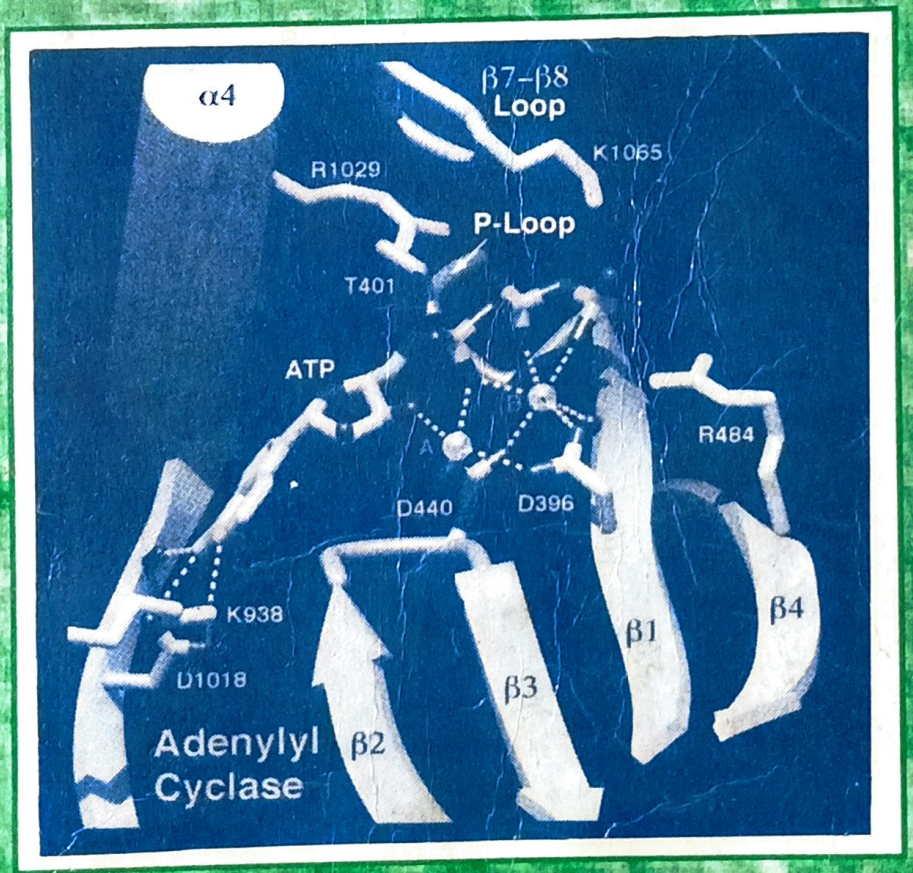
A TEXT BOOK OF MEDICINAL CHEMISTRY

(Synthetic & Biochemical Approach)

[Vol - I]



Surendra N. Pandeya

CHAPTER 16

NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

Many drugs that are not steroids can cure or prevent inflammation. Such drugs include penicillin when given for a streptococcal sore throat, colchicine when given for acute gout or allopurinol when given for chronic gout. Each of these drugs, under their clinical circumstances, might be called a non-steroidal antiinflammatory drug or NSAID.

These agents can be divided chemically into the following groups :

1. Carboxylic acids :

a. Salicylates (Aspirin) b. Acetic acids : Indomethacin c. Propionic acids : Ibuprofen d. Fenamates : Meclofenamic acid

2. Pyrazoles : Phenylbutazone

3. Oxicams : Piroxicam

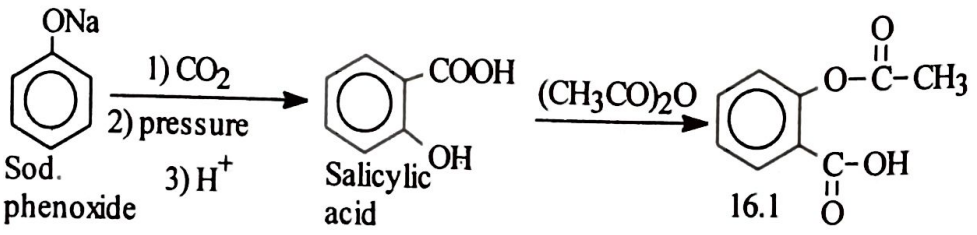
1. Carboxylic acids

a. Salicylates

These are derivatives of salicylic acid and used for initial therapy for active rheumatoid arthritis, jaundice arthritis, and osteoarthritis and is the most commonly used analgetic-antipyretic. It is used in the treatment of diseases associated with platelet hyperaggregability e.g. coronary artery disease and post operative deep vein thrombosis.

Acetyl salicylic acid (ASA) (aspirin, 16.1) is a prodrug of salicylic acid.

Synthesis (Scheme 16.1)

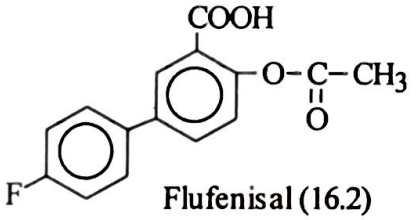


Scheme 16.1

The development of gastric damage is the most prevalent side effect associated

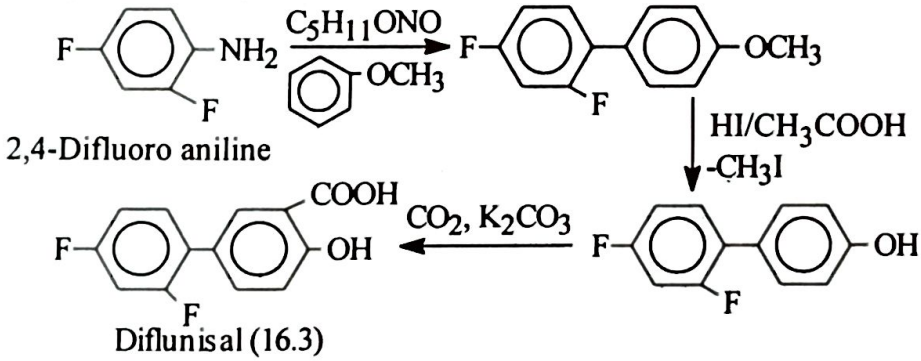
with ASA therapy. Daily blood loss of 2 to 6 ml occurs in at least 50% of the general population consuming 1 to 3 g of aspirin daily. It is widely used to relieve headache, muscle and joint aches and dysmenorrhoea. The used dose is 0.6g every 4h, but a more desirable dose is 0.3g every 3h.

The simplest active antiinflammatory compound is the salicylic acid anion. The carboxyl group is necessary for activity, and the hydroxyl group must be adjacent to it. Halogenated derivatives are active but toxic. Synthesis of aspirin derivatives containing a hydrophobic aryl group in position 5 has led to greater antiinflammatory activity than is found with aspirin. Modification systematically made on the aromatic ring of salicylic acid led to O-acetyl-4-fluorophenyl salicylic acid (flufenisal 16.2) a compound twice as potent as ASA in animal models of inflammation. 2,4-Difluorophenyl analog (Diflunisal 16.3) indicated to be more potent and has weak gastrointestinal side effects associated with aspirin. A long plasm half-life in man, 7.5 to 12 h allows the administration of diflunisal first twice a day.



Flufenisal (16.2)

Synthesis (Scheme 16.2)



2,4-Difluoro aniline

Diflunisal (16.3)

Scheme **16.2**

Diflunisal is reported not to bring about intestinal bleeding.

Salicylic acid I.P.

Properties and uses : colorless, feathery powder with a sweetish taste. Soluble in boiling water and freely soluble in alcohol, melting range 158-161°C.

Identification : Gives the test of salicylates.

Limits of Impurities : Heavy metals. Test with 1.0g of the substance using H_2S solution and standard lead solution. Iron. A sample (12.0g) is dissolved in dilute ammonia solution (14ml) and water (35ml), adjust pH 5-6. Any pink colour is not deeper than the obtained by boiling 2.0g of the standard iron solution. Sulphated Ash. Not more than 0.1 percent. Loss on drying not more than 0.5 percent. Readily

carbonisable substances. A sample (0.5g) is dissolved in sulphuric acid (5ml); the solution is not more coloured than a mixture of 0.1ml of cobalt chloride, 0.5ml of ferric chloride, 0.1ml of copper sulphate and 4.2ml of water.

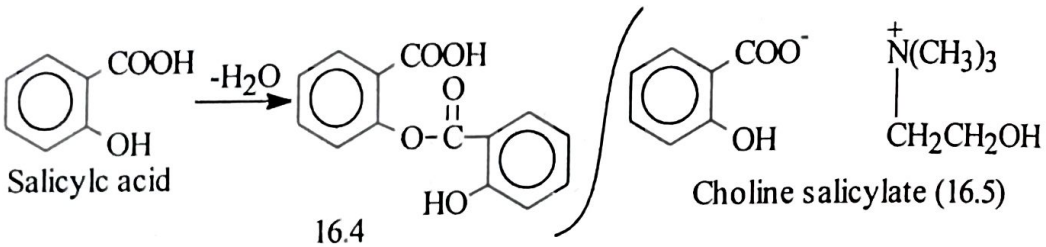
Assay : A sample (2.0g) is dissolved in warm alcohol (15ml), add water (20ml), and titrate with 0.5N NaOH, using phenol red solution.

1 ml of 0.5N NaOH = 0.06905g of salicylic acid.

Other salicylic acid derivatives include :

Salasalate (Duragesic 16.4)

It is a dimer of salicylic acid in which the carboxyl group of one salicylate molecule is linked to the hydroxyl group of several salicylate molecules, in effect producing a prodrug of salicylic acid. Toleration of salsalate has been observed to be better than that of ASA, with a lower incidence of gastric irritation and fecal blood loss.



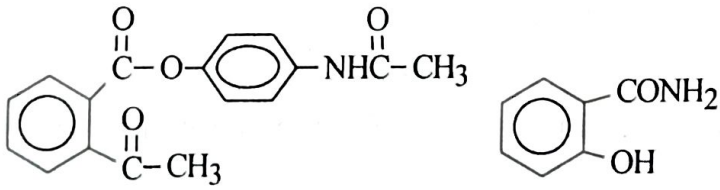
Salicylc acid 16.4 Choline salicylate (16.5)

Choline Salicylate (16.5)

It has been used in cases of jaundice rheumatoid arthritis in which aspirin did not give adequate control or caused gastric irritation. It is very soluble in water and is absorbed faster than aspirin.

Benorylate (Benorsal)

It is an ester of acetate/salicylic acid with acetaminophen 16.6. Salicylamide 16.7 has been suggested as an effective substitute for aspirin in rheumatic disease.

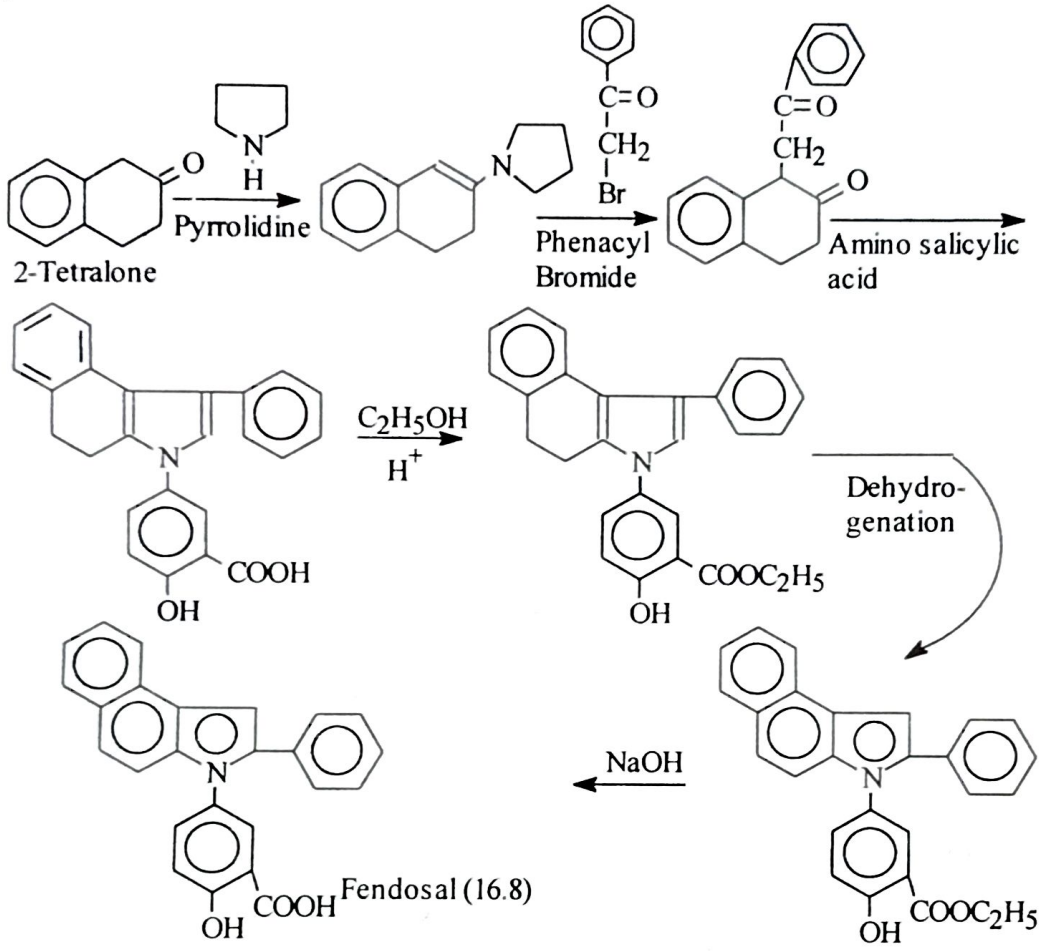


16.6 16.7

Fendosal (16.8)

It is an indole salicylic acid. Introduction of a bulky group into the salicylic acid molecule, that exhibits anti-inflammatory and analgesic activity in animals slightly greater than that of ASA.

