Pharmaceutical Chemistry

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Synthesis of Essential Drugs

By *R.S. Vardanyan* and *V.J. Hruby*, Elsevier, 2006

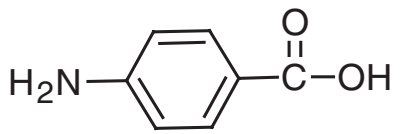
33. Antimicrobial Drugs

33.1 SULFONAMIDE DRUGS AND TRIMETHOPRIM

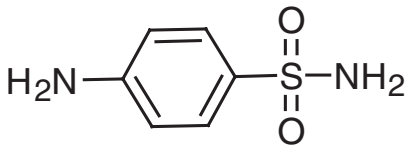
Sulfonamide drugs are a group of synthetic antimicrobial drugs that have a broad spectrum of use with respect to Gram-positive and Gram-negative microorganisms. They were introduced into medical practice even before the discovery of penicillins.

Sulfonamide drugs are derivatives of sulfanilamide (*p*-aminobenzenesulfonamide), which is a structural analog of *p*-aminobenzoic acid (component necessary in bacteria for synthesizing folic acid), the precursor of purine, nucleic acids, and especially DNA.

Animal cells are not able to synthesize folic acid by themselves—it must be obtained through the consumption of food.



p-aminobenzoic acid

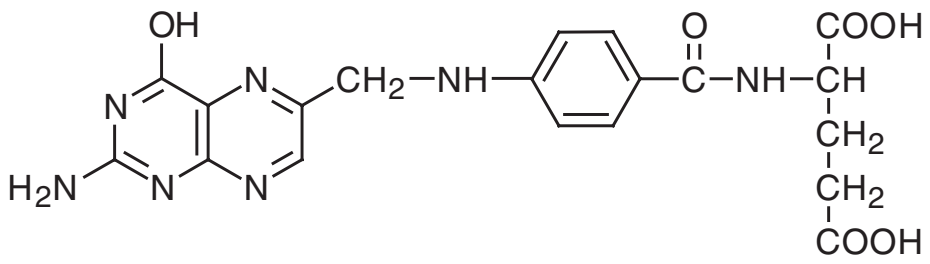


sulfanilamide

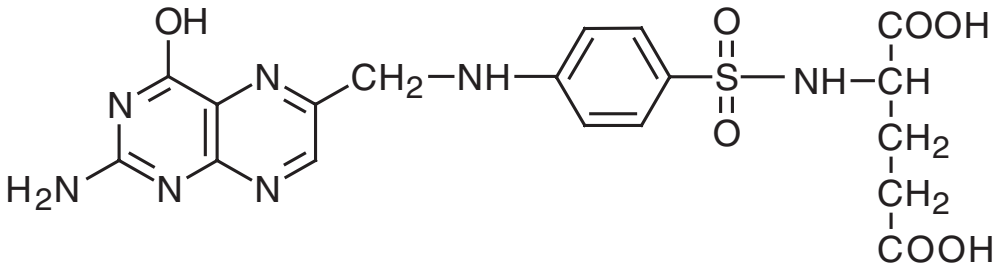
In addition, most bacteria are not able to utilize folic acid of exogen origin, so they synthesize the folic acid necessary for vital functions by themselves. This is the difference between bacterial and animal cells, and it is the reason behind the selective toxicity of sulfonamides.

Sulfanilamide, whose structure is similar to the structure of *p*-aminobenzoic acid, competes with *p*-aminobenzoic acid for inclusion in the folic acid molecule. In short, by taking the place of *p*-aminobenzoic acid, it “interferes” with the biosynthesis of folic acid.

As a result, the “misled” enzymes construct a “false” molecule of folic acid, which is not able to carry out the vital function of true folic acid.



folic acid



“false folic acid”

Sulfonamides are bacteriostatic drugs that inhibit bacterial growth by interfering with the microbial synthesis of folic acid.

More specifically, sulfonamides block the biosynthetic pathway of folic acid synthesis, thus competitively inhibiting the transformation of *p*-aminobenzoic acid to folic acid (mediated by the enzyme dihydropteroate synthetase), which allows them to be considered as antimetabolites.

Currently, various sulfanilamide drugs are used in medicine, the choice of which depends on various factors: the type of stimulant, course of the disease, speed in which the drug is absorbed from the gastrointestinal tract, the speed in which it is excreted, and its ability to diffuse into different organs and tissues.

Sulfonamides have a broad spectrum of antimicrobial activity, including *Staphylococcus aureus,* nonenterococcal types of *Streptococcus*, *Listeria monocytogenes*, *Nocardia*, *Neisseria*, *Haemophilius influenzae*, enteric Gram-negative types of *E. coli*, *Proteus mirabilis*, and a few forms of anaerobic bacteria.

Sulfonamides are also used for treating uncomplicated infections of the urinary tract, infections caused by *Nocardia asteroids*, streptococcal pharyngitis, menigococcal diseases, toxoplasmosis, and others.

Resistance to such drugs does develop during long-term use. Bacterial resistance to sulfonamides can develop as a result of mutations expressed either in the overproduction of *p*-aminobenzoic acid, or in changes in dehydroproteorate synthetase itself, which becomes more sensitive to the drugs.

Resistance can also be mediated by plasmids that code for dehydroproteorate synthetase, or by reduced diffusion of the drug through bacterial cell membranes.

Sulfanilamide drugs do not currently have a clear classification. However, they are grouped as **systemic** (absorptive action) and **local**.

They are subdivided into:

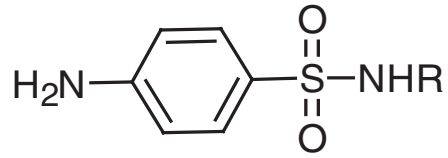
- short-lasting (sulfacytine, sulfadiazin, sulfamerazine, sulfametazine, sulfametizole, sulfisoxazole);
- moderate-lasting (sulfamethoxazole, sulfapyridine);
- long-lasting (sulfamethoxypiridazine, sulfamter), which, are no longer used as independent drugs because of extremely rare hypersensitivity reactions.

Drugs for local use include:

- ophthalmological use (sulfacetamide, sulfozoxazol);
- vaginal use (sulfabenzamide, sulfacetamide, sulfathiazole, sulfizoxazol);
- external use (maphenid, silver sulfadiazine).

This group also includes sulfasalazine and phthalylsulfathiazole, a drug that acts in the lumen of the intestines, but which is poorly absorbed from the gastrointestinal tract.

In terms of chemistry, sulfanilamide drugs can be represented by the following simple formula (except for rare exceptions, such as phthalazol):



In terms of determining a correlation between structure and activity, the free *p*-amino group in the benzene ring is necessary for the exhibition of antibacterial activity.

Replacing one of the hydrogen atoms on the nitrogen atom in the sulfonamide region of the molecule leads to a significant change in the activity and solubility of the compounds.

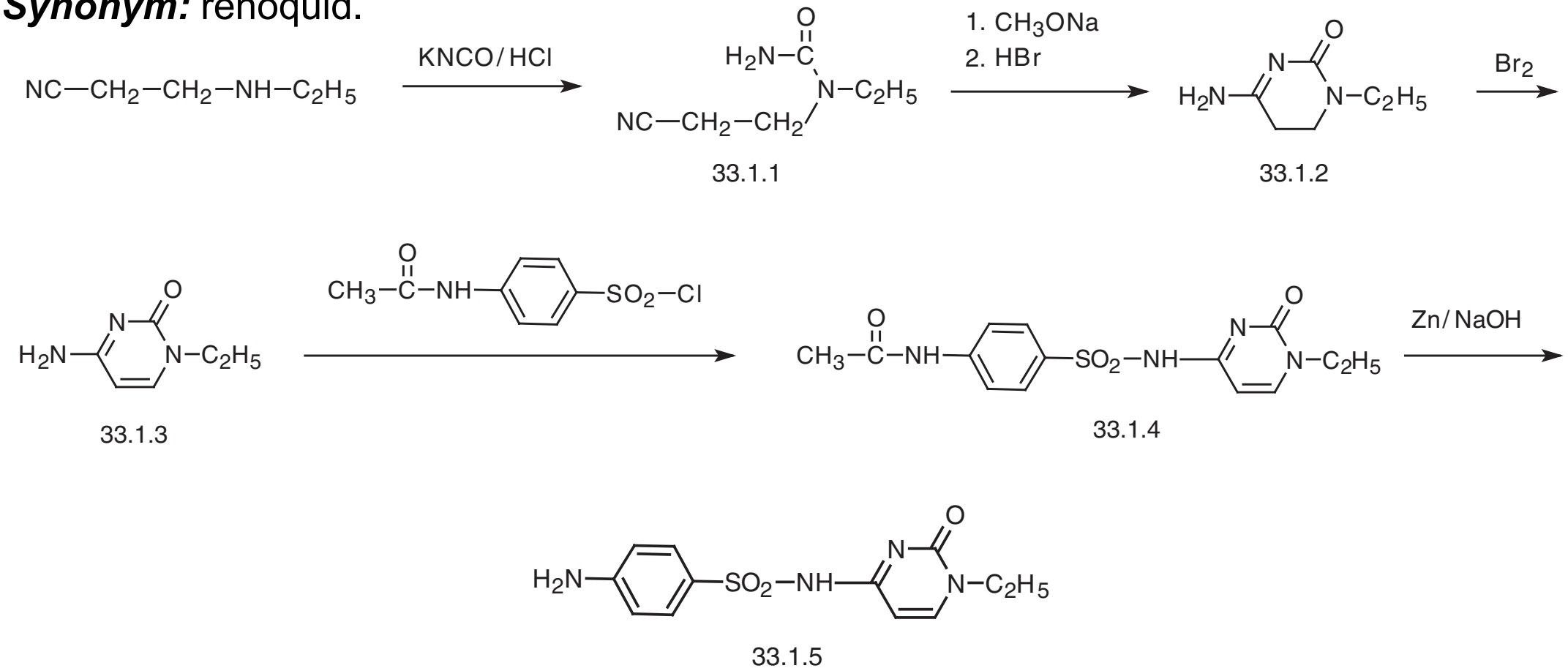
The presence of an additional substituent in the *o*- and *m*-positions of the benzene ring reduces the activity of the given series of compounds as antibacterial agents.

The nature of the substituent in the sulfonyl radical determines the antimicrobial activity and the pharmacokinetic features of each of the individual compound.

Sulfacytine

This drug is effective for infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus. Sulfacytine is used for pneumonia, cerebral meningitis, staphylococcal and streptococcal sepsis, and other infectious diseases.

Synonym: renoquid.



