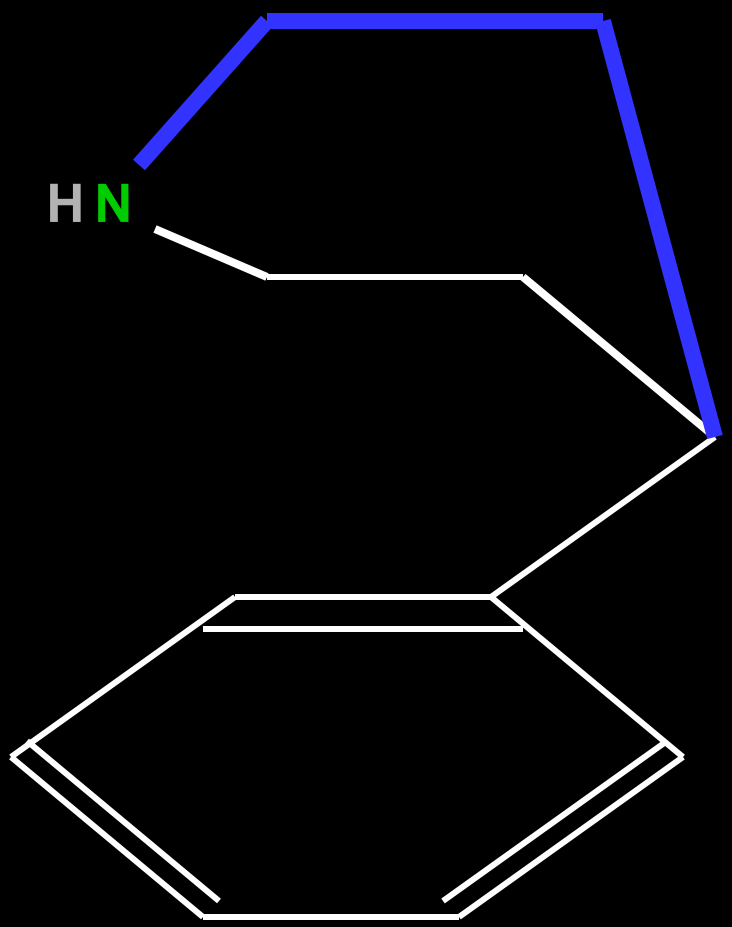
phenylpropylamine



The phenylpropylamine molecule and its three-dimensional shape form the basis of a sequence of more complex molecules that nevertheless conform to the same geometric plan.

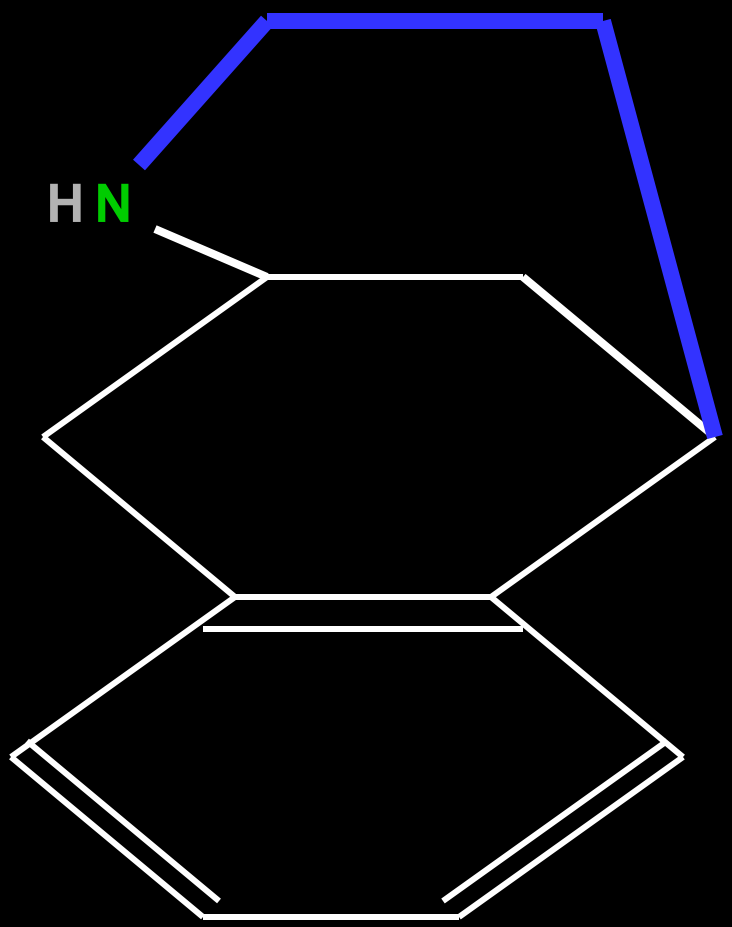
If we join up the bottom of the propylamine chain to form a ring called piperidine, we get the next molecule.

phenylpiperidine



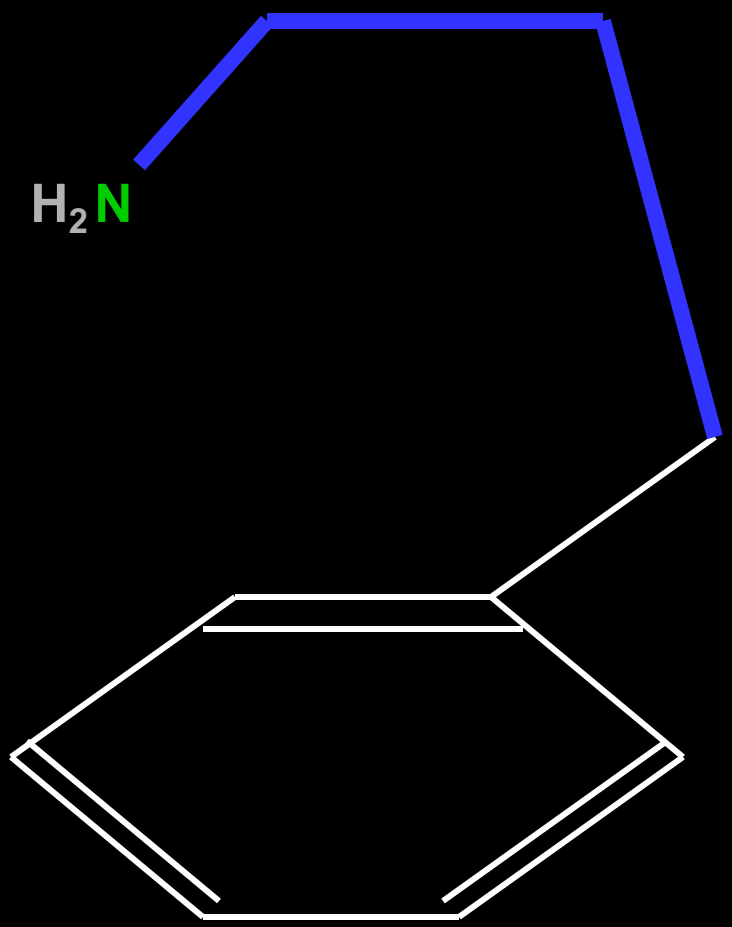
If we next join the piperidine ring to the phenyl ring, we get…

benzomorphan

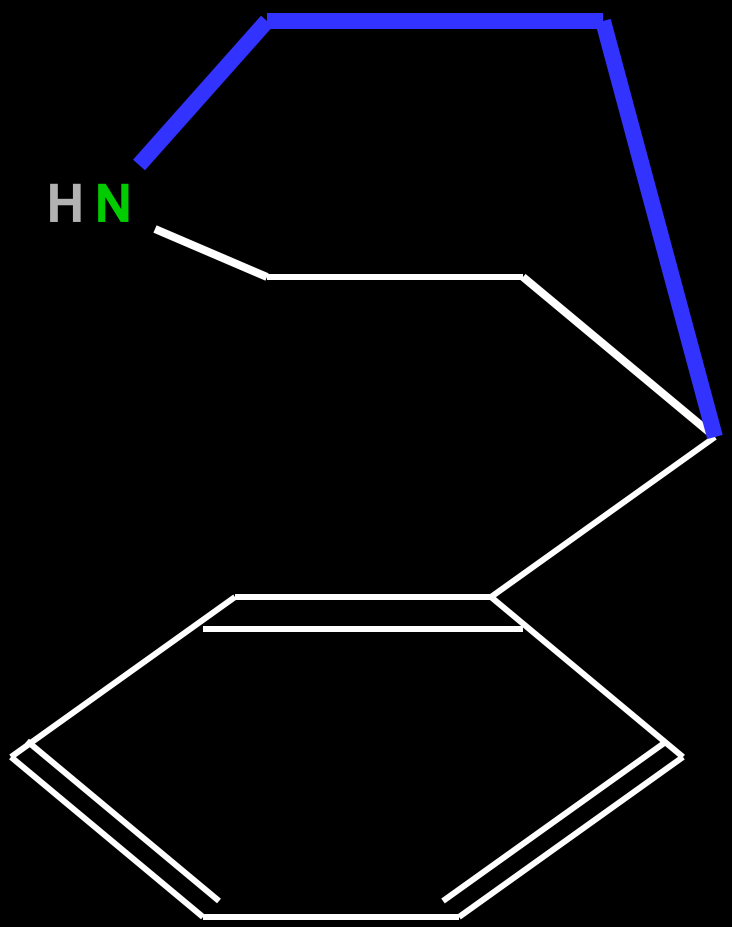


Run through the next sequence of figure (until the blank) to see how the three molecules are related. [If you do so rapidly, you get a “movie” effect.]