Synthesis (Scheme 16.3)



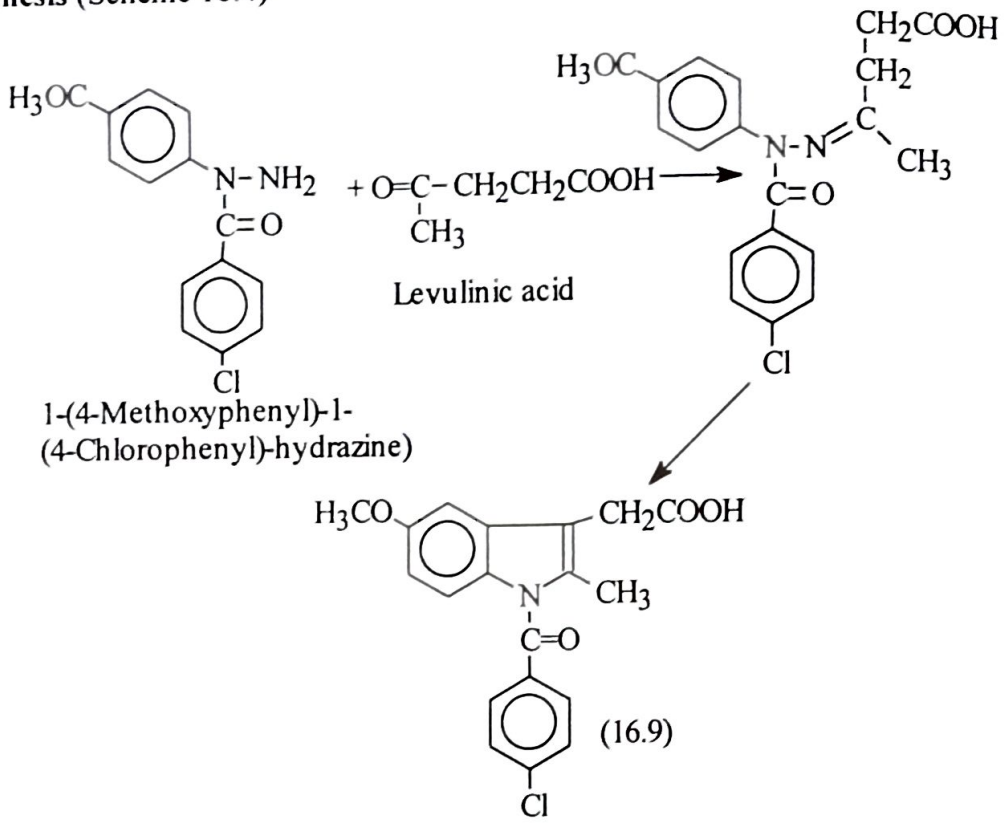
Scheme **16.3**

(b) Acetic acids

Indomethacin I.P. (Indocin) : 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (16.9)

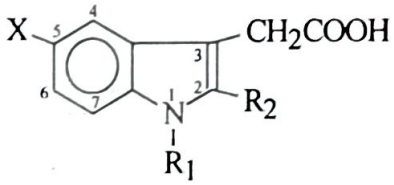
It is among the earliest non-salicylate compounds to be discovered and developed for use as an antiinflammatory agent. It can be synthesized from a 1,1-disubstituted hydrazine and levulinic acid.

Synthesis (Scheme 16.4)



Scheme **16.4**

Structure Activity Relationship



(i) Substituents R_1 useful for increasing antiinflammatory activity are ranked as $R'C_6H_4CH_2$ > alkyl > H; (ii) R_2 substituents for improved activity are ranked CH_3 > H; (iii) X substituents are ranked 5-OCH_3 > $(CH_3)_2N$ > CH_3 > H. The carboxyl group is necessary for antiinflammatory activity. A para halogen for halogen equivalent, such as CF_3 or SCH_3, substituted in the 1-benzoyl group provides the greatest activity. At position 2, a methyl group is better than an aryl group. At the alpha position of the side chain, a hydrogen and a methyl group are roughly equivalent. At position 5 of the ring methoxy, allyloxy, dimethylamino, acetyl, methyl, and fluoro functions are superior to hydrogen or chlorine. The 3-acetic acid side chain is free to rotate to assume different conformations. In a-methyl analog, anti-inflammatory activity was displayed only by the dextrorotatory enantiomorphs with similar absolute configuration. It has 25 times the activity of phenylbutazone.

Properties and uses : Pale yellow, crystalline powder without any taste, practically insoluble in water, melting range 158-162°C.

It benefits 25% of rheumatoid arthritis patients by relieving pain, reducing

swelling and tenderness of the joints. A typical dosage schedule is 25mg twice daily. Side effects headache, nausea and diarrhoea. Peptic and jejunal ulcers have been reported.

Identification : (a) Prepare a solution of the sample (0.3g) in methyl alcohol (15ml). (i) To one portion add sodium hydroxide (5ml of 0.1N NaOH), the colour changes from yellow to greenish yellow and finally to very pale yellow. (ii) Another portion is treated with HCl (2.5ml) a white precipitate is produced and the supernatant liquid becomes very pale yellow. (b) A Solution is prepared in dilute sodium hydroxide solution in 100ml water. A small portion is treated with sodium nitrite and sulphuric acid, a deep yellow colour is produced.

Limits of Impurities : Heavy metals. Not more than 20ppm. Sulphated ash. Not more than 0.2 percent. Loss on drying. Not more than 0.5 percent. Foreign substances. Determine by TLC method using silica gel HF254 and solvent ether (70ml), light petroleum (40^{o}-60^{o} 30 ml) as a mobile phase. Maxima at 254nm. Alkaline Hydrolysis - refer to assay in which the difference of standard solution and sample solution volumes should be between 27.25-28.25ml.

Assay : Dissolve the sample (0.45g) in CO_2 free-nitrogen methyl alcohol (75ml). The entire operation is done in the nitrogen atmosphere. Add water (75ml) and titrate with 0.1N NaOH using phenolphthalein. Similarly a blank experiment is also run.

1ml of 0.1N NaOH = 0.03578g of indomethacin.

Storage : well-closed, light resistant containers.

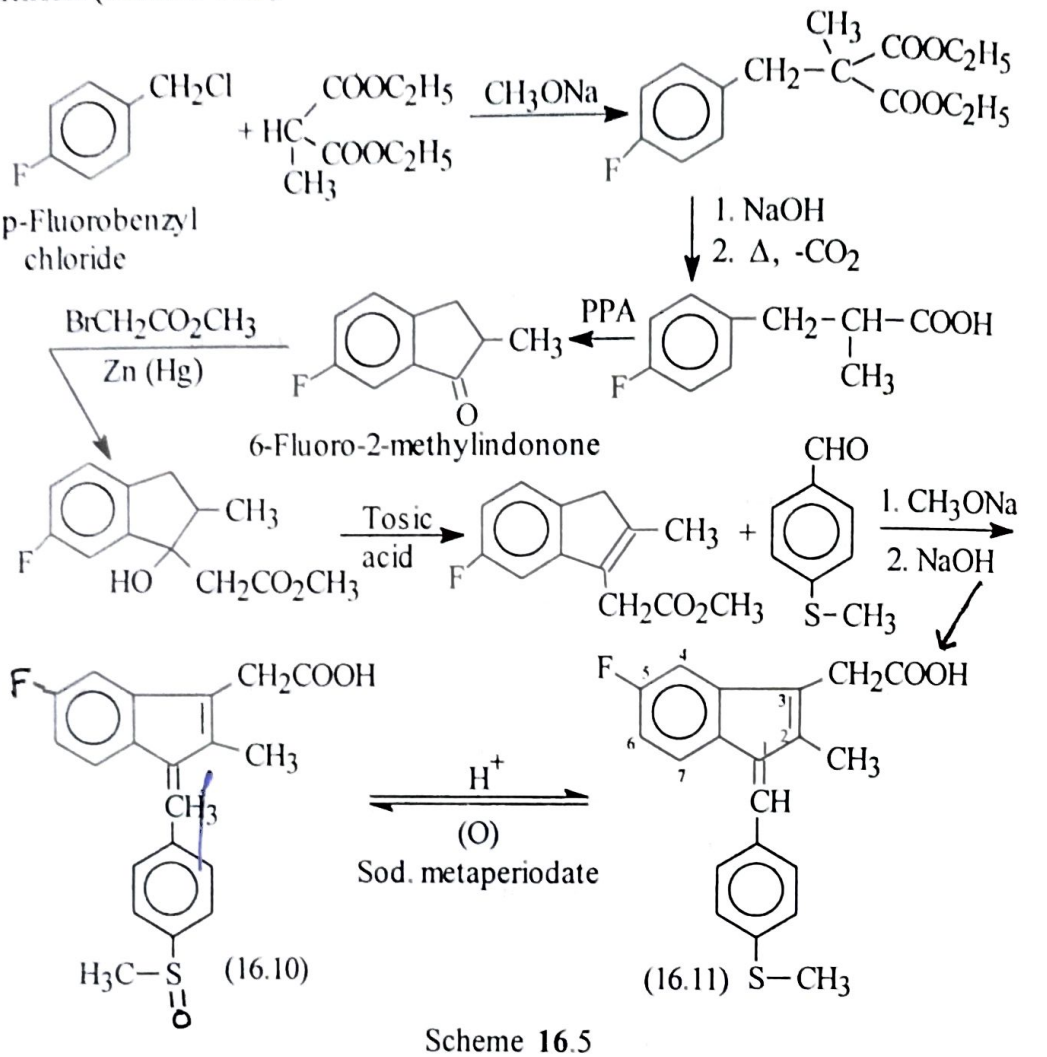
Preparation : Indomethacin capsules I.P. 25mg.

Dose : 75-100mg daily, in divided doses.

Sulindac (Clinoril) : cis-5-fluoro-2-methyl-1-(p-methyl-sulfinyl) benzylidene) indene-3-acetic acid (16.10)

In an effort to produce a nonindole NSAID with reduced central nervous system and gastric irritancy side effect of Indomethacin, some benzylidene indene acetic acids were synthesised. These compounds are considered electronically isosteric with N-acyl indole structure of indomethacin 16.9. The cis-isomer is five times as potent as the trans-isomer. Further molecular modification of the indene isostere by substitution of a fluorine atom and a methylsulfinyl group in order to increase the solubility while retaining the potency, gave sulindac.

Synthesis (Scheme 16.5)



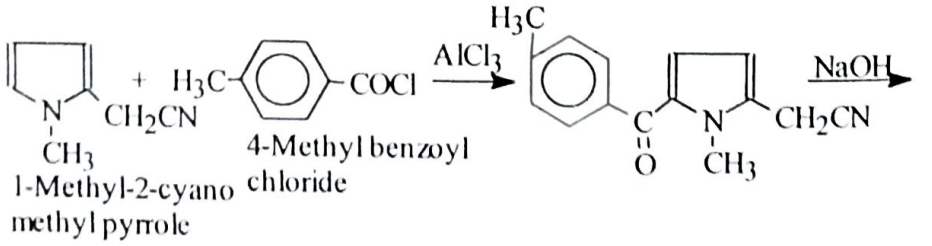
Scheme **16**.5

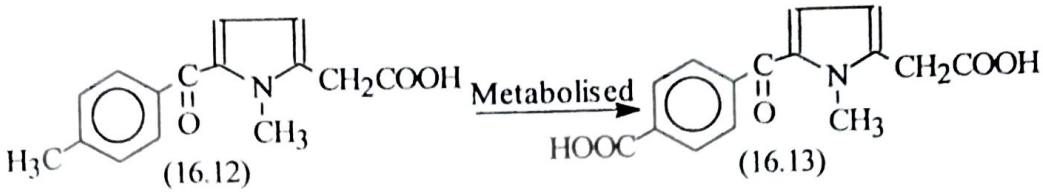
In humans, sulindac behaves as a prodrug for the more active sulfide metabolite (16.11), which is generally more potent than sulindac. The metabolism of sulindac to the long acting sulfide (18 hrs) leads to prolonged therapeutic effect for sulindac, which allows it to be given only twice daily (300-400mg).