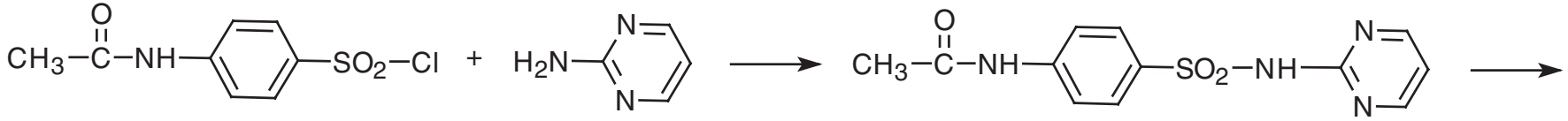
Sulfadiazine

Like sulfacytine, this drug is effective for infections caused by streptococci, gonococci, pneumococci, staphylococci, and colon bacillus. Sulfadiazine is used for pneumonia, cerebral meningitis, staphylococcal and streptococcal sepsis, even for nocardiosis.

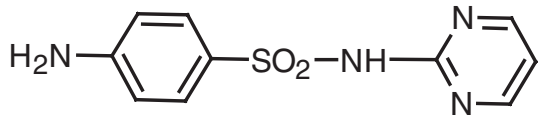
This drug is not recommended for urinary tract infections because of its low solubility and certain nephrotoxicity.

It is used in the form of silver salts (sulfadiazine silver) as an external antibacterial agent, primarily for treating burns. It is believed that the presence of the silver ion in the molecule facilitates increased antimicrobial and wound-healing action.

Synonym: flammazine, sterinor, and terfonil



33.1.6

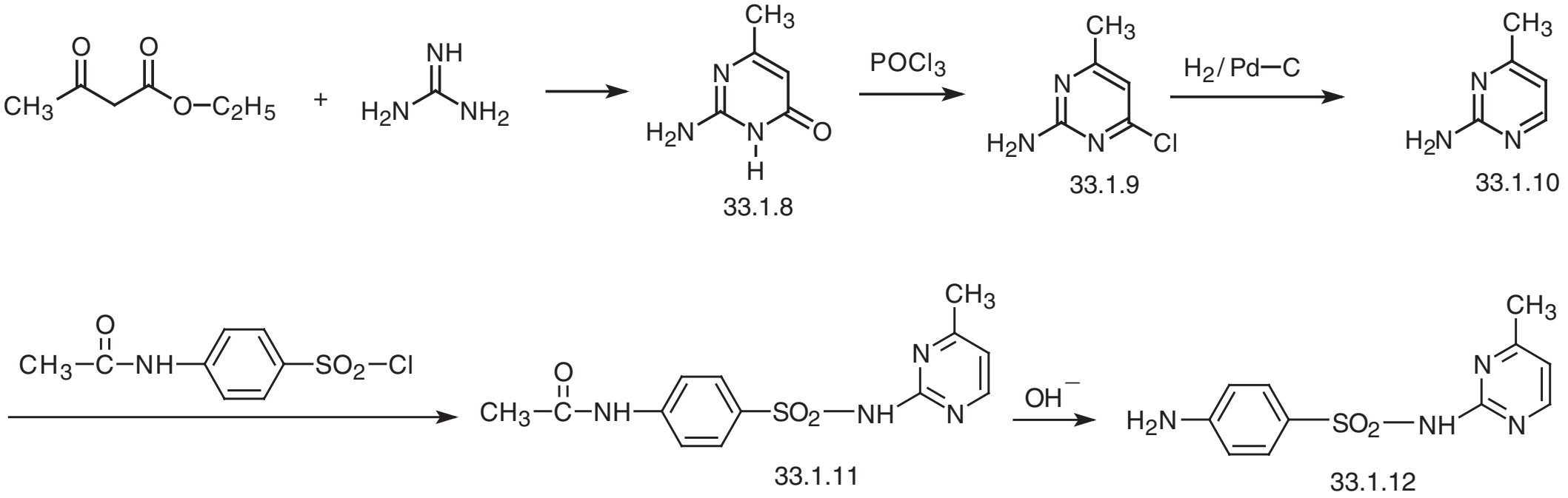


33.1.7

Sulfamerazine

This drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus.

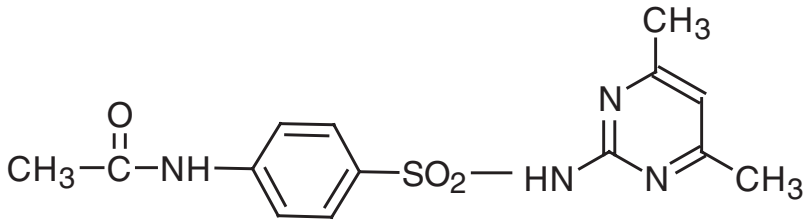
Synonym: dosulfin, polagin, and romezin



Sulfamethazine

This drug is used for pneumococcal, staphylococcal, and streptococcal infections as well as for sepsis, gonorrhea, and other infectious diseases.

Synonym: sulfadiamezin and sulfadimidin.



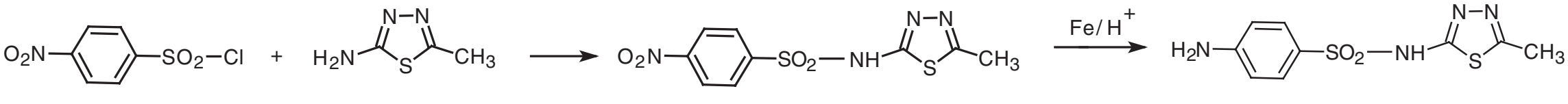
33.1.13

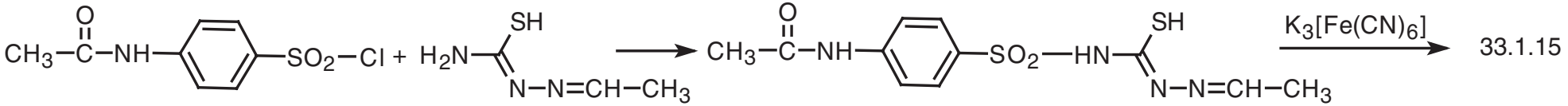
Sulfamethizole

This drug has antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and others. It is not very toxic.

It is generally used for acute, uncomplicated infections of the urinary tract that are caused by sensitive organisms. Because it is removed quickly from the organism by the kidneys, the level of drug in the plasma remains low, and therefore it is not used for treating infections that are localized in the urinary tract. Sulfisoxazole is the more preferred drug.

Synonym: urosol, rufol, and thiosulfil



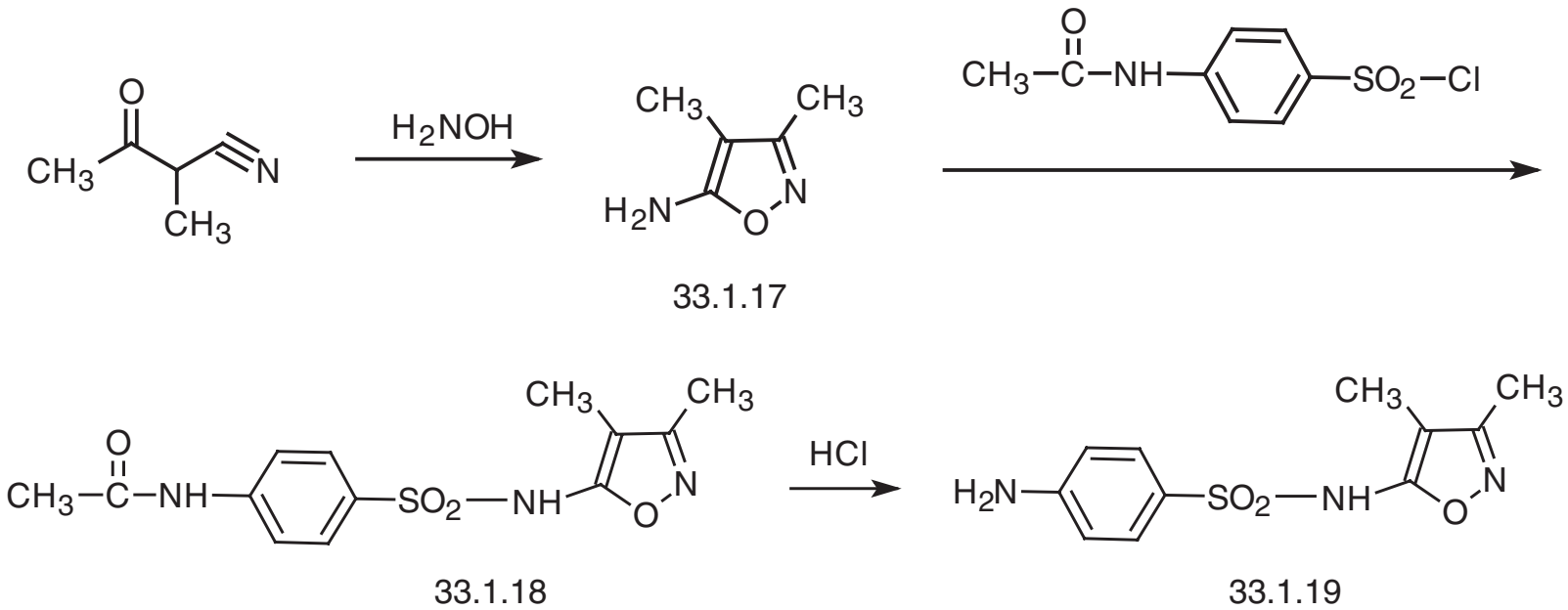


Sulfisoxazole

This drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus.

However, about 90% of it binds with proteins in the plasma after oral administration, and it diffuses mostly to tissues and tissue fluids, which makes it the drug of choice for many systemic infections.

Synonym: gantrisin, fultrxin, sulfazin, and sulfolar



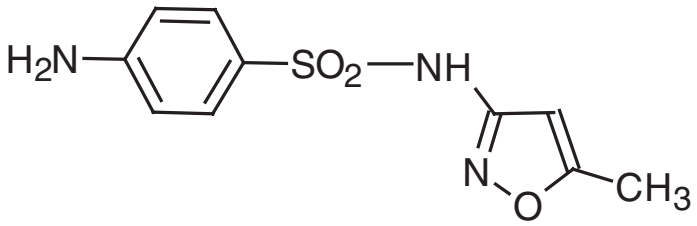
Sulfamethoxazole

Like sulfisoxazole, this drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci as well as colon bacillus.

Unlike sulfisoxazole, only about 70% of it binds with proteins in the plasma after oral administration, and it diffuses mostly to tissues and tissue fluids. However, since it is removed **much slowe**r than sulfisoxazole, it does **not require frequent administration** and is also the drug of choice for many systemic infections.

Moreover, it is an ingredient of a combined drug named bactrim, biseptol, and so on, which has a fixed correlation with trimethoprim.

Synonym: gantanol, sinomin, and sulfisomezole

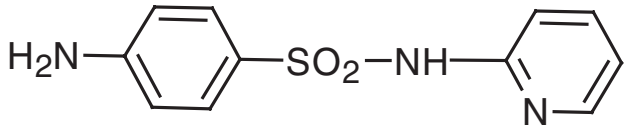


33.1.20

Sulfapyridine

Like all sulfanilamides, this drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and so on. It is a long-lasting drug.

