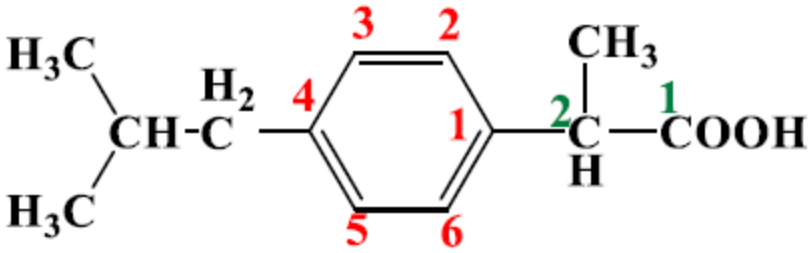
# Organic Pharmaceutical Chemistry II

# Phenyl propionic acid derivatives

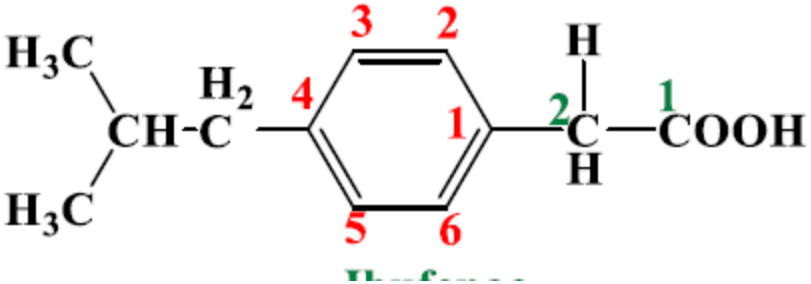
## •Ibuprofen




**Ibuprofen**

**2-(4-isobutylphenyl)propionic acid**

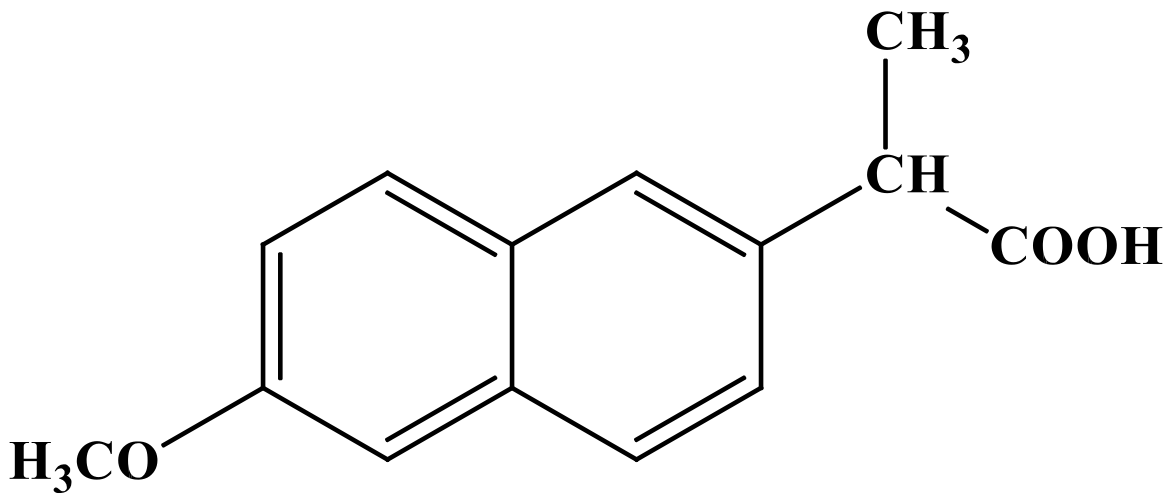
**It appears to be comparable to aspirin in the treatment of RA, with a lower incidence of side effect**