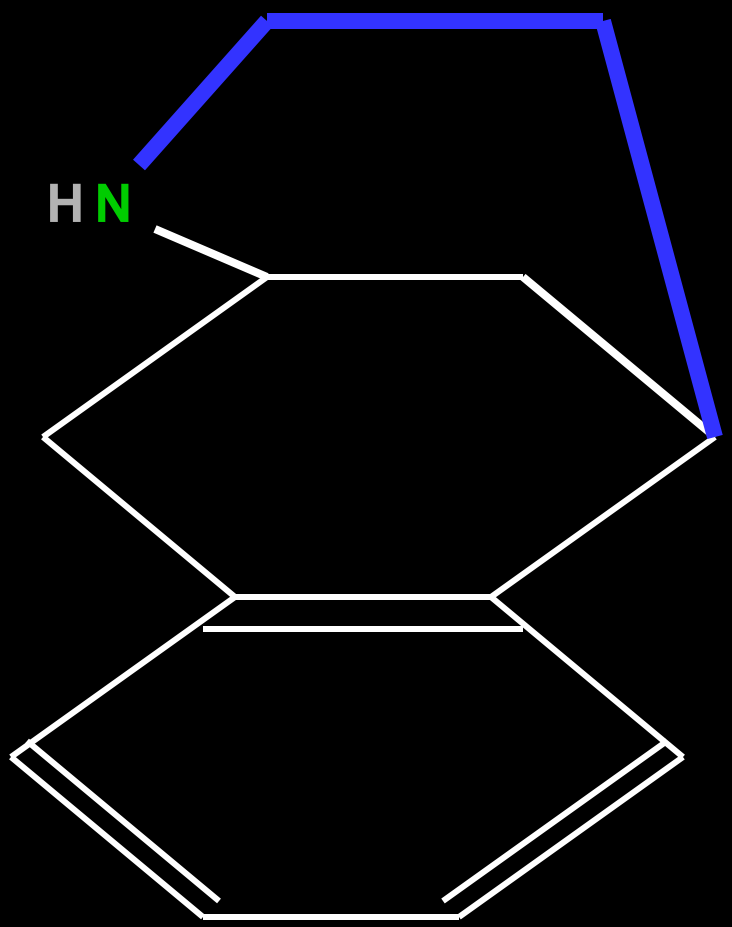
phenylpropylamine



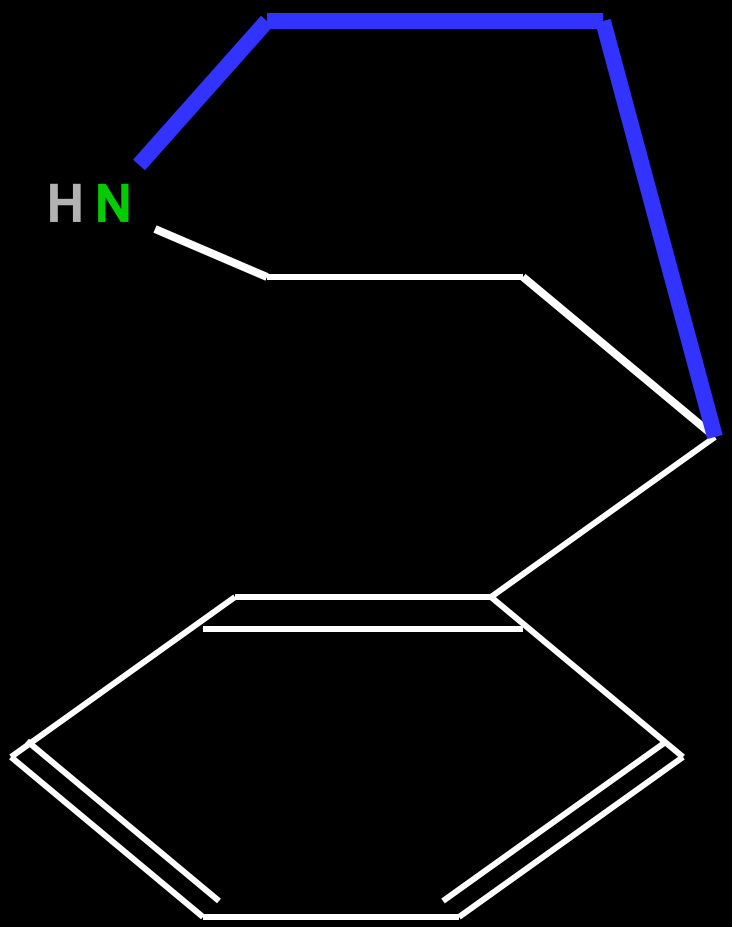
phenylpiperidine



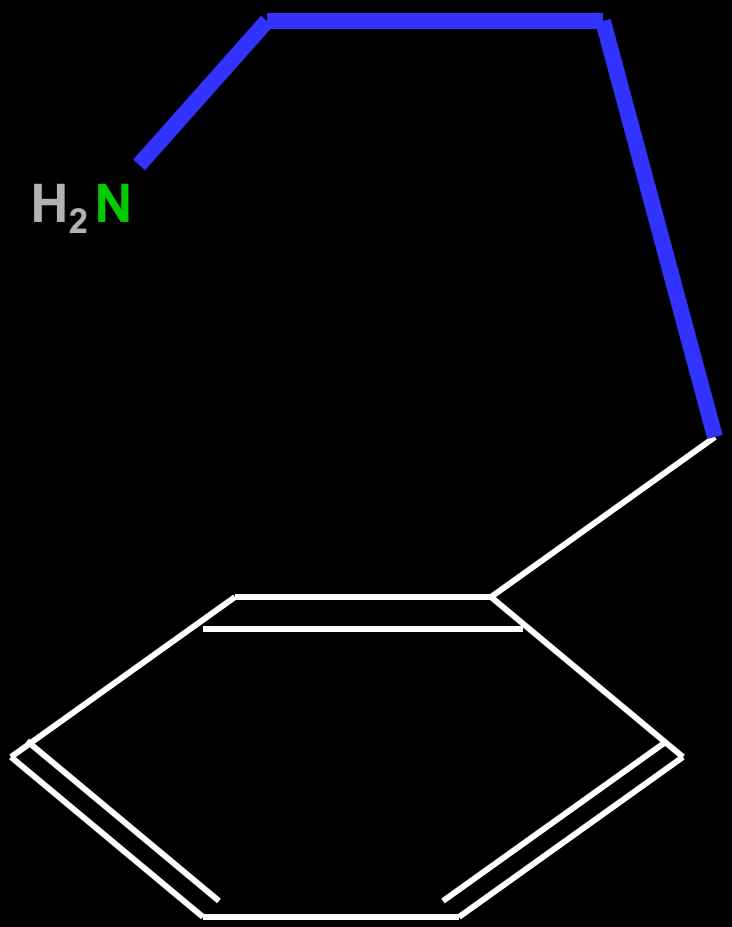
benzomorphan



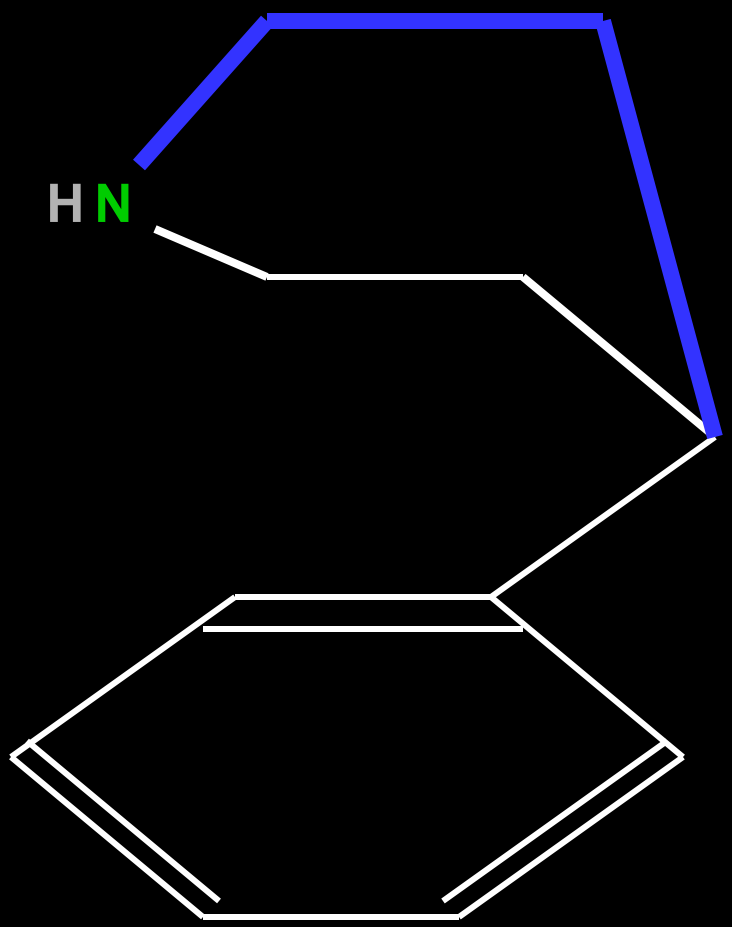
phenylpiperidine



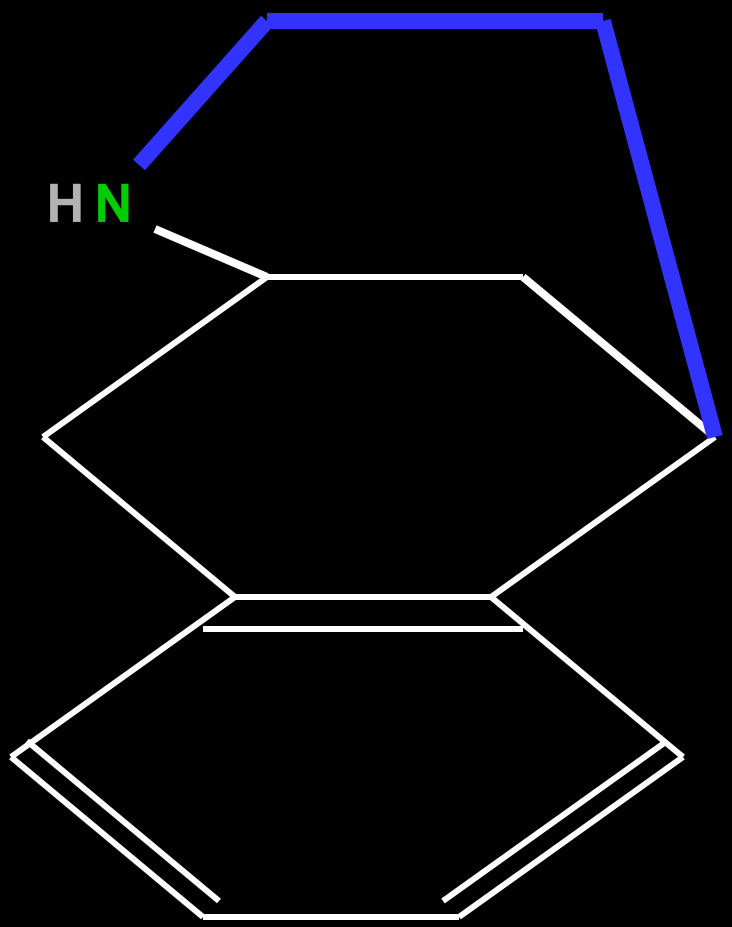
phenylpropylamine



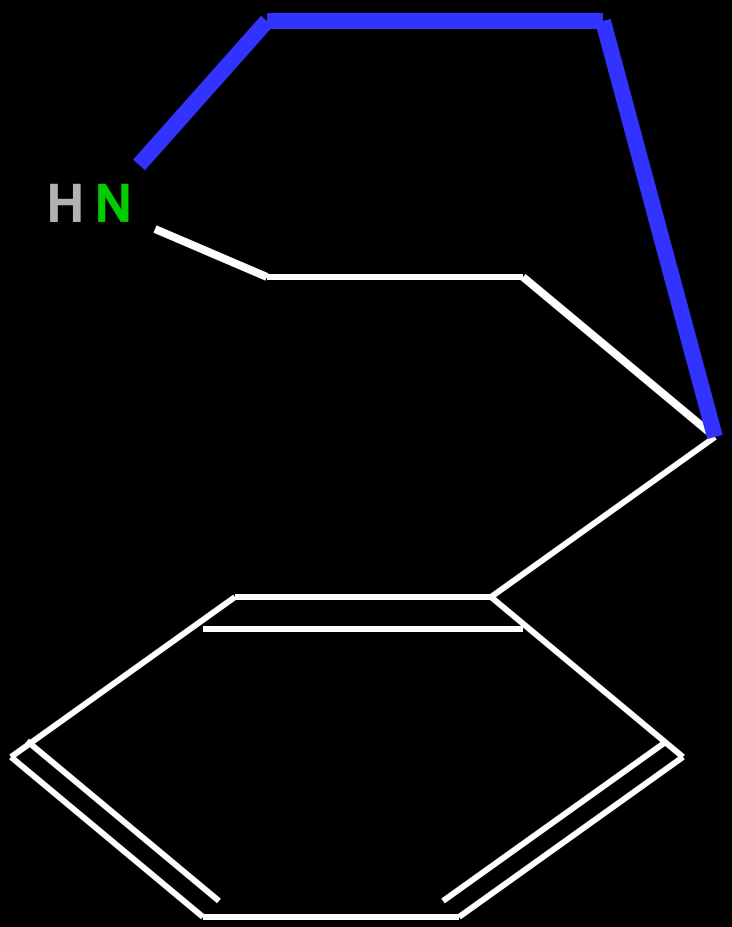
phenylpiperidine



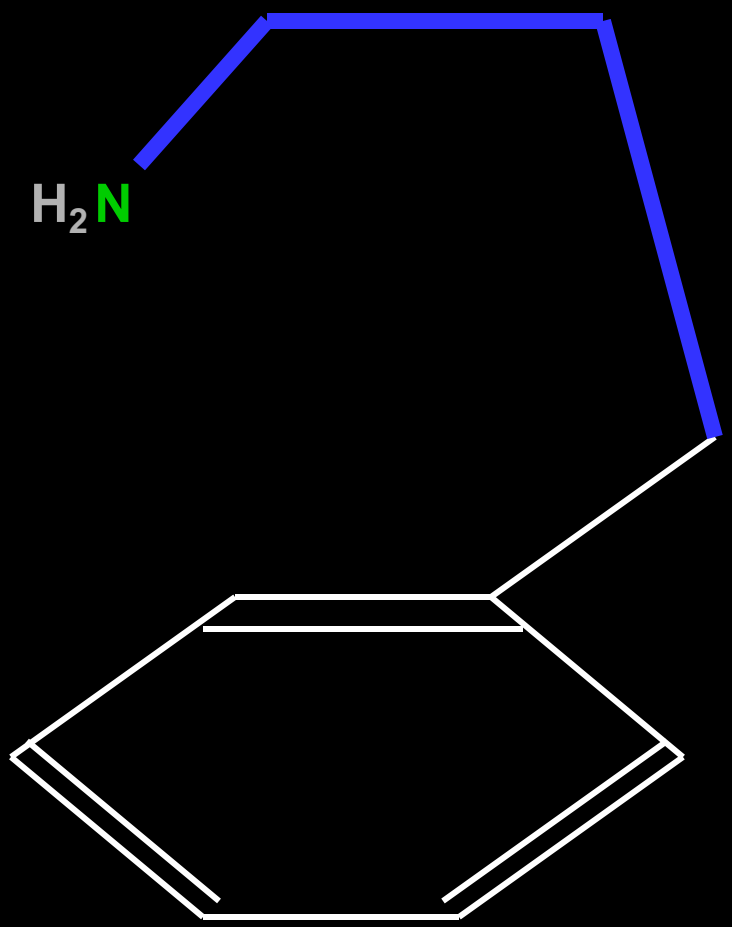
benzomorphan



phenylpiperidine



phenylpropylamine



The significance of these three molecules is that they give rise to three families of opioids:

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phenylpropylamine

methadone

dextropropoxyphene

The significance of these three molecules is that they give rise to three families of opioids:

phenylpropylamine	**methadone**
	dextropropoxyphene
phenylpiperidine	**pethidine**
	fentanyl

The significance of these three molecules is that they give rise to three families of opioids:

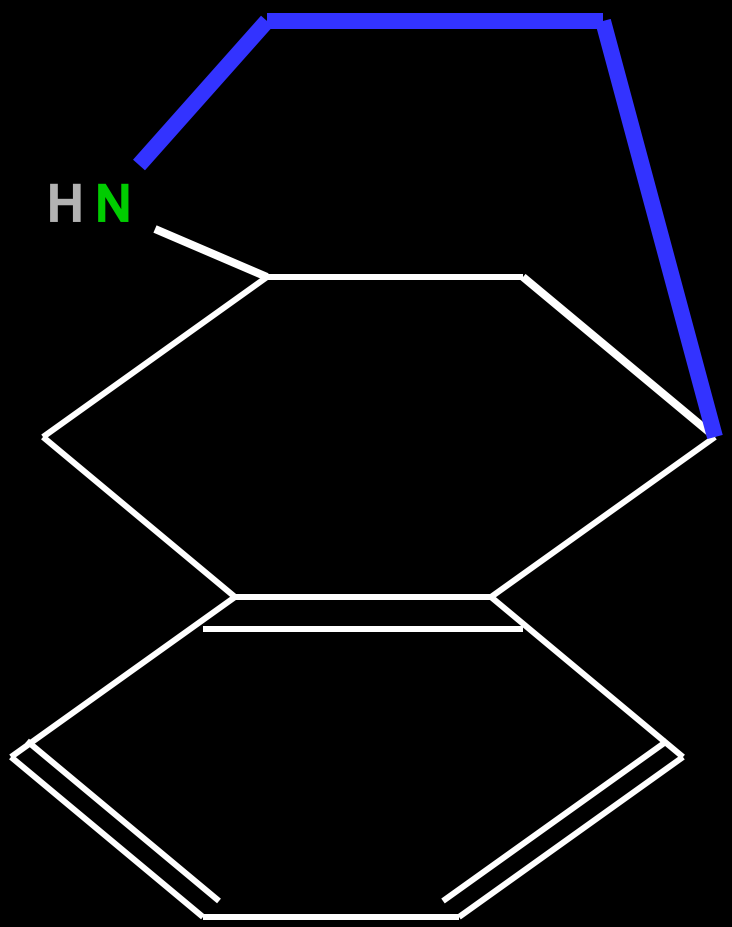
phenylpropylamine	methadone
	dextropropoxyphene
phenylpiperidine	pethidine
	fentanyl
benzomorphan	morphine
	codeine

Observe the structures of the following opioids.

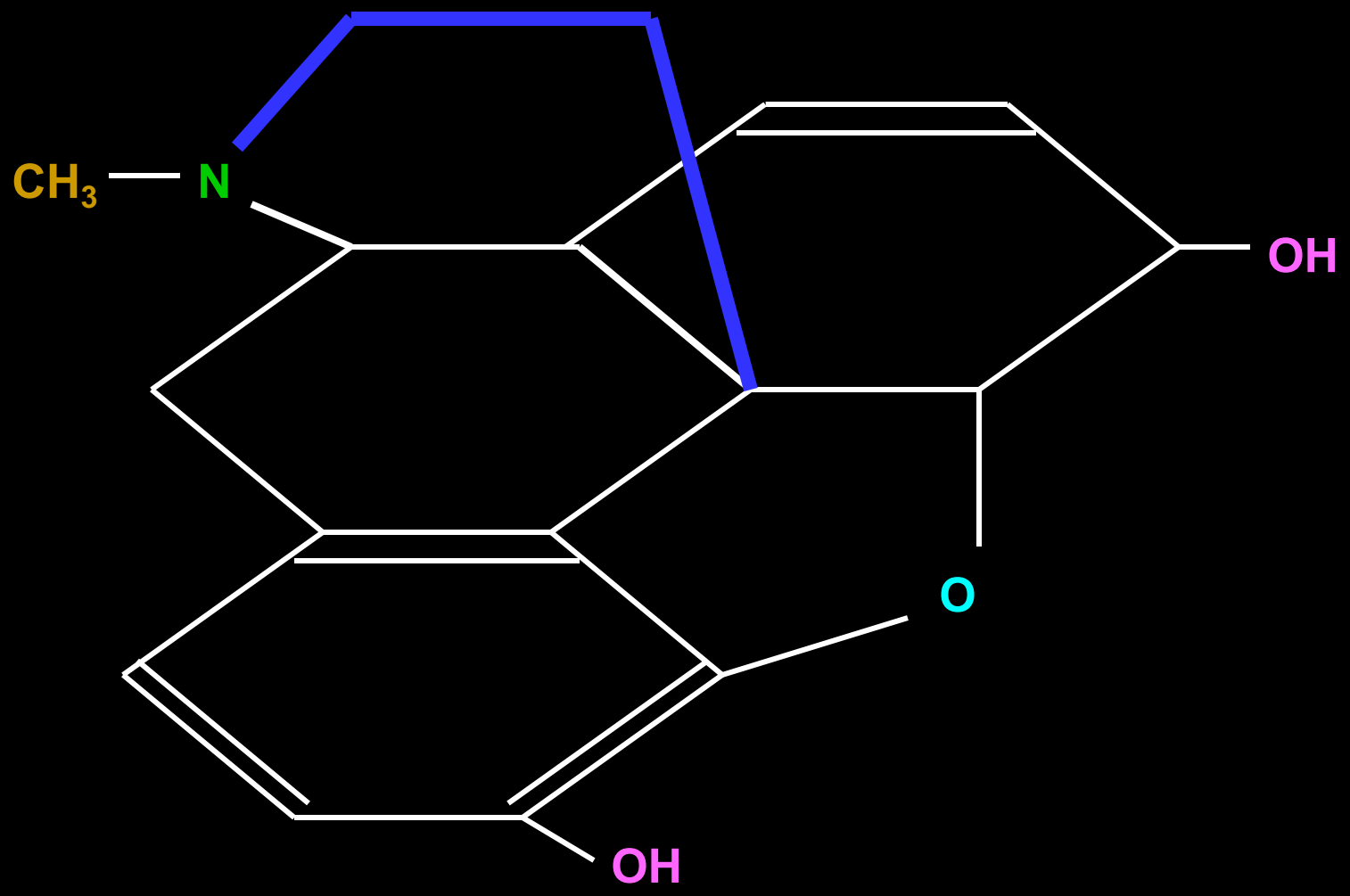
Recognize the base molecule (phenylpropylamine, phenylpiperidine, or benzomorphan).

See how various chains, part rings, or rings are added to the basic stem to complete the new molecule.

benzomorphan



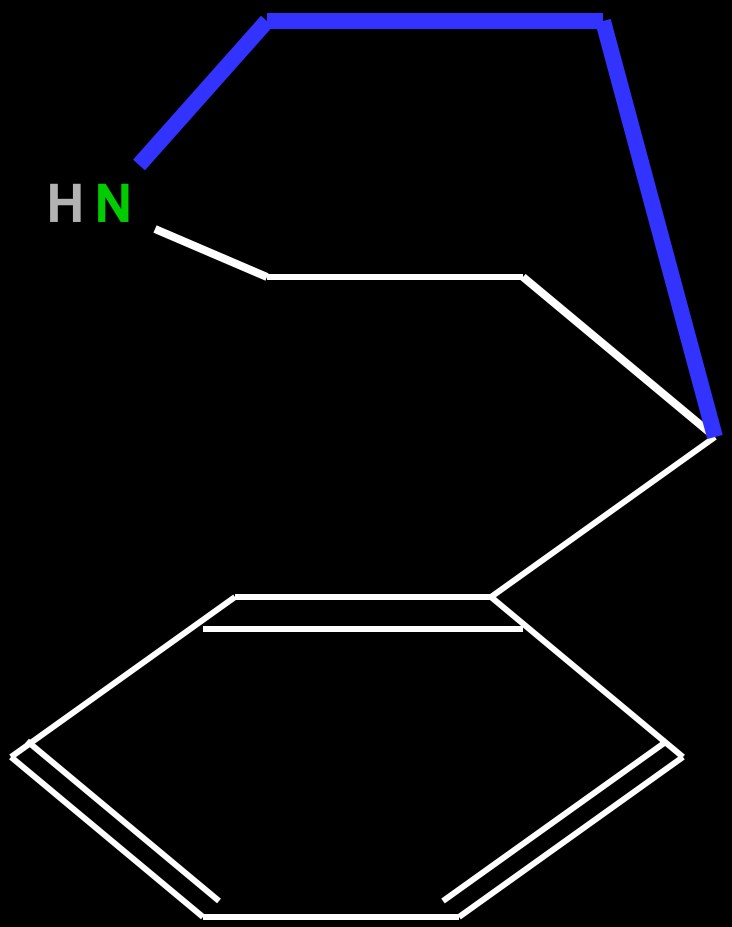
morphine



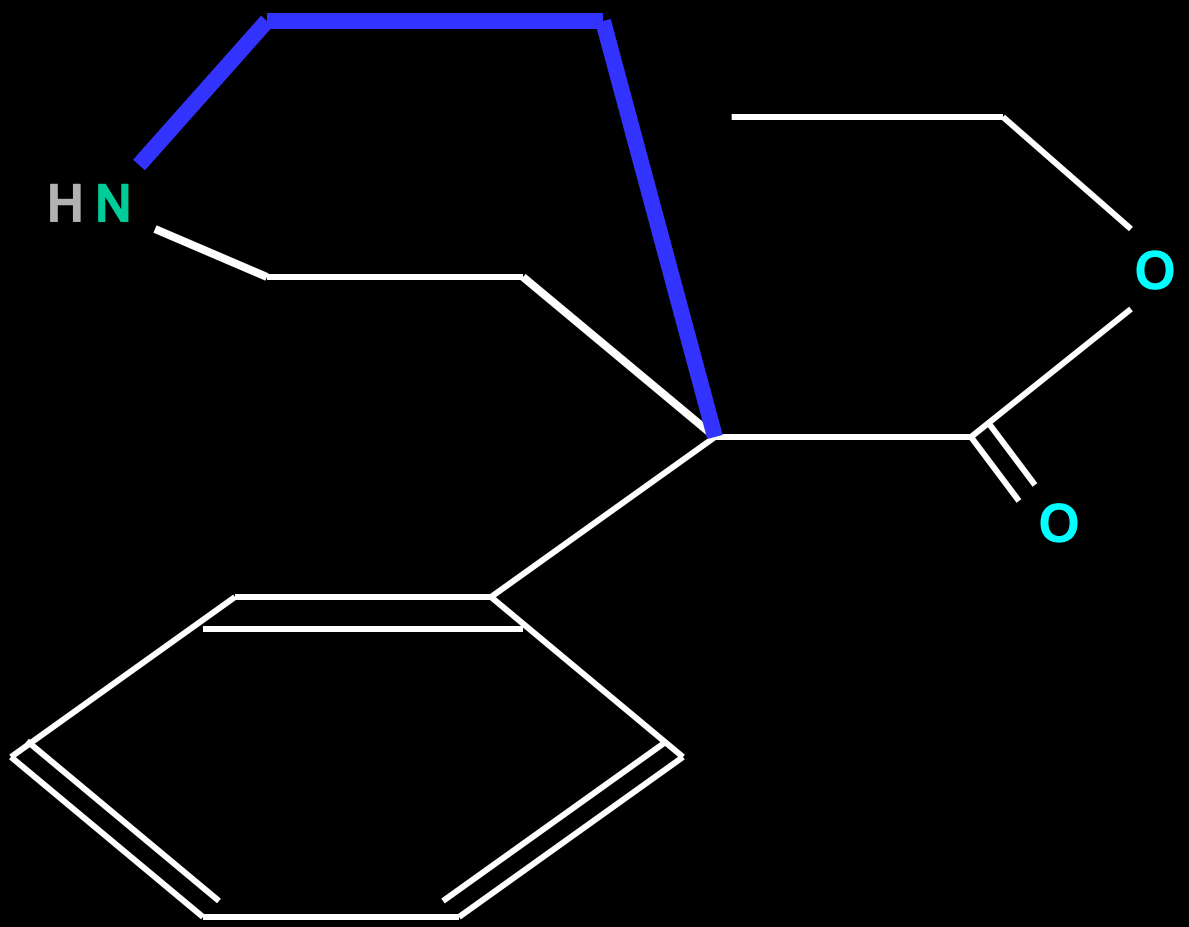
Morphine is a benzomorphan with a third 6-carbon ring attached to the bottom of the piperidine ring, and held to the phenyl ring by an oxygen bond.