Synonym: bacillopirin, plurazol, sulfidin, and thiaseptol



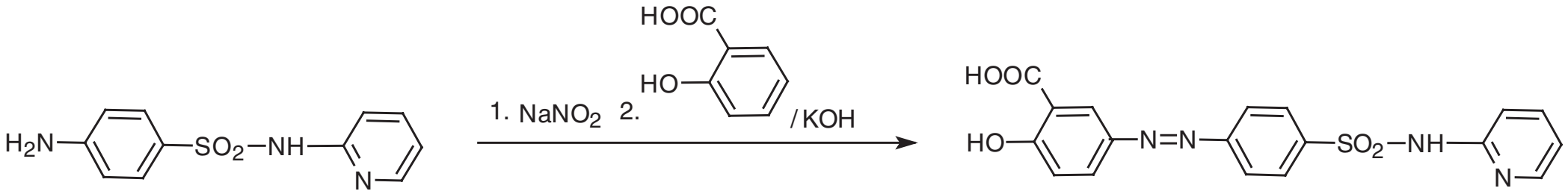
33.1.21

Sulfasalazine

This drug possesses antibacterial activity with respect to a few cocci and colon bacillus. It exhibits a simultaneous, pronounced healing effect in patients with nonspecific ulcerative colitis, which is explained by the degradation in the body of 5-aminosalicylic acid and sulfapyridine, which possess anti-inflammatory and antibacterial properties.

It is used for ulcerative colitis, chronic rheumatoid arthritis as well as acute and subacute inflammatory diseases.

Synonym: slazopyrin and salazosulfapyridine



33.1.21 33.1.22

Phthalylsulfathiazolee

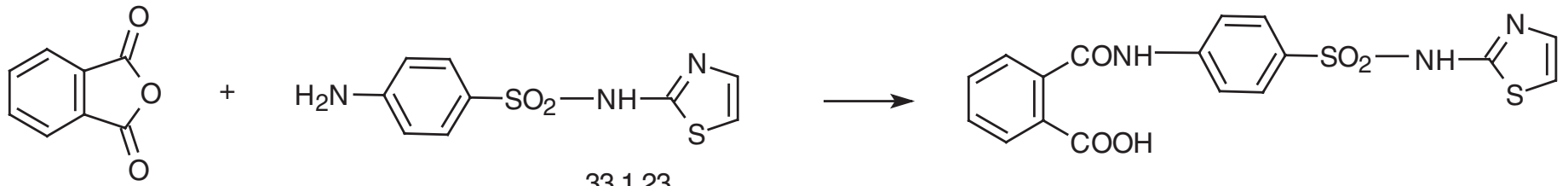
This drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and others.

Phthalylsulfathiazolee is slowly absorbed from the gastrointestinal tract, and its initial mass upon oral administration is retained in the intestines, where it is slowly broken down.

As is the case with sulfasalazinee, a large concentration of sulfanilamide is created in the intestine, which explains its high activity with respect to intestinal infections.

It is used for dysentery, colitis, gastroenteritis, and operational interventions on the intestines in order to prevent purulent complications.

Synonym: phthalazol, enterozol, sulfazole, and talazol



33.1.23

33.1.24

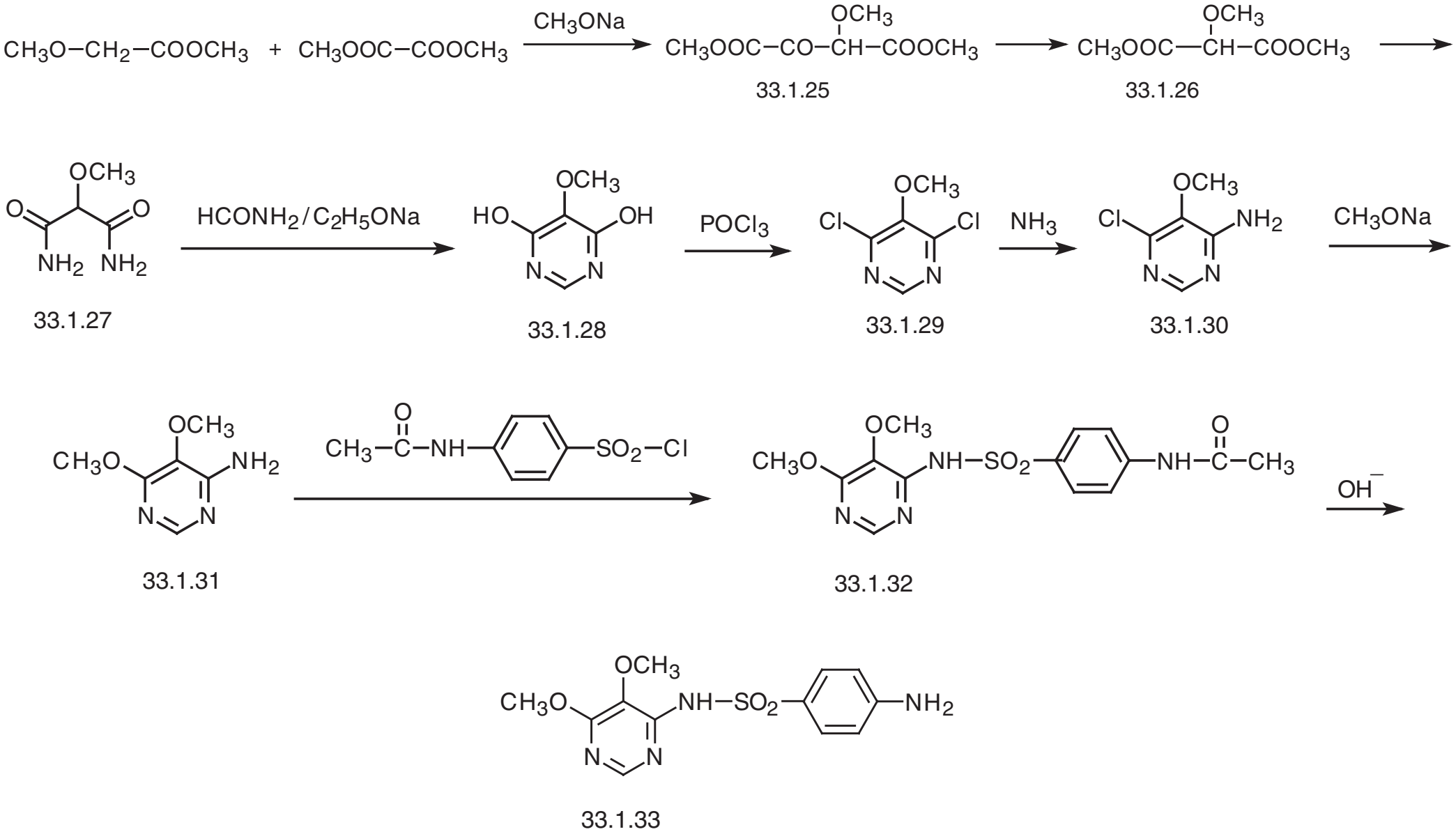
Sulfadoxine

In terms of antibacterial action, this drug is analogous to other sulfanilamides; however, it possesses very prolonged action. Its half-life is from 120 to 200 h.

Sulfadoxine is used for infectious diseases caused by microorganisms that are sensitive to the sulfanilamide drugs, such as infections of respiratory organs, gastric and urinary tracts; purulent infections of various localization, osteomyelitis, sinusitis, and other infections.

It is used in combination with antimalarial drugs.

Synonym: sulfarmethoxine, fanasil, and fansidar


CH3O–CH2–COOCH3 + CH3OOC–COOCH3
CH3ONa
CH3OOC–CO–CH–COOCH3
OCH3
33.1.25
CH3OOC–CH–COOCH3
33.1.26
NH2 NH2
33.1.27
HCONH2/C2H5ONa
HO OH
33.1.28
POCl3
Cl Cl
33.1.29
NH3
Cl NH2
33.1.30
CH3ONa
CH3O NH2
33.1.31
CH3–C–NH
SO2–Cl
NH–SO2
NH–C–CH3
33.1.32
OH–
NH–SO2
NH2
33.1.33

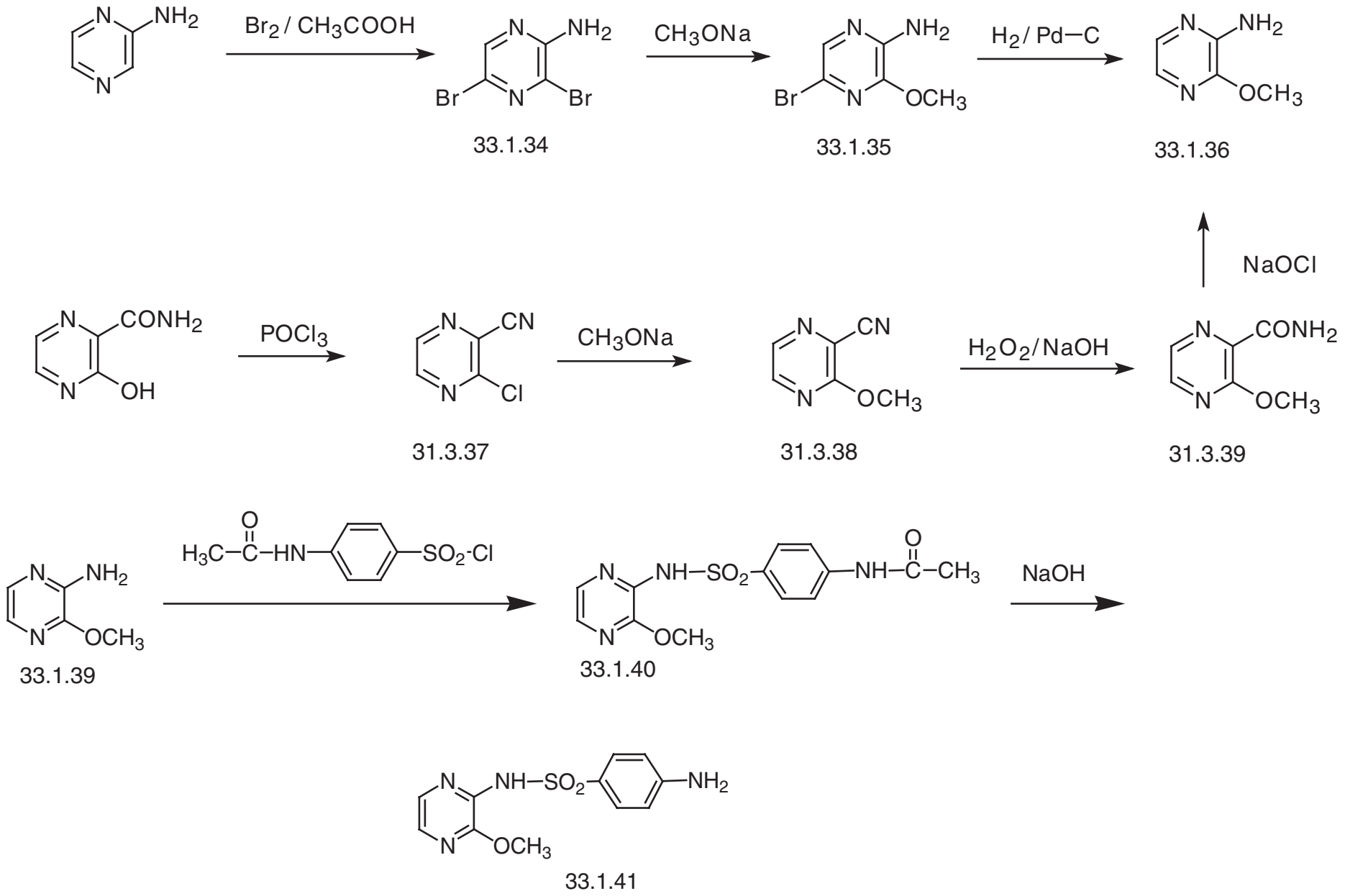
Sulfalene

Sulfalene is also a very long-lasting bacteriostatic sulfanilamide with a broad spectrum of antimicrobial activity.