**Ibufenac**

**less potent with hepatotoxicity**

# Naproxen•



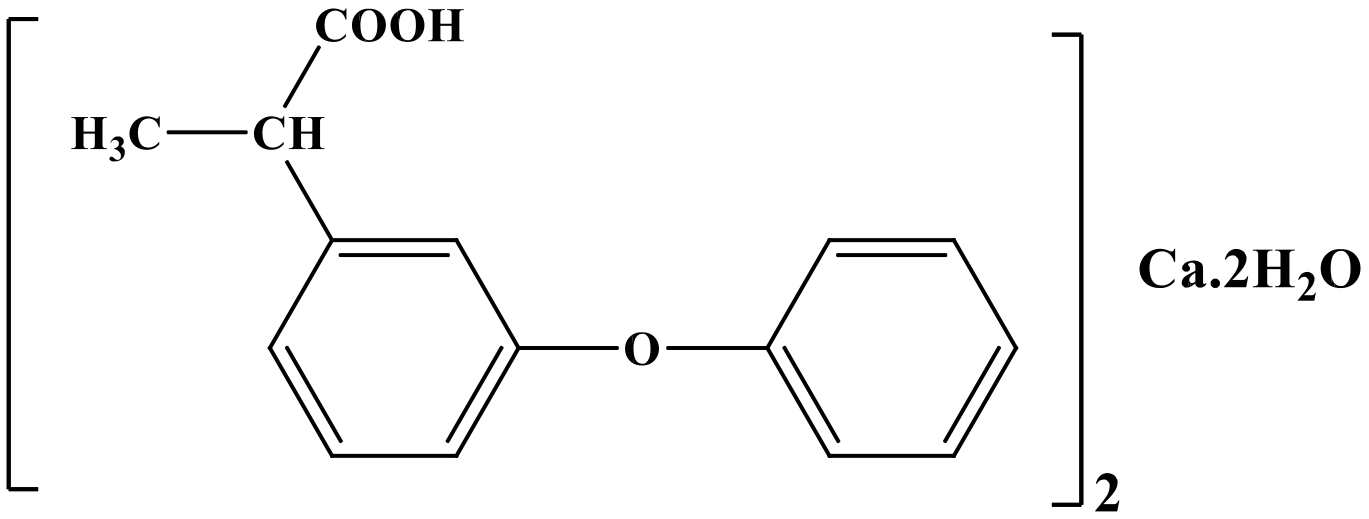

**Naproxen**

**(+ )-6-methoxy-α-methyl-2-naphthaleneacetic acid**

**Uses:- Naproxen is recommended for use in rheumatoid and gouty arthritis.**

**S/E:- It reportedly produces dizziness, drowsiness and nausea, with infrequent mention of GIT irritation.**

# Fenoprofen calcium

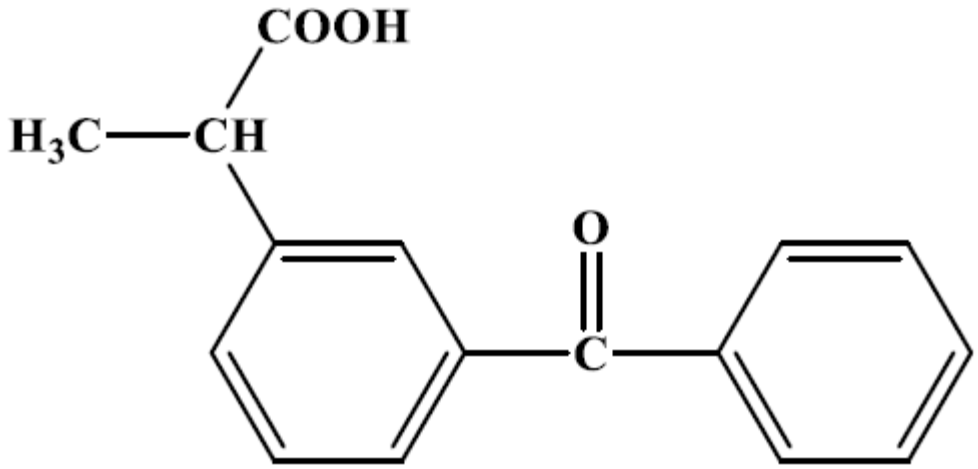



α-methyl-3-phenoxybenzeneacetic acid dihydrate calcium

**Uses: - RA and OA**

**S/E: - Gastrointestinal bleeding ,ulcers, dyspepsia, nausea, sleepiness, and dizziness.**

# Ketoprofen

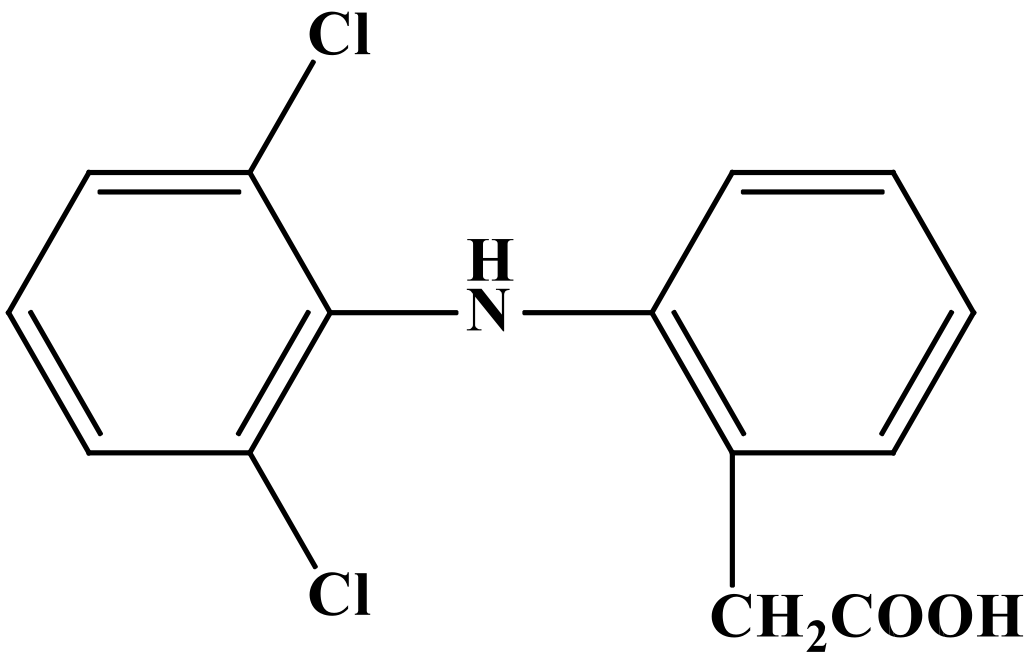



**α-methyl-3-benzoylbenzeneacetic acid**

**It is closely related to fenoprofen in structure, properties and indicator**

# Phenyl acetic acid derivative

## Diclofenac potassium and sodium

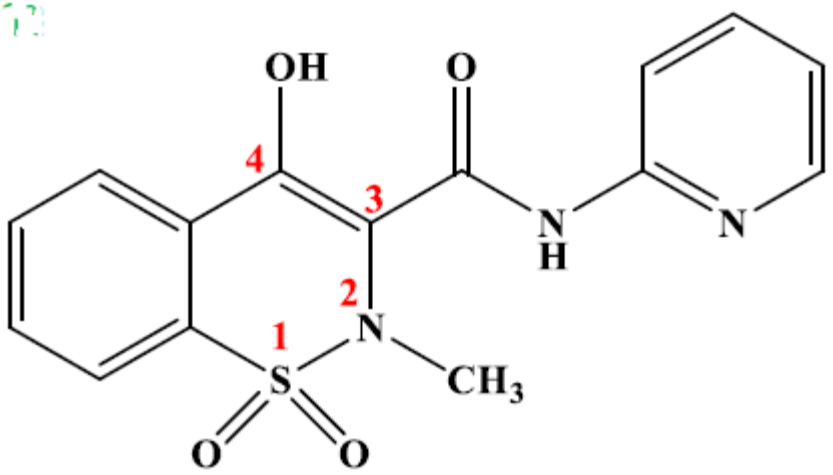



**[o-(2,6-dichloroanilino)phenyl]acetate**

**Uses- : RA and OA**

# Oxicams

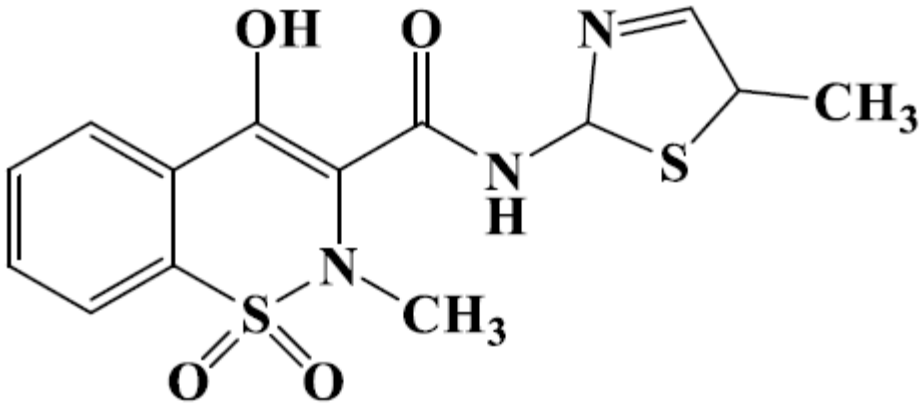
## •Piroxicam




**4-hydroxy-2-methyl-N-2-pyridyl-**
**2H- I,2-benzothiazine-3-carboximide- 1,1 -dioxide**

**It represents a new class of acidic inhibitors of prostaglandin synthetase, although it does not antagonize PGE2 directly. This drug is very long acting, and given once daily.**

