Coronary vascular dilators

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Ischemic heart disease

- when lumen of coronary artery is restricted (due to atherosclerotic changes, spasm or inflammatory reaction), supplying of myocard with oxygen and nutrients is insufficient
- primary symptom is **Angina pectoris** – sudden, severe pain originating in the chest and radiating to the left shoulder and arm

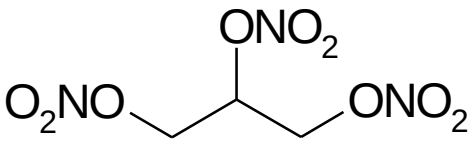
Ischemic heart disease therapy

- vasodilators – direct (NO releasing agents, xanthine derivatives, nicotinic acid, chromone derivatives, prostaglandines, trimetazidin) indirect (Ca^{2+}inhibitors, ACE inhibitors, angiotensin II receptor antagonists)
- drugs preventing myocardial infarction (anicoagulants, antithrombotics)

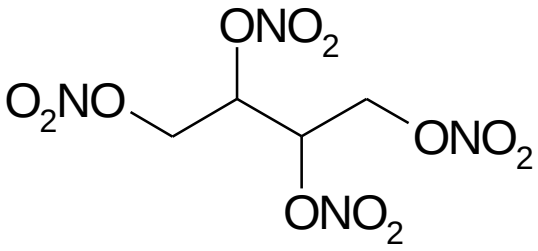
Organic nitrates

- prodrugs releasing NO
- NO is endotelial guanylatcyclase activator
- increased intracelular cGMP decrease Ca^{2+} levels → vessel wall smooth muscle relaxation → vasodilatation