Tolmetin (Tolectin) : Sodium-1-methyl-5-p-toluoylpyrrole-2-acetic dihydrate. 16.12.

Replacement of the indole ring system of indomethacin by a pyrrole ring produces the pyrrole acetic acid, tolmetin (16.42). It is metabolized to the dicarboxylic acid 16.13.

Synthesis (Scheme 16.6)



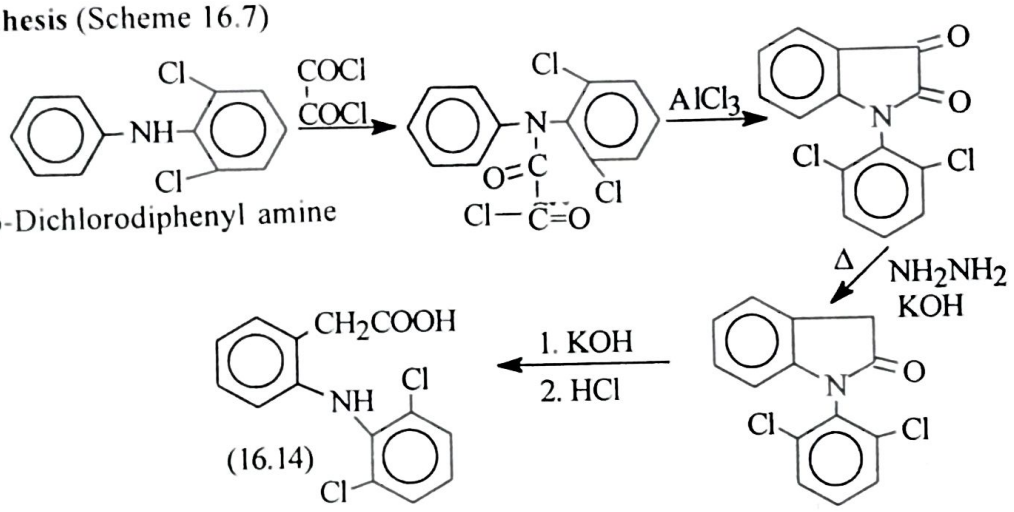


Scheme **16.6**

Doses of Tolectin in human trials range between 800-1200mg/day given in 3 or 4 divided doses.

Diclofenac sodium (voltaren sodium) : o-(2,6-dichloroanilino)-phenyl) acetate (16.14)

Synthesis (Scheme 16.7)

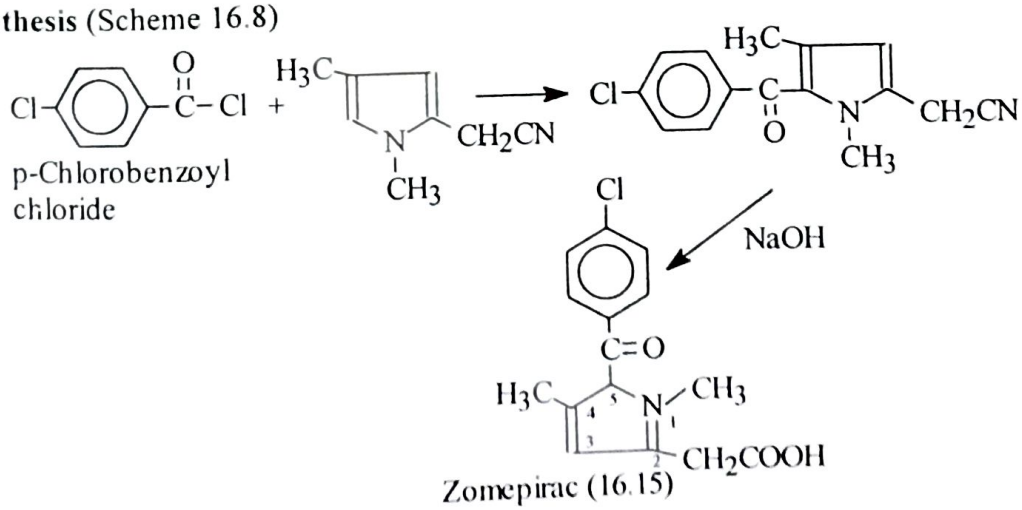


Scheme **16.7**

A relatively low recommended daily dose of 75 to 150mg for treating arthritic patients is evidenced of its high antiinflammatory potency. It ranks second in sales (1983) world wide.

Zomepirac : (Zomax) : 5-(p-chlorobenzoyl)-1,4-dimethyl-pyrrole-2-acetic acid (16.15).

Synthesis (Scheme 16.8)



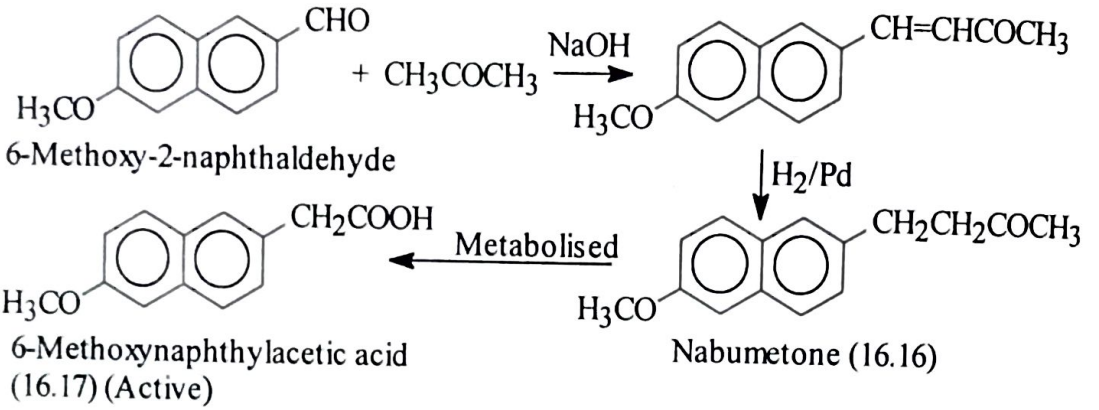
Scheme **16.8**

A greater degree of analgesia for severe pain is claimed for zomepirac.

Nabumetone (Relafen) 16.16; 4-(6-Methoxy-2-naphthyl)-2-butanone

Prodrug approach is therapeutically useful in the development of less gastrotoxic NSAIDS, since after oral administration, the GI tract is exposed primarily to the pharmacologically inactive prodrug, while the active NSAID is ultimately generated *in vitro* for systemic activity. Nabumetone is a non-acidic, prodrug and is converted by first-pass biotransformation in the liver to 6-methoxynaphthyl acetic acid (16.17), an effective inhibitor of prostaglandin synthesis and cyclooxygenase.

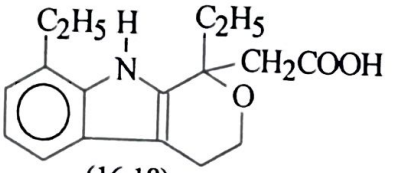
Synthesis (Scheme 16.9)



Scheme 16.9

Nabumetone is indicated in the treatment of acute and chronic treatment of osteoarthritis and rheumatoid arthritis. The recommended starting dose is 1g as a single dose with or without food once or twice daily.

Etodolac (16.18)



(16.18)

It has antiinflammatory activity and inhibits cyclooxygenase. It is used in the treatment of osteoarthritis and rheumatoid arthritis. Gastrointestinal irritation and ulceration is less with this drug than other drugs.

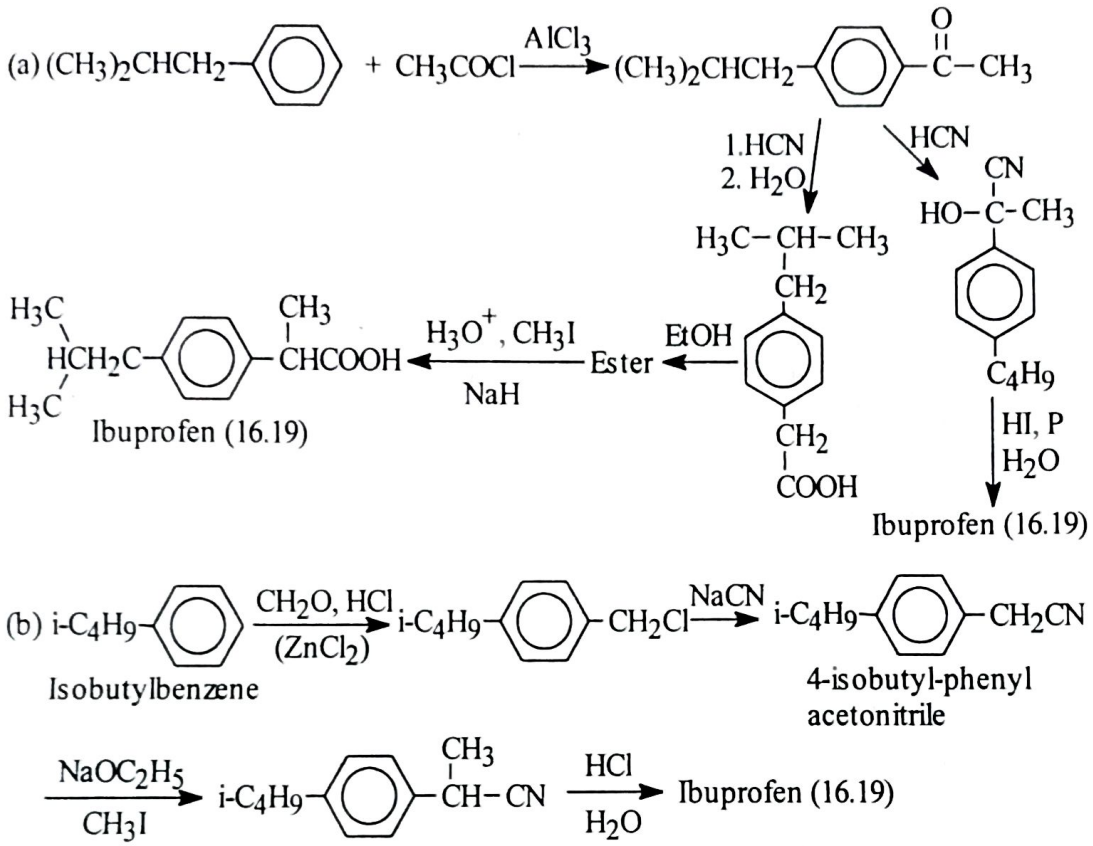
(c) Propionic acids

The ending "Profen" denotes phenylpropionic acid.

Ibuprofen I.P. (Motrin, 16.19)

It is one in a series of antiinflammatory phenyl alkanoic acids and is most widely used NSAID in the world.

Synthesis (Scheme 16.10)



Scheme **16**.10

Properties and uses : white, crystals, insoluble in water and freely soluble in alcohol. Melting range 75-78°C. Useful as analgesic, antiinflammatory and anti-pyretic property. It is indicated for relief of symptoms of rheumatoid arthritis and osteoarthritis. It can inhibit platelet function and prolong bleeding time and may cause less gastric distress than does aspirin. The usual recommended dosage form is (a 800mg tablet given upto four times a day).

Identification : A sodium hydroxide solution (0.1N) exhibit maxima at 264 and 273 nm with extinction coefficient 0.47 and 0.39 respectively.

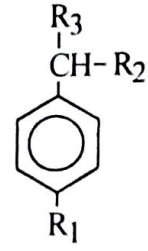
Limits of Impurities : Heavy metals. Not more than 10 ppm. Sulphated Ash. Not more than 0.1 percent. Loss on drying. Not more than 0.5 percent. Related substances. Determined using TLC method. Solvent system : n-hexane; ethyl acetate : glacial acetic acid : 15 : 5 : 1. A standard sample with 0.1 percent solution is also prepared. The two are compared. There should not be any other spot besides the principal spot of ibuprofen.

Assay : A sample (0.5g) is dissolved in alcohol (100ml). Titrate with 0.1N NaOH using phenolphthalein solution as indicator.