# Meloxicam(Mobic)•

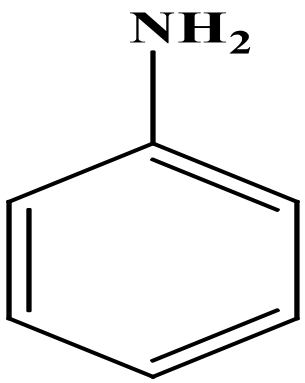



**4-hydroxy-2-methyl-N-(5-methyl-2-thiazoyl)-2H- I ,2-benzothiazine-3-carboxamide- 1,1-dioxid**

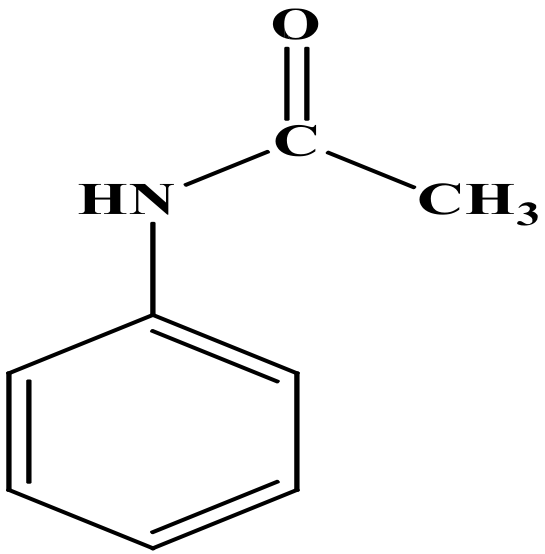
**Uses-: treatment of OA**

# Aniline and p-Aminophenol Derivatives

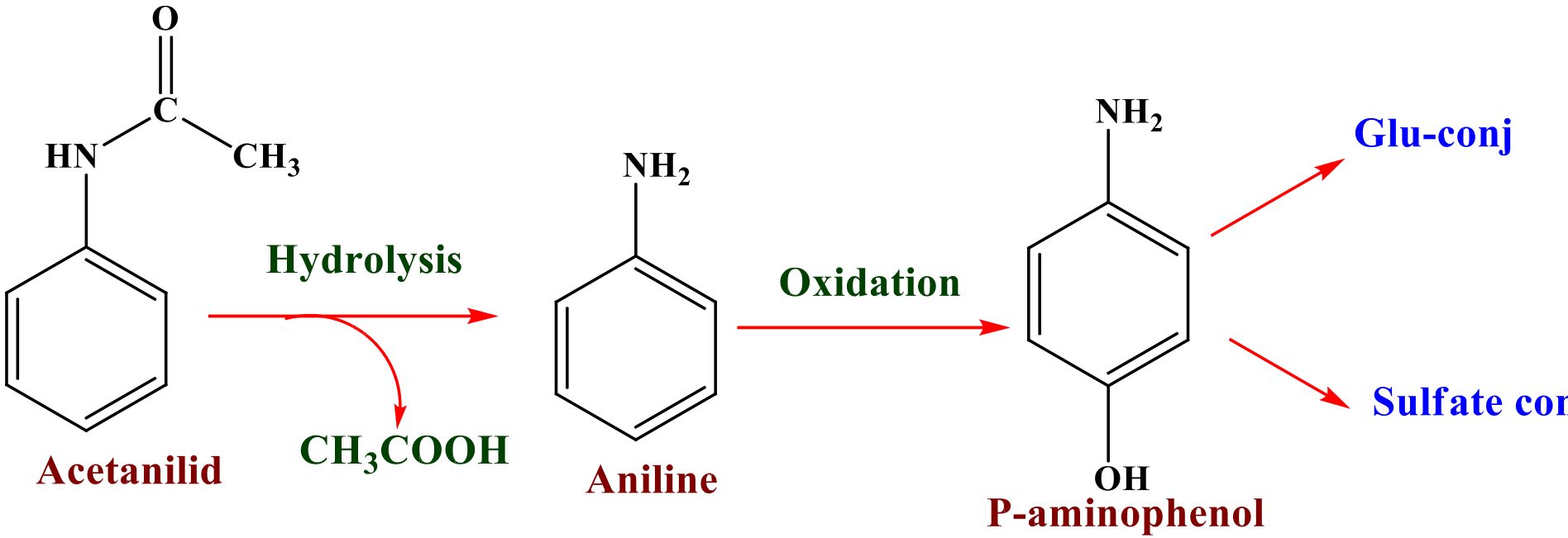
**Cahn and Hebb in 1886 discover that aniline and acetanilide, both have powered antipyretic properties, but aniline is toxic and cause methemoglobinemia. The acyl derivatives of aniline were thought to exert their analgesic and antipyretic effects by first being hydrolyzed to aniline and the corresponding acid, after which the aniline was oxidized to p-aminophenol. This is then excreted in combination with glucuronic or sulfuric acid.**




**Aniline methemoglobinemia**



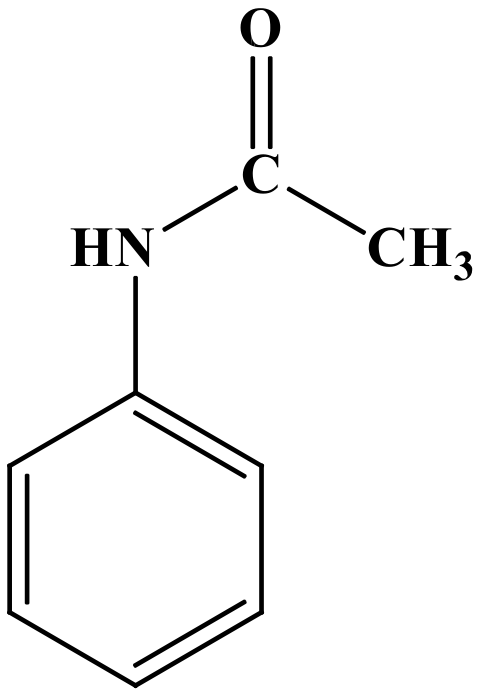

**Acetanilid**


O
C
HN
CH3
Acetanilid
Hydrolysis
CH3COOH
NH2
Aniline
Oxidation
NH2
OH
P-aminophenol
Glu-conj
Sulfate cor