The third ring is not complete in other opioid molecules but elements of it are evident in the derivatives of phenylpropylamine and phenylpiperidine.

phenylpiperidine



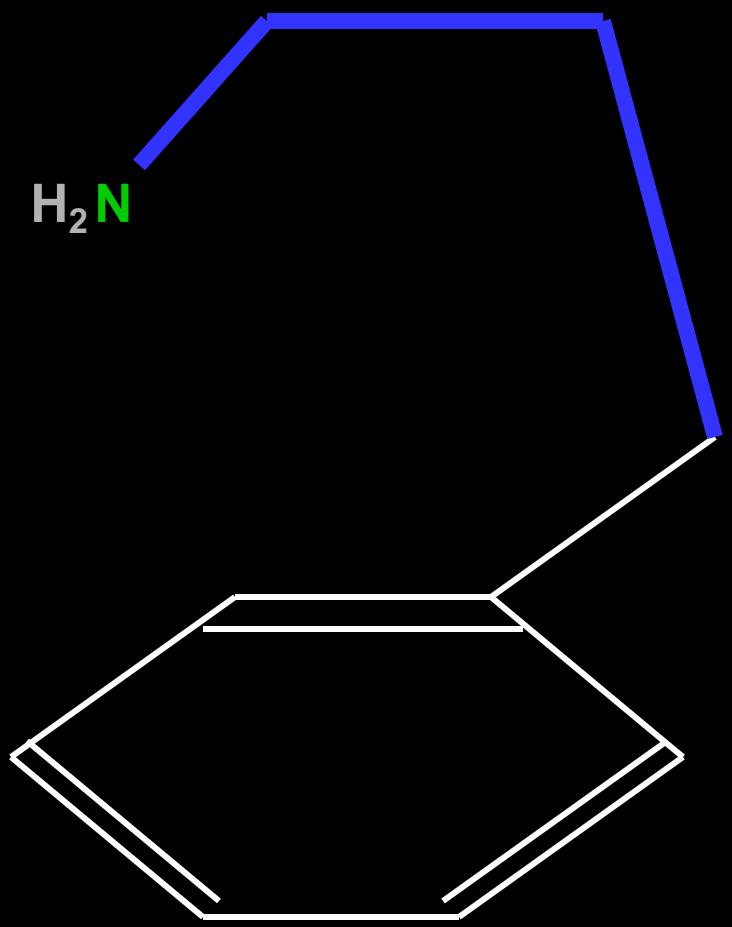
pethidine



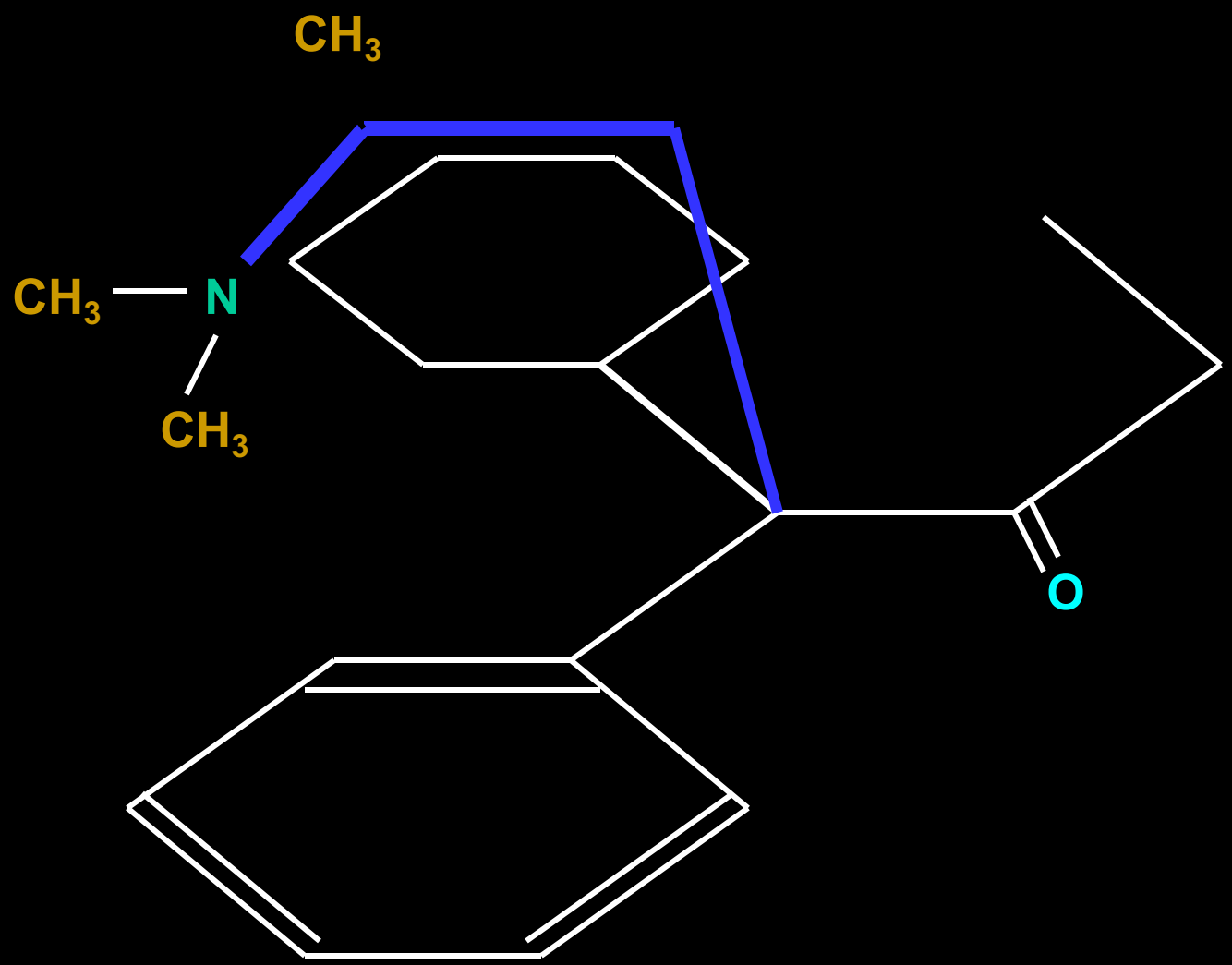
Pethidine has almost a complete third ring.

The C6 carbon is replaced by an oxygen.

phenylpropylamine



methadone



Methadone has less of a third ring, but has a side-chain bearing another phenyl ring, displaced away from the foot plate.

PART 3:

THE CHEMISTRY OF MORPHINE

The structure of morphine provides a frame of reference for discussing and describing other opioids.

The following description consists of

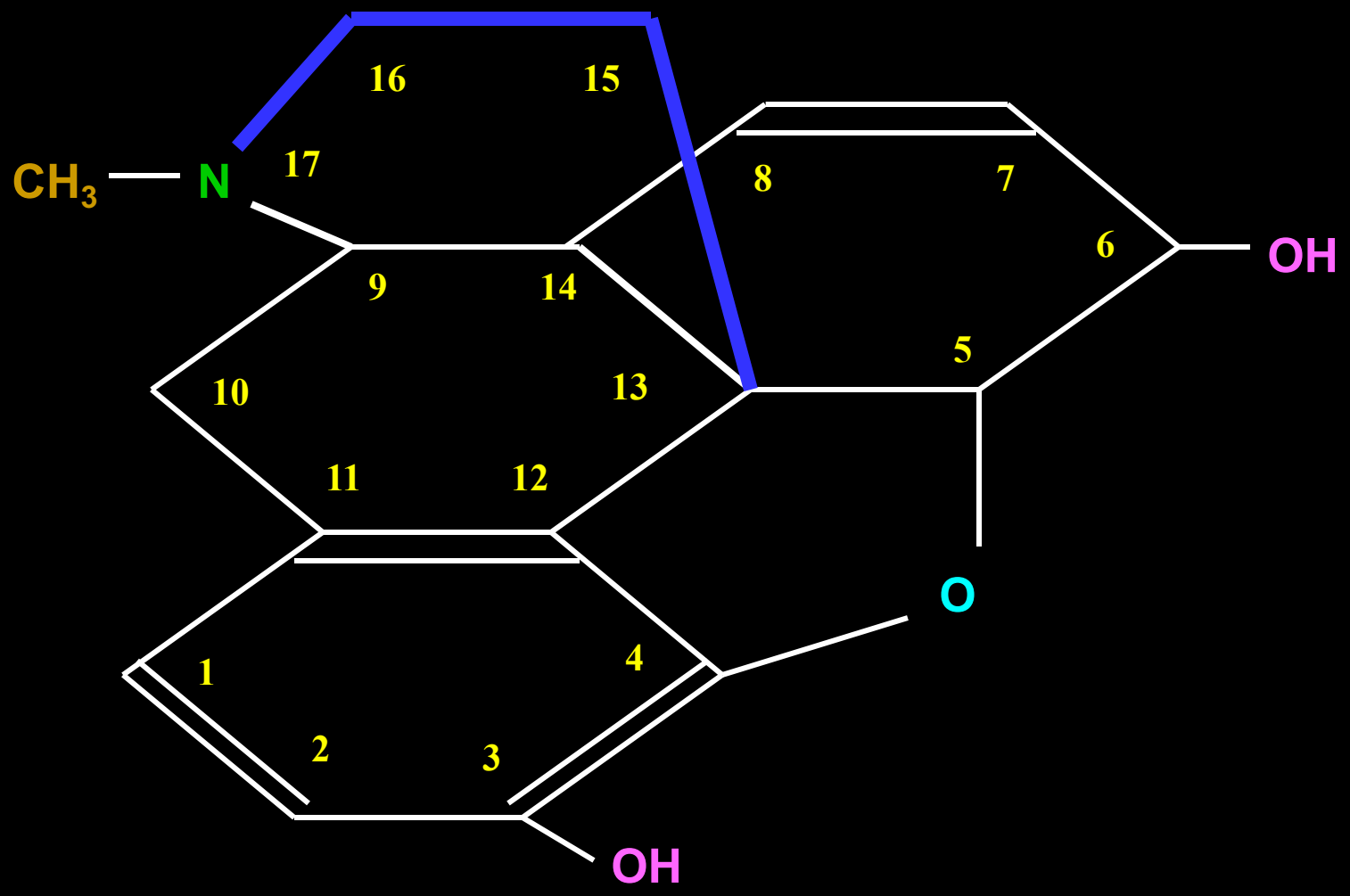
- **the formal nomenclature,**
- **an appreciation of the key elements**
- **manipulation of the key elements.**

NOMENCLATURE

The carbon atoms of the morphine molecule are numbered.

The numbering starts in the phenyl ring, and then proceeds around the perimeter of the molecule; it continues into the centre of the molecule, and finally up into the propylamine chain.

morphine



In formal terms, morphine

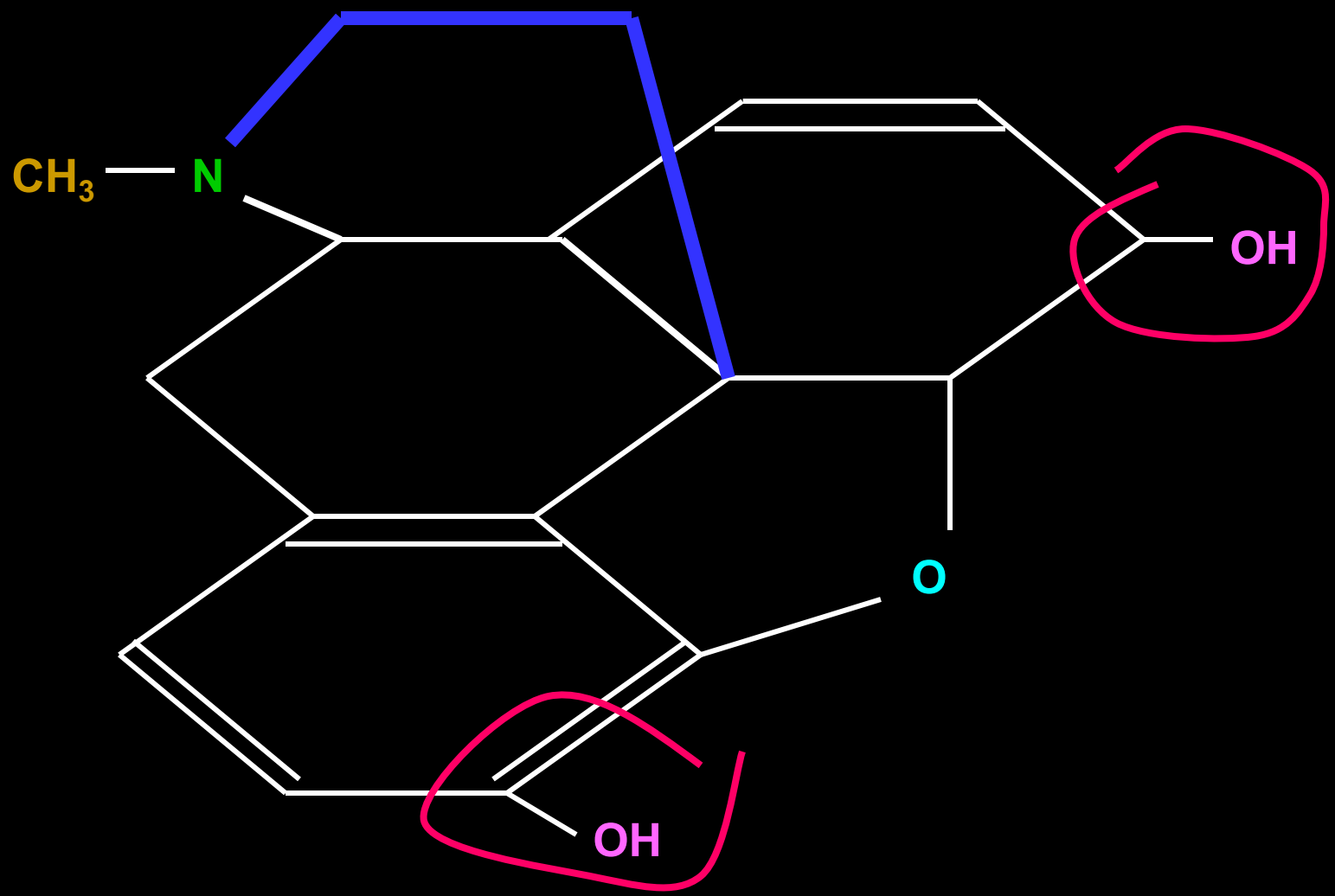
- **carries a hydroxyl at its number 3 and number 6 carbons;**
- **a double bond between its number 7 and number 8 carbons;**
- **carries the nitrogen at is number 17 position.**

These sites, and the number 14 position are key to the chemistry of morphine and its derivatives.