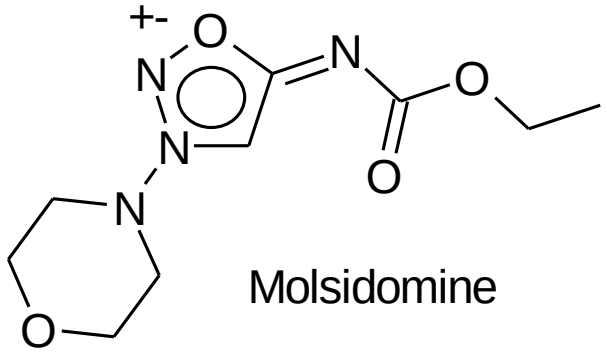
Organic nitrates



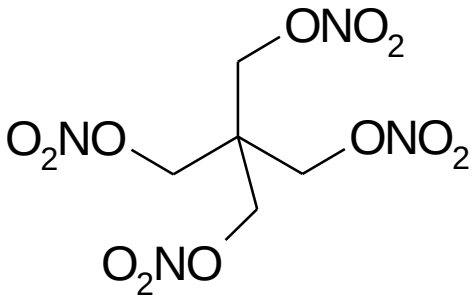
glyceryl trinitrate



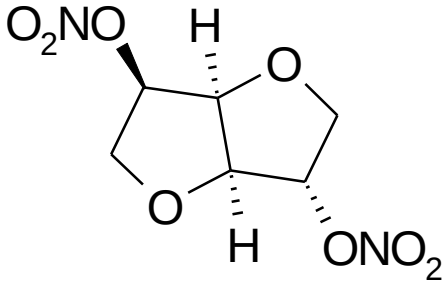
erithrityl tetranitrate



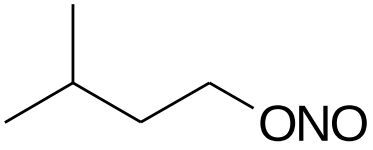
Molsidomine



pentaerythritol tetranitrate

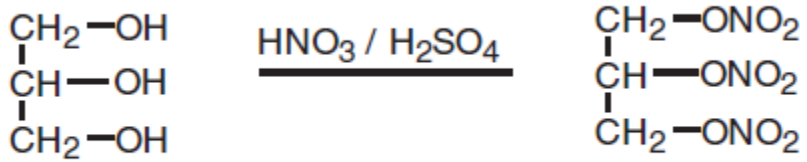


isosorbide dinitrate

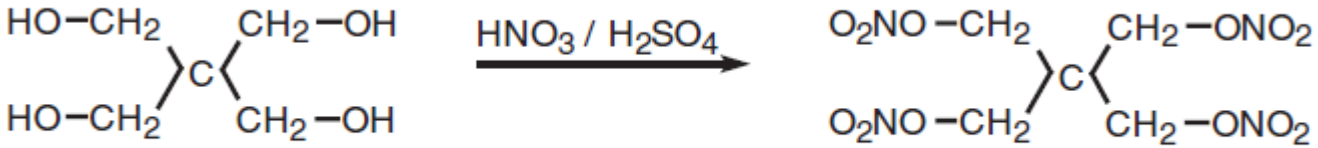


amyl nitrite

Organic nitrates synthesis



19.1.1



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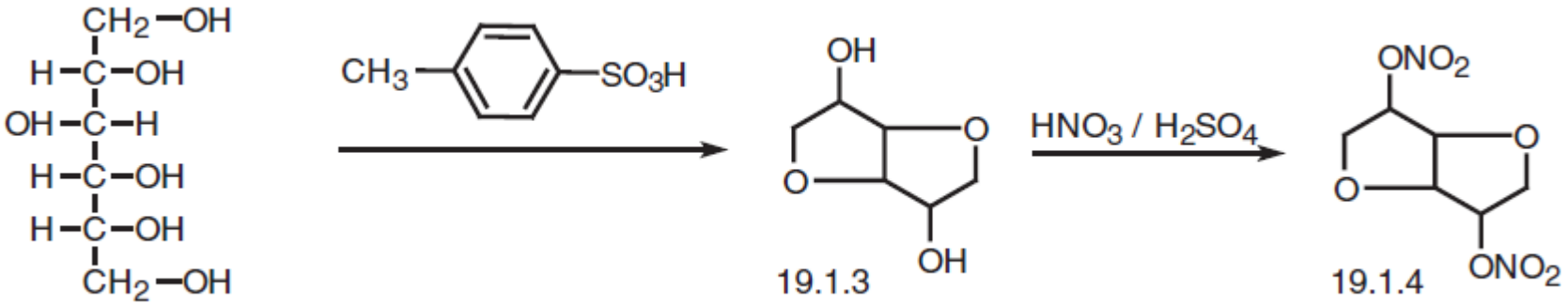
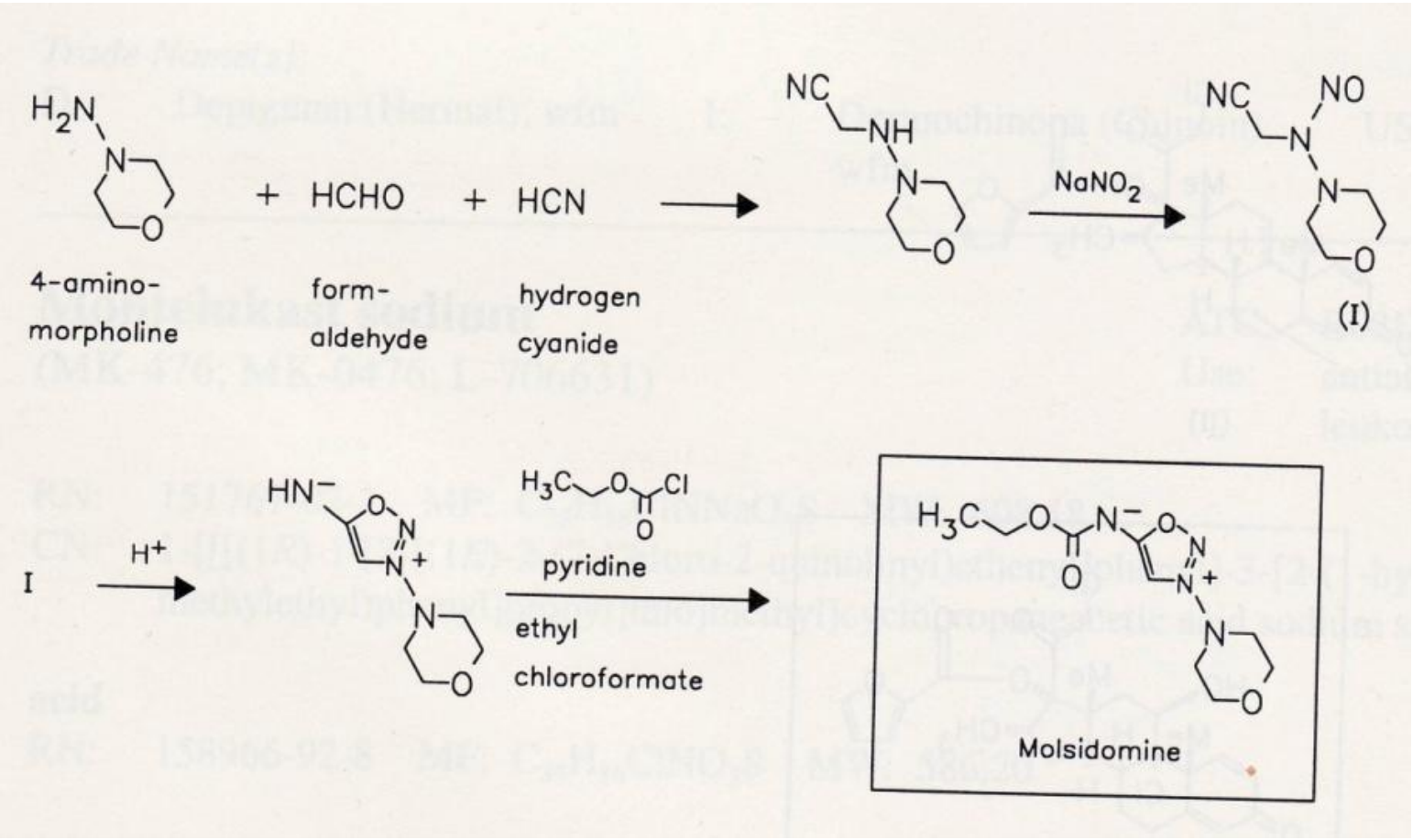