1ml of 0.1N NaOH ≡ 0.02063g of ibuprofen.

Storage : in well-closed containers. **Preparation** : Ibuprofen Tablets I.P. 0.2g.

Structure Activity Relationship



(1) The size of the substituent R_1 : Maximum activity was present in the isobutyl substituent, with reduced activity for small substituents (e.g. $-CH_3$, $-CH_2CH_3$) and sharply reduced activity for longer R_1 substituents (e.g. $(-CH_2)_4-CH_3$) and $(CH_2)_5-CH_3$).

(2) The maximal activity is found with $R_2 = CH_3$. Smaller (R_2 = H) / larger ($R_2 = CH_2CH_3$) or ($CH_2CH_2CH_3$) diminish activities.

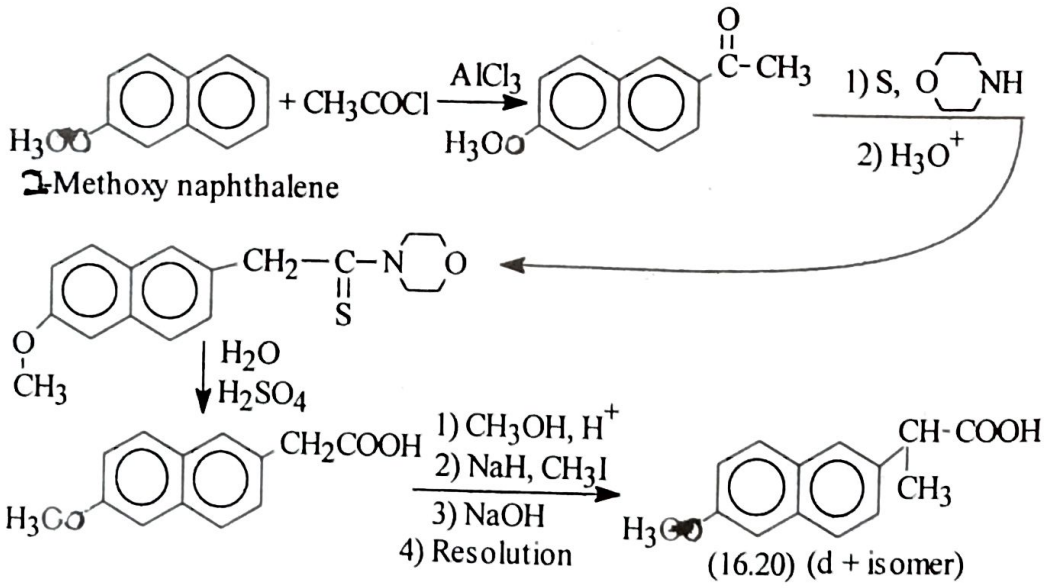
(3) Replacement of the carboxylic function by an ester ($COOC_2H_5$), alcohol (CH_2OH), amide ($R_3 = CONH_2$), hydroxamic acid (R_3 = NHOH) or tetrazole ($R_3 = CHN_4$) generally produces less active compounds.

(4) The anti-inflammatory activity resides in the S(+) isomer.

Naproxan (Naprosyn) : ((+)-2-(6-methoxy-2-naphthyl)-propionic acid 16.20.

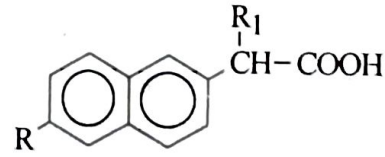
Naproxen was designed not to contain a nitrogen atom, which may be responsible for some of the observed side effects of indomethacin.

Synthesis (Scheme 16.11)



Scheme 16.11

Structure Activity Relationship



1. Activity is reduced when $OCH_3(SCH_3)$ is larger as R.
2. The carboxyl group may be replaced by alcohol and aldehyde.
3. Dextro-rotatory isomer is 11 times more active than phenylbutazone.

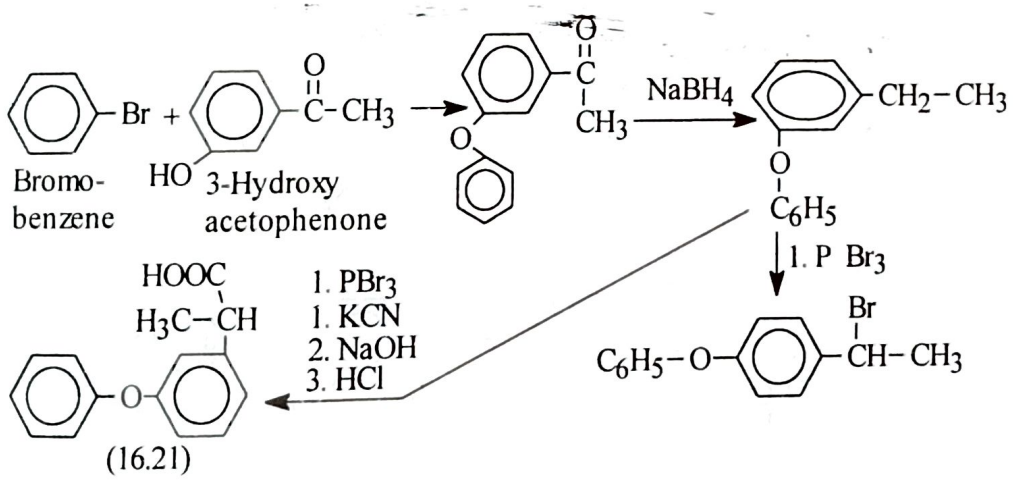
The recommended starting dose of naproxen in rheumatoid arthritis is 250mg orally, twice daily. The metabolising naproxen produces the demethylated compound, its glucuronide and sulfate derivatives, and naproxen glucuronide. The sodium salt of naproxen (Flanx) is being marketed as an analgesic agent.

Fenoprofen calcium (Nalfon) : Calcium (±)-2-(3-phenoxyphenyl) propionic acid.16.21.

A phenyl propionic acid with an m-phenoxy substituent, is structurally similar to ibuprofen.

Increasingly larger α-substituents produce compounds with decreasing activity. Clearly, propionic acid derivatives in this family of compounds are more active than acetic acid derivatives. Fenoprofen calcium (Nalfon), is a white crystalline powder. The recommended oral dose is 600mg four times a day. The ester, amide, amine and alcohol analogs of fenoprofen are all potent. It is metabolically converted to a hydroxylated product and to a glucuronide conjugate of the carboxylic function.

Synthesis (16.12)

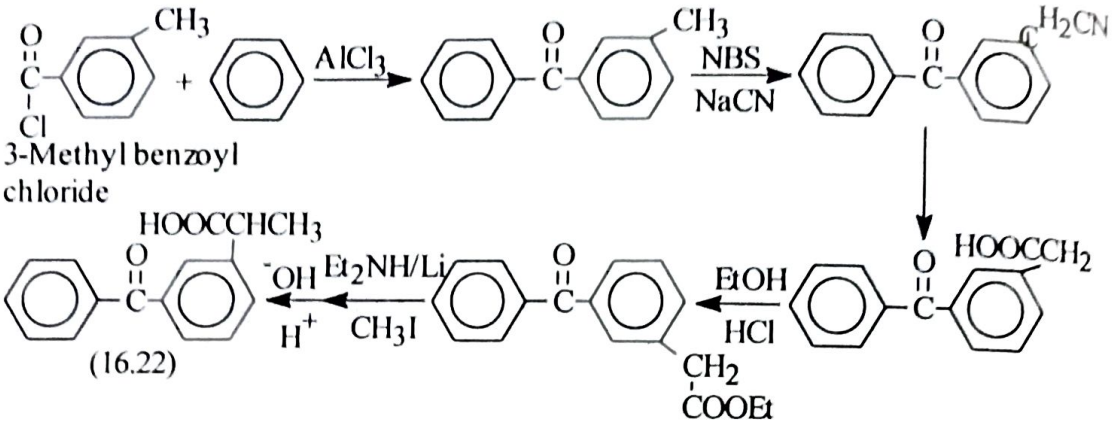


Scheme **16.12**

Ketoprofen : (Orudis) : 2-(3-Benzoylphenyl) propionic acid (16.22)

Addition of a 3-benzoyl function to phenyl propionic acid produces ketoprofen. Ketoprofen is as active as indomethacin. Metabolism of ketoprofen occurs mainly to yield hydroxylated products and a glucorinide of the parent product. At daily doses of 150mg. ketoprofen is an effective anti-inflammatory agent in humans.

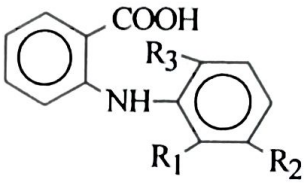
Synthesis (Scheme 16.13)



Scheme **16**.13

(d) Fenamates : (N-Arylanthranilic acids). The ending 'Fenac' indicates its origin as phenyl acetic acid.

Derivatives of anthranilic acid are potent analgesic and anti-inflammatory agents. These are nitrogen analogs of salicylic acid.



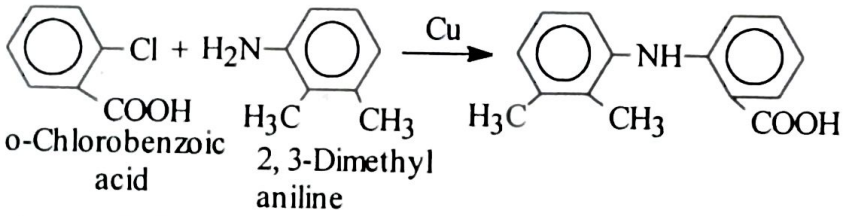
(a) Mefenamic acid (16.23) $R_1 = R_2 = CH_3$; $R_3 = H$

(b) Flufenamic acid (16.24) $R_1 = H$; $R_2 = CF_3$; $R_3 = H$

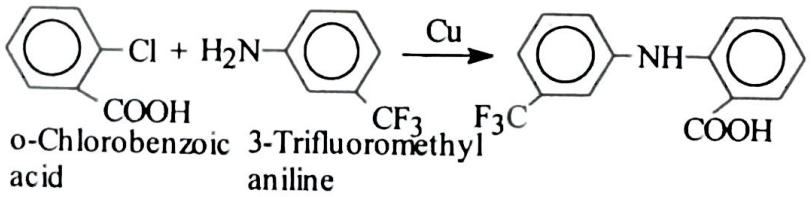
(c) Meclofenamic acid (16.25) $R_1 = R_3 = Cl$; $R_2 = CH_3$

Synthesis (Scheme 16.14)

1) Mefenamic acid (16.23)



2) Flufenamic acid (16.24)



Scheme **16**.14

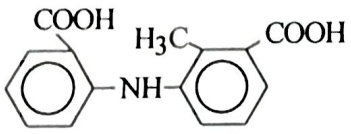
Structure Activity Relationship

1. The most active anthranilic acid derivatives have substituents at positions 2,3 and 6 of the ring attached to the anthranilic acid nitrogen from 2,3-disubstitution pattern usually improves activity over the 2-substituted com-

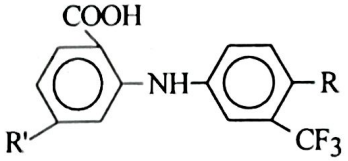
pounds. A substituent at position 3- is common to virtually all potent analogs in this series.

2. Replacing the -NH- function in fenamic acids produces less active compounds. Thus the ethers, ketones, and thioether are essentially inactive.
3. The carboxylic function is required at the 2-position for biological activity. Isomeric 3-carboxy or 4-carboxy derivatives are inactive. A tetrazole function can substitute for a carboxylic acid function with retention of anti-inflammatory activity.

Mefenamic acid is given 500mg an initial dose, followed by 250mg every 6h as needed. Flufenamic acid is recommended at a usual daily dose of 600mg. The principal metabolic products of mefenamic acid come from stepwise oxidation of the 3'-methyl group, forming first the alcohol and then the carboxyl group forming the diacid 16.26. Hydroxylation of each of the aromatic systems in flufenamic acid gives rise to two major hydroxylated metabolites (16.27) in humans.