It is used for the same indications as sulfadoxine. Its half-life is about 150–200 h.

This drug binds to proteins in the plasma to a lesser degree than other sulfanilamides, which ensures its high concentration in the blood in a free form. Therefore, only one dose of sulfalene needs to be taken one time per week.

Synonym: celfizin, sulfamethopyrazine, and sulfamethoxypyrazine


Br2 / CH3COOH
CH3ONa
H2 / Pd—C
33.1.34
33.1.35
33.1.36
NaOCl
POCl3
CH3ONa
H2O2/NaOH
31.3.37
31.3.38
31.3.39
33.1.39
NaOH
33.1.40
33.1.41

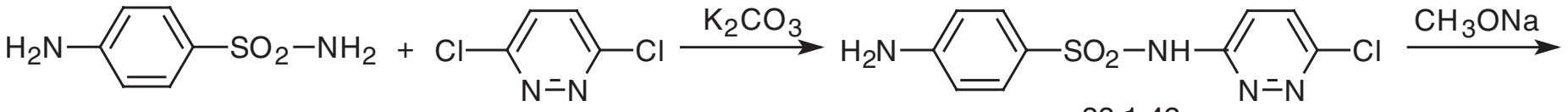
Sulfamethoxypyridazine

This drug possesses antibacterial activity with respect to a few cocci and colon bacillus.

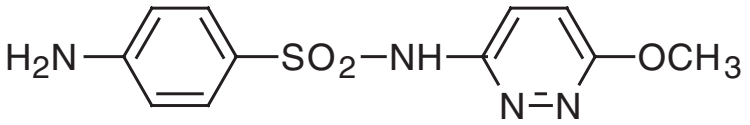
It is a long-lasting drug.

It is used for treating pneumonia, bronchitis, tonsillitis, purulent otitis and meningitis, purulent infections of the urinary tract, dysentery, and others.

Synonym: sulfapyridazine, sufalex, and retasulfin



33.1.42



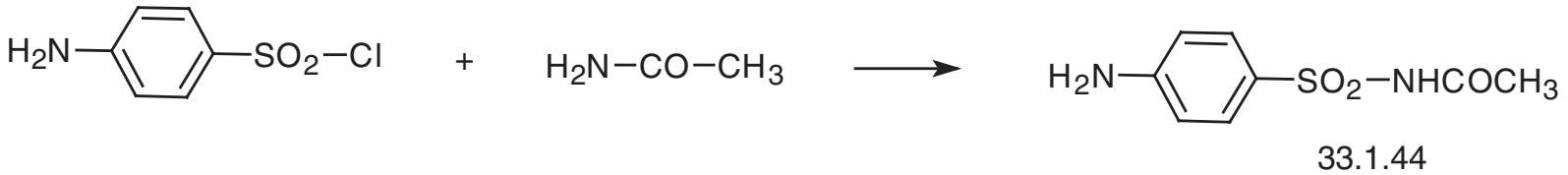
33.1.43

Sulfacetamide

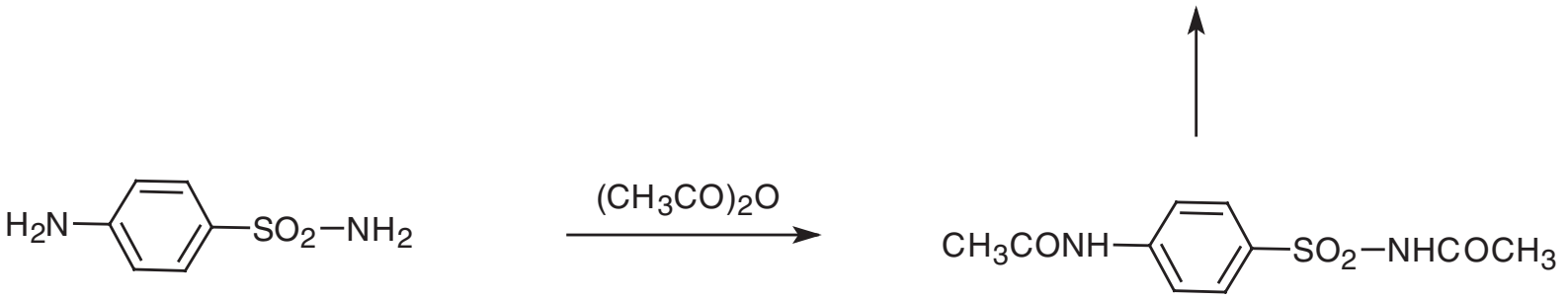
This drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, and gonococci.

It is used for treating pneumonia, purulent tracheobronchitis, urinary tract infections, gonorrheal diseases of the eyes in newborns and adults, and so on.

Synonym: albucid, cetamide, prontamide, and sebizon



33.1.44

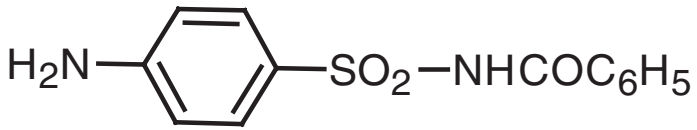


33.1.45

Sulfabenzamide

It is used for the same indications, primarily in the form of ointments for vaginal infections.

Synonym: sulfabenzide

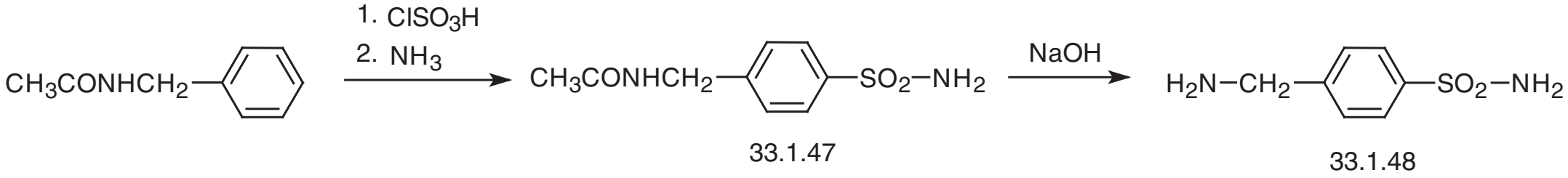


33.1.46

Maphenide

Maphenide is structurally somewhat different from all drugs examined above in that the amino group in the *p*-position to the sulfonamide group is distanced from the benzene ring by one methyl group.

Synonym: marfanil, mezudin, ambamide, and septicid.



33.1.47

33.1.48

Currently, the most widely used are sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfamethizole, and trisulfapyrimidine (a mixture of sulfamerazine, sulfamethazine, and sulfadiazine).

The long-lasting sulfonamide (sulfadioxin) is used only in combination with pyrimethamine (an antagonist of folic acid) for prevention and treatment of tropical fever.

In combination with pyrimethamine or trimethoprim, sulfanilamides are active with respect to a few protozoal infections, including *Toxoplasma*, *Plasmodium falciparum*, and *Pneumocystis carinii.*

33.1.1 Diaminopyrimidines (trimethoprim, pyrimethamine, trimethoprim-sulfamethoxazole)

The diaminopyrimidines, trimethoprim and pyrimethamine, are synthetic antibacterial drugs and inhibitors of dihydrofolate reductase that are used both independently and in combination with sulfanilamides, in particular, with sulfamethoxazole (cotrimoxazole, bactrim, biseptol, sulfatrim, and many others).

Diaminopyrimidines (trimethoprim, pyrimethamine) were suggested as medicinal and preventative agents against malarial infections.

All of the strong dihydrofolate reductase inhibitors could disable the malarial parasite with relatively minor consequences to the host.

The closest structural similarity of these drugs (as well as structural similarity between pteridine ring of folic acid and the diaminopyrimide fragment of pyrimethamine) is most likely the reason of the affinity of this compound to receptive regions of dihydrofolate reductase.

All of these compounds are inhibitors of dihydrofolate reductase in bacteria, plasmodia, and humans. Fortunately, they have a significantly higher affinity to bacterial and protozoal dihydrofolate reductase.

Pyrimethamine inhibits dihydrofolate reductase in parasites in concentrations that are a several hundred times lower than that required to inhibit dihydrofolate reductase in humans. This is the basis of their selective toxicity.

Selective toxicity can be elevated upon the host organism's production of folic acid, which parasites are not able to use.

Trimethoprim acts in the body by interfering with the action of hydrofolate reductase, an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid. This process is necessary for purine biosynthesis of live organisms and DNA, respectively.

Reducing the dihydrofolic acid to tetrahydrofolic acid is also catalyzed in humans by dihydrofolate reductase.

However, trimethoprim has thousands of more inhibitory effects with respect to bacterial enzymes than with respect of analogous enzymes of mammals, which is the main benefit of trimethoprim.

Various sulfonyl amides inhibit one of the stages of this biosynthetic pathway, which is by adding dihydrofolic acid in the place of *n*-aminobenzoic acid in sulfanilamide.

Subsequent blockage of one or the other biosynthetic pathways by two drugs (sulfanilamide and trimethoprim at the same time) differs in the high degree of synergism with respect to a broad spectrum of microorganisms.

A very strong effect is exhibited with respect to many microorganisms when used in combination with sulfomethoxazole. A ratio of 20:1 sulfamethoxazole/trimethoprim is considered to be optimal.

Trimethoprim

Trimethoprim has a broad spectrum of antimicrobial activity. It is 20–100 times more active than sulfamethoxazole with respect to most bacterial forms.

Trimethoprim is active with respect to Gram-positive, aerobic bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and various types of *Streptococcus* and *Listeria monocytogenes*.