# SAR of aniline

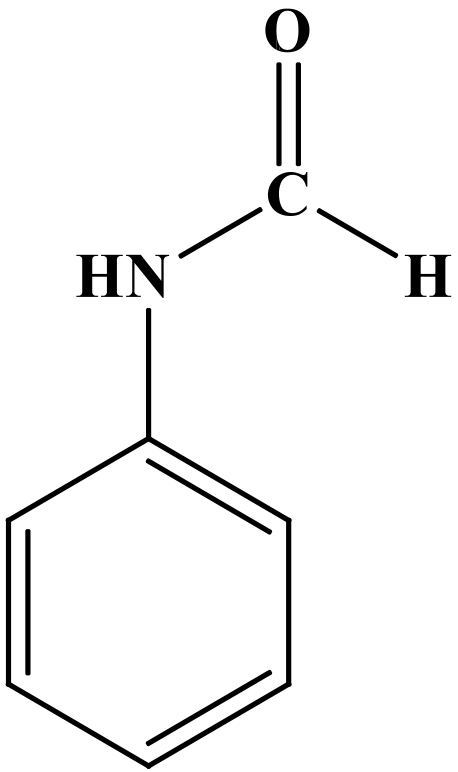
**In general, any type of substitution on the amino group that reduces its basicity also lowers its physiological activity.**

- **Acylation decrease the basicity as, acetanilid , but its toxic in large doses, but when administered in analgesic doses, it is probably without significant harm.**



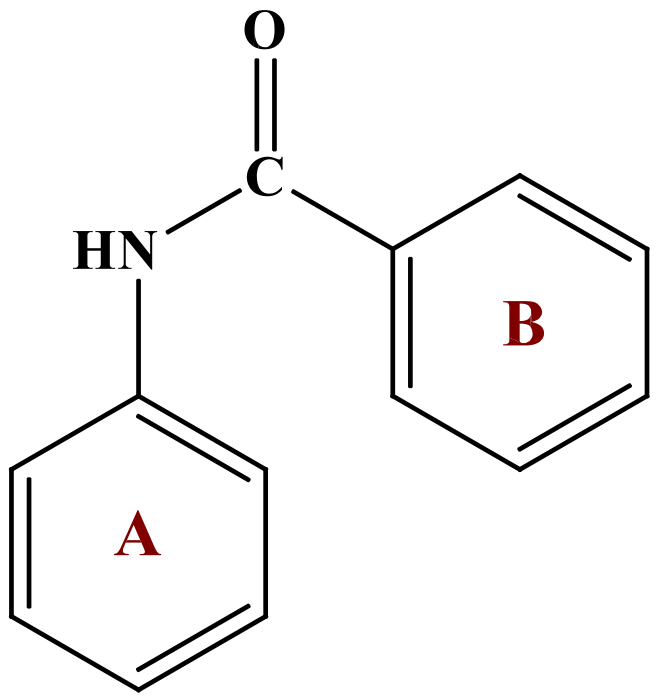

**Acetanilid**

**Formanilid is readily hydrolyzed and too irritant• .**



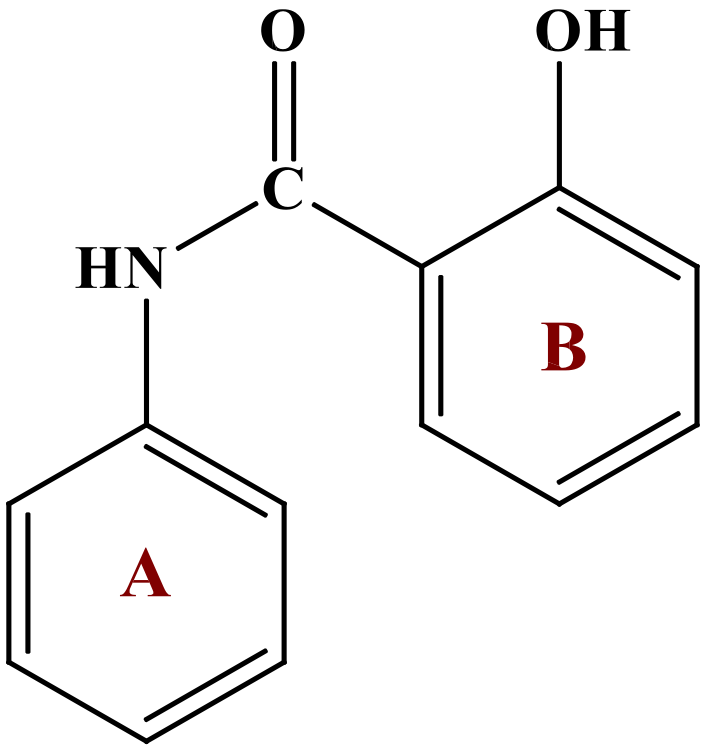

**Formanilid**

**Replacement of (H) atom of formanilid by• benzene ring to give benzeanilid, results in compound without analgesic and antipyretic activity and less toxic**



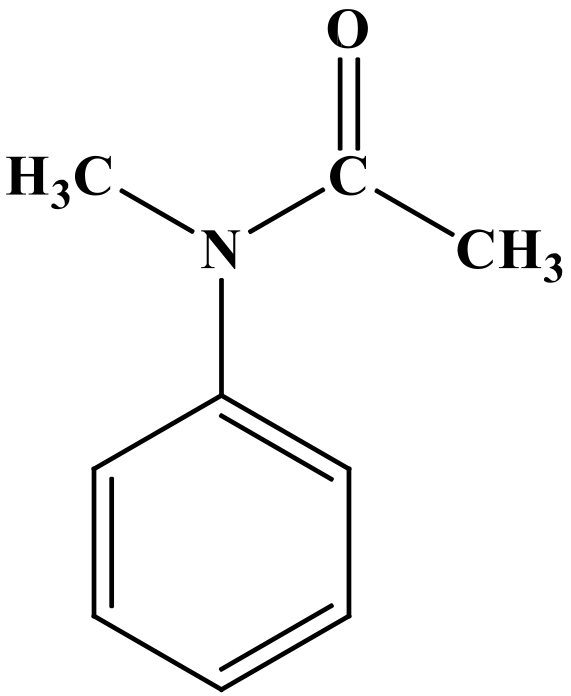

**Benzanilid**

- O-hydroxy substitution on the B phenyl ring of Benzanilid to give salicylanilid compound which is not an analgesic but is an antifungal.