Consequently, appreciate the foci of the morphine molecule…

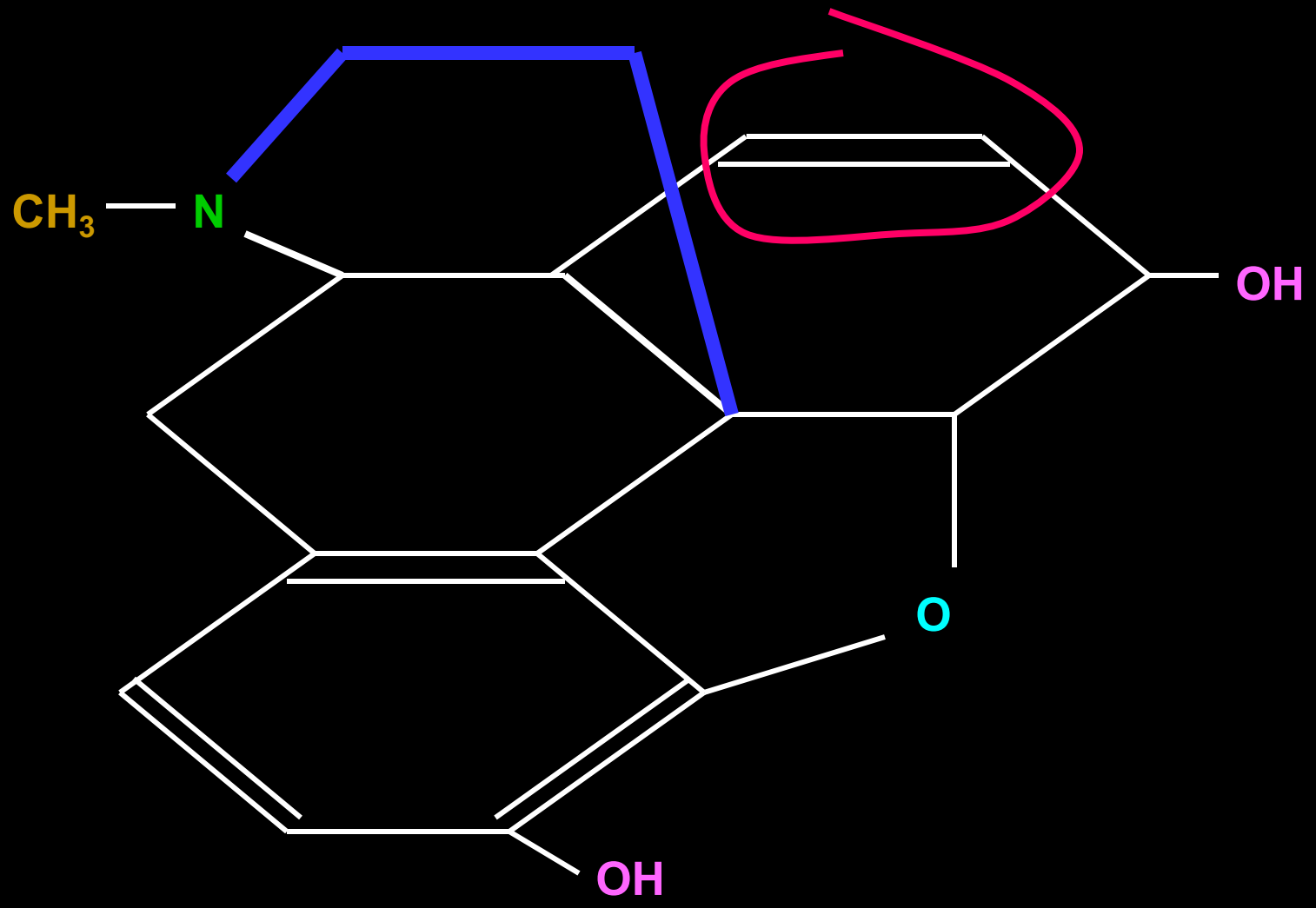
morphine

the 3 and 6 hydroxyls



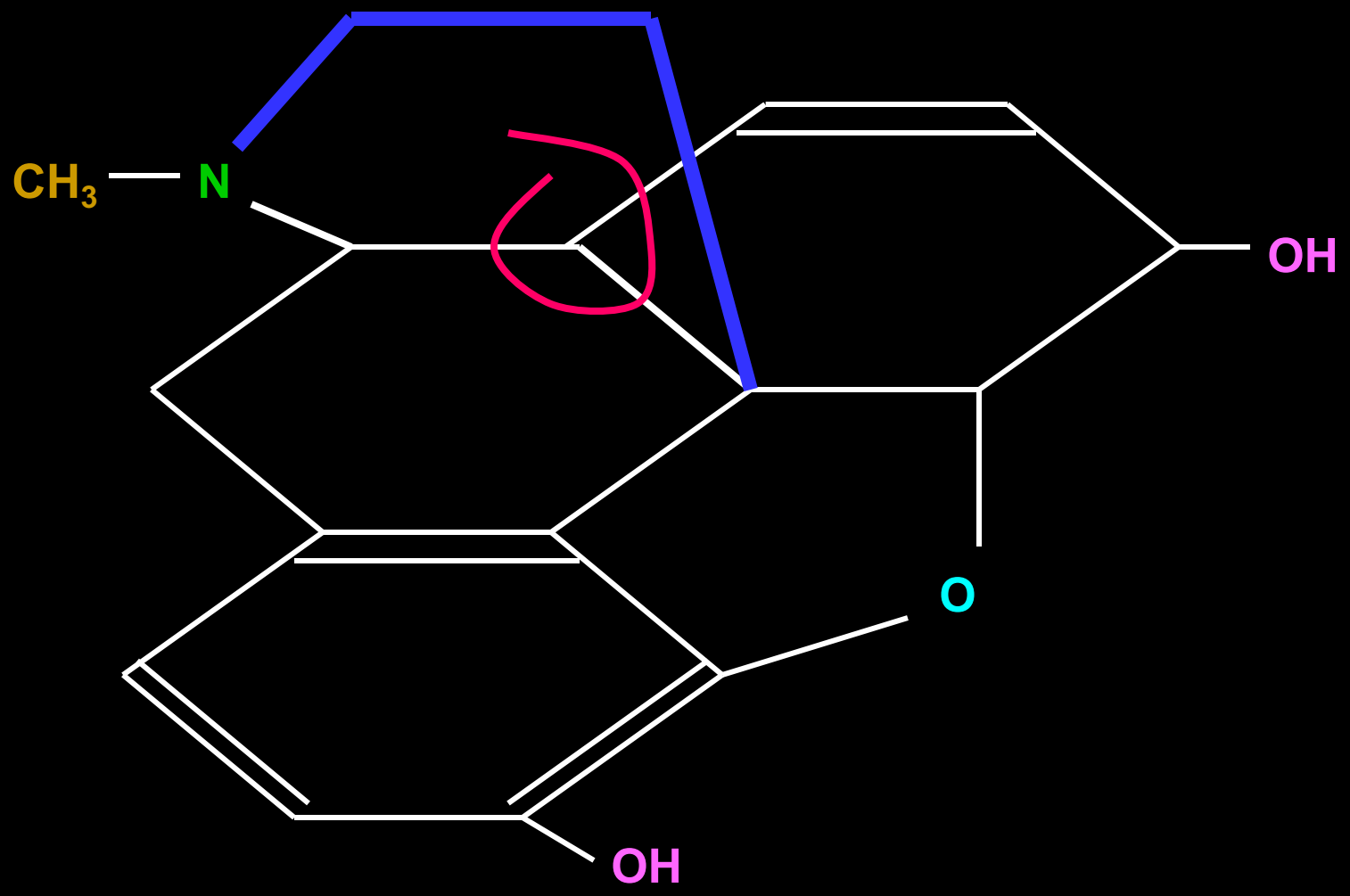
morphine

the 7,8 double bond



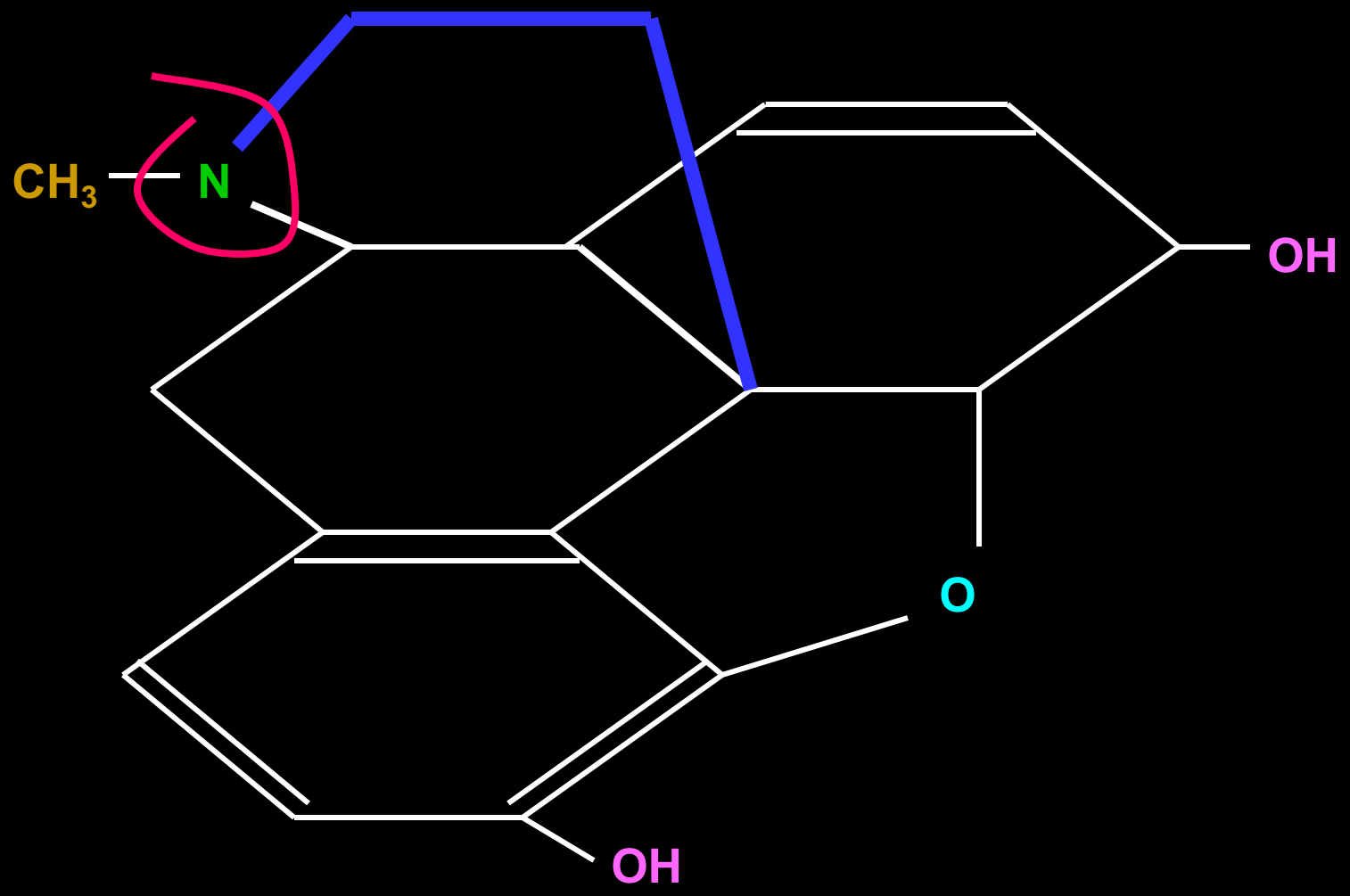
morphine

the C14 carbon



morphine

the C17 nitrogen



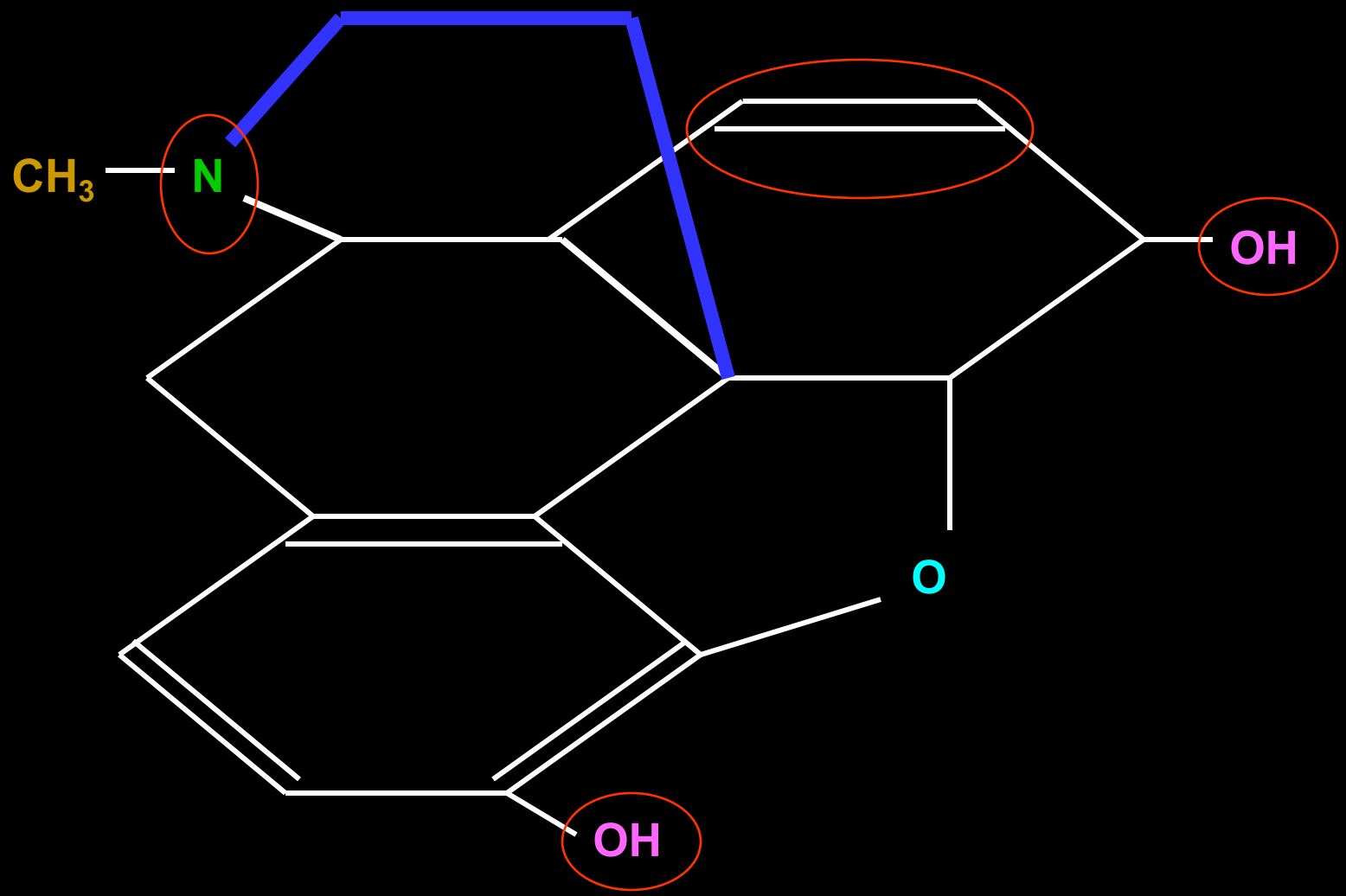
Develop an appreciation that

the C3 and C6 sites, are “electric” and relatively polar, because of the hydroxy radicles. They are hydrophilic, and can bind to other structures.

The C17 nitrogen is also relatively polar.

The C7,8 double bond is a hydrophobic but lipophilic region.

morphine



The key sites of the morphine molecule are

- **the 3 and 6 hydroxy sites**
- **the 7,8 double bond**
- **the 17 nitrogen**
- **and the C14 carbon.**

[The C14 carbon is inconspicuous in the native molecule, but its location is important.]

All these sites lie at the "bottom" of the molecule. It is with that bottom that the molecule binds to the receptor.

Consequently, modifying the bottom changes the binding and, therefore the potency of the drug.

Extending the C3 radicle decreases binding, and produces a less potent agonist.

By the same token, the resultant molecule is resistant to degradative enzymes. Therefore, its bioavailability is increased.

Polarizing the C6 carbon, with glucuronide or sulphate,

- **increases potency,**
- **but decreases lipophilicity.**

Therefore, although more potent, the drug cannot get into the CNS where it acts.

Hydrogenation of the C7,C8 double bond

- increases lipophilicity
- which results in greater potency

Similar effects are achieved by oxidation of the C6 carbon.

Hydroxylation of the C14 increases the potency of the drug

(ostensibly by increasing the binding capacity of the footplate).

However, extending the radicle on the C14 hydroxyl

- produces antagonists

Extending the radicles on the 17 nitrogen

- **produces strong antagonists**

(ostensibly by compromising the polarity of the “head” of the molecule).

By inspecting the structure of the commonly used opioids,

see how these various rules underlie their clinical properties.

Start with morphine, and see how its derivatives progress.

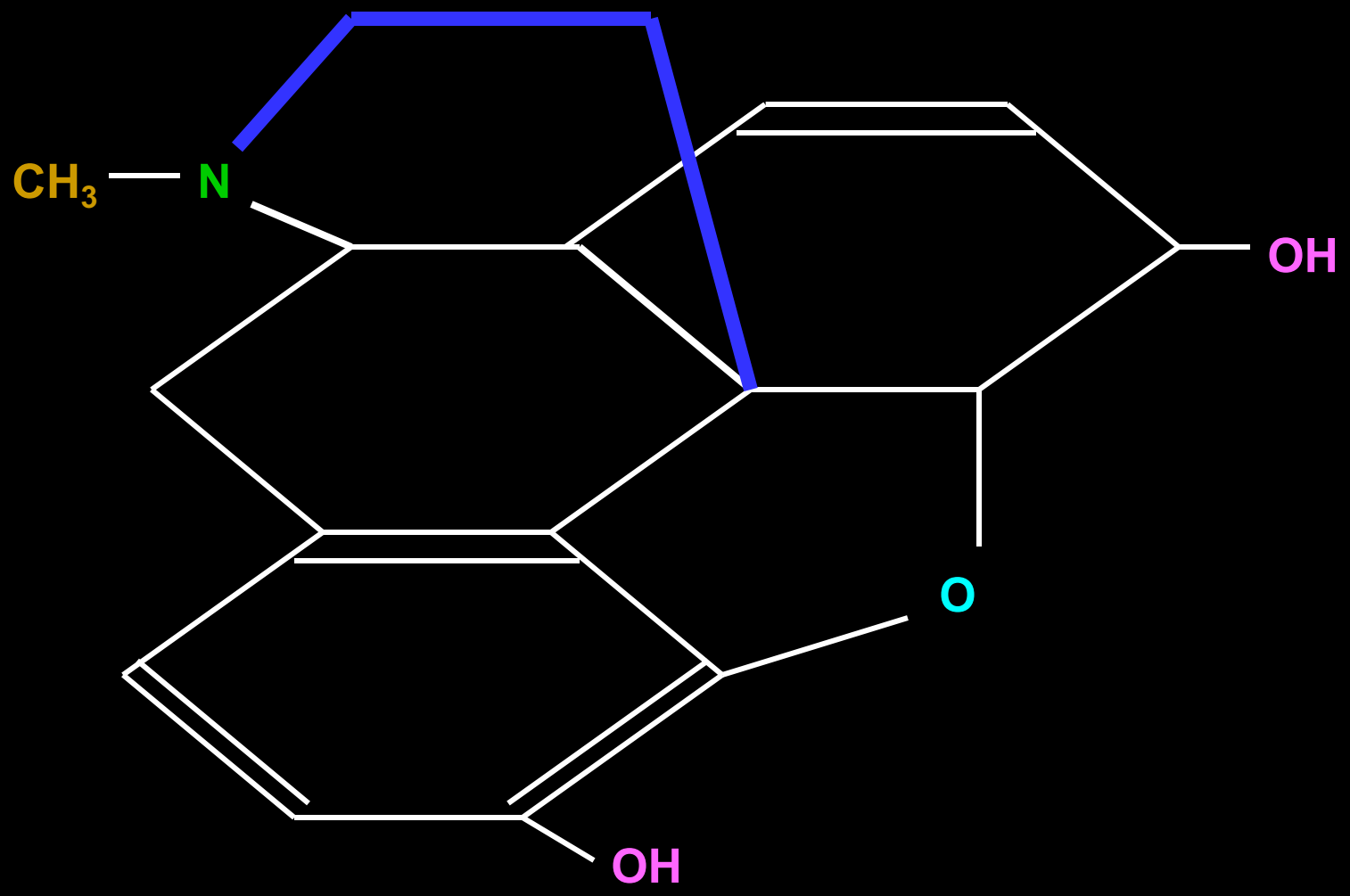
Then inspect the propylamine and piperidine derivatives.

PART 4:

THE STRUCTURES OF OPIOIDS

MORPHINE DERIVATIVES

morphine



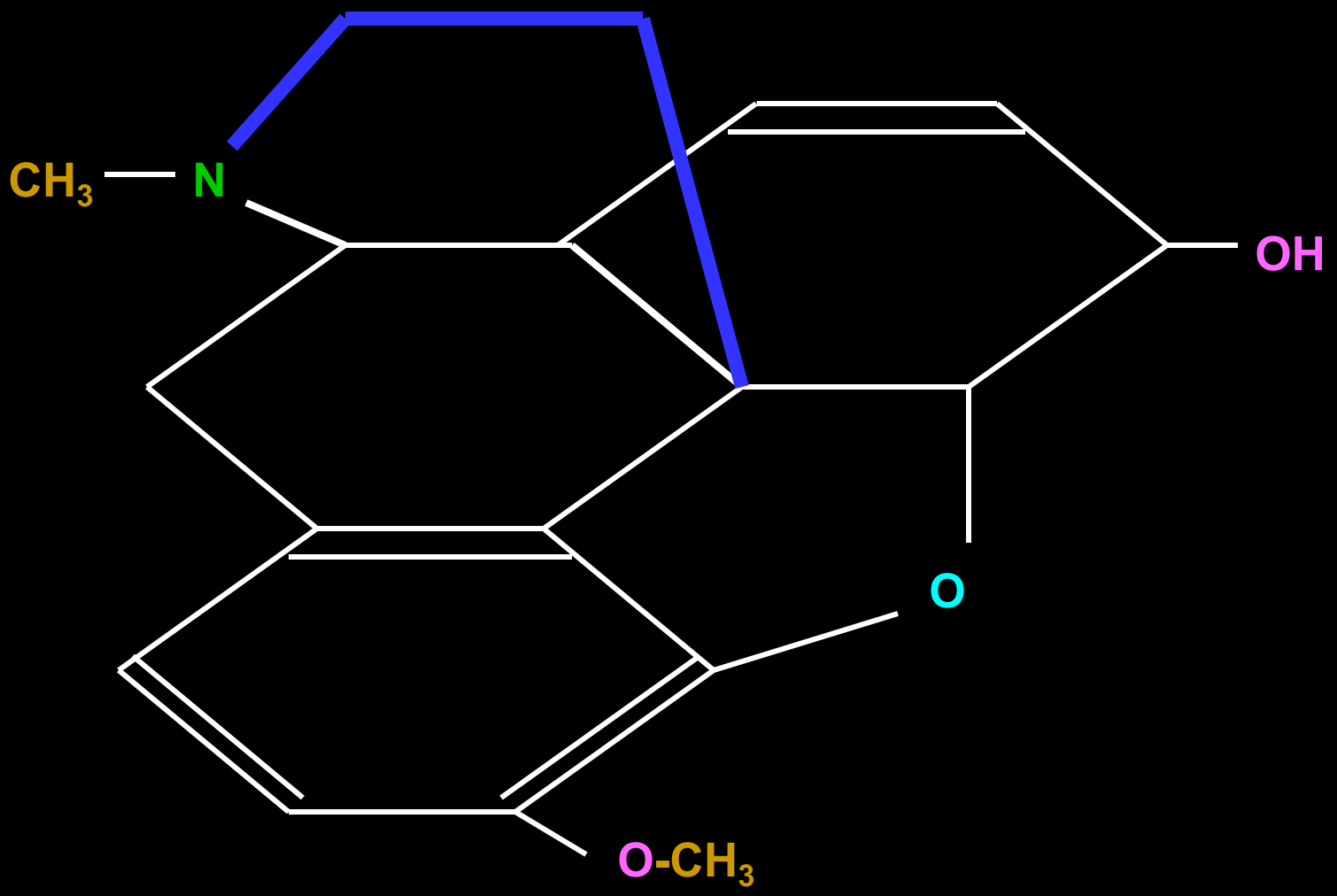
By simply adding a methyl to the C3 hydroxyl, we get a drug

that is less potent, but with greater bioavailability,

which, therefore, can be used orally.