Trimethoprim is inferior to sulfonamides against forms of *Nocardia*.

It is active with respect to Gram-negative, aerobic bacteria such as most *E. coli*, *Enterobacter*, *Proteus*, *Klebsiella*, *Providencia*, *Morganella*, *Serratia marcescens*, *Citrobacter*, *Salmonella*, *Shigella*, *Yersinia enterocolitica* that are sensitive to trimethoprim.

Trimethoprim is also active with respect to *Legionella*, *Acinetobacter*, *Vibrio*, *Aeromonas*, *Pseudomonas maltophila*, *P. cepacia*, although ***P. aeruginosa*** **is resistant to trimethoprim**.

Haemophilus influenzae and *H. ducreyi* are sensitive to trimethoprim.

Pathogenic *Neisseria* (meningococci and gonococci) and *Branhamella catarrhalis* are moderately resistant to trimethoprim, although they are very sensitive to a combination of trimethoprim and sulfamethoxazole.

Anaerobic bacteria in general are resistant to trimethoprim, although a combination of trimethoprim-sulfamethoxazole does have an effect on them.

Pneumocystis carinii is also sensitive to that combination.

Bacterial resistance to trimethoprim can originate because of a number of reasons:

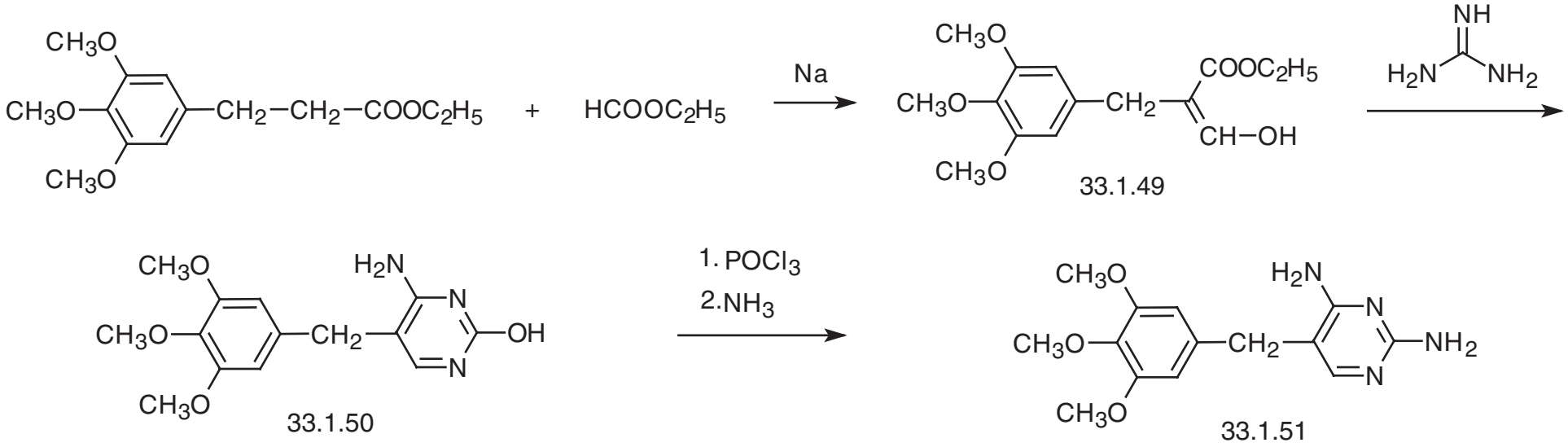
(1) inability of the drug to penetrate through the membrane (*P. aeruginosa*);

(2) the presence of dihydrofolate reductase that is not sensitive to inhibition by trimethoprim;

(3) overproduction of dihydrofolate reductase and mutation expressed as thyminic dependence, when the organism requires exogenic thymine for synthesizing DNA, i.e. bypassing metabolic blockage caused by trimethoprim.

Resistance to a **combination** of trimethoprim-sulfamethoxazole is always less frequent than when any of these drugs is used separately.

This combination of drugs, which is known by the commercial names cotrimoxazole, bactrim, biseptol, sulfatrim, and many others, is used for treating infections of the respiratory tract, infections of the urinary tract, gastric infections, surgical infections, enteritis, meningitis, and other diseases.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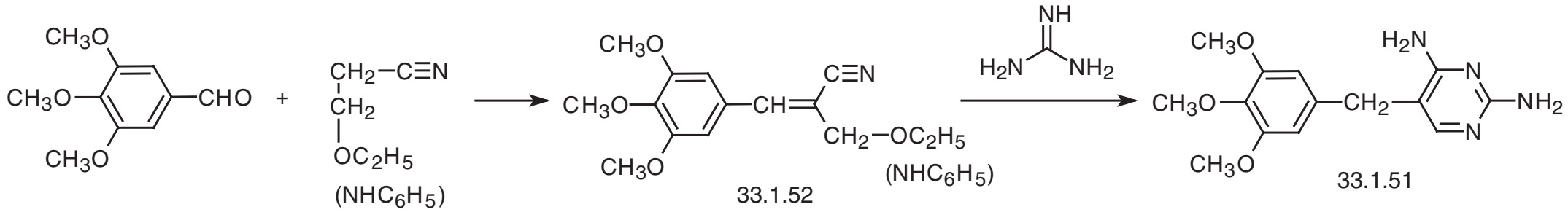
CH3O
CH3O
CH2–CH2–COOC2H5
+
HCOOC2H5
Na
COOC2H5
CH2
CH–OH
33.1.49
NH
H2N
NH2
1. POCl3
2.NH3
H2N
N
OH
33.1.50
NH2
33.1.51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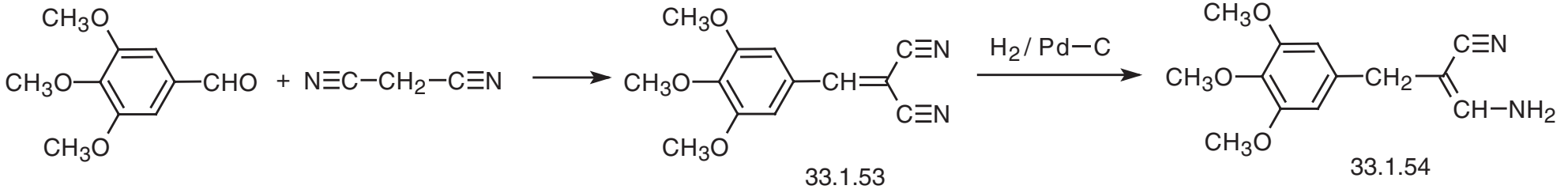
CHO
+
CH2–C≡N
CH2
OC2H5
(NHC6H5)
C≡N
CH
CH2–OC2H5
33.1.52
NH
H2N
NH2
H2N
N
NH2
33.1.51



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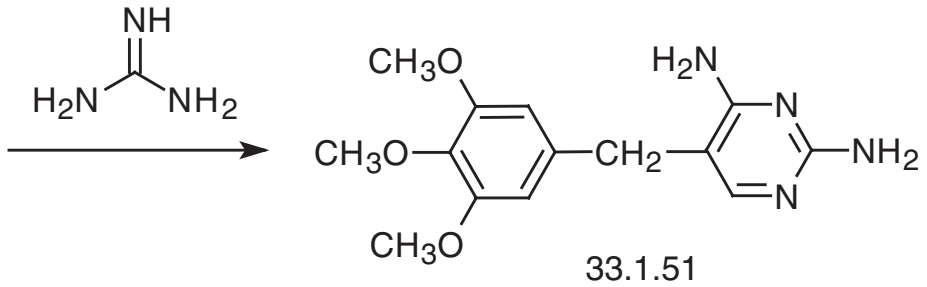

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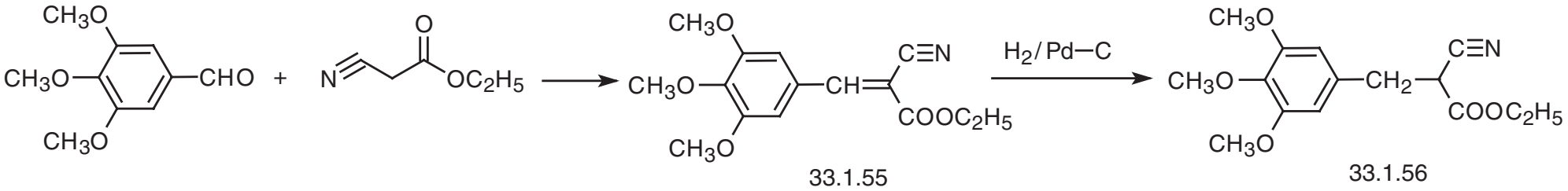

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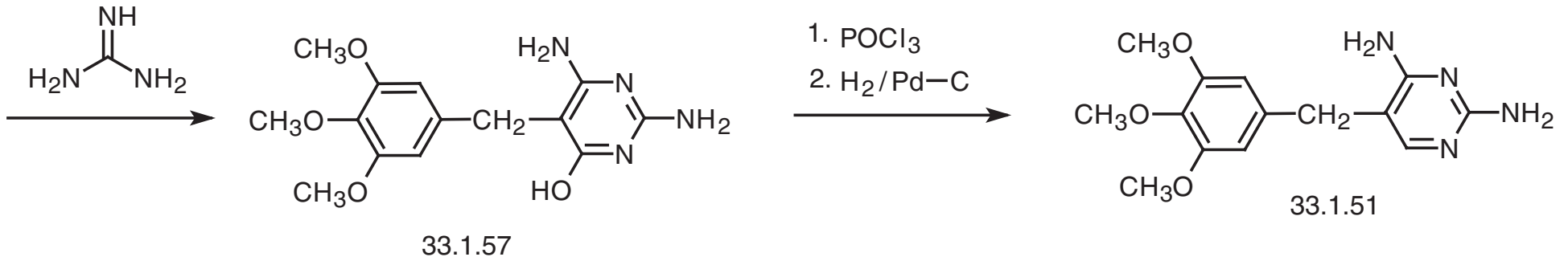

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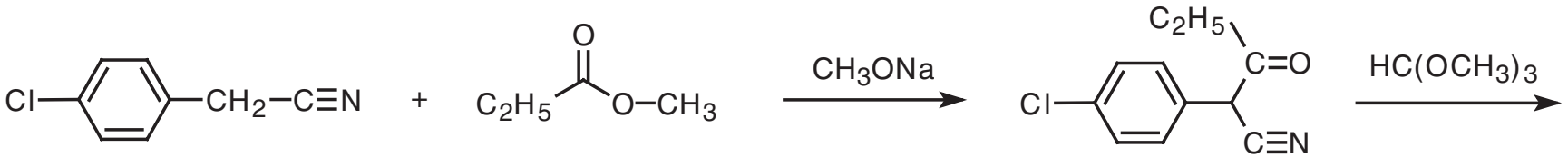
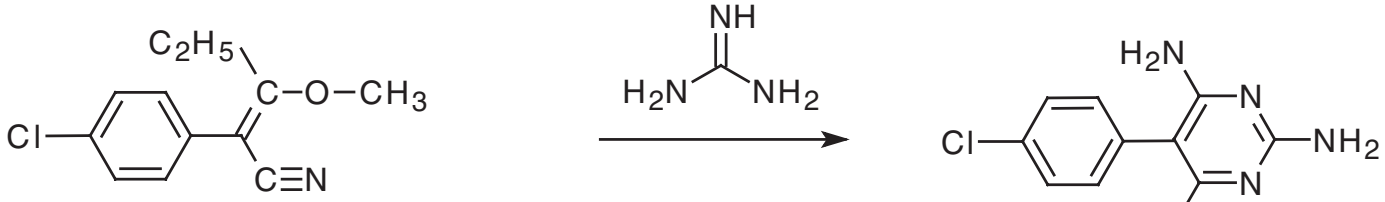
Pyrimethamine

Pyrimethamine, a folic acid antagonist, exhibits antimicrobial action against the causative agent of malaria and possesses sporontocidal action.