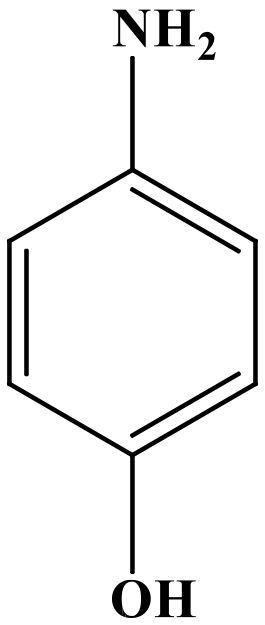

**Salicylanilid**
**antifungal without analgesic activity**

**N-methyl substitution of acetanilide to give exalgin• which is too toxic.**




**Exalgin (too toxic)**

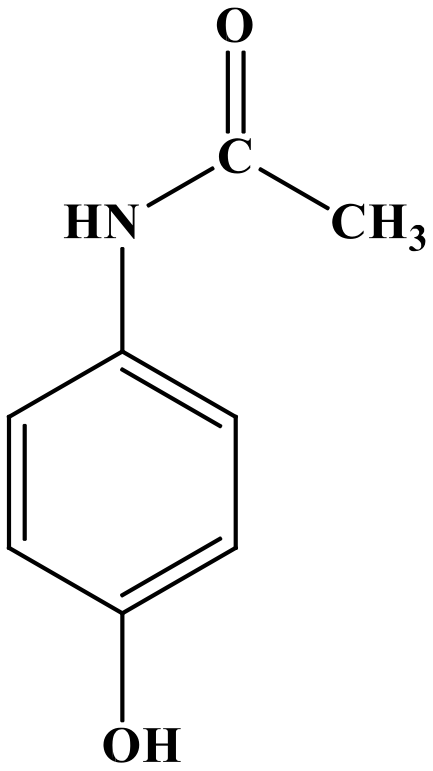
**The hydroxylated anilines (o, m, p), better known as the• aminophenols, are less toxic than aniline. The para compound (p-aminophenol) is the metabolic product of aniline, and it is the least toxic of the three possible aminophenols. It also possesses a strong antipyretic and analgesic action. It is too toxic to serve as a drug, however, and therefore, numerous modifications were attempted.**




***P*-aminophenol**

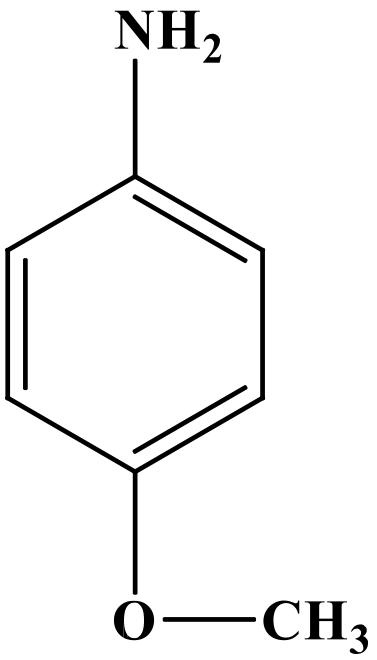
# SAR of p-aminophenol

- The acetylation of the amine group to provide N-acetyl-p-aminophenol (acetaminophen), which is a good analgesic agent.

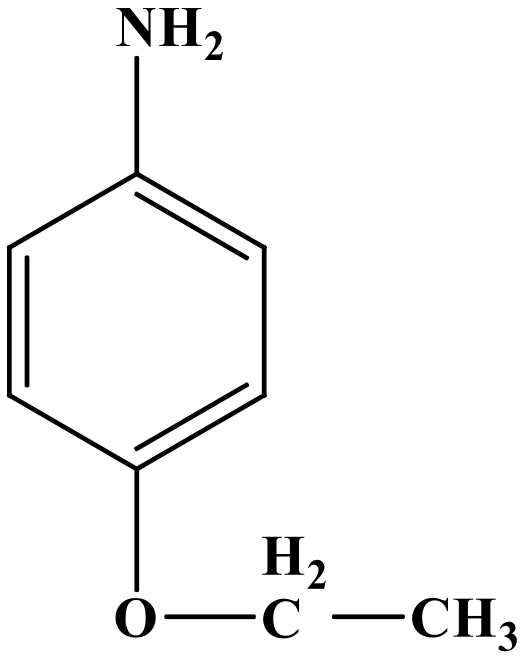



**Acetaminophen**
**N-acetyl-*p*-aminophenol**

Etherfication of the phenolic group this results in• detoxification of p-aminophenol like, anisidine and phenetidine), which are methyl and ethyl ethers, respectively, but the free amino group, cause MetHb in addition to antipyretic effect.

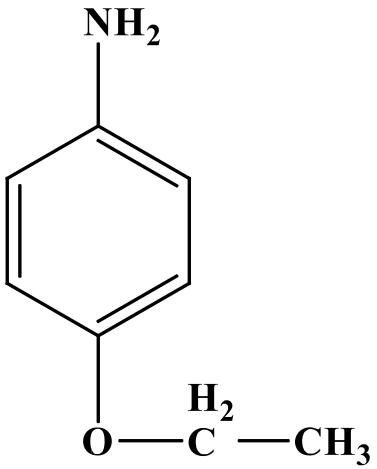



Anisidine

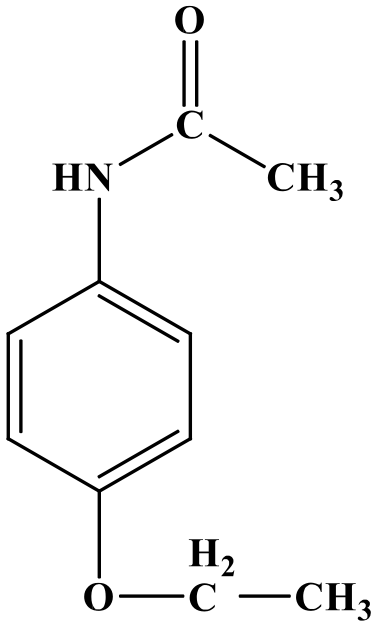



Phenetidine

**The ethyl ether derivative of acetaminophen• (phenacetine), does not cause MetHb because it not contain free amine group.**