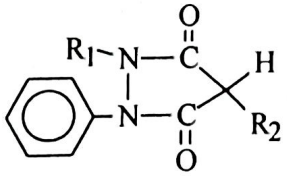


Metabolites (16.26)



R = OH; R' = H (16.27)
R = H; R' = OH (16.27)

2. Pyrazoles : 3,5-Pyrazolidinedione Derivatives



Phenylbutazone (Butazolidin) 16.28 : $R_1 = C_6H_5$; $R_2 = nC_4H_9$;

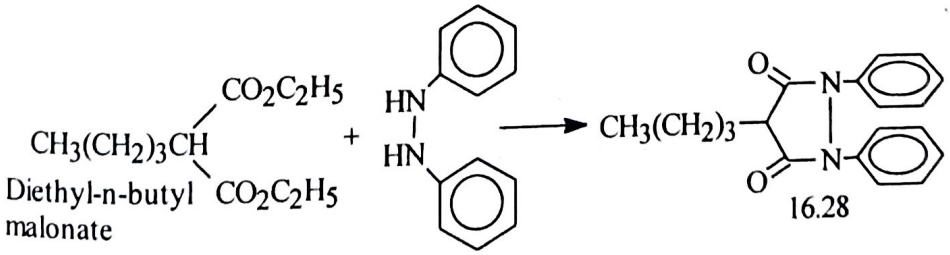
Oxyphenbutazone (Tandearil) 16.29 : $R_1 = p\text{-}HOC_6H_4$; $R_2 = nC_4H_9$;

Sulfinpyrazone (Anturane) 16.30 : $R_1 = C_6H_5$, $R_2 = CH_2\text{-}CH_2\text{-}SC_6H_5$

Synthesis (Scheme 16.15)

Phenylbutazone (16.28) : Diphenyl-4-n-butyl-3, 5-pyrazolidine-dione

It is obtained in a straight forward manner by condensation of diethyl n-butylmalonate with hydrazobenzene in the presence of base.



Diethyl-n-butyl malonate

Hydrazobenzene

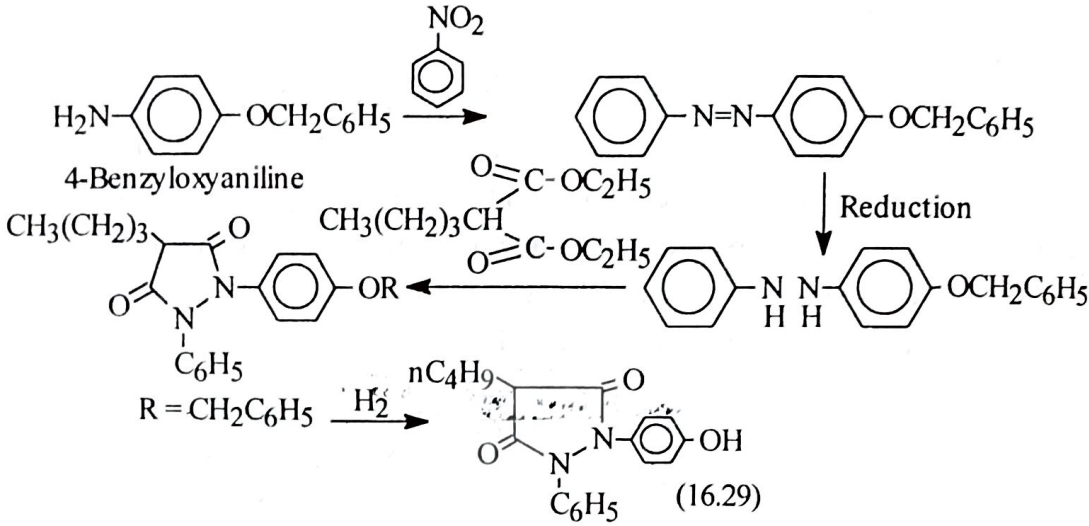
16.28

Scheme 16.15

Oxyphenbutazone (16.29)

Synthesis (16.16)

Condensation of the protected aminophenol with nitroaniline affords the corresponding azo compound; reduction gives the hydrazobenzene. Condensation of this with diethyl butyl malonate gives the heterocycle. Removal of the benzyl group by hydrogenolysis gives oxyphenbutazone 16.29.



Scheme **16**.16

Structure Activity Relationship

1. The butyl group of carbon 4 may be replaced by a propyl or allyl group.
2. The presence of a keto group in the gama position of the butyl side chain produces the active compound.
3. Meta substitution of the aryl rings of phenylbutazone gives uniformly inactive compounds. Para-substitution such as methyl, chloro, nitro or OH of one or both rings retains activity.
4. Replacement of one of the nitrogen atoms in the pyrazolidines with an oxygen atom yields an isoxazole analog, which is as active as pyrazolidine derivative.
5. A parabolic relationship was derived between lipophilicity (partition coefficients) and antiinflammatory activity. The optimal logarithmic partition coefficient (log P) value of 0.7 is the value obtained for the most active compound.
6. Decreasing pKa values of phenylbutazone analogs correlate with shorter half-lives.
7. An enolizable β-dicarbonyl system is essential, because substitution of the hydrogen at carbon 4 of phenylbutazone by a methyl group destroys antiinflammatory activity.

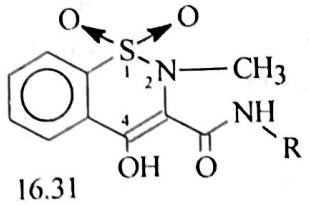
Phenylbutazone is more often used in therapy with so-called rheumatoid variants, ankylosing spondylitis, psoriatic arthritis, arthritis associated with ulcerative colitis. Osteoarthritis and particularly its acute exacerbations are relieved by phe-

nylbutazone. The therapeutic action of phenylbutazone is lysis of fever, and dimunition of swelling, tenderness and local heat. The initial doze is of 300 to 600mg divided into three or four equal doses.

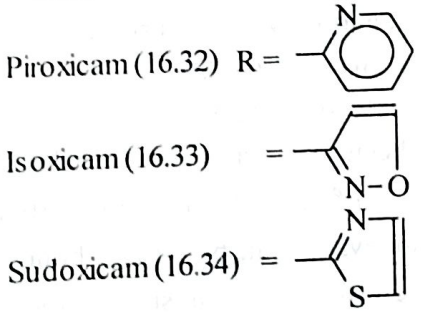
In man, phenylbutazone is slowly and almost completely metabolised by liver microsomal enzymes to oxyphenbutazone, which is an equally potent anti-inflammatory agent and less toxic.

3. Oxicams : Enolic Acids

This new class of 4-hydroxy-benzothiazine-3-carboxamide-1,1-dioxide derivatives (16.31) is characterized by long-acting and often very potent antiinflammatory activity. The potency, convenience of once-daily dosing, and safety of piroxicam have caused it to become one of the most widely used NSAID.

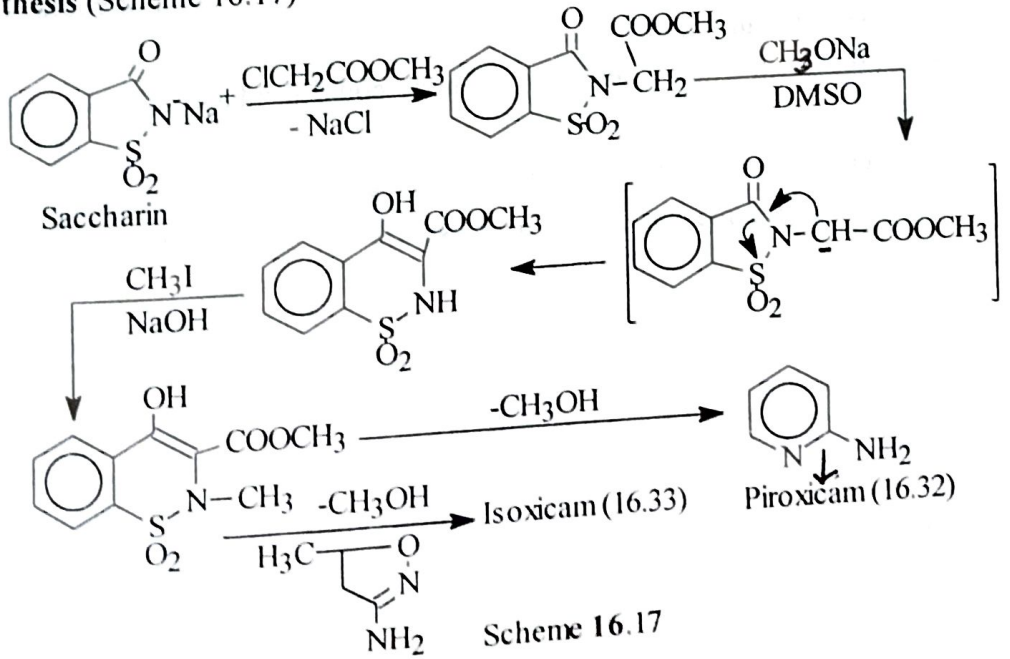


16.31



Piroxicam (Feldene) : 4-Hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide (16.32).

Synthesis (Scheme 16.17)



Scheme 16.17

Structure Activity Relationship

1. The most active analogs have the substituent CH_3 on the nitrogen and electron withdrawing substituents on the anilide phenyl group such as chloro and trifluoromethyl.
2. The introduction of a heterocyclic ring in the amide oxide chain significantly increases antiinflammatory activity. 2-Thiazolyl derivative Sudoxicam (dose 0.1-0.3mg/kg) is more potent than indomethacin.
3. Most active benzothiazines have acidities in the pKa range of 6 to 8.

Properties and uses

Piroxicam is effective in the symptomatic treatment of rheumatoid arthritis and osteoarthritis. It is also indicated in ankylosing spondylitis and acute gouty arthritis. Dose of 20mg daily is as effective as aspirin 4.7g daily. It has reduced ulcerogenocity (one-third to one half the value of indomethacin), long plasma half life in dogs (36 hrs) and humans (45 hrs), and high oral LD_{50} values (300-500 mg/kg) in rodents. It is among the least irritating of the NSAID.

Piroxicam is metabolised in the liver primarily by hydroxylation of the pyridine ring and subsequent conjugation with glucuronic acid. According to figures (1983) available it ranks first in sales worldwide.

Common Unwanted Effects of NSAIDs

The NSAIDs have been used particularly in the elderly in large doses in joint diseases. A high incidence of side effects-more particularly in the gastrointestinal tract but also in liver, kidney, spleen, blood and bone marrow have been observed.

(i) Gastrointestinal side effects. The most common effects are dyspepsia, nausea and vomiting, Diarrhoea also occurs. At least one in five patients will have ulcer crater disease.

(ii) Renal disease, chronic consumption of phenacetin or paracetamol could cause chronic nephritis and renal papillary necrosis.

(iii) Skin reactions. Mefenamic acid and sulindac could produce mild skin rashes, urticaria.

(iv) Other effects include bone marrow disturbance and liver disorders.

A comparison of some commonly used NSAIDs is given in Table 16.1.

Table 16.1 : Comaparison of some commonly used NSAIDs

Drug	Plasma $t_{\frac{1}{2}}$ (hours)	Action: Analg	Antipyr	Anti-infl	Comments
Salicylic acids					
Aspirin	3–5	+	+	+	Fairly marked GIT upsets and haemorrhage. Tinnitus. Hypersensitivity reactions. Cheap and effective. A drug of first choice for mild analgesia. An encephalitis can be precipitated in children with viral infections.
Diflunisal	8–13	+	–	+	10 times more potent in anti-inflammatory and analgesic effect than aspirin but only 1.5 times more potent in antipyresis. Less GIT irritation than aspirin.
Benorylate		+	+	+	Aspirin–paracetamol ester; broken down in liver; less GIT irritation than with aspirin.
Propionic acids					All have very similar actions and side effects. Metabolised in liver. Effective and better tolerated than most other NSAIDs. As inhibitors of cyclo-oxygenase naproxen is 20 times more potent than aspirin, the others are equipotent. Ibuprofen is a drug of first choice for inflammatory joint disease because it has the lowest incidence of unwanted effects. Fenbufen is a pro-drug, activated in the liver; less likely to cause bleeding in GIT
Naproxen	13	+	+	+	
Ibuprofen	2	+	+	+	
Flurbiprofen	4	+	+	+	
Fenbufen	10	+	+	–	
Ketoprofen	2	+	+	+	
Acetic acids					
Indomethacin	2	+	+	+ +	One of the most potent inhibitors of cyclo-oxygenase in vitro. Clinically effective but high incidence of side effects. Headache, dizziness and GIT upsets common.
Sulindac	7 (18)*	+	+	+	A pro-drug manifesting reversible activation, i.e. inter-convertible with its active sulphide metabolite; long duration of action. Enterohepatic cycling. About half the potency of indomethacin.
Fenamates					
Mefenamic acid	2	+	+	+	Moderate anti-inflammatory actions. GIT upsets. Diarrhoea likely. Haemolytic anaemia has been reported.
Meclofenamic acid	4	+	+	±	
Oxicams					
Piroxicam	45	+	±	+ +	Piroxicam is used world-wide for chronic inflammatory conditions. GIT irritation in 20% patients. Tinnitus. Rashes. Metabolised in the liver. Is given once daily. Multiple peaks in plasma suggest enterohepatic recycling. No accumulation in the elderly or in patients with renal impairment.
Tenoxicam	42–98	+	+	+ +	Long $t_{\frac{1}{2}}$ means steady-state plasma concentration only after 2 weeks. Marginally less toxic than piroxicam.
Pyrazolones					
Phenylbutazone	50–100	±	+	+ +	Very potent. More toxic than other NSAIDs. In UK use restricted to ankylosing spondylitis.
Azapropazone	20	+	+	+	Moderate efficacy. Mild GIT irritation.
Paracetamol	2–4	+	+	–	Safe and effective mild analgesic in therapeutic doses, less analgesic efficacy in inflammatory conditions. Chronic use can cause kidney damage. Overdose causes serious hepatotoxicity.
Tolmetin	1	+	+	+	Rapidly absorbed. Excreted in urine within 24 hours. Fairly high incidence of side effects.