19.1.3 19.1.4

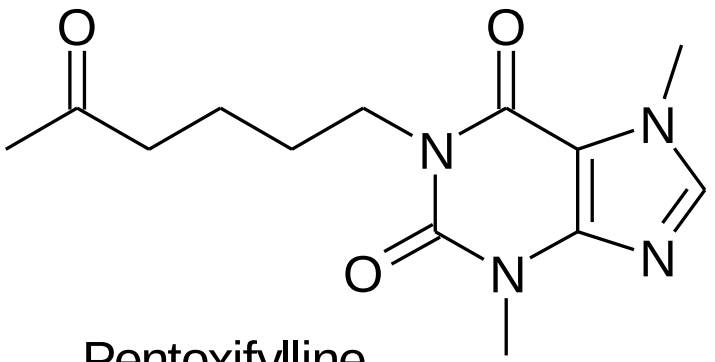
Molsidomine synthesis



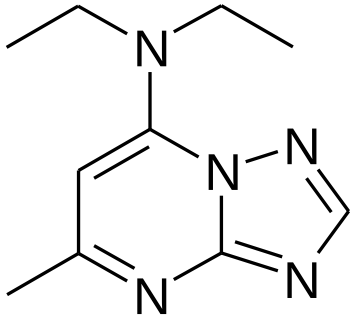
Xanthin derivatives

- nature xanthines – theophylin, theobromin, coffein
- all are central stimulants, vasodilators, bronchodilators, diuretics
- theophylin has enhanced smooth muscle relaxing activity
- synthetic analogues are vasodilators and bronchodilators

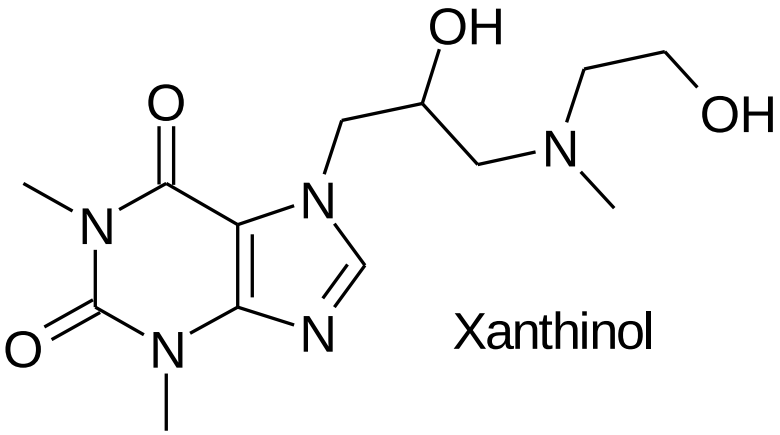
Xanthin derivatives



Pentoxifylline