It is also effective with respect to the causative agent of toxoplasmosis. It is used for preventing malaria and treating toxoplasmosis.



33.1.58



33.1.59

33.1.60

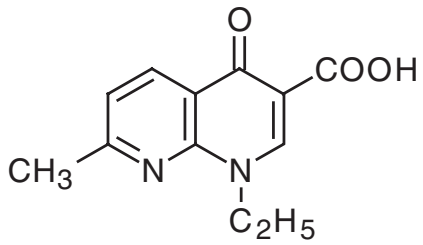
33.2 QUINOLONES

Quinolones are a group of structurally similar antimicrobial drugs that exhibit high activity against many microorganisms.

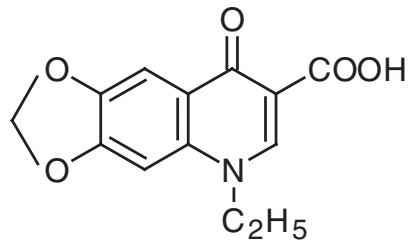
The first representative of the new class of antimicrobial drugs (called drugs of the quinolone series, which are derivatives of naphthiridine), was nalidixic acid (nevigramon), which was synthesized in 1962 and was suggested for treating urinary tract infections.

The main spectrum of its use includes Gram-negative bacteria. It is also effective with respect to colon bacillus, proteus, klebisella, shigella, and salmonella.

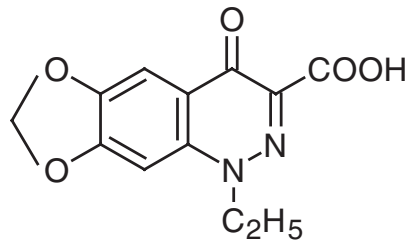
In recent years, a number of chemically similar compounds have been synthesized, such as oxolinic acid and cinoxacin, although all of them had a relatively narrow antimicrobial spectrum.



nalidixic acid



oxolinic acid



cinoxacin

Enormous progress was made in the 1980s due to the introduction of a fluorine atom to the C6 position of 4-quinolone and a piperazine fragment to the C7 position.

Introducing a fluorine atom in the indicated position dramatically increased the activity of the drug with respect to Gram-positive microorganisms, which broadened its spectrum of action to include Gram-negative microorganisms.

Introducing the piperazine fragment to C7 ensured activity of this group of drugs with respect to *Pseudomonas aeruginosa.* The substituents at the nitrogen atom of the quinolone structure and in the piperazine ring may vary from drug to drug.

All fluoroquinolones are usable in medical practice: ciprofloxacin, enoxacin, norfloxacin, and ofloxacin have approximately the same antimicrobial spectrum, which includes most aerobic Gram-negative and a few Gram-positive bacteria.

Fluoroquinolones are highly active against most enterobacteria, including *E. coli*, *Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Providencia*, *Citrobacter* and *Serratia.*

They are also active with respect to *Pseudomonas aeruginosa*, including strains resistant to other antibacterial drugs. Most strains of *Acinetobacter*, aerobic Gram-negative microorganisms are sensitive to fluoroquinolones.

Fluoroquinolones are highly active against most Gram-negative bacterial pathogens of the gastrointestinal tract, such as *Shigella*, *Salmonella*, *Yersinia enterocolitica*, *Aeromonas species*, and *Vibrio species*.

Gram-negative coccobacteria *Haemophilus influenzae*, *Haemophilus ducreyi* and Gram-negative cocci *Neisseria meningitides*, *N. gonorrhoeae*, and *Moraxella* are also very sensitive to fluoroquinolones.

Fluoroquinolones are also active with respect to most Gram-positive bacteria, *Staphylococcus aureus* and *S. epidermidis*, although the concentrations used must be somewhat higher than for Gram-negative bacterial pathogens.

Fluoroquinolones are powerful bactericidal drugs that change the structure and function of bacterial DNA by affecting the enzyme DNA-gyrase (topoisomerase II).

This enzyme is responsible for negative supercoiling twisting (negative supercoiling) to covalently closed, circular DNA as well as breaking up the repeating compounds (catenation, decatenation) of DNA coils linked to the chain.

DNA-gyrase is capable of breaking down bacterial DNA that has an approximate length of 1300 μm, such as in *E. coli*, inside a cell whose size ranges from 2 to 3 μm. This enzyme is necessary for replication, restoration, and transcription of certain DNA operons.

DNA-gyrase is made up of two A and two B subunits. Quinolones have a direct effect on the function of A subunits.

Drugs of this series have a similar antimicrobial spectrum, which includes most aerobic Gram-negative and a few Gram-positive bacteria. The specific difference in activity of these drugs is observed with respect to a few specific microorganisms, their relative toxicity, pharmacokinetic features, and so on.

For example, ciprofloxacin and norfloxacin have a similar antimicrobial spectrum; however, depending on the type of microorganisms, norfloxacin can turn out to be 2–8 times weaker.

Two mechanisms of resistance have been discovered with respect to fluoroquinolones:

(a) a change in subunits A of DNA-gyrase, and

(b) reduced permeability of the outer membrane of the bacteria.

Resistance is mediated by chromosomes, and not plasmids in the bacteria. The development of resistance while using the drugs is very rarely observed.

Because of its pharmacokinetic features (pronounced bioaccessability upon oral use, diffusion to tissues and permeation into them, broad spectrum of antibacterial activity, and so on), fluoroquinolones have considerable potential for treating infections of practically any anatomic localization.

Fluoroquinolones are very effective in treating infections of the respiratory tract, urinary tract, bones, skin, soft tissues, and so on.

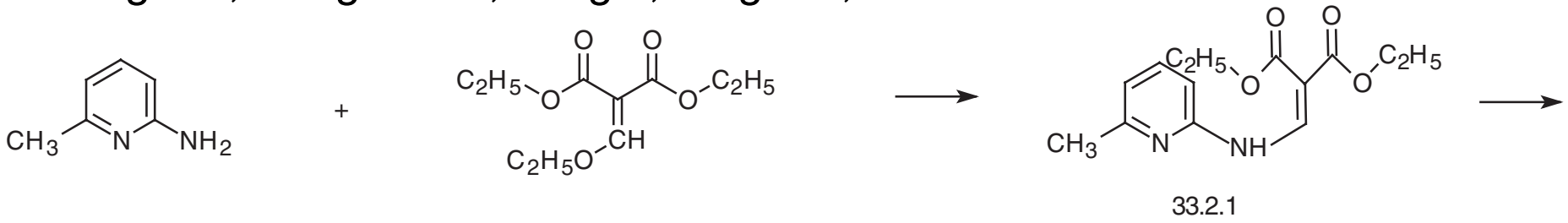
Nalidixic acid

It has a bactericidal or bacteriostaic effect depending on the sensitivity of the microorganism and the concentration.

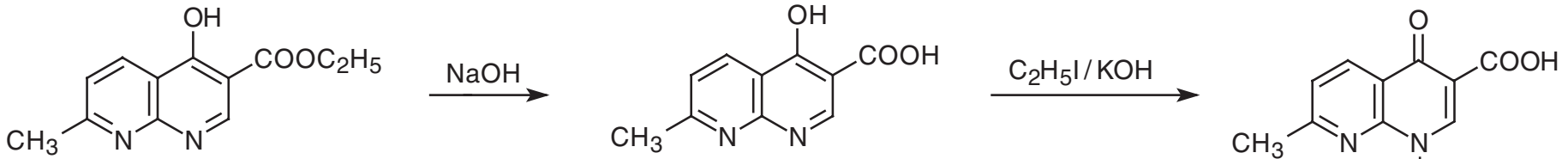
It is effective with respect to Gram-negative microorganisms, such as colon bacillus, salmonella, shigella, proteus, and Fridlender's bacillus.

It is used for pyeolonephritis, cystitis, urethritis, prostatitis, and gastrointestinal tract infections.

Synonym: negram, nevigramon, uralgin, urogram, and vintron



33.2.1

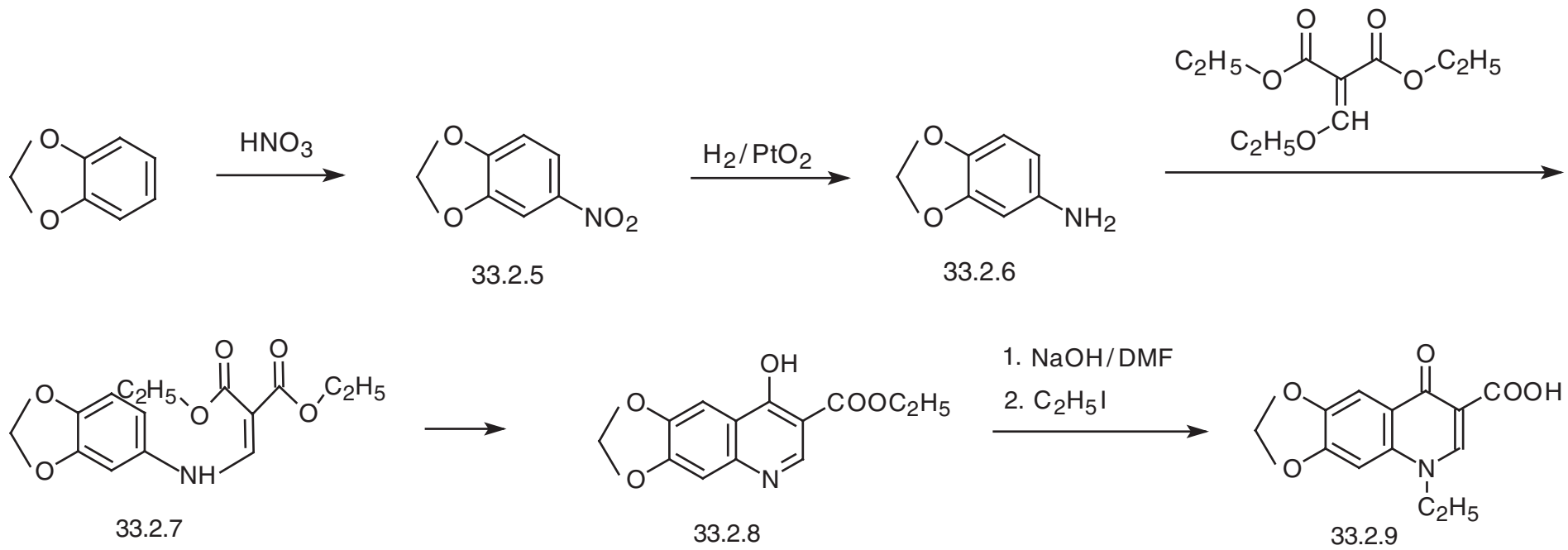


33.2.2 33.2.3 33.2.4

Oxolinic acid

Like nalidixic acid, this drug is effective with respect to Gram-negative microorganisms and is used for the same indications.