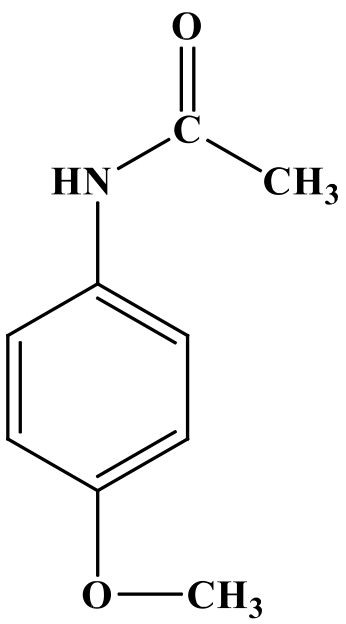


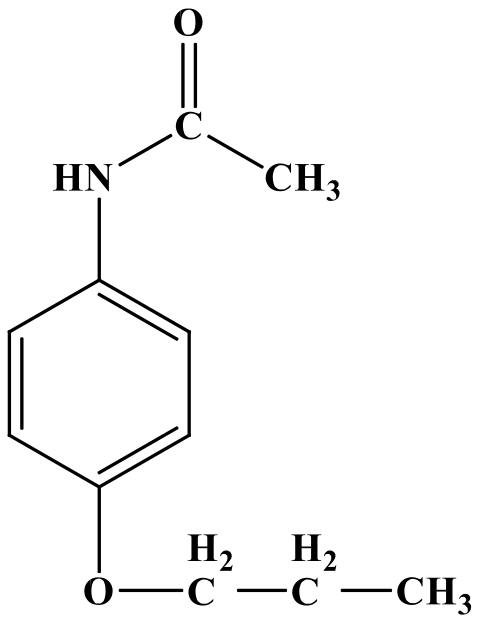

Phenetidine




Phenacetine

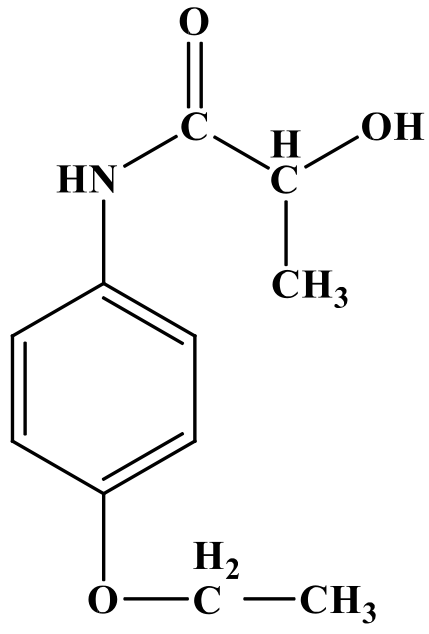
**Methyl and propyl analogs of phenacetin, are undesirable since they cause emesis, salivation, and diuresis.**



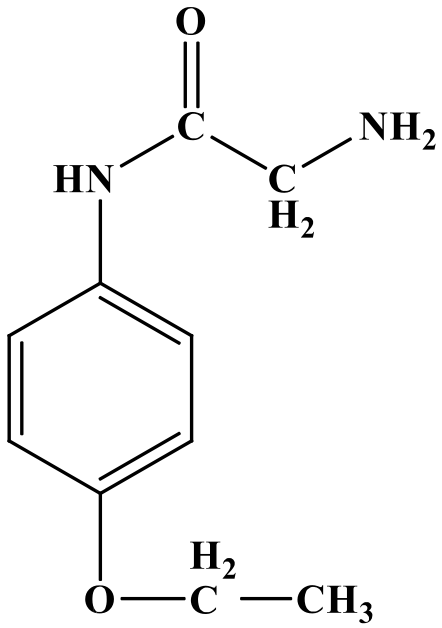




**Alkylation of the nitrogen with a methyl group potentiates the analgesic action but, has a highly irritant action on mucous membranes**

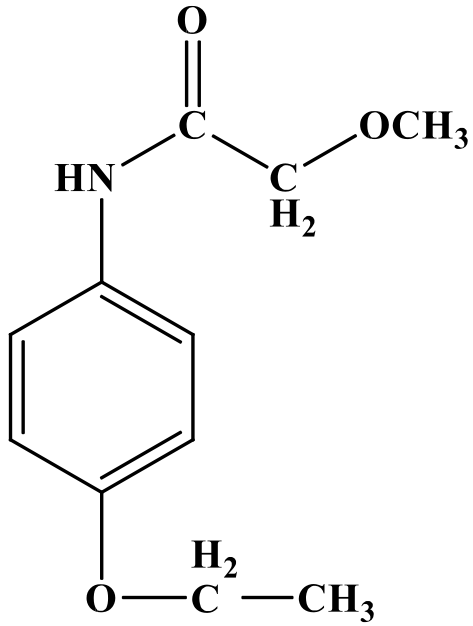
**The phenacetin molecule has been modified by• changing the acyl group on the nitrogen by –CO-C(OH -$CH_3$ (lactylphenetidin)- ,(CO-$CH_2NH_2$(phenocoll ), -CO -$CH_2$-O-$CH_3$ kryofine . None of these, however, is in current use.**