The drug is codeine…

codeine

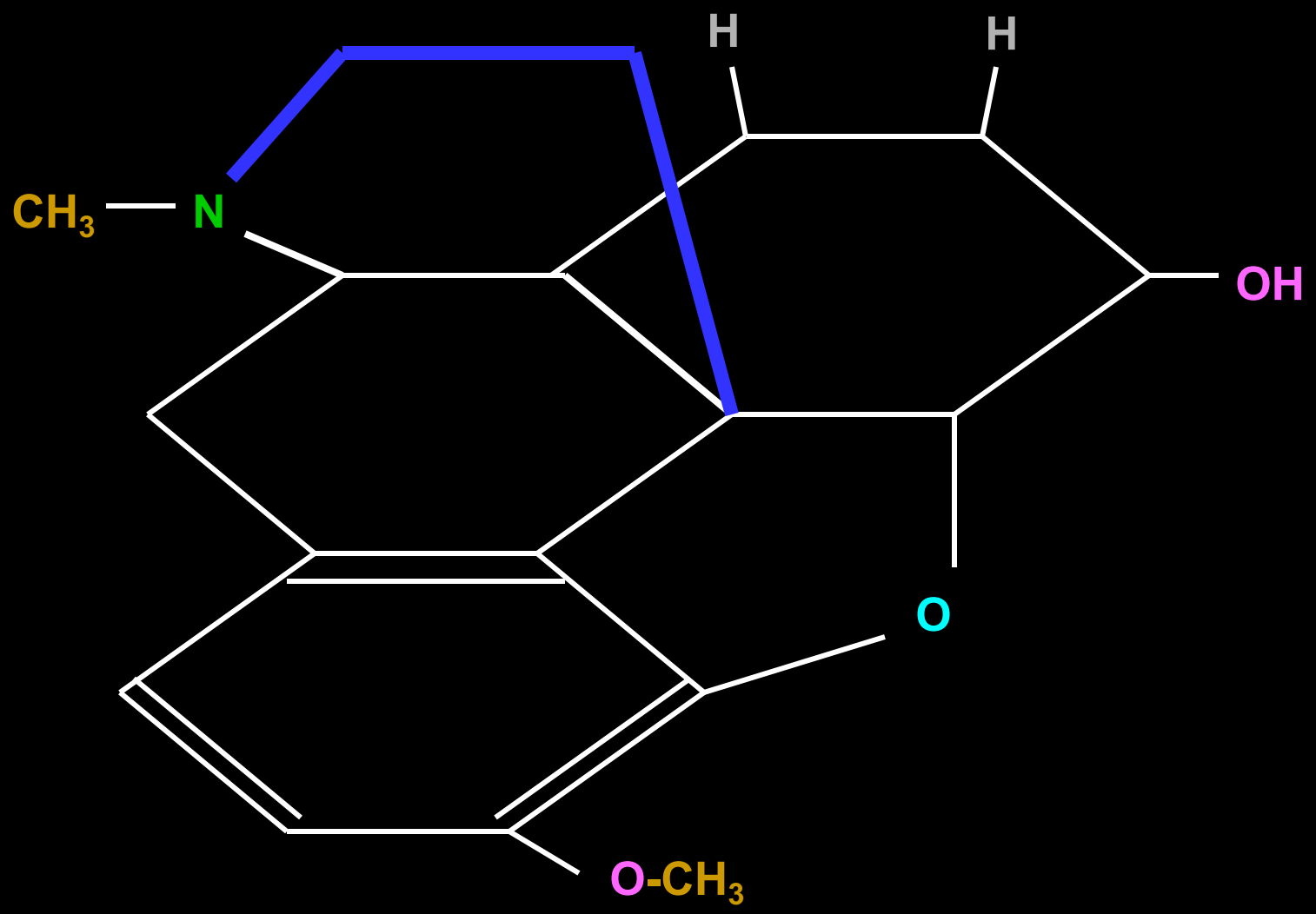


By hydrogenating the C7,C8 double bond of codeine, we get

a drug that is more lipophilic and more potent, viz.

dihydrocodeine…

dihydrocodeine

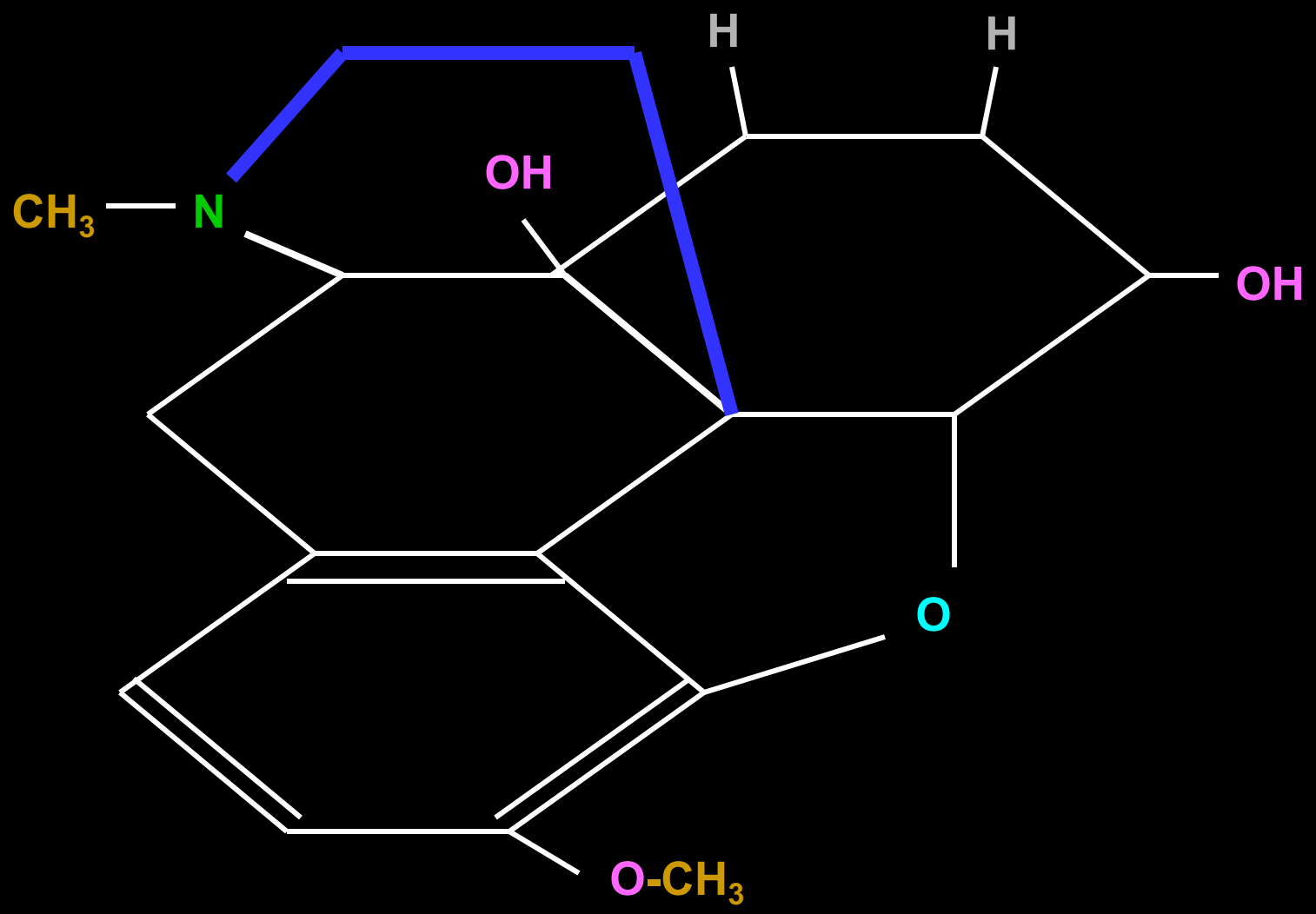


If, now, we hydroxylate the C14 carbon, we get

a more potent drug,

oxycodone…

oxydrocodone



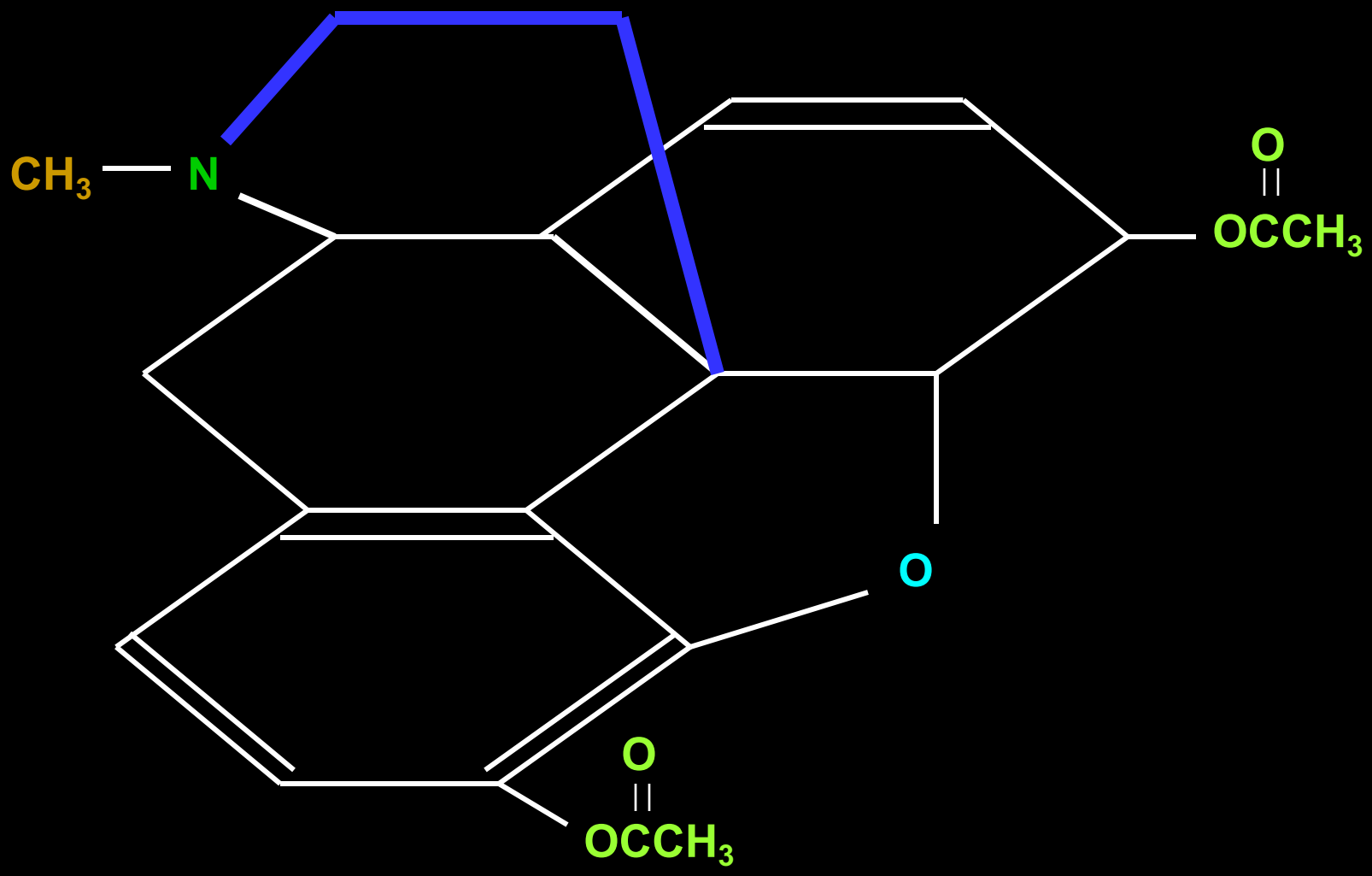
Heroin is simply morphine with vinegar on its handlebars.

It is 3,6 diacetyl morphine.

The acetate radicles are rapidly removed, to convert heroin into morphine.

Therefore, heroin has no greater potency than morphine, for the active molecule has not been modified.

heroin: 3,6 diacetyl morphine



PHENYL PIPERIDINE DERIVATIVES

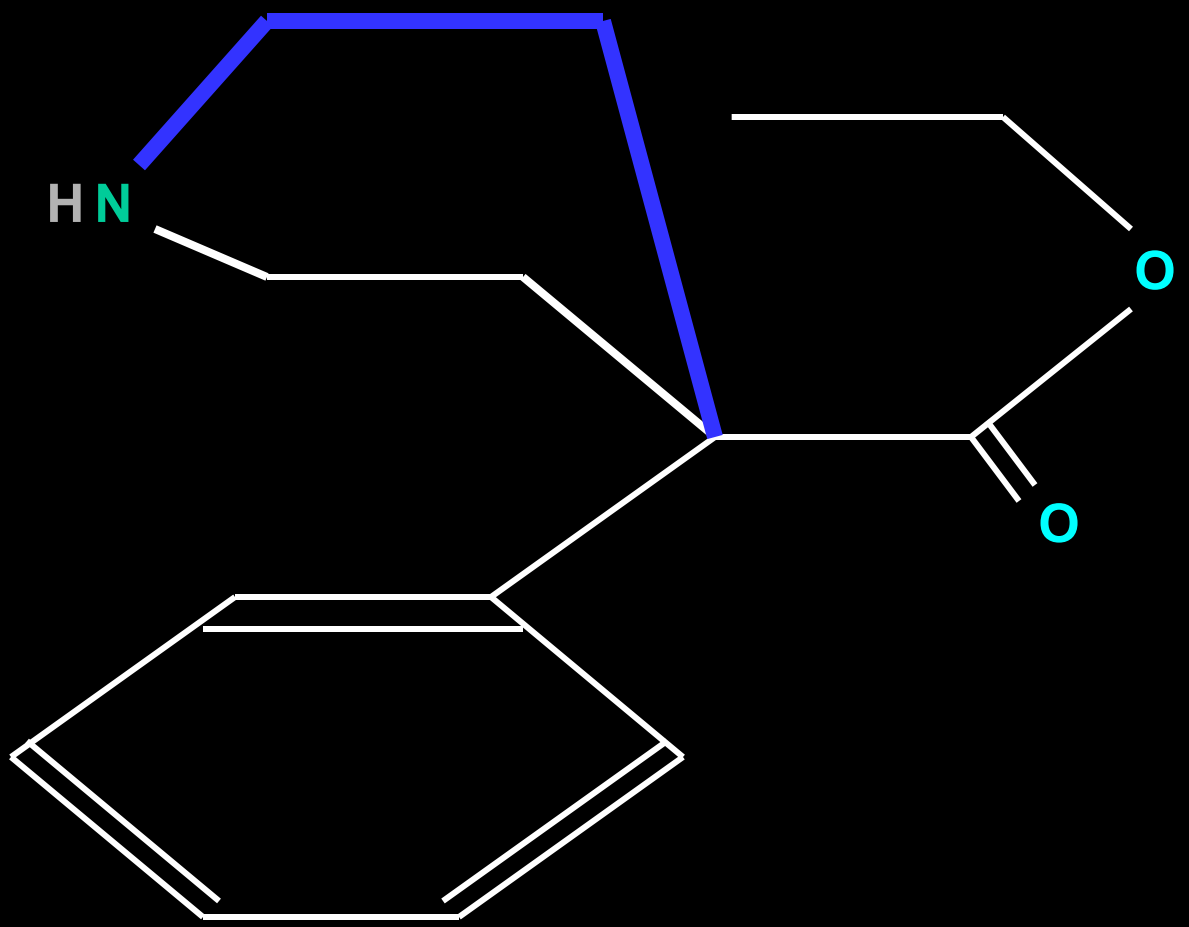
Pethidine is almost like a morphine molecule, but

it lacks a lot of the “bottom”, and

an oxygen replaces the C6 carbon…

(Perhaps the lack of a complete bottom, explains the shorter duration of action of pethidine, i.e. it does not bind to the receptor as avidly or for as long.)

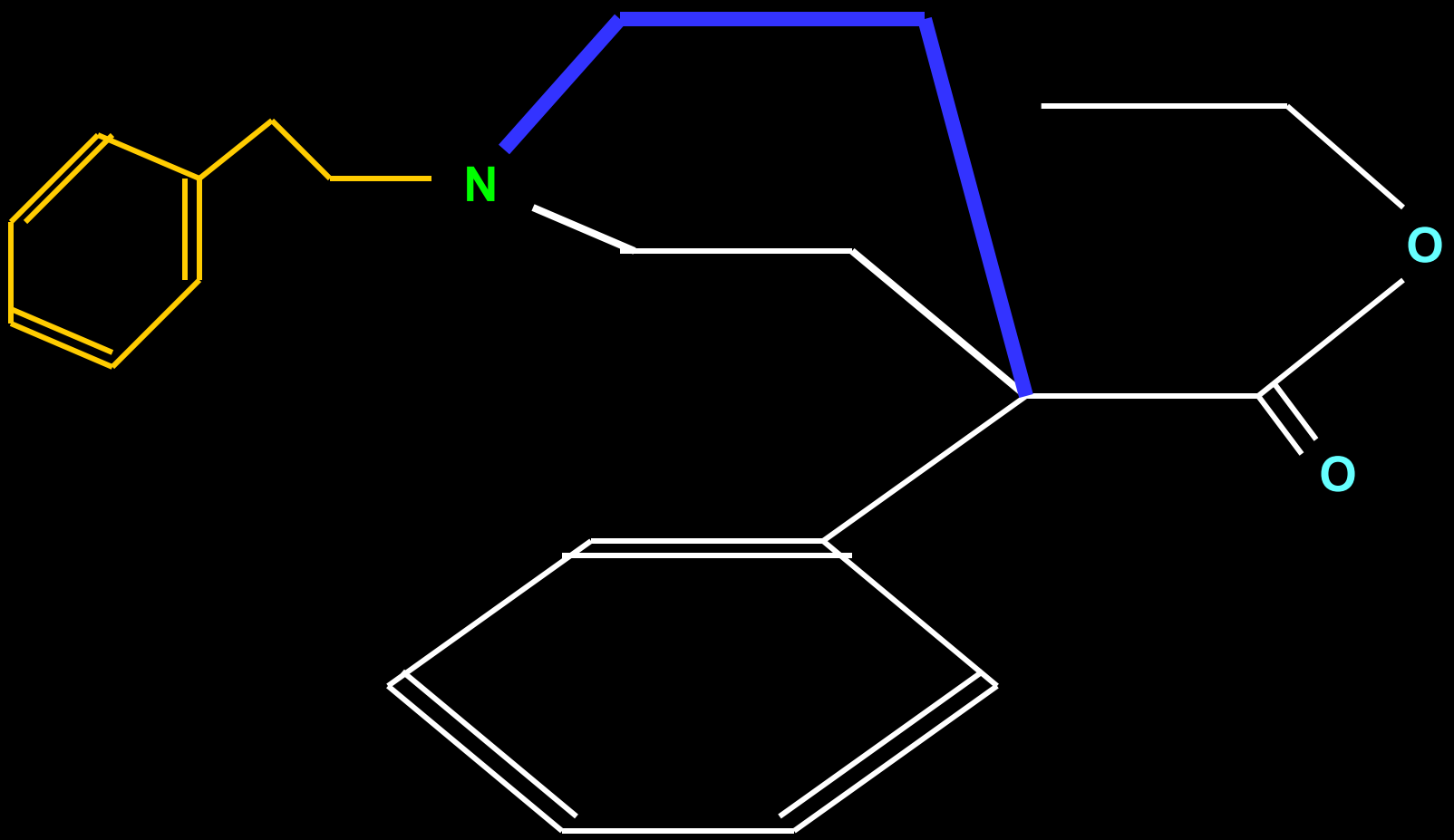
pethidine



Fentanyl is pethidine with a long aromatic chain on its head.

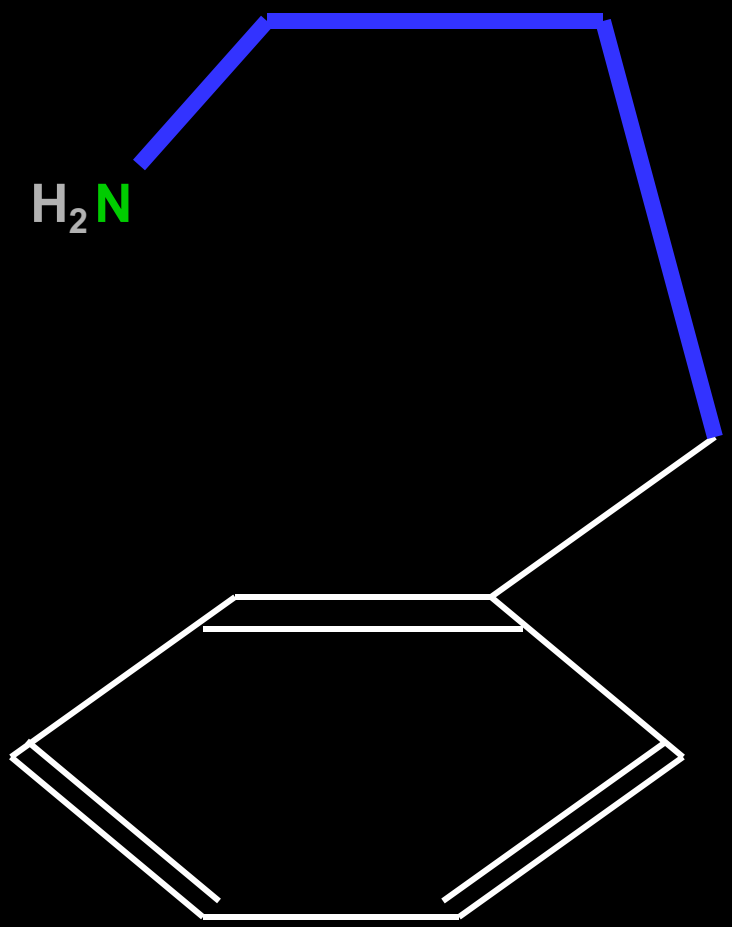
Since extending the 17N as rule produces antagonists, perhaps the presence of this cranial extension explains the rapid and short acting nature of fentanyl.