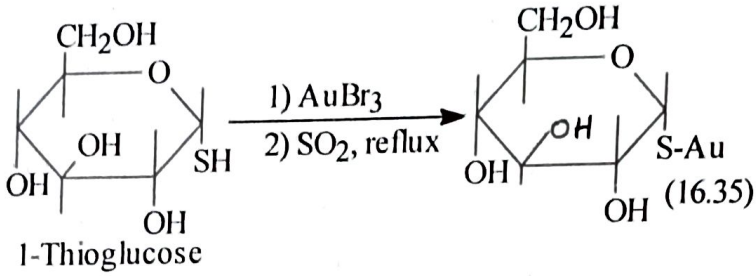
*Half-life of active metabolite
Analg = analgesic; Antipyr = antipyretic; Anti-infl = anti-inflammatory; GIT = gastrointestinal tract
See text for details of unwanted effects (p. 287)

Gold Preparation

Crysotherapy was introduced for the treatment of rheumatoid arthritis because of its similarity with tuberculosis. The first gold compound, goldthioglucose was used to relieve joint pain in 1927. Gold compounds are used in treatment of early stages and progressive state of rheumatoid arthritis.

Gold thioglucose (Solganal) : (1-Thio-D-pyrasato) gold, 16.35

Synthesis (Scheme 16.18)

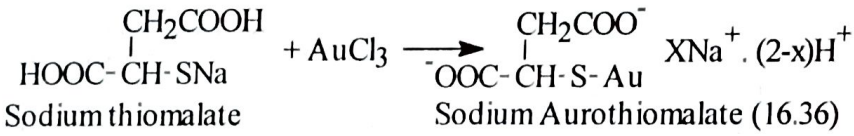


Scheme **16**.18

It occurs as a yellow powder and is odorless and stable in air, soluble in water. The gold content is 50%. Aurothioglucose injection is a suspension in seasam oil containing 2% aluminium monostearate and 1mg propyl paraben/ml. Initial dose of 10mg is given upto a total of 800mg to 1g.

Gold sodium thiomalate (Mychrysine) : Mercapto succinic acid, monogold (1+) sodium salt, 16.36.

Synthesis (Scheme 16.19)

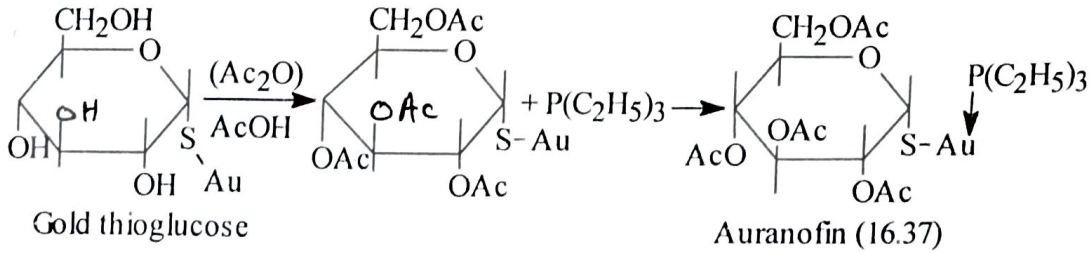


Scheme **16**.19

It is a white to yellowish-white, odorless, fine powder with a metallic taste. It is soluble in water and light sensitive. The intramuscular dosage regimen is similar to god thiomalate

Auranofin : (Ridaura) : (SK and FD-39162) : 2,3,4,6-Tetra-o-acetyl-1-thio-β-D-glucopyranosato-S-)-(triethylphosphine gold), 16.37.

Synthesis (Scheme 16.20)



Scheme **16**.20

In auranofin, 16.37, the gold atom is linked to both sulfur and phosphorous by covalent bonds with identical bond lengths. The gold content is 20%. It is slightly

soluble in water, more in lipids. It is administered orally with a dosage of 3mg twice a day or 6mg once daily. Blood dyscrasias and kidney damage are serious adverse effects. The control of toxic effects can be brought out by use of chelating agents, dimercaprol or penicillamine. The gold compounds have several possible mechanism of action.

1. Inhibition of leukocyte chemotoxins
2. Alter the properties of collagen
3. Inhibition of lysosomal enzymes, with possibility of a reversible bonding to sulphydryl groups.
4. *In vivo* inhibition of prostaglandin synthesis.
5. Uncoupling of oxidative phosphorylation.

Mode of Action of NSAIDs

Prostaglandins emerged as putative mediation of inflammation. The major site of NSAIDs action is very likely the step that converts arachidonic acid to prostaglandins by the catalytic activity of prostaglandin synthesis. The NSAI drugs inhibit the cyclooxygenase step, thereby preventing the formation of prostaglandin endoperoxides (PGG_2 and PGH_2) (and thromboxane A_2) and other prostaglandins, and consequently reducing the signs and symptoms of inflammation (Scheme 16.21).

Besides inhibiting prostaglandin biosynthesis, NSAIAs also inhibit the synthesis of leukotriens, histamine and monopolysaccharides, and some biological processes such as phagocytosis, complement system, and platelet aggregation. Other possible mechanisms of NSAIAs are kinin antagonism, prevention of leukocyte accumulation, stabilization of lysosome membranes, uncoupling of oxidative phosphorylation, and oxygen radical scavenger action.

On the basis of structure-activity relationships for indomethacin and other NSAID, and anti-inflammatory receptor site consisting of two noncoplaner hydrophobic regions and a cationic center has been proposed. This receptor consists of a largely flat area, a trough to accomodate an out-of-plane group (such as an aryl ring acting possibly by a charge-transfer type of interaction, and a cationic site to accomodate an acidic anion (or unprotonated amine).

The topography of the receptor for NSAIDs is depicted below : Fig. 16.1.

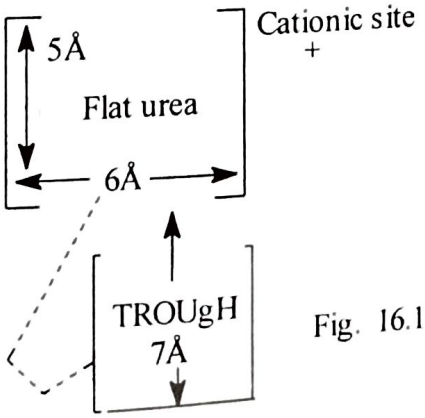


Fig. 16.1

A. Inhibition of cyclooxygenase enzyme can occur by different mechanisms.

(i) An irreversible inactivation of the enzyme, e.g. aspirin (Scheme 16.21)

(ii) A rapid reversible non-competitive inhibition involves antioxidant or free radical trapping properties. This effect is significant since it reduces the hydroperoxides, which are believed to have an essential role in cylo-oxygenase activity. This action is negated by leucocyte-generated hydroperoxides. e.g. paracetamol. This drug has analgesic-antipyretic action but very weak antiinflammatory action.

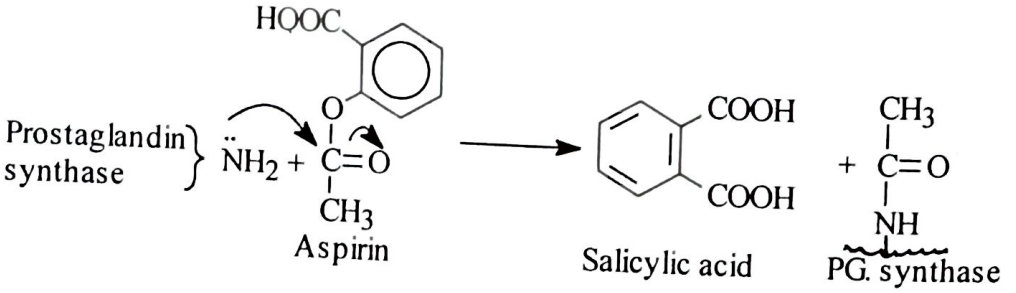
(iii) A rapid, reversible competitive inhibition is manifested by the propionic acid NSAIDs, such as ibuprofen (16.9) which binds reversibly to the enzyme cyclo-oxygenase (Kd 5 x 10 mol/l) competing with the natural substrate, arachidonic acid (Kd 2 x 10^{-6} mol/l). Hydrophobic forces are important in this interaction. The oxicams, such as piroxicam, have a similar mechanism of action.

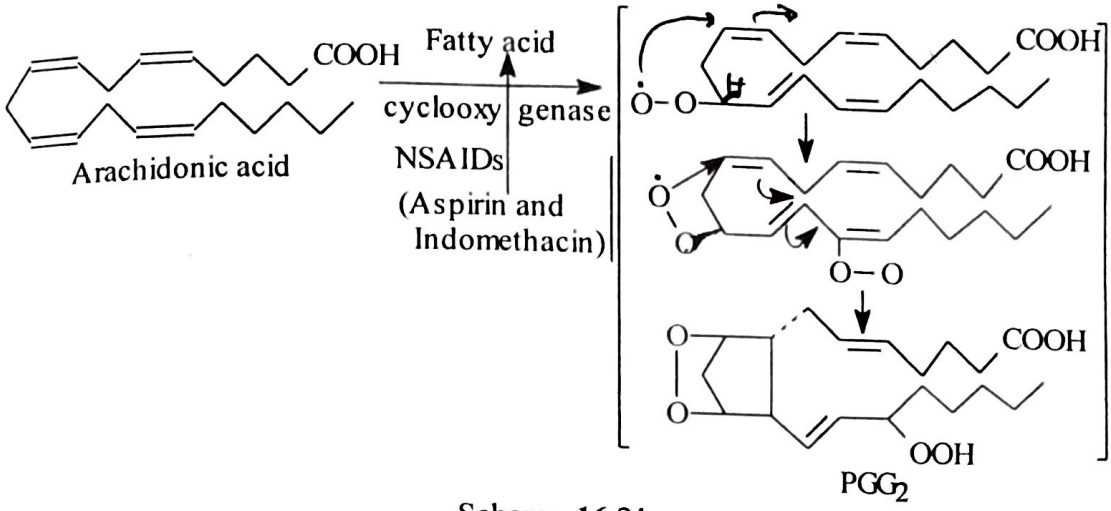
B. (iv) Other action besides inhibition of cyclo-oxygenase may contribute to the anti-inflammatory effects of some NSAIDs.

(a) Reactive oxygen radicals produced by neutrophils and macrophages are thought to be implicated not only in eicosanoid production but in *tissue damage* in some conditions, and NSAIDs that have particularly strong O_2 radical scavenging effects as well as cyclo-oxygenase inhibitory activity may decrease tissue damage e.g. phenylbutazone and sulindac.

(b) Some NSAIDs may interfere with the binding of mediators (such as the chemotactic peptides, peptides derived from bacteria) to their receptors on inflammatory cells, e.g. pyrazolones.

The primary action of aspirin is inactivation of cyclooxygenase by irreversible acetylation of the serine 530, residue of this component of the multienzyme complex known as prostaglanding synthase, the enzyme that catalyzes the first phase of prostaglandin biosynthesis from arachidonic acid.





Scheme **16.21**

Besides inhibiting prostaglandin biosynthesis, aspirin-like drugs also inhibit the synthesis of histamine, leukotrienes and platelet aggregation. They also help uncoupling of oxidative phosphorylation, oxygen radical scavenging and prevention of leukocyte accumulation.

Peripheral Analgesic - Antipyretics

Analgetic-Antipyretics : are drugs that relieve mild to moderate pain, such as headache, myalgia, and anthralgia, and lower body temperature in fever. Some of them alleviate symptoms of gout and rheumatic fever. They are without significant addiction liability. They belong to a heterogenous groups of compounds. Several of these are also used as anti-inflammatory agents. The main adverse effects of most analgetic-antipyretics are gastrointestinal irritation and ulceration, decreased renal functions, inhibition of platelet aggregation with consequent prolonged bleeding time. Analgetic-antipyretics can be divided into the following chemical classes :

(i) para aminophenol derivatives : paracetamol, phenacetin.