Lactylphenetidine



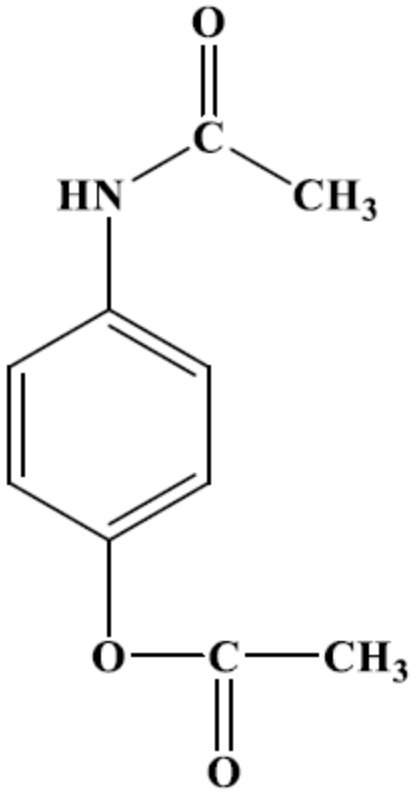

Phenocoll



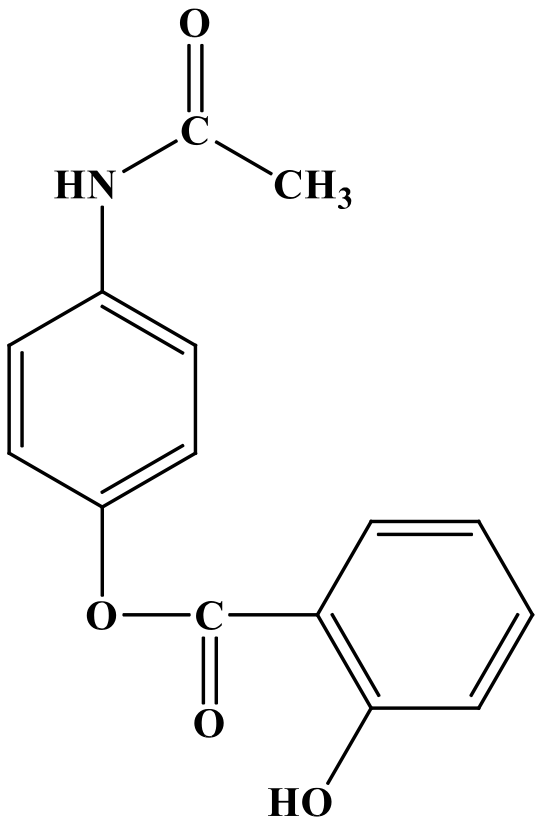

Kryofine

**Changing the ether group of phenacetin to an acyl type of• ' derivative has not always been successful.**

**•p-Acetoxyacetanilid has about the same activity and disadvantage as the free phenol.**

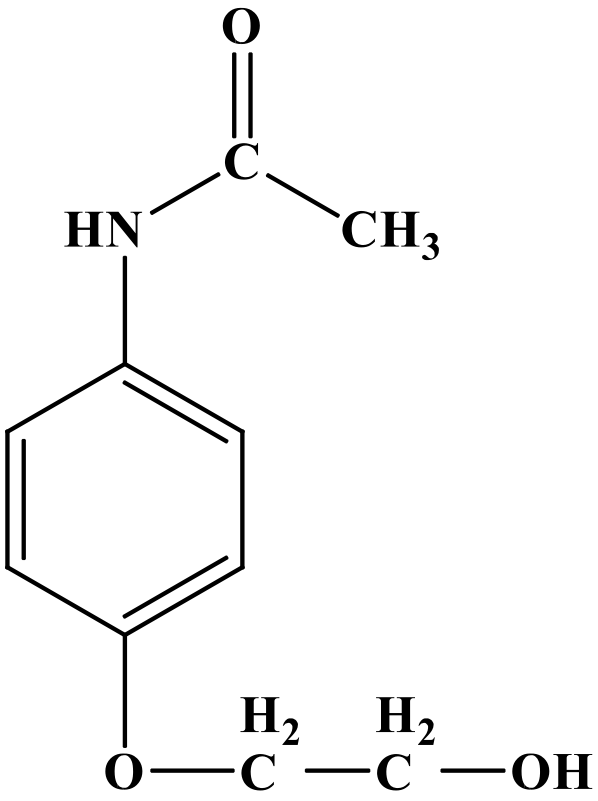


**The salicyl ester of phenacetine, which is called• phenetsal have less toxicity and increased antipyretic activity.**

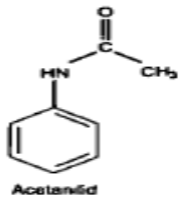



**Phenetsal**

**Pertonal is a somewhat different type in which glycol has been• used to etherify the phenolic hydroxyl group. It is very similar to phenacetin.**

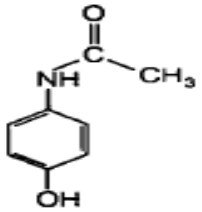



**Pertonal**



Acetanilid

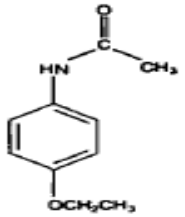
CYP 450



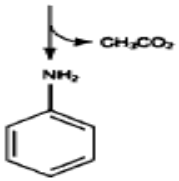
Acetaminophen

CYP450

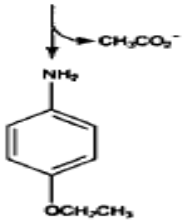
$CH_3CHO$



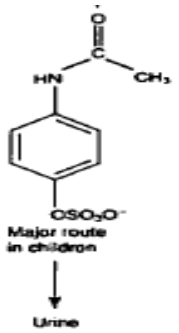
Phenacetin



Aniline
Methemoglobinemia; hemolytic anemia

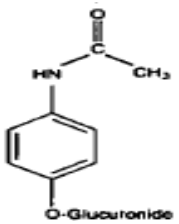


P-phenelidin
Methemoglobinemia; hemolytic anemia; nephrophathy

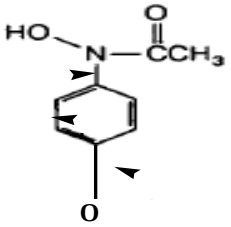


Major route in children

Urine



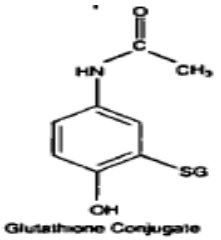
O-Glucuronide



H

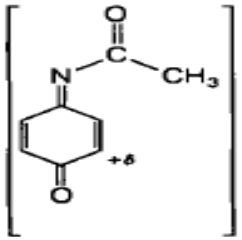
N-hydroxyacetaminophen

Direct renal excretion



Glutathione Conjugate

GSH



*N*-Acetylimidoquinone

Pathway when %70of the liver glutathione is depleted

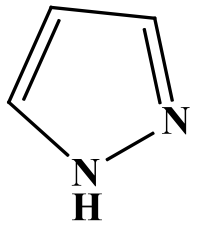
Covalent binding to the hepatic liver cell structure

Hepatic necrosis ; renal failure

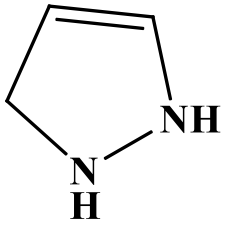
## Pyrazolone and Pyrazolidinedione derivatives

**The simple doubly unsaturated compound containing two nitrogen and three carbon atoms in the ring, with the nitrogen atoms neighboring, is known us pyrazole. The reduction**

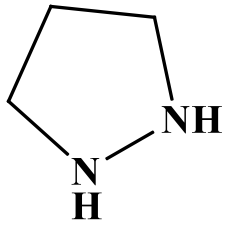
**Products, named as are other rings of five atoms, arepyrazoline and pyrazolidine. Several pyrazoline substitution products are used in medicine. Many of these are derivatives 5-pyrazolone. Some can be related to 3.5-pyrazolidinedionc**