fentanyl



PHENYLPROPYLAMINE DERIVATIVES

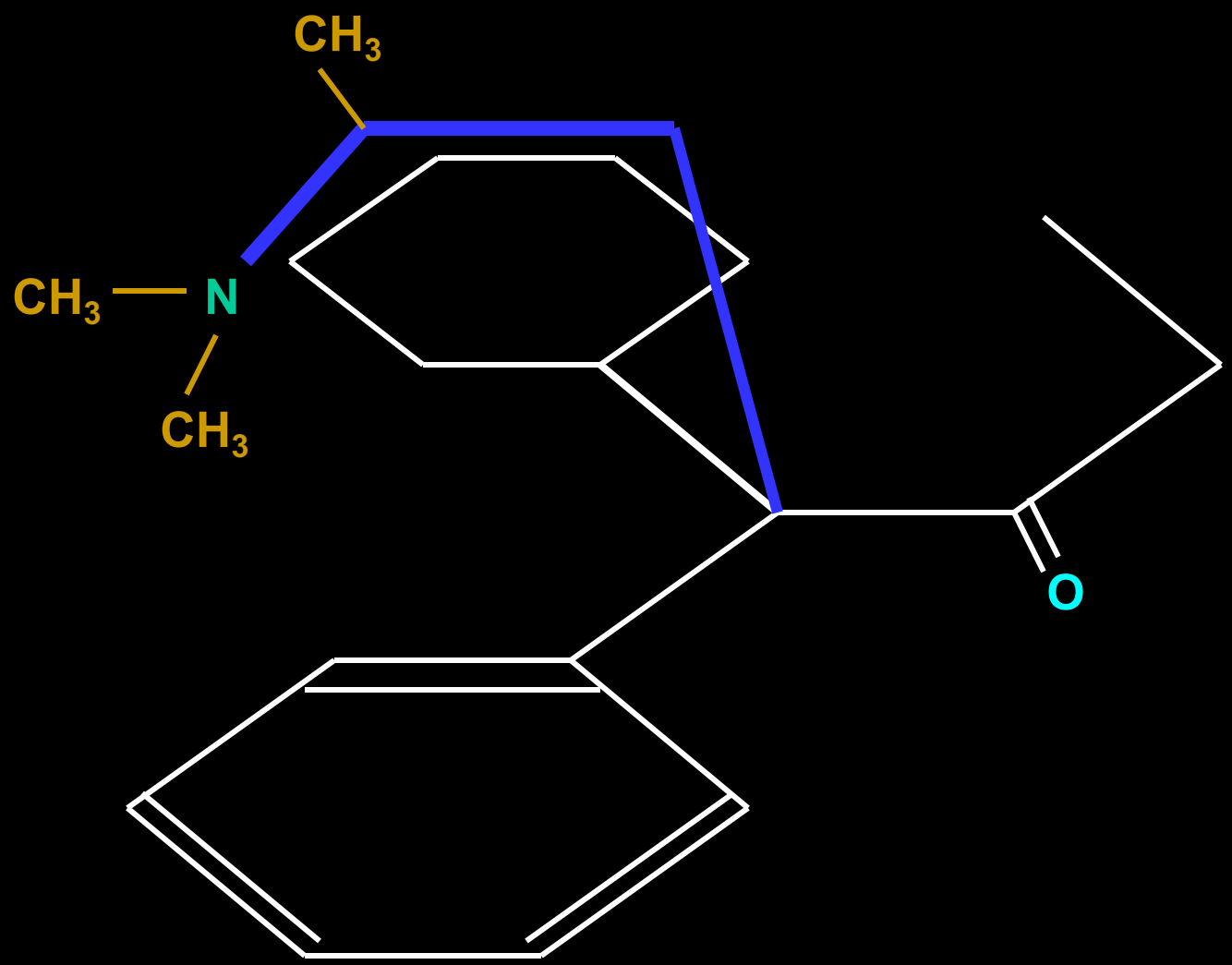
phenylpropylamine



Methadone has

- **an incomplete third ring**
- **a bunch of methyl radicles scattered around N17 and the propyl chain, and**
- **a new phenyl group way out to the other side…**

methadone



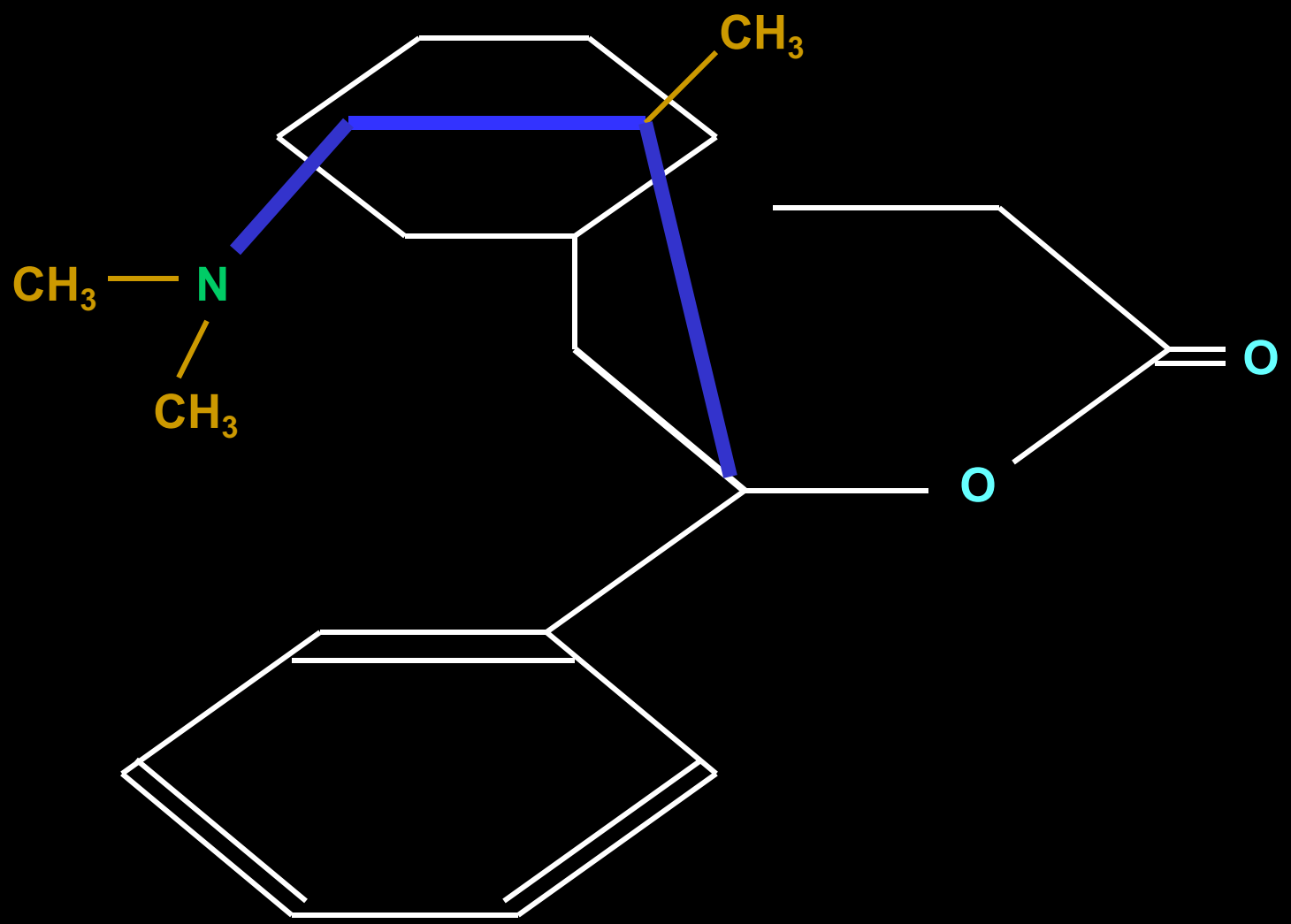
Dextropropoxyphene resembles methadone, but

- **has more of a third ring,**
- **has more oxygens in the third ring, and**

a new phenyl ring, way out to the side

(further away than in methadone because of an extra carbon in the link).

dextropropoxyphene



PART 5:

WHY OPIOIDS ARE ANALGESICS

Opioids act on opioid receptors, but

opioids are not naturally occurring substances in the human body.

The natural ligand of opioid receptors are the enkephalins.

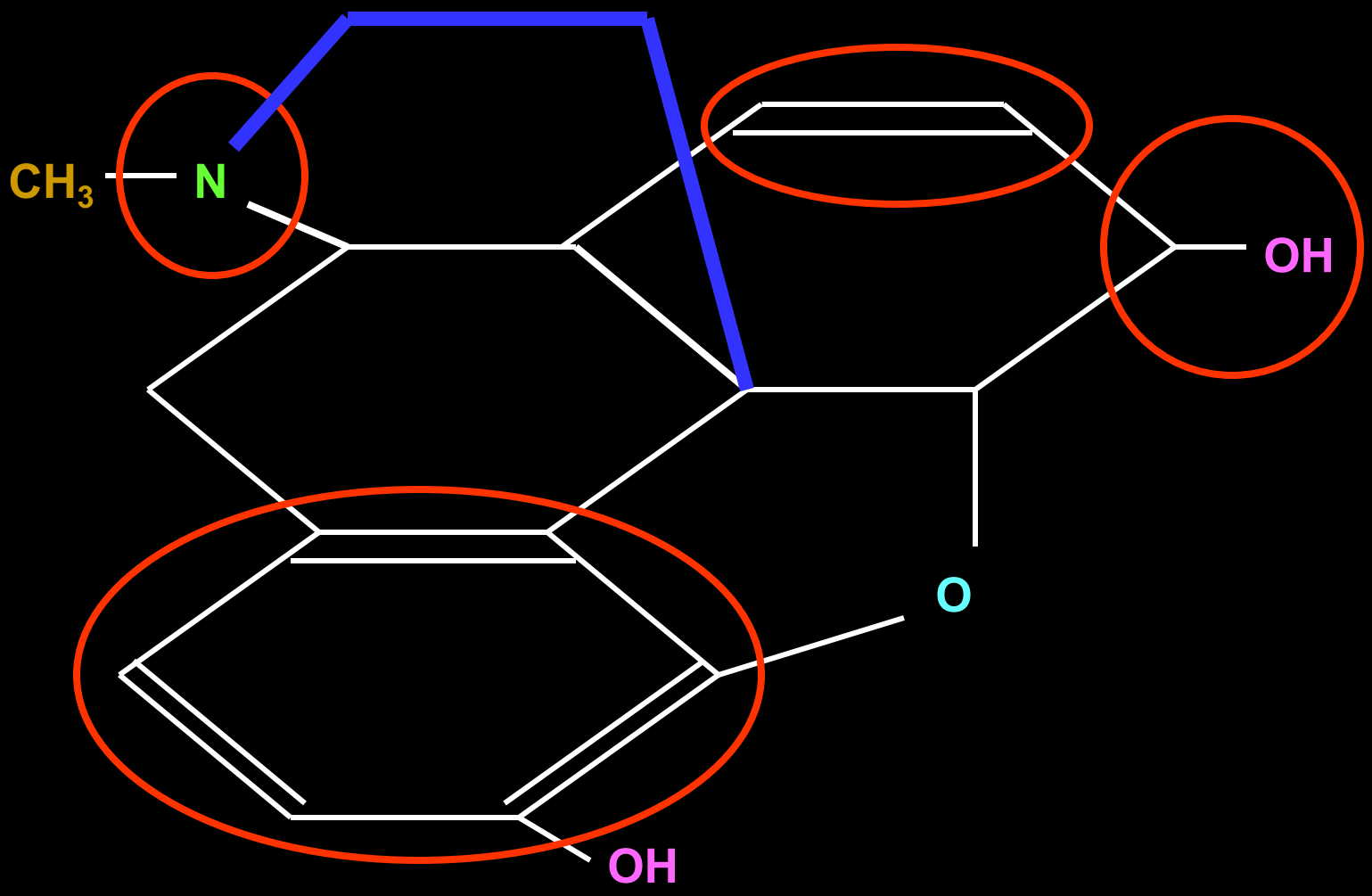
But enkephalin is a five amino acid peptide.

How is it that an exogenous alkaloid can mimic the effect of an endogenous peptide?

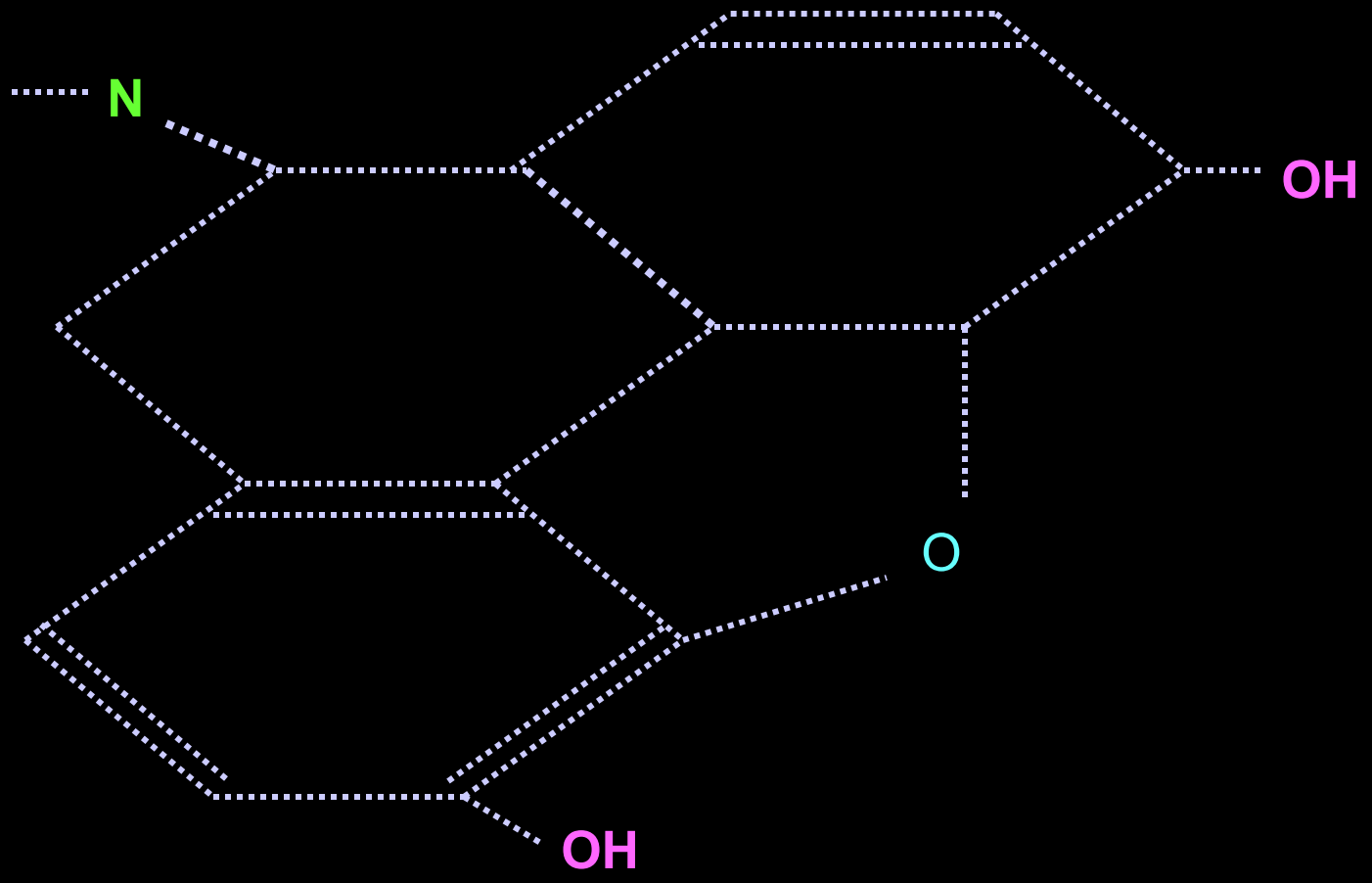
If you revise the key structure of morphine, you find that the key sites are

- **the phenyl ring of the footplate,**
- **a hydroxylated C16 carbon, at the right rear of the molecule,**
- **the N17 head,**
- **and the hydrophobic region of the C7, C8 carbons.**

Note the relative spatial arrangement of these sites, viz…


CH3
N
OH
O
OH

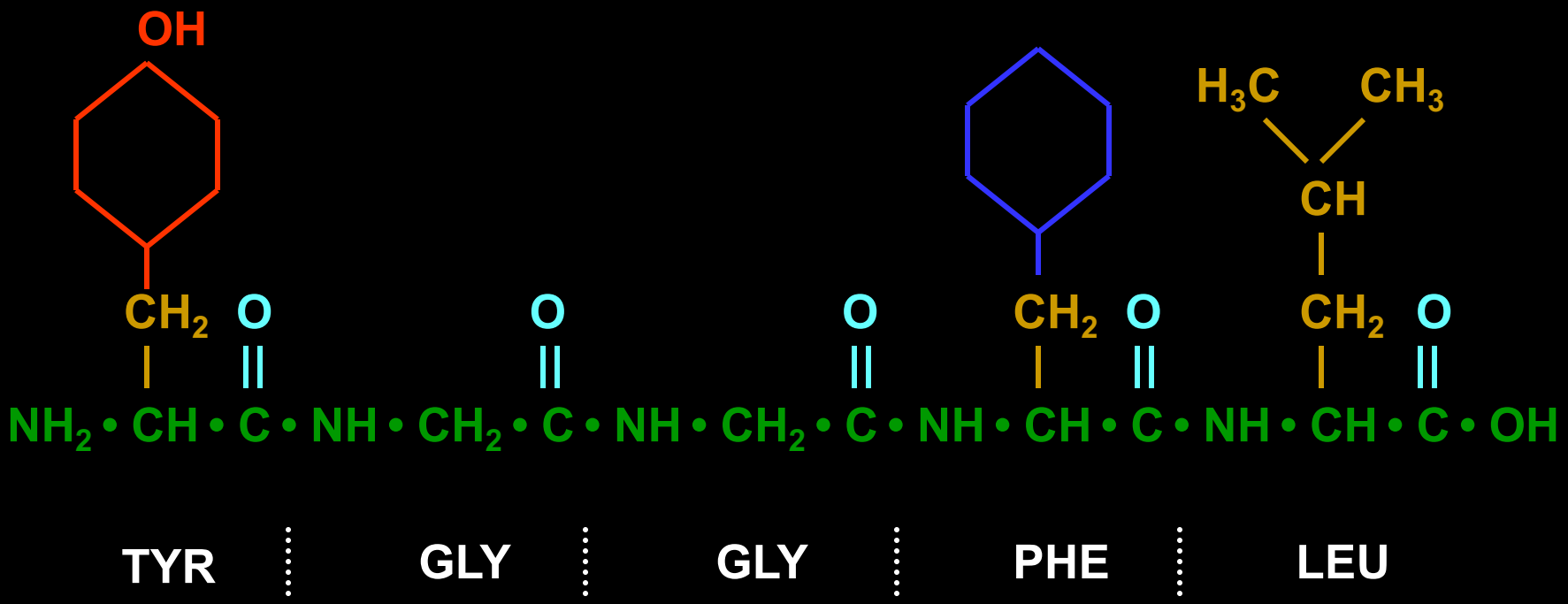
Picture these sites as forming a phantom template…


N
OH
O
OH

Now consider the leucine enkephalin molecule.

If we we just consider its primary structure we see only a string of amino acids…

LEU-ENKEPHALIN



But now view the molecule with insight, greater than what you ever were accustomed to having when originally studying biochemistry.