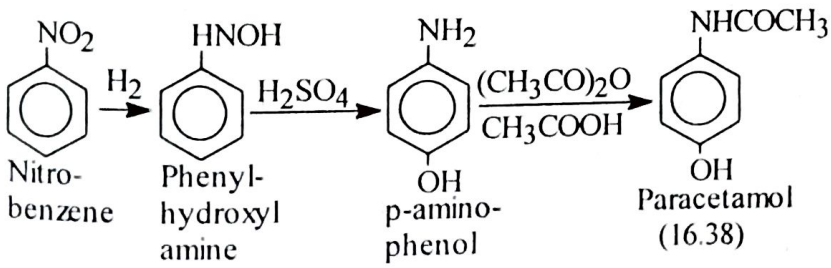
(ii) 5-pyrazolone derivatives : antipyrine, analgin, sulfinpyrazone,

(iii) Miscellaneous agents; allopurinol, colchicine, probenecid.

Paracetamol I.P. : Acetaminophen : (Tylenol) : N-(4-hydroxyphenyl) acetamide (16.38).

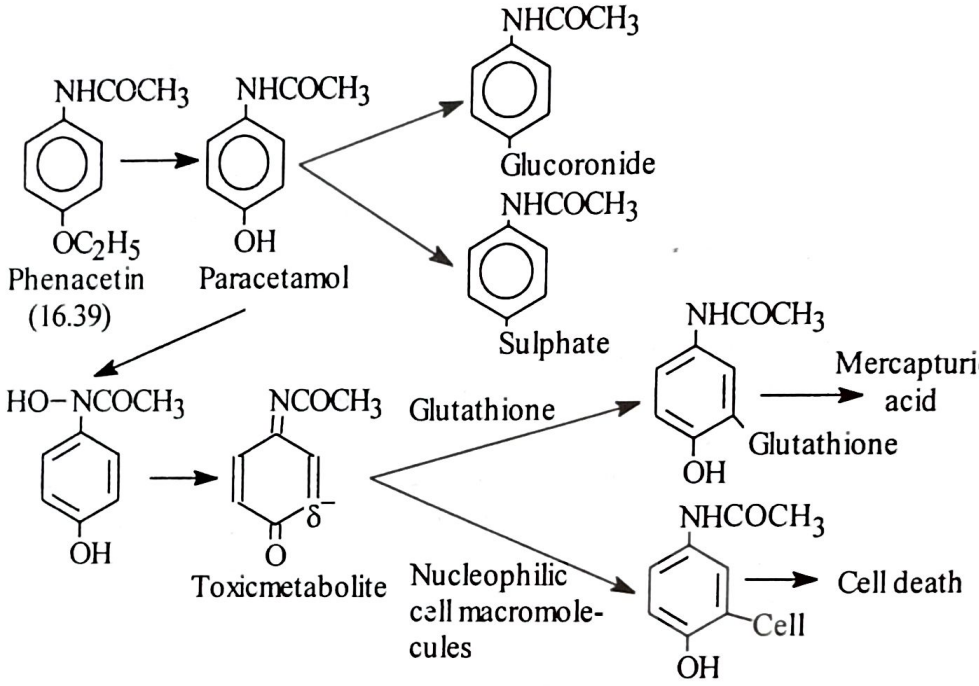
Synthesis (Scheme 16.22)

Electrolytic reduction of nitrobenzene gives phenylhydroxylamine, which on treatment with sulfuric acid is rearranged to p-aminophenol, which can be acetylated by a mixture of acetic anhydride and glacial acetic acid to give acetaminophen.



Scheme **16.22**

Properties and uses : white, crystals with slightly bitter taste. Sparingly soluble in water and freely soluble in alcohol. Melting range 169-172°C. pH between 5.3 and 16.5. It is effective in a wide variety of arthritic and rheumatic condition involving musculoskeletal pain as well as the pain of headache, myalgia and neuralgia. It is particularly useful as an analgesic-antipyretic in patients sensitive to aspirin. The half-life is 3 hours. It acts centrally to reduce fever. **Dose** : 325 to 650 mg at 4 hour intervals. It is a metabolite of phenacetin and acetanilid. (Scheme 16.23)



Scheme **16**.23 Metabolism of Phenacetin

The toxic effects of overdose include hepatotoxicity, necrosis.

Identificaiton : (i) A sample gives a violet blue colour with ferric chloride (Test for phenol) (ii) A sample is boiled with HCl (1ml), on addition of water, no precipitate is produced. Add potassium dichromate, a violet colour slowly develops. (iii) A p-nitrobenzoyl derivative is prepared (m.pt. 210°C). p-Nitrobenzoylchloride is condensed with paracetomol in presence of pyridine. The precipitate is washed with water and sodium carbonate solution.

Limits of Impurities : Heavy metals. Not more than 10 ppm. Sulphated ash. Not more than 0.1 percent. Loss on drying. Not more than 0.5percent. 4-Aminophenol. Not more than 0.005 percent. A sample (0.5g) is dissolved in a mixture of methyl alcohol and water (10ml). An alkaline sodium nitroprusside solution (0.2ml) is mixed and the solution kept for 30 minutes. A separate standard solution is prepared using 0.5ml of a 0.005 percent w/v solution of 4-aminophenol using 0.5g of 4-aminophenol free paracetamol. The intensity of the sample solution is not more intense than the standard. 4-Chloroacetamide determined using TLC method.

Assay : A sample (0.3g) is dissolved in a mixture of water (10ml) and 2N H_2SO_4 (30ml). The mixture is boiled under reflux for one hour, cooled and diluted to 100ml with water. 20ml of the solution is mixed with water (40ml), ice (40g), 2N HCl (15 ml) and titrated with 0.1N ceric ammonium sulphate using ferrous sulphate solution as indicator. Similarly a parallel blank is also done.

1ml of 0.1N ceric ammonium sulphate ≡ 0.00756g of paracetamol.

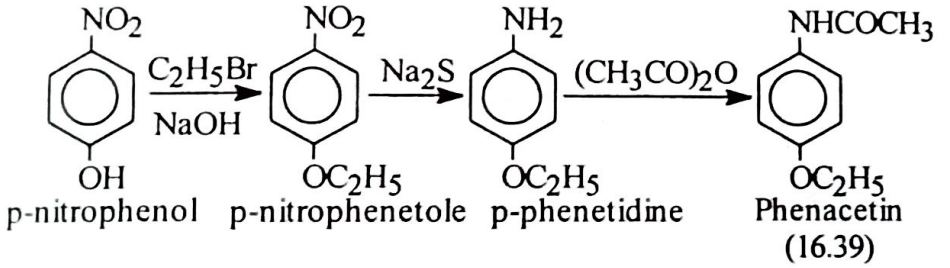
Storage : in well-closed, light resistant containers.

Preparations : Paracetamol Tablets I.P. 300mg, 500mg.

Phenacetin (Acetophenetidin) : N-(4-ethoxyphenyl) acetamide.

Synthesis (Scheme 16.24)

p-Nitrophenol is condensed with ethyl bromide in presence of sodium hydroxide to give p-nitrophenetole, which is reduced with sodium sulfide. The resulting p-phenetidine is acetylated by refluxing with acetic anhydride.

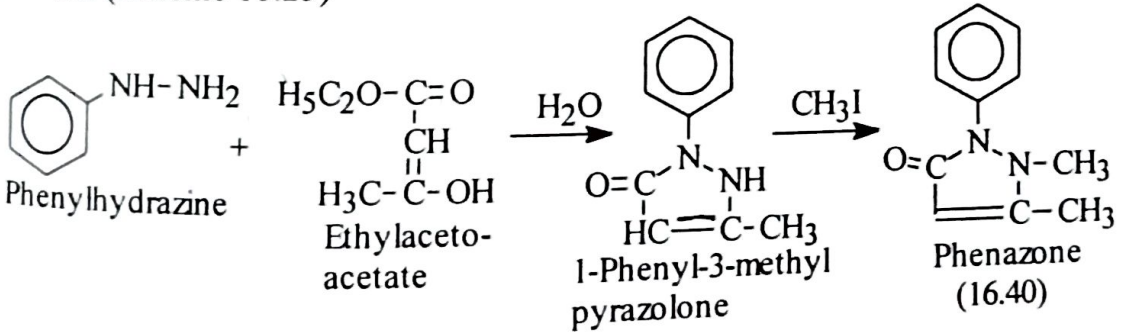


Scheme **16.24**

It is a white, glistening powder with a bitter taste. Sparingly soluble in water, soluble in chloroform. It is mainly used for mild to moderate pain. It is metabolised to active metabolite acetaminophen. It is more toxic than paracetamol and produces methemoglobinemia and hemolytic anemia. Dose : 300 mg to 2g per day.

Antipyrine (Phenazone) : 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one (16.40).

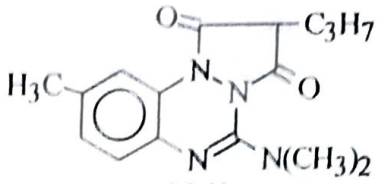
Synthesis (Scheme 16.25)



Scheme **16.25**

It is a colorless, odorless, crystalline powder, freely soluble in water, alcohol, chloroform. It is an oral analgesic, antipyretic, now no more in use. A solution of antipyrine (5.4%) and benzocaine (1.4) in anhydrous glycerine is used topically as ear drops.

Apazone (Azapropazone) 16.41.



16.41

It is a pyrazolon with atiinflammatory, analgesic and antipyretic action. It is also useful in the treatment of rheumatoid arthritis and osteoarthritis. The half-life is about 20-24 hours. It is an inhibitor of cyclooxygenase. It is well-tolerated. The useful dose is 1200mg per day in divided doses.

Drugs used in the treatment of Gout

Gout is a genetically determined metabolic disease in which there is overproduction of purines. It is characterised by intermittent attacks of acute arthritis produced by the deposition of crystals of sodium urate in the synovial tissue of joints. Sodium urate is a product of purine metabolism. An inflammatory response is evoked, involving activation of the kinin, complement and plasmin systems, generation of lipoxygenase products such as LTB_4 and local accumulation of neutrophil granulocytes. These engulf the crystals by phagocytosis, which causes generation of tissue-damaging toxic oxygen metabolites and subsequently lysis of the cells with release of proteolytic enzymes.

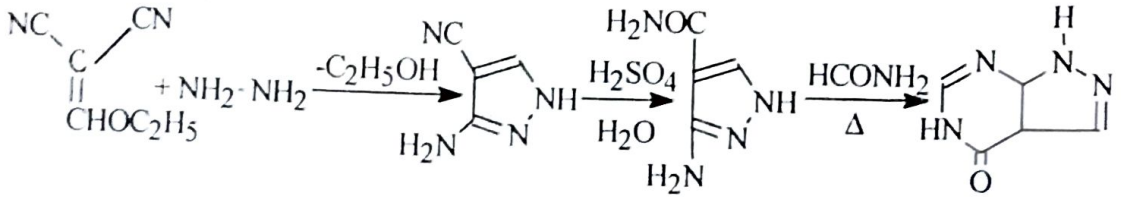
Drugs used to treat gout may act in the following ways :

(i) by inhibiting uric acid synthesis (allopurinol).
(ii) by increasing uric acid secretion (uricosuric agents : probenecid, sulphinpyrazone).
(iii) by inhibiting leucocyte migration into the joint (colchicine).
(iv) by general anti-inflammatory and analgesic effects (NSAIDs).

Allopurinol I.P. (Zyloprin) : 1,5-Dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-one 16.42.

Synthesis (Scheme 16.26)

Hydrazine is reacted with ethoxymethylene malonitrile (I) to give 3-amino-4-cyanopyrazole(II). Treatment with H_2SO_4 results in hydrolysis of cyano group to the corresponding carboxamide derivative (III). This derivative is condensed with formamide to yield allopurinol (16.42).