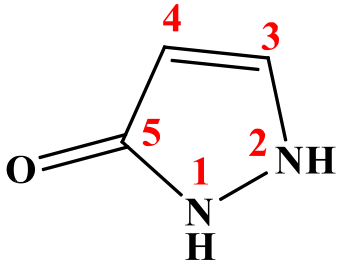

Pyrazole



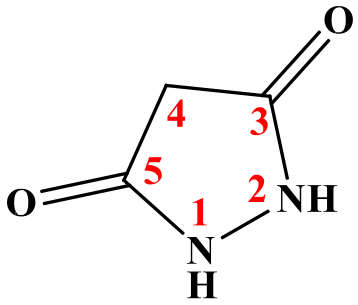

Pyrazoline




Pyrazolidine

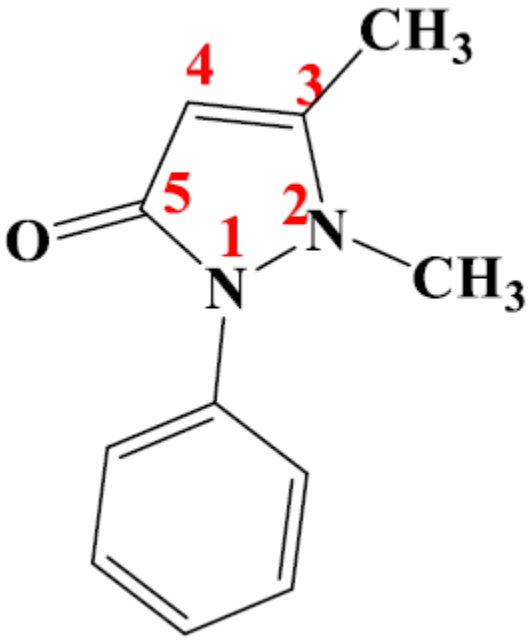



5-Pyrazolone




3,5-Pyrazolidinedione

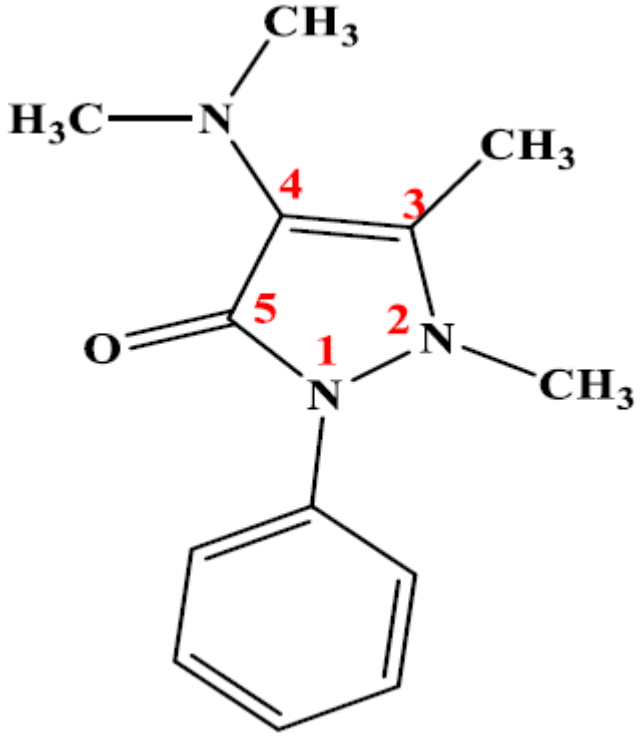
# Antipyrine•




**2,3-dimethyl-l-phenyl-3-pyrazolin-5-one**

**used to reduce It pain, fever in neuralgia, the myalgias, migraine, other headaches, chronic rheumatism, and neuritis, but it is less effective than salicylates and more toxic.**

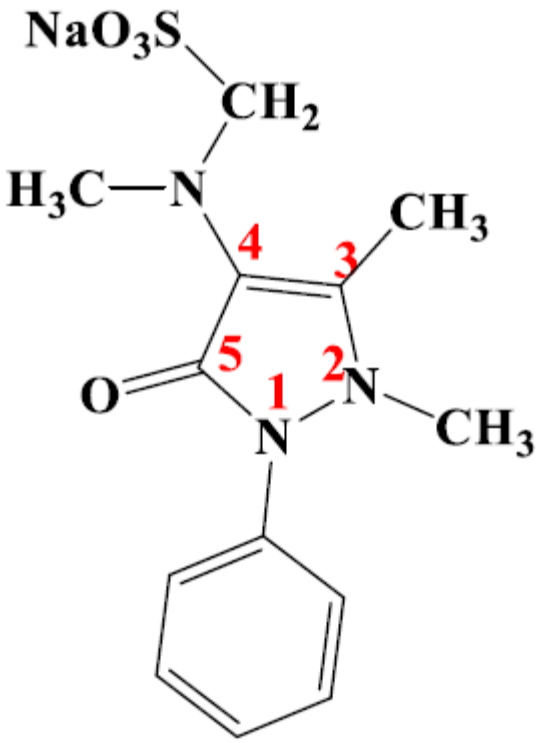
# Aminopyrine•




**2,3-dimethyl-4-dimethylamino-l-phenyl-3-pyrazolin-5-one**

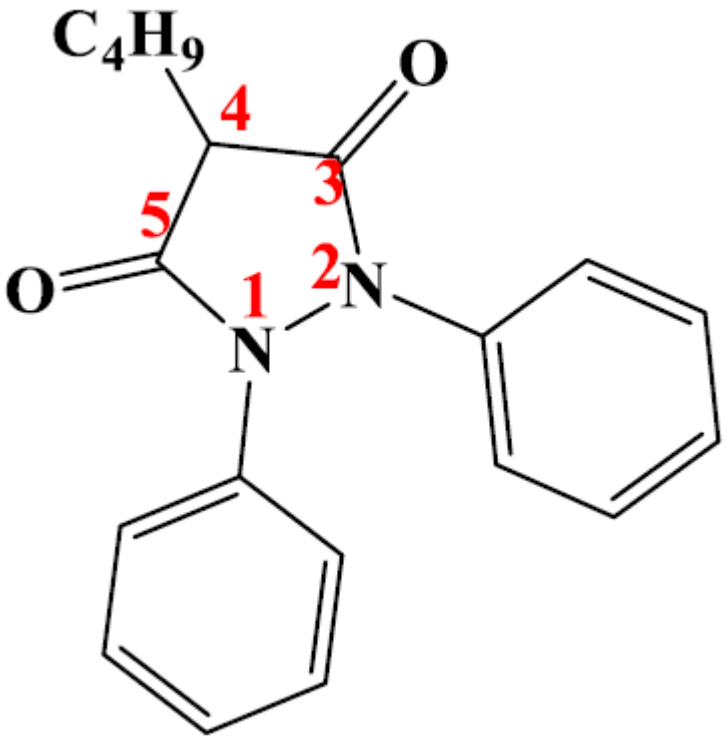
**It has more powerful, longer duration but slower onset of analgesic action than antipyrine.**

# Dipyrone •




**It is used as an analgesic, an antipyretic, and an antirheumatic.**

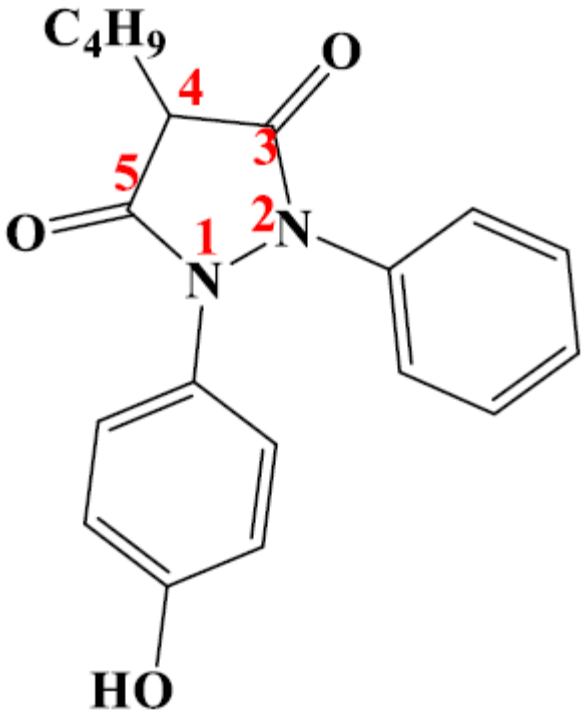
# Phenylbutazone•




**4-butyl-1,2-diphenyl-3,5-pyrazolidinedione**

**it is used in treatment of painful symptoms associated with gout, rheumatoid arthritis and spondylitis and painful shoulder.**

# Oxyphenbutazone•




**4-butyl-1-(p-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione**

Exactly similar to phenylbutazone