- **A string of amino acids has a relatively featureless and innocuous core chain, consisting of repeated sequences of**

[- NH – CH – COO -] - [- NH – CH – COO -] –

- **The key to a peptide lies in its radicles.**

Enkephalin presents three radicles:

- **the phenol group of the tyrosine**
- **the phenyl group of the phenylalanine**
- **the hydrophobic group of the leucine**

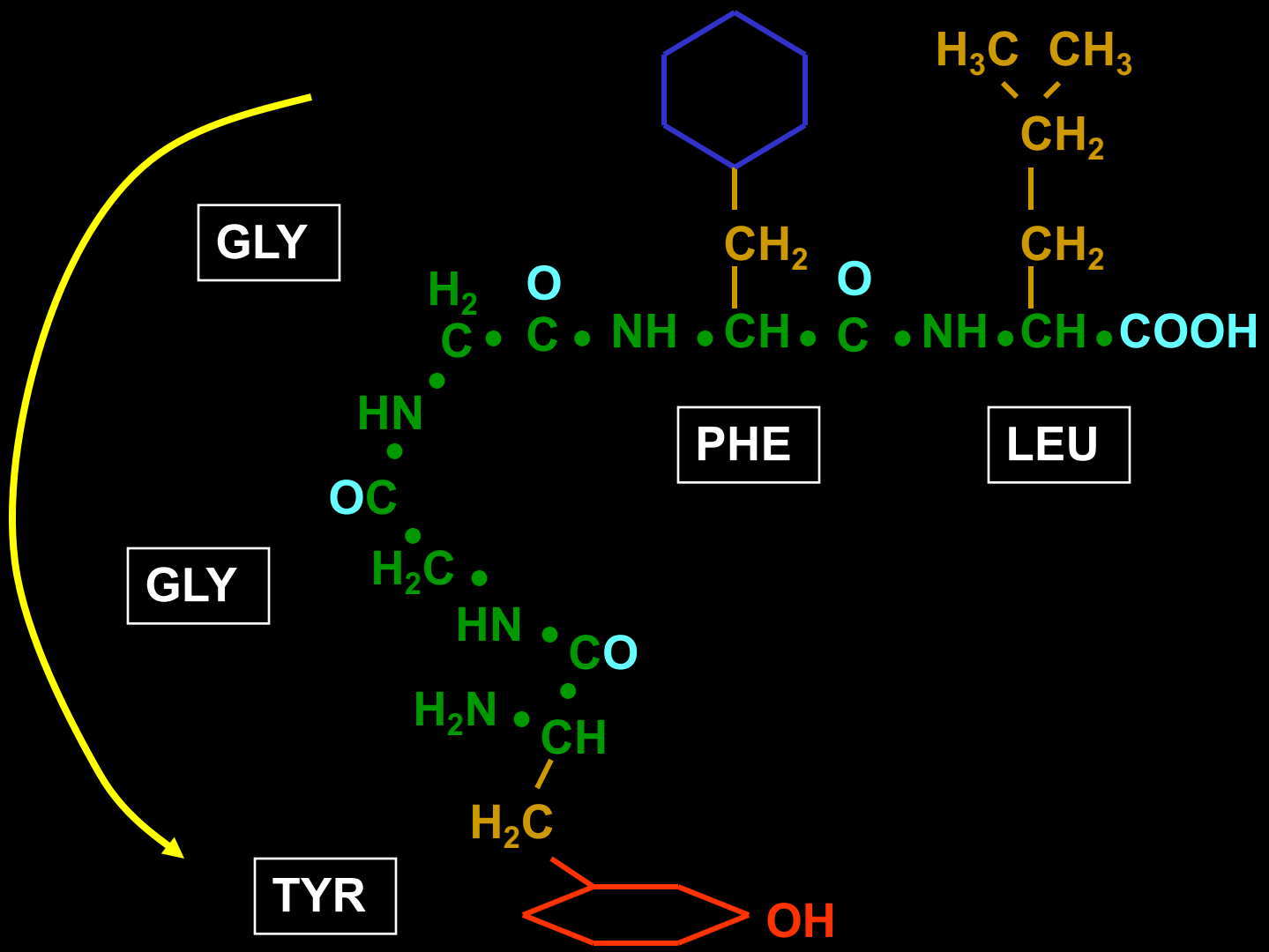
[Does this ring a bell?]

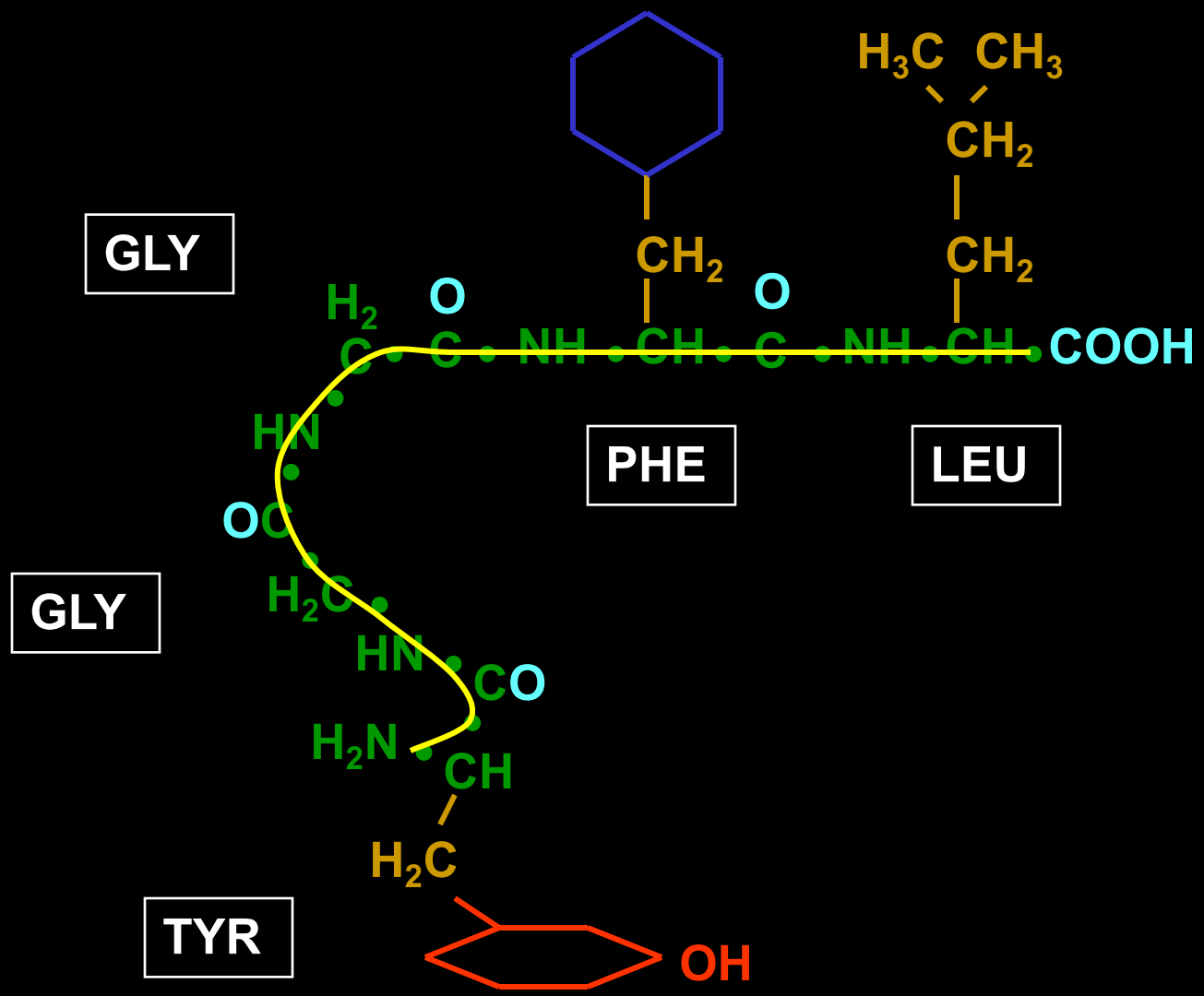
These radicles correspond to the key elements of the morphine molecule; but they are not arranged spatially as in the morphine molecule. That illusion arises when you view only the primary structure of enkephalin.

The core chain of a peptide is not as featureless and useless as it might seem. That chain is pliable. Its bonds allow the chain to twist and turn. Its function is to bend so as to bring the side-chains into a better spatial relationship. In particular, glycine lacks side-chains and so, does not contribute "external" properties; but it serves very well to allow twists and bends.

Also, the carboxy oxygens and the amino nitrogens are relatively polar; they can form hydrogen bonds. They can be used to hold the molecule in shape once it has twisted.

So, see what happens when we twist an enkephalin molecule…


GLY
GLY
TYR
PHE
LEU
H2
O
C
C
NH
CH
C
NH
CH
COOH
HN
OC
H2C
HN
CO
H2N
CH
H2C
OH
CH2
CH2
CH2
H3C
CH3

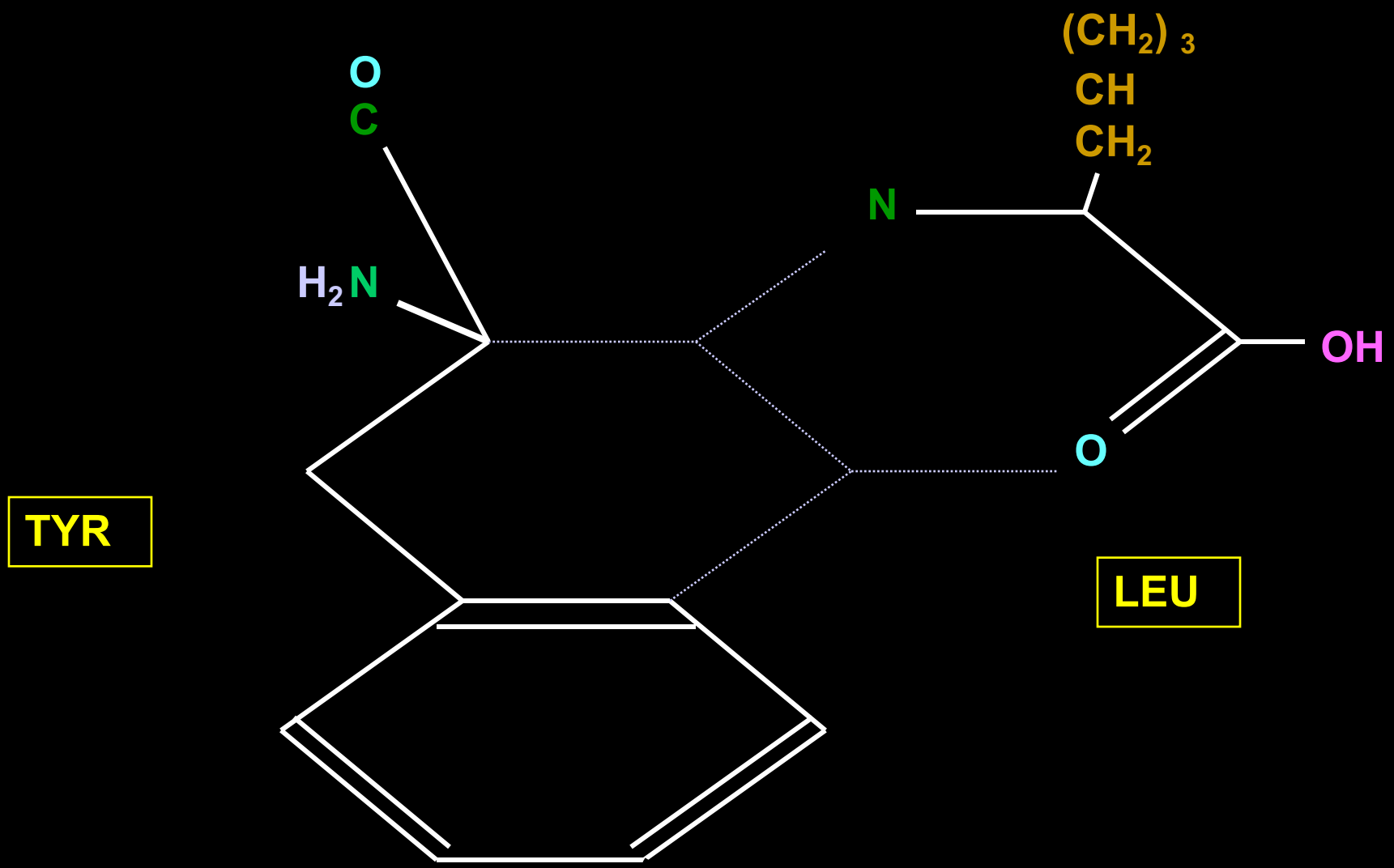

GLY
GLY
TYR
PHE
LEU
COOH
OH

Leaving the leucine and phenylalanine in place, we bend the amino end of the chain downwards and towards you, capitalizing on the pliability of the glycine-glycine sequence.

That brings the phenol of the tyrosine into place, as a foot.

Meanwhile, the terminal nitrogen of the peptide chain is also brought down.

Recognize how this now places the key sites of the enkephalin molecule into a spatial arrangement that fits onto the template of the morphine molecule…


O
C
$(CH_2)_3$
CH
CH_2
N
H_2N
OH
O
TYR
LEU

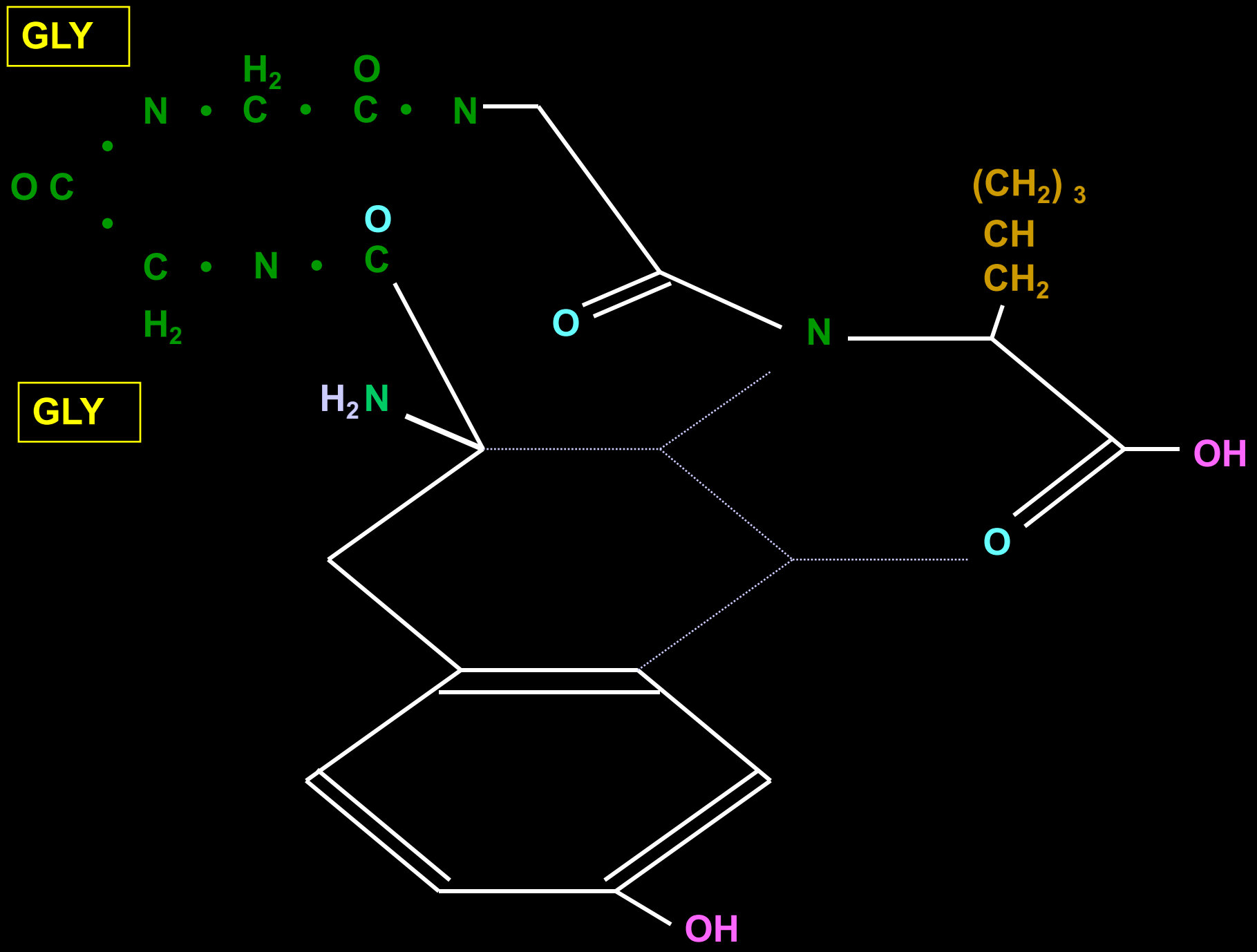
The phenol group of the tyrosine fits into place, providing the phenyl ring and the C3 hydroxyl of morphine;

The amino nitrogen of tyrosine corresponds to the N17 of morphine;

The hydrophobic dimethyl ethyl chain of leucine is not a double bond, but corresponds to the C7,C8 hydrophobic region of morphine;

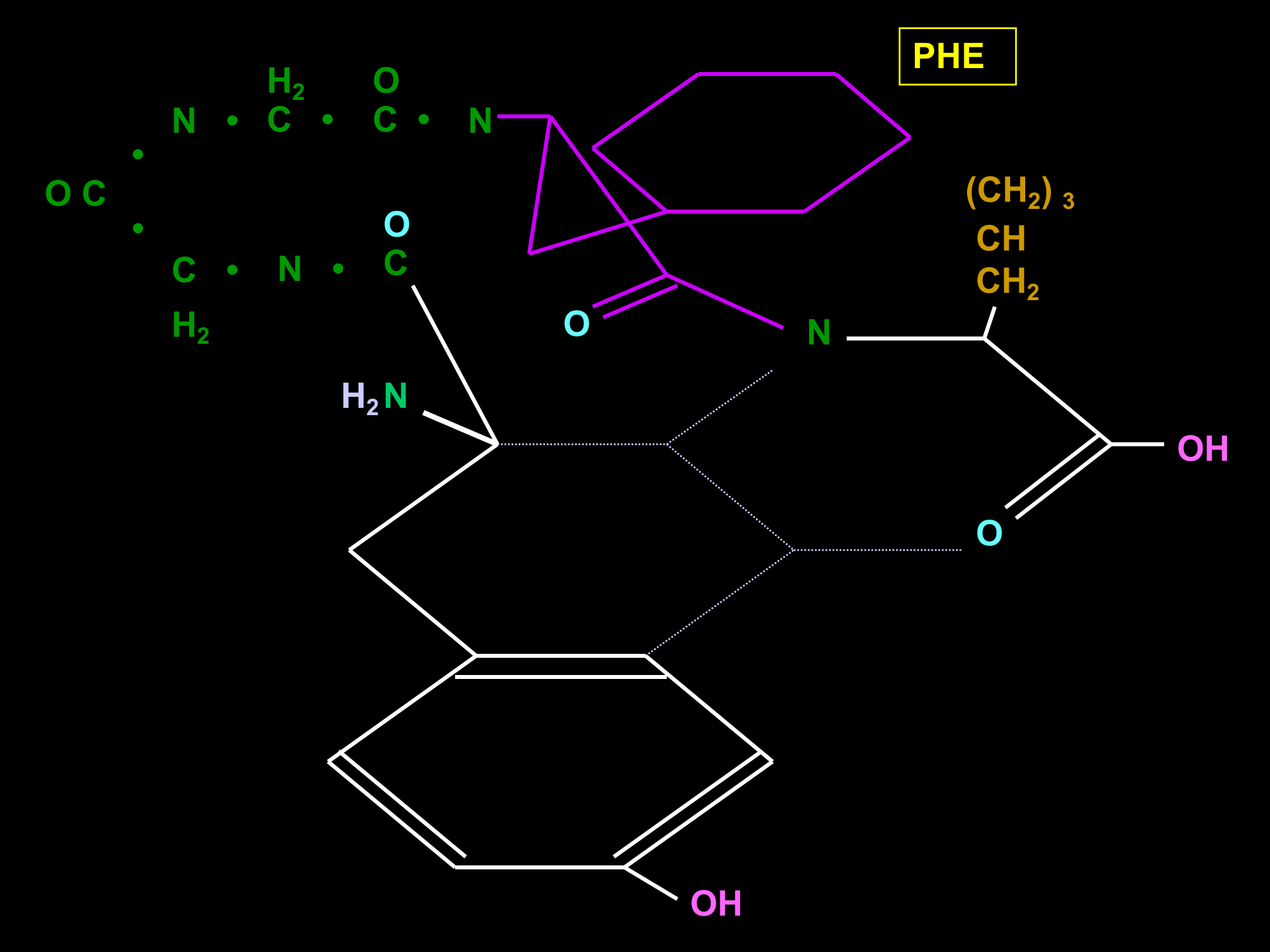
The carboxyl radicle of leucine furnishes the C6 hydroxyl of morphine, and the oxygens seen in the third ring of other opioids.