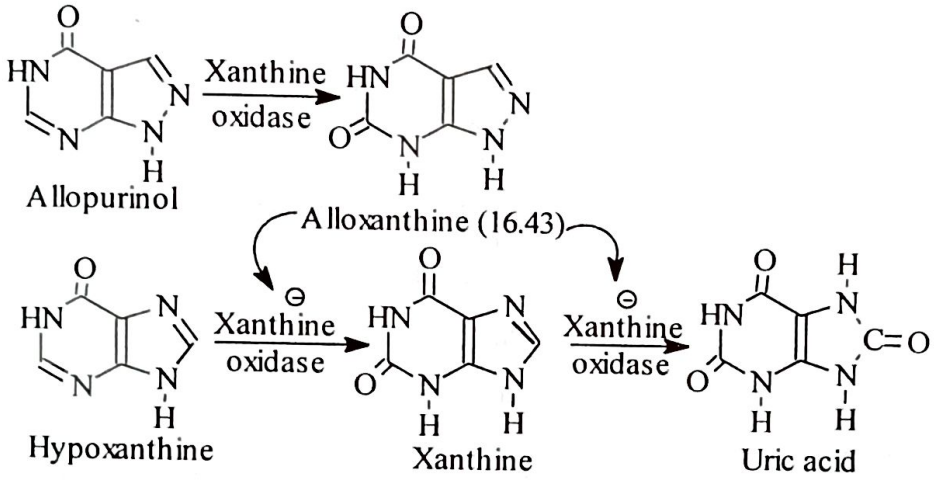


I II III IV

Scheme 16.26

Properties and uses

It is an odorless, white fluffy powder, very slightly soluble in water and alcohol. It is used in the treatment of gout and prevention of urate deposition in patients with leukemia receiving anticancer drugs, which cause increasing serum uric acid levels. Allopurinol is metabolised to oxypurinol (alloxanthene 16.43), which has got a longer half-life (18-30 hours) than allopurinol (less than 2 hours). This accounts for its long duration of action and need for single dose daily. Allopurinol together with its primary metabolite, prevents the terminal step in uric acid synthesis by inhibiting the enzyme xanthine oxidase, which converts xanthine or hypoxanthine to uric acid (Scheme 16.27). Dose : Adults : 100 to 800mg daily; children; oral, 100mg 3 times a day.



Scheme **16**.27 : Inhibition of uric acid synthesis by allopurinol

Identification : (i) A sample is reacted with lithium and sodium molybdophosphotungastate, dilute sodium hydroxide in presence of sodium carbonate when blue-grey colour is formed. (iii) A small sample of the drug is dissolved in dilute sodium hydroxide solution. Alkaline potassium mercuric iodide solution is added and the mixture boiled. After standing the solution turns into flocculent yellow precipitate.

Limits of Impurities : Sulphated ash. Not more than 0.1 percent. Loss on drying. Not more than 0.5 percent. Related compounds. By TLC, n-Butyl alcohol with dilute ammonia solution is the mobile phase. Two separate solutions are prepared. A 2.5 percent solution of the substance under examination is prepared (Solution A). Another solution of 0.0025 percent w/v 3-aminopyrazole-4-carboxamide hemi sulphate (Solution B). Take 10ml of each of the solution on the chromatogram and view the spots under u.v. lamp of about 250nm. Any spot in the chromatogram of solution A, other than the principal spot, is not more intense than the spot in the chromatogram of solution B.

Assay : A sample (0.2g) is dissolved in dimethylformamide (50 ml) and titrated with 0.1N CH_3ONa using thymol blue in methyl alcohol as indicator.

1ml of 0.1N $CH_3ONa \equiv 0.01361g$ of allopurinol.

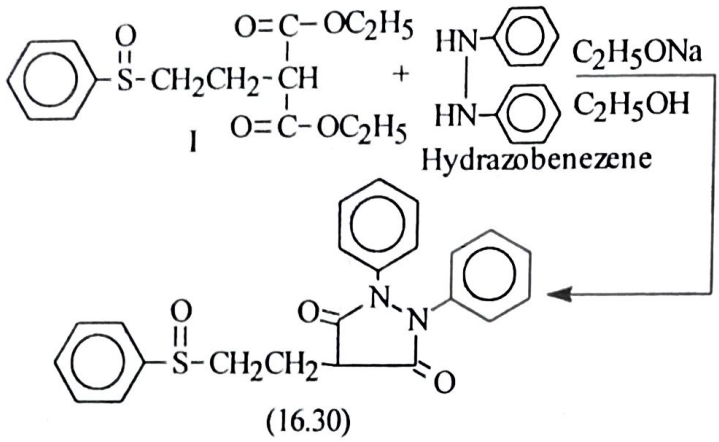
Storage : in well-closed containers.

Preparation : Allopurinol Tablets, I.P. 100mg.

Sulfinpyrazone (Anturane, Aprazone) : 1,2-Diphenyl-4-[2-phenylsulfinyl) ethyl]-3,5-pyrazolidinedione (16.30).

Synthesis (Scheme 16.28)

2-(Phenylsulfinyl) ethyl malonic acid diethyl ester (I) is condensed with hydrozobenzene in presence of sodium ethoxide in ethanol. The resulting reaction mixture is heated at about 130°C with xylene to remove ethanol.



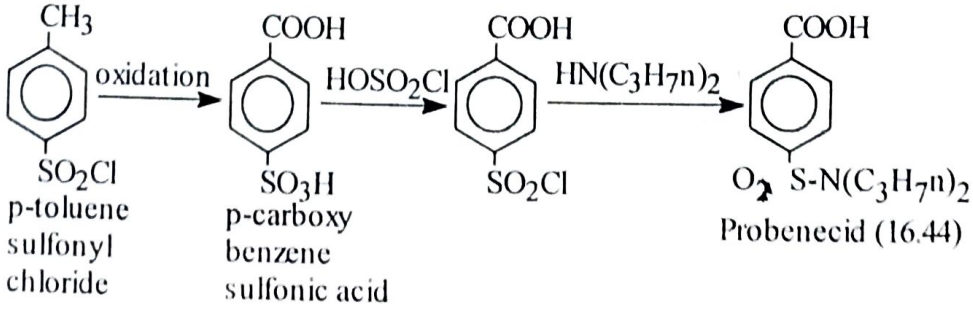
Scheme **16.28**

It is a white powder, practically insoluble in water. It is used as a potent uricosuric agent in the prevention, rather than the treatment of acute gouty arthritis. Caution is advised in case the patient is on sulfa drugs, and sulfonylureas. Sulfinpyrazone inhibits the proximal tubular reabsorption of uric acid. A hydroxy metabolite is also a potent uricosuric agent. Dose : Oral, 200 to 800mg daily with meals or milk.

Probenecid (Benemid) : 4-[(Dipropylamino) sulfonyl]-benzoic acid (16.44)

Synthesis (Scheme 16.29)

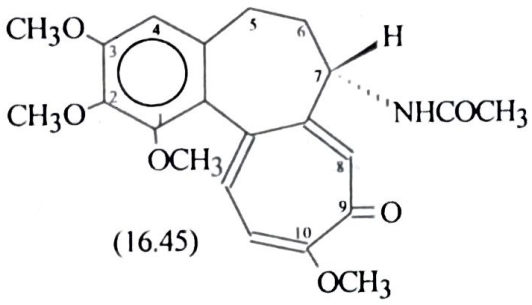
p-Carboxybenzenesulfonic acid is obtained by the oxidation of p-toluenesulfonyl chloride. Further treatment with chlorosulfonic acid yields p-chlorocarboxybenzene sulfonyl chloride, which on condensation with di-n-propylamine gives probenecid.



Scheme **16.29**

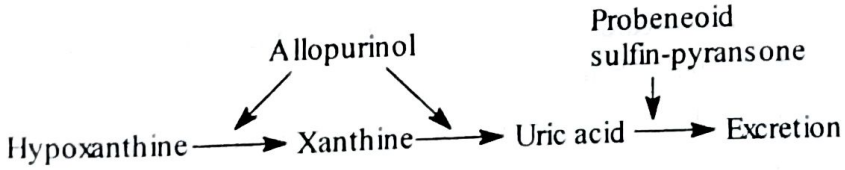
It is a fine, white, odorless, crystalline powder, insoluble in water and soluble in alcohol and chloroform. Because it selectively blocks both inward and outward renal transport of weak acids, it is an effective usicosuric agent for the treatment of gout and gouty arthritis (Scheme 16.30) and an agent to prolong the effects of penicillins. It has no analgesic activity. The plasma-half ranges from 4 to 17 hours. Dose : oral, adults, 500mg to 2g daily, not recommended for children.

Colchicine : N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a] heptalen-7-yl)-acetamide (S), 16.45.



(16.45)

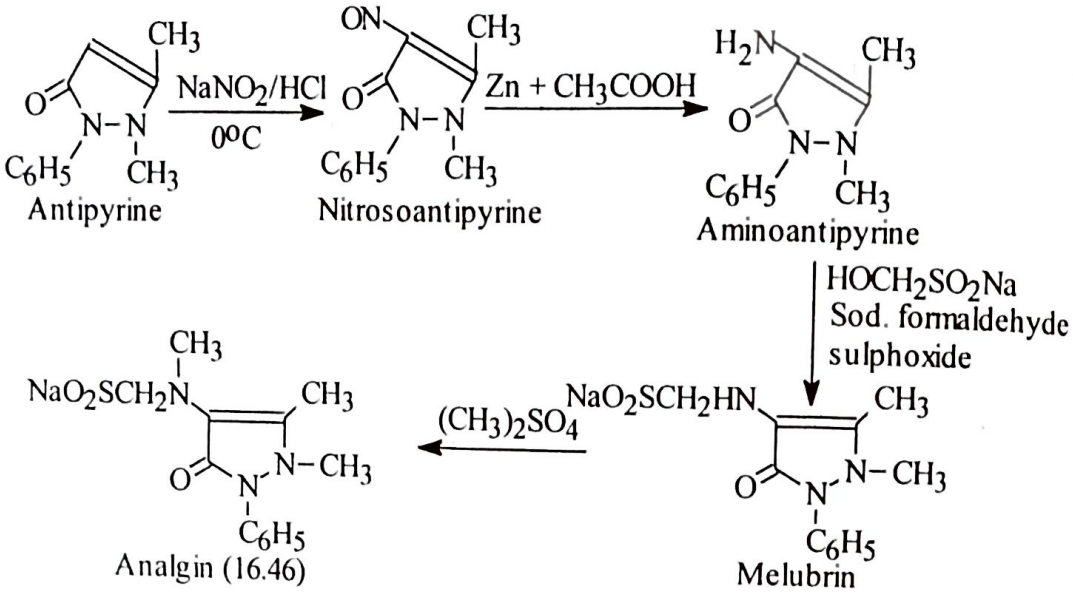
It is an alkaloid obtained from various species of Colchicum automnale. It occurs as pale yellow, amorphous powder and darkens on exposure to ligh. Soluble in water, alcohol and chloroform. It is effective in the treatment of acute attacks of gout and is also effective if given prophylactically to prevent such attacks. It inhibits the migration of polymorphonuclear leukocytes to the inflammatory area. It also blocks cell division by binding to mitotic spindles. Colchicine is extremely poisonous and nausea, vomiting, and abdominal pain with diarrhoea are warning signals for toxicity. Dose : oral, adults, 0.5 to 0.65mg once a day for 1 to 4 days each week.



Scheme 16.30 : Mechanism of action of antigout agents

Analgin (Metamizol, Novalgin, dipyrone): sodium N-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-N-methylamino methane sulfonate monohydrate 16.46.

Synthesis (Scheme 16.31)



Scheme 16.31

It is a white, odorless, crystalline powder with a scarcely perceptible yellowish tings, with a bitter taste, insoluble in chloroform. It has antipyretic action i.e. it lowers the body temperature in case of fever. It is also used to subside headache and body pains.

Dose : 0.5 to 3g daily, in divided doses.

Suggested Readings

1. T.T. Harrison, C. Beard, L. Kirkham, B. Leuis, I.M. Jamieson, W. Rooks, and J.H. Fried; J. Med. Chem., **11**, 868 (1968).
2. M. Verderame, Ed. Cardiovascular and Anti-inflammatory agents, CRC Press, Boca Raton, Fla. 1986.
3. J.G. Lombardino, Nonsteroidal Anti-inflammatory Drugs, Willey, New york, 1985.
4. Emerson, BT : Drug control of Gout and hyperuricemia, Drugs. **16**, 158 (1978).
5. Boss, G.R., Seegmiller, J.E. : Hyperuricemia and Gout : Classification, complications and management, N. Engl. J. Med. 300 : 1459 (1979).
6. Roberts, W.N., Liang, M.H. and Stern, S.H. : Colchicine in acute gout. J.A.M.A., **257**, 1920-1922 (1987).

7. Rainsford, K.O.(Ed.) : Newer Anti-inflammatory drugs., Vol. II. CRC Press, Boca Raton, Fla., 1985.
8. Clissold, S.P., Paracetamol and phenacetin, Drugs, 32 (Suppl. 4) 46-59 (1986).
9. Cash, J.M., and Klippel, J.H., Second line drug therapy for rheumatoid arthritis. New. Engl. J. Med.; 330, 1368-1375 (1994).
10. Patrono, C., Aspirin as an antiplatelet drug. N. Engl. J. Med., 330 : 1287-1294(1994).
11. Vane, J.R. and Botteng, R.H., New insights into the mode of action of anti-inflammatory drugs. Inflamm. Res., 44 : 1-40 (1995).