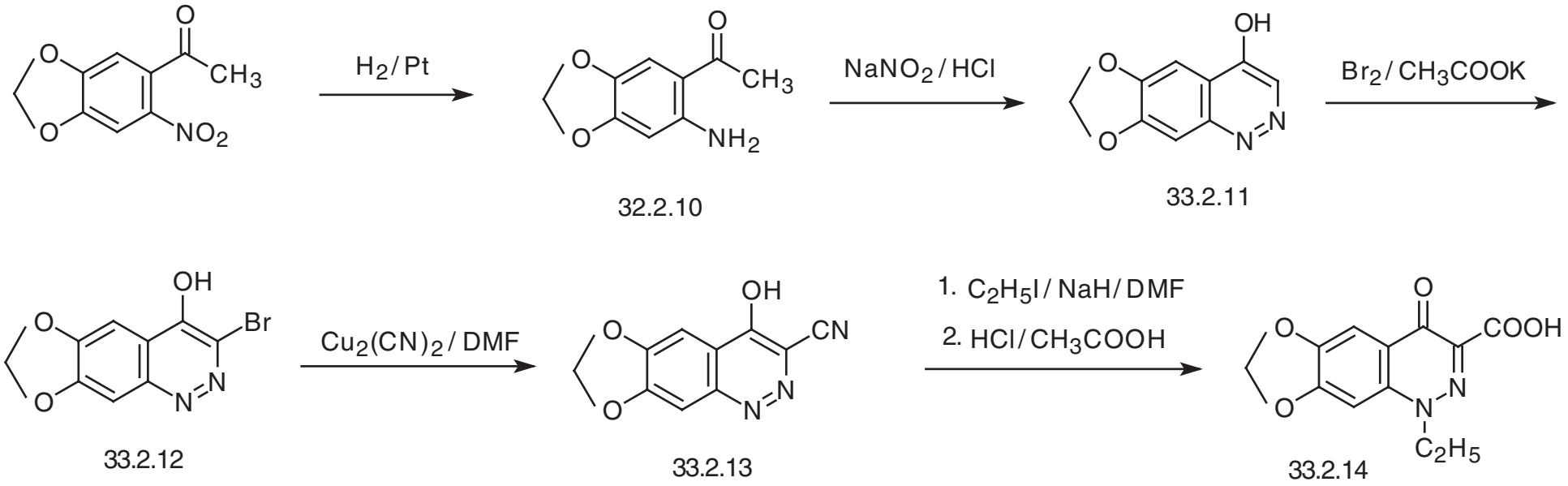
Synonym: nidantin, prodoxol, ocolin, and uroxol



Cinoxacin; Azolinic acid

This drug is effective with respect to Gram-negative microorganisms and is used for the same indications as nalidixic and oxolinic acids.

Synonym: cinobactin, nossacin, and uronorm



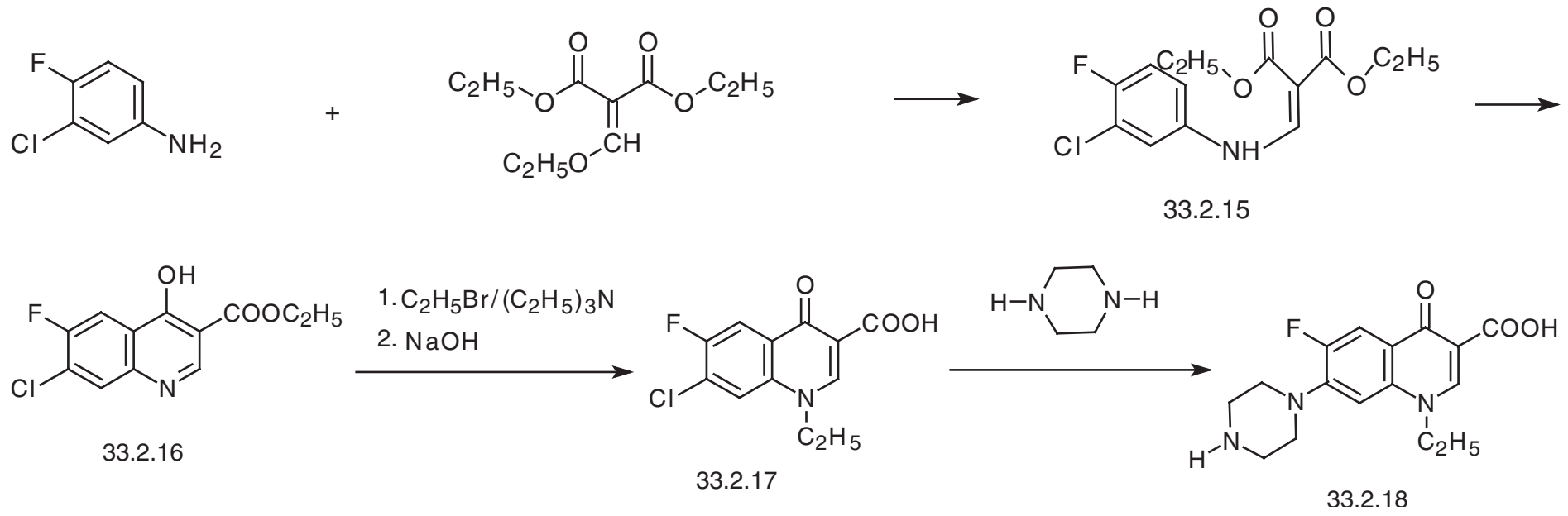
Norfloxacin

It possesses a broad spectrum of bactericidal action. It is highly active with respect to most Gram-negative and a few Gram-positive microorganisms.

Anaerobic bacteria are not sensitive to this drug, while enterococci and akinetobacter are not very sensitive.

It is used for bacterial infections of the urinary tract, prostate gland, gastrointestinal tract, gonorrhea, and traveler's diarrhea.

Synonyms: noroxin, barazan, fulgram, and bacidal



Ciprofloxacin

It possesses a broad spectrum of antimicrobial action, highly effective against Gram-negative microorganisms, such as blue-pus bacillus, hemophilic and colon bacillus, shigella, salmonella, meningococci, gonococci, and a few forms of enterococci.

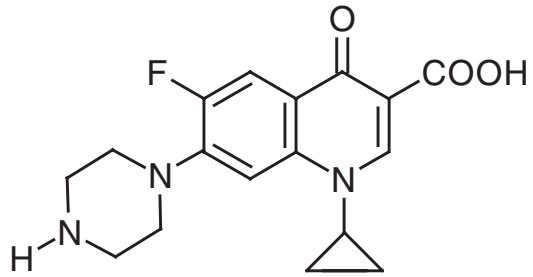
It is also active with respect to many strains of staphylococci, camphylobacter, legionella, mycoplasma, chlamydia, and mycobacteria. *Ureaplasma urealyticum*, *Clostridium difficile*, and *Nocardia asteroids* are resistant to it.

It is used for infections of the urinary tract, respiratory tract, biliary tract, infective-inflammatory diseases of the abdominal cavity and organs, pelvis minor, bones, joints, and skin, bacterial prostatitis, noncomplicated gonorrhea, osteomyelitis, and pulmonary infections.

It is effective in treating acute infectious diarrhea, including traveler's diarrhea and enteritis.

Side effects are rarely seen when taking this drug.

Synonym: ciproquin, ciprolet, cipropan, ciproxan, and ciprocinal

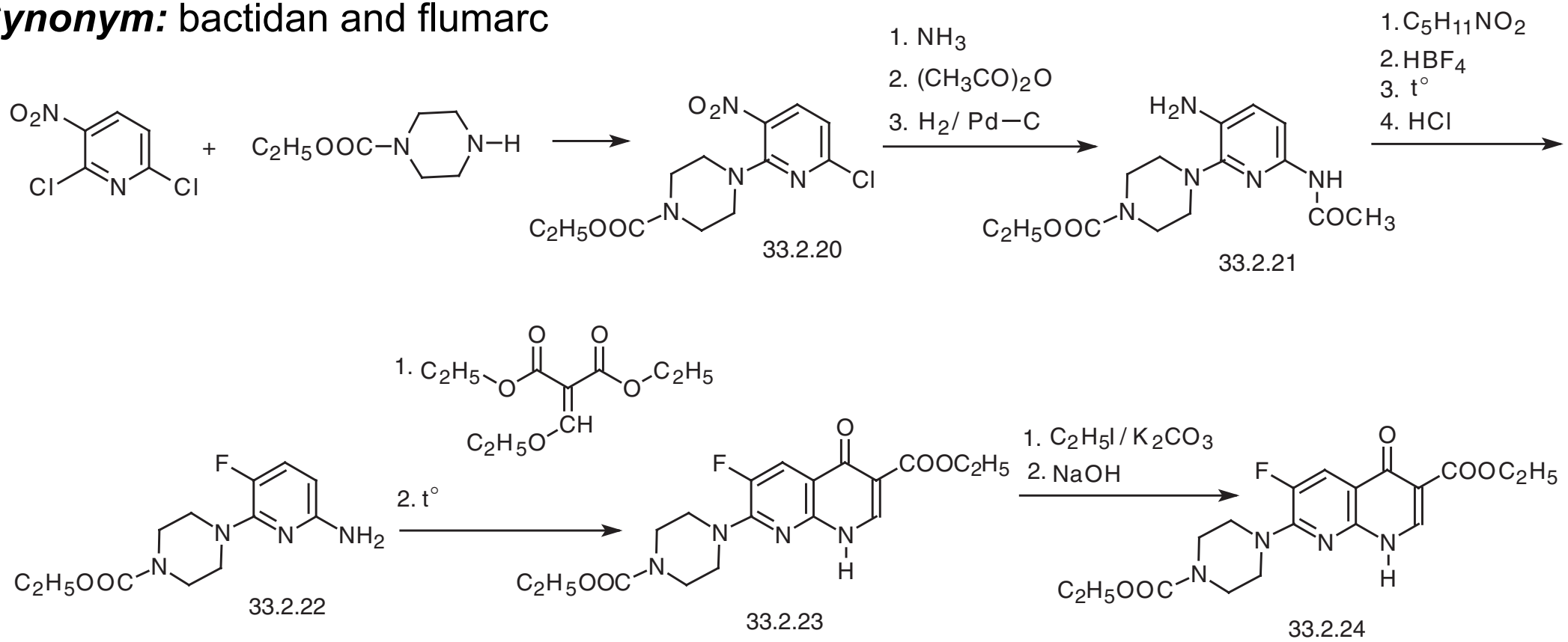


33.2.19

Enoxacin

In terms of the antibacterial spectrum and region of use, enoxacin basically exhibits the same properties as norfloxacin. However, it is better absorbed from the gastrointestinal tract and has a longer half-life.