The glycine chain serves parenthetically just to link the two "active" ends of the enkephalin chain, and is basically out of the plane of the "morphine molecule" where it does not interfere with the activity of the footplate…

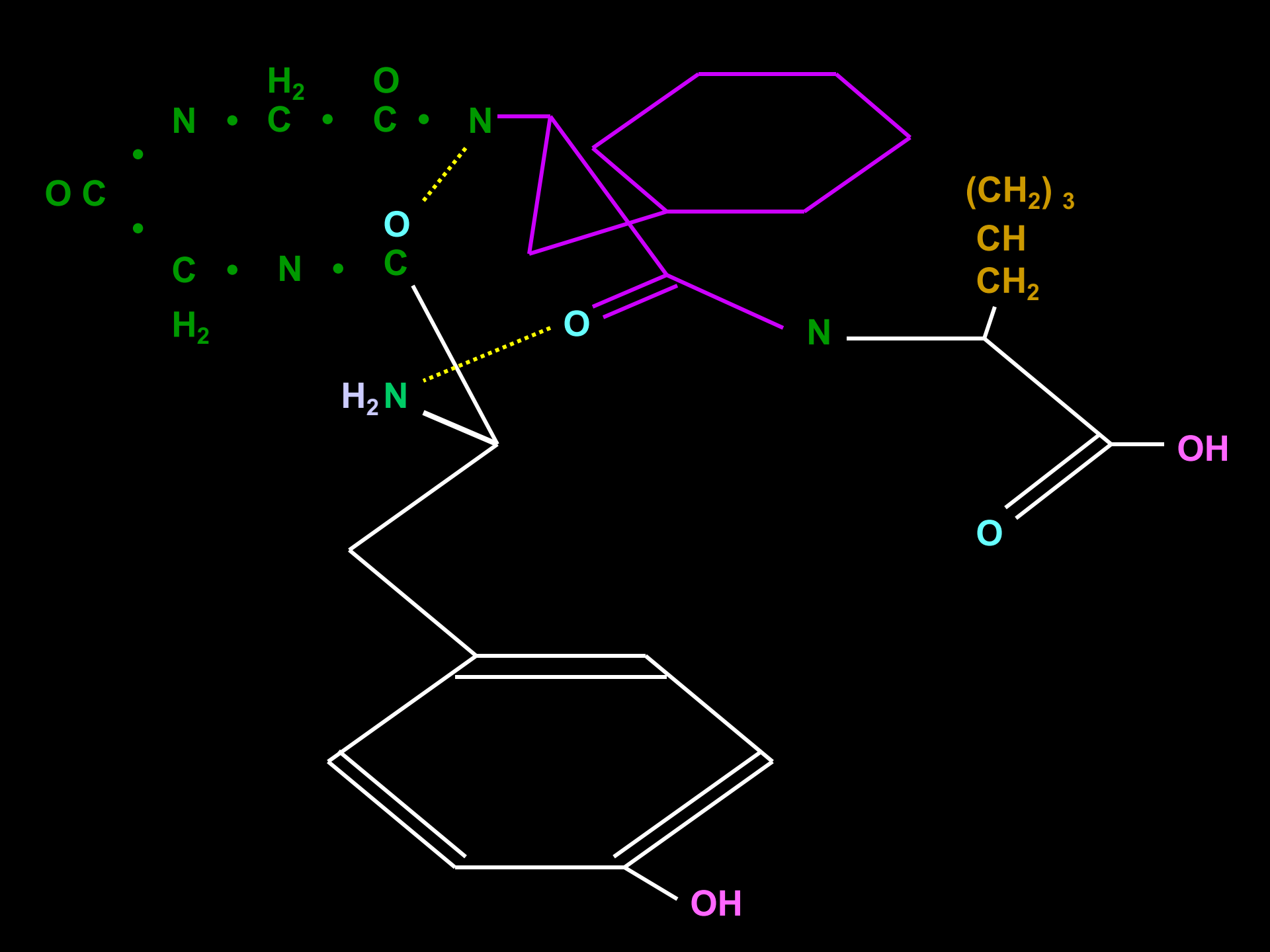

GLY
GLY
OH
OH

The phenyl group of the phenylalanine is an optional extra.

It does not have an analogue in the morphine molecule, but it is evident as the additional phenyl ring of methadone and of dextropropoxyphene…

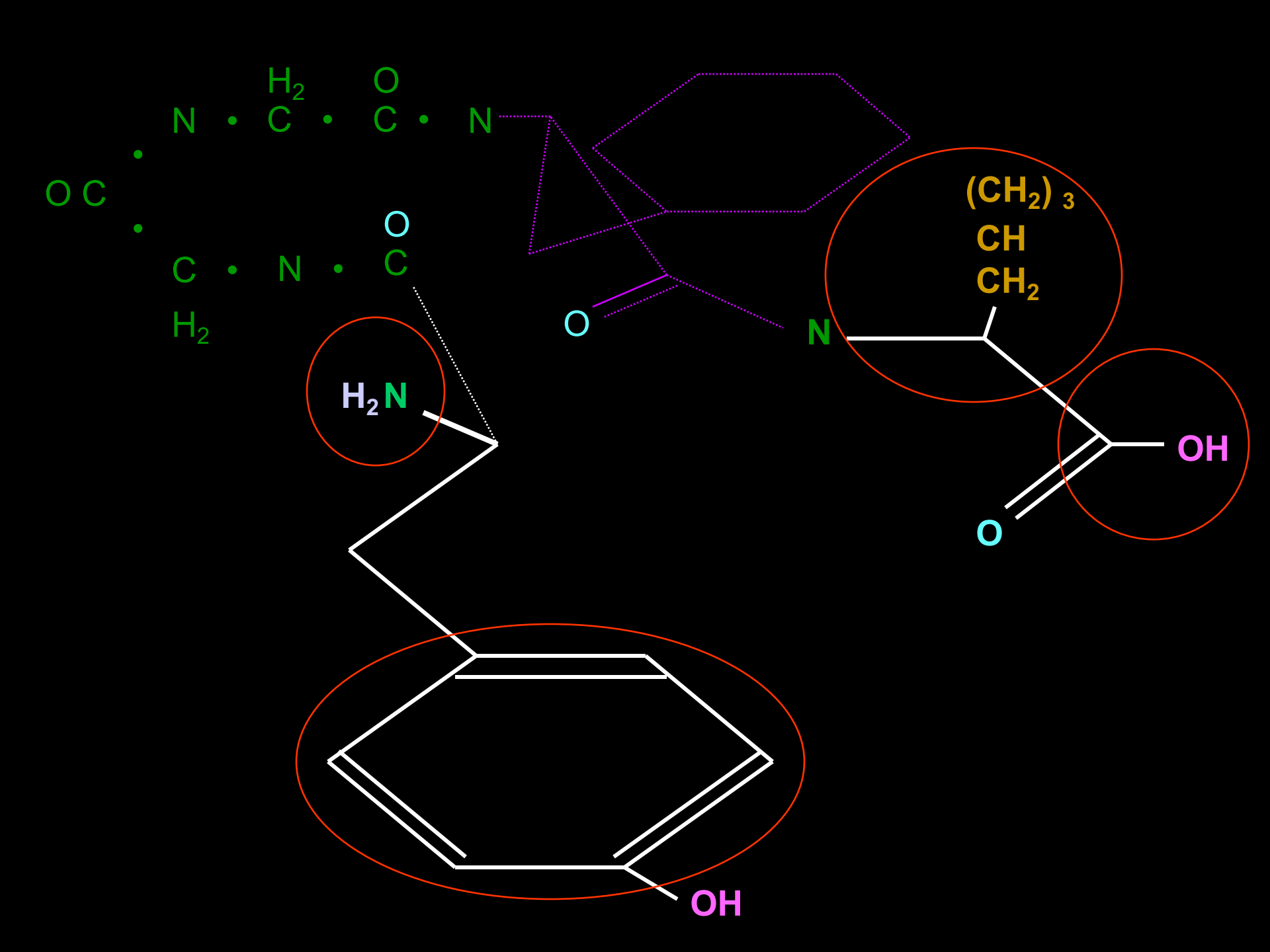

PHE
H2
O
N
C
C
N
O C
O
C
N
C
H2
O
N
(CH2) 3
CH
CH2
H2N
OH
O
OH

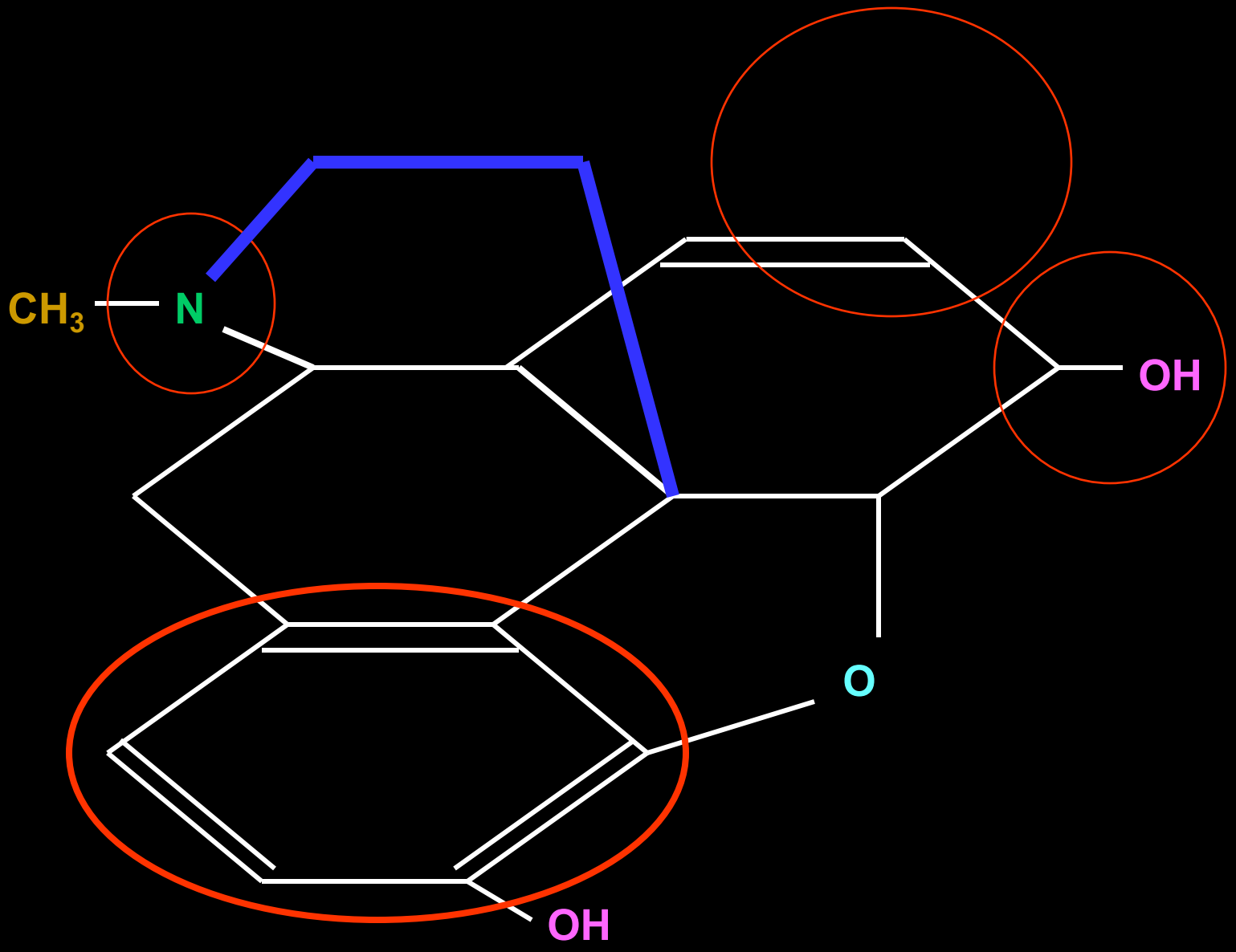
Finally, the hydrogen bonds of the glycine chain hold the molecule in shape, to retain the spatial relationship of its "active" components…

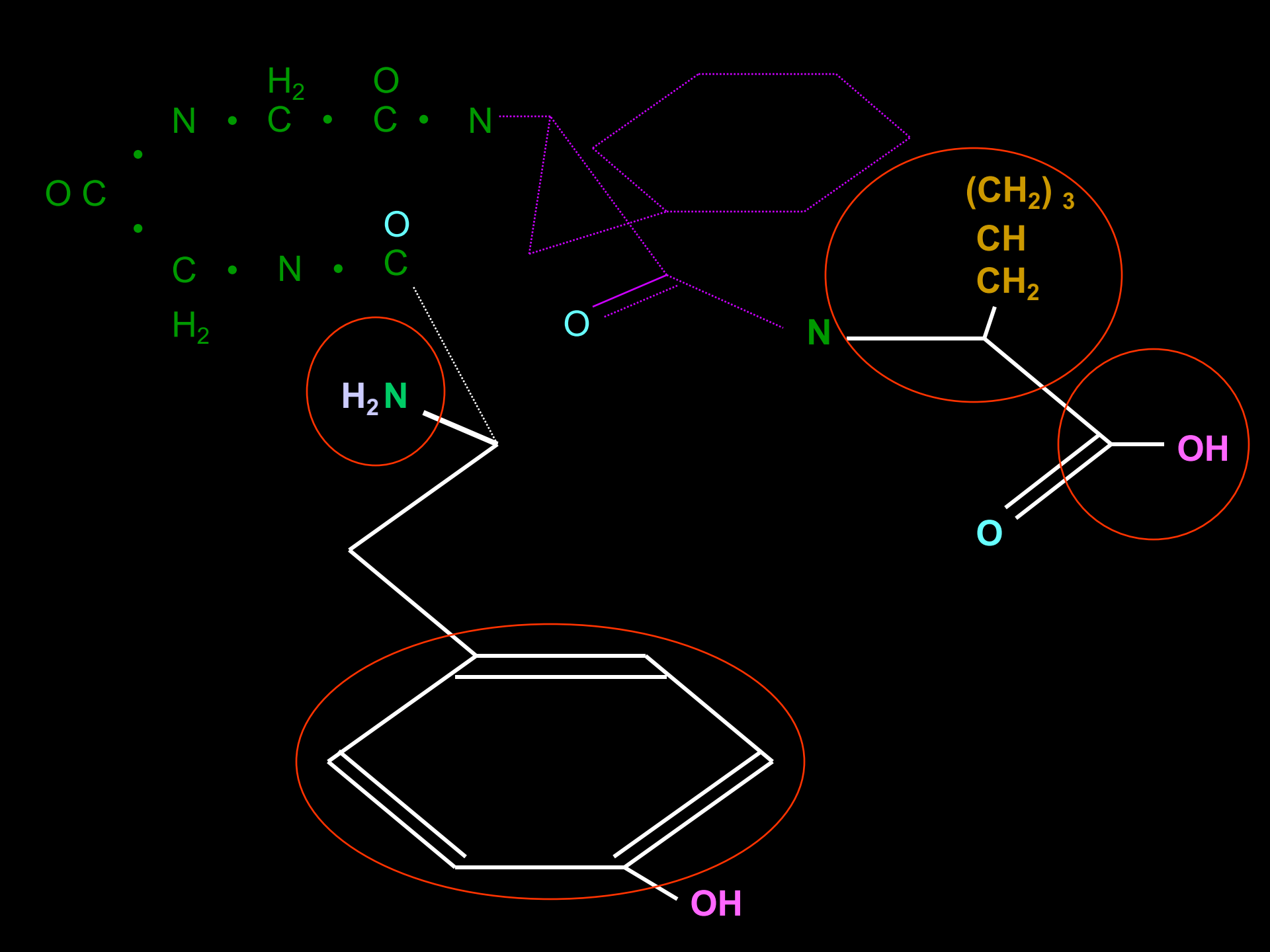

H2
O
N
C
C
N
O C
O
C
N
C
H2
O
N
(CH2) 3
CH
CH2
H2N
OH
O
OH

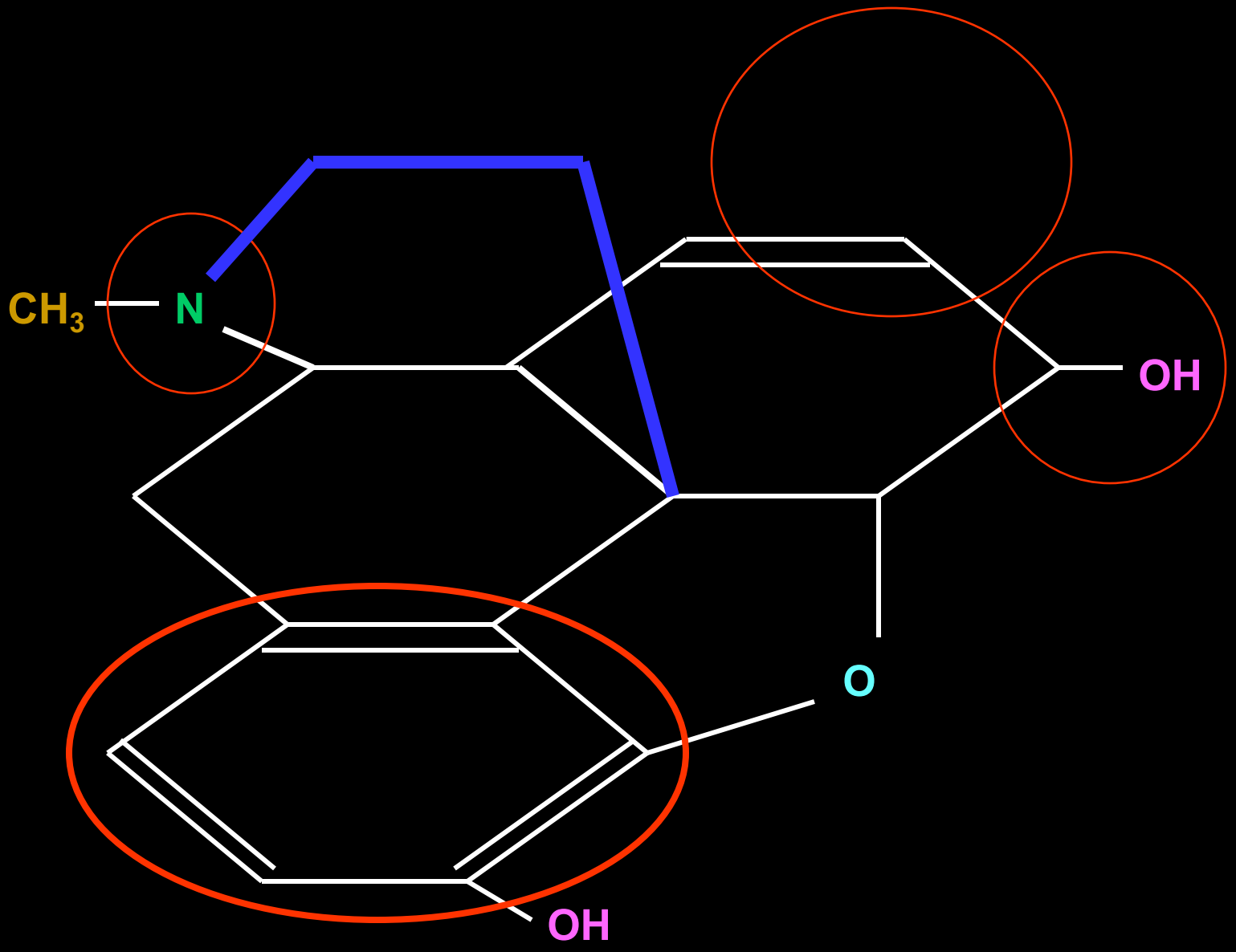
Thus, although proteins and alkaloids are different chemically, an enkephalin molecule can be contorted in such a way as to deliver into an appropriate three-dimensional configuration, the active components of the morphine molecule.

By alternating between the last four slides, see the spatial homology of the two molecules…


H2
O
N • C • C • N
O C
O
C • N • C
H2
O
N
(CH2) 3
CH
CH2
H2N
OH
O
OH


CH3
N
OH
O
OH


H2
O
N • C • C • N
O C
O
C • N • C
H2
O
N
(CH2) 3
CH
CH2
H2N
OH
O
OH


CH3
N
OH
O
OH