Synonym: bactidan and flumarc

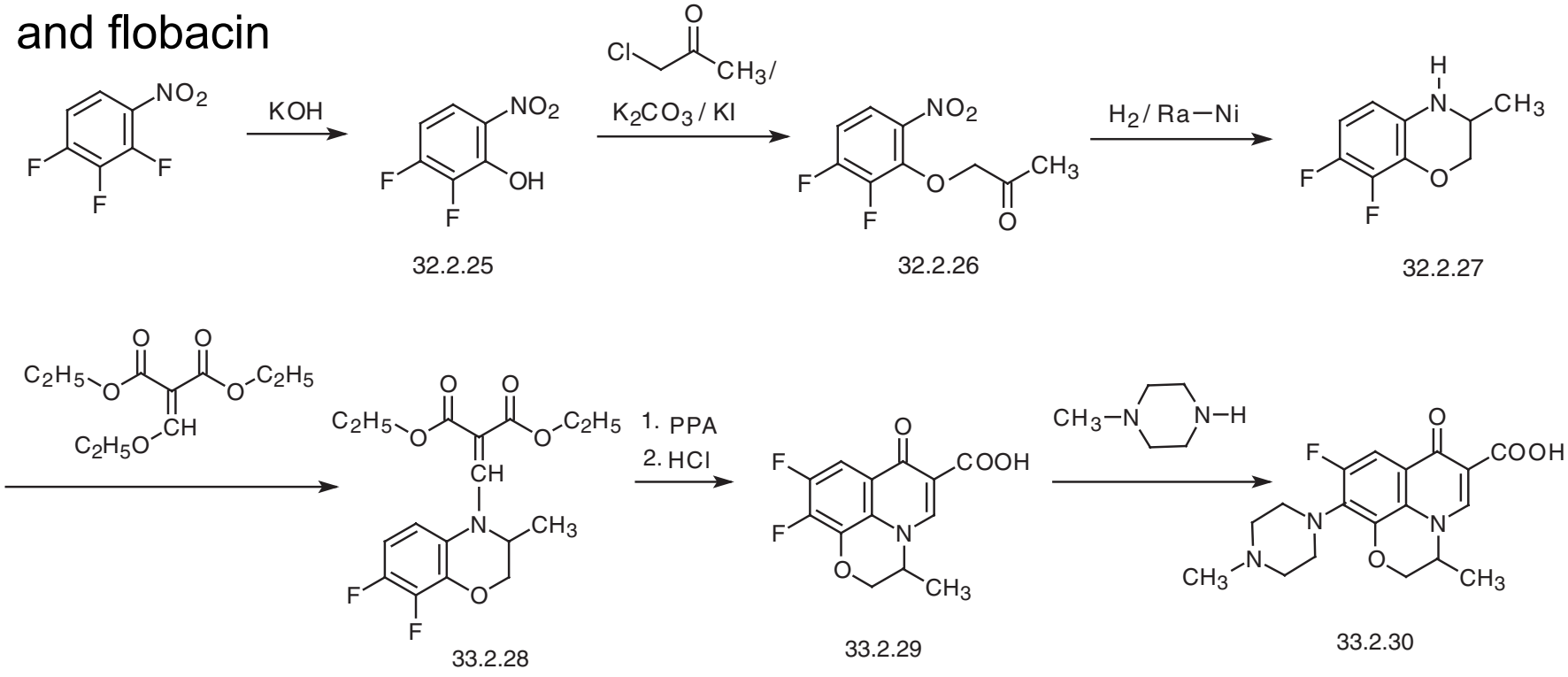


Ofloxacin

It possesses a broad spectrum of antimicrobial action, highly active with respect to Gram-negative microorganisms such as blue-pus bacillus, hemophilic and colon bacillus, shigella, salmonella, and chlamydia.

It is used for infections of the respiratory tract, ears, throat, nose, skin, soft tissue, bones, joints, infective-inflammatory diseases of the abdominal cavity organs (kidneys, urinary tract), and organs of the pelvis minor (genitalia), and for gonorrhea.

Synonym: tarivid and flobacin



33.3 NITROFURANES

A few nitrofurane derivatives possess pronounced antimicrobial activity. All of these compounds are characterized by the fact that they are derivatives of 5-nitrofurfurol, which are synthesized by reacting various compounds that contain a hydrazine functional group.

Nitrofuranes are effective with respect to Gram-positive and Gram-negative microorganisms as well as trichomonad and lambliosis.

In small concentrations, these drugs act bacteriostatically, while in high concentrations they act bactericidally.

They are most effective against a few strains of *E. coli*, *Klebsiella*, *Enterobacter* and *Citrobacter.* They can also be effective against a few microorganisms that are resistant to antibiotics and sulfonamides.

Nitrofurazone, furazolidon, and nitrofurantion are the most widely used. Derivatives of nitrofurane are used both orally and as external drugs.

Drugs of this series accumulate in the urine and bile. The speed of absorption depends heavily on the crystallized form of the drug.

Nitrofuranes are used predominantly as antiseptics for external use (nitrofurazone) as well as for treating infections of the urinary tract and intestines.

The exact mechanism of action of these drugs has not been established. However, it seems likely that they inhibit a number of bacterial enzyme systems, most likely by damaging their DNA.

It is presumed that the enzyme nitroreductase transforms these drugs to short-lived, intermediate radicals, which react with DNA of bacteria and damage the process of twisting.

Resistance, which is rarely observed, can originate as a result of mutations linked to a loss of nitroreductase activity.

Nitrofurazone

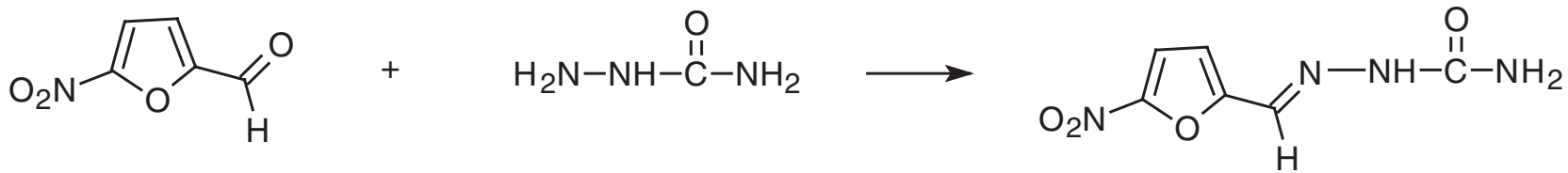
It is an effective drug that acts on a number of Gram-positive and Gram-negative microorganisms (staphylococci, streptococci, dysentery bacillus, colon bacillus, paratyphoid bacillus, and others).

It is generally used externally for treating and preventing the pyoinflammatory processes, and internally for treating bacterial dysentery.

Wounds are irrigated and wet bandages are synthesized using nitrofurazone.

It is used in the form of eye drops for practically all suppurative processes that require use of antibacterial drugs.

Synonym: furacillin, furacin, antibioptal, and vabrocid



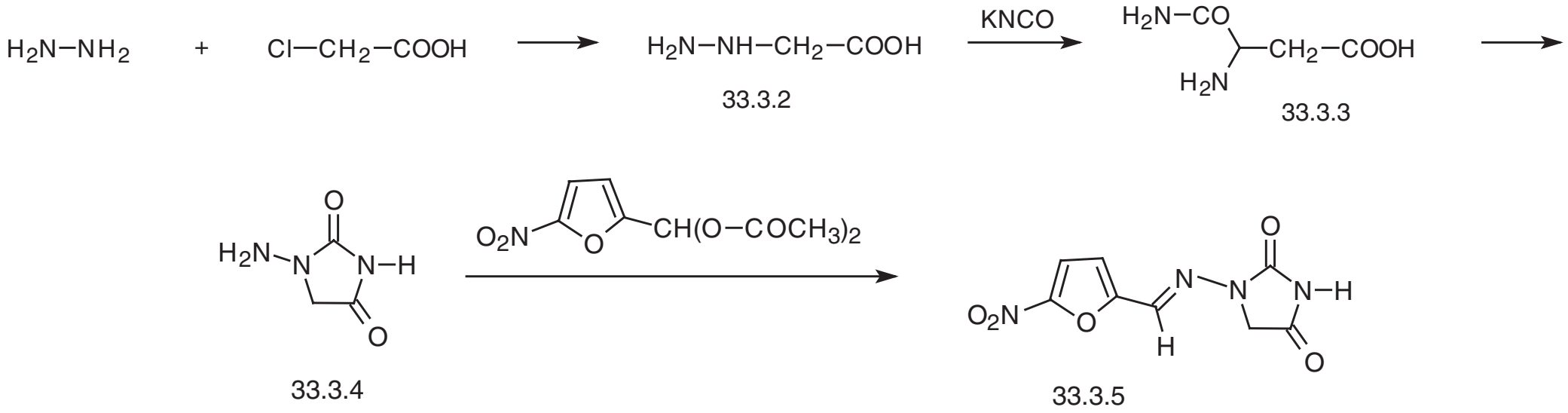
33.3.1

Nitrofurantoin

Like nitrofurazone, nitrofurantoin is an effective drug that acts on a number of Gram-positive and Gram-negative microorganisms (staphylococci, streptococci, dysentery bacillus, colon bacillus, paratyphoid bacillus, and others).

It is primarily used for treating infectious diseases of the urinary tract (pyelitis, pyelonephritis, cystitis, urethritis).

Synonym: furadonin, ituran, phenurin, urolong, cistofuran, and nitrofurin



33.3.2 33.3.3 33.3.4 33.3.5

Furazolidone

Furazolidone is effective against Gram-positive and Gram-negative microorganisms. However, it also possesses antitrichomonal activity and is effective in treating lambliosis.

In comparison with nitrofurazone and nitrofurantoin, furazolidone is more active with respect to Gram-negative microorganisms, and at the same time it is less toxic.

Furazolidone is used internally and locally for the same indications as nitrofurazone and nitrofurantoin.

Synonym: diafuron, furoxan, itifur, vaginol, and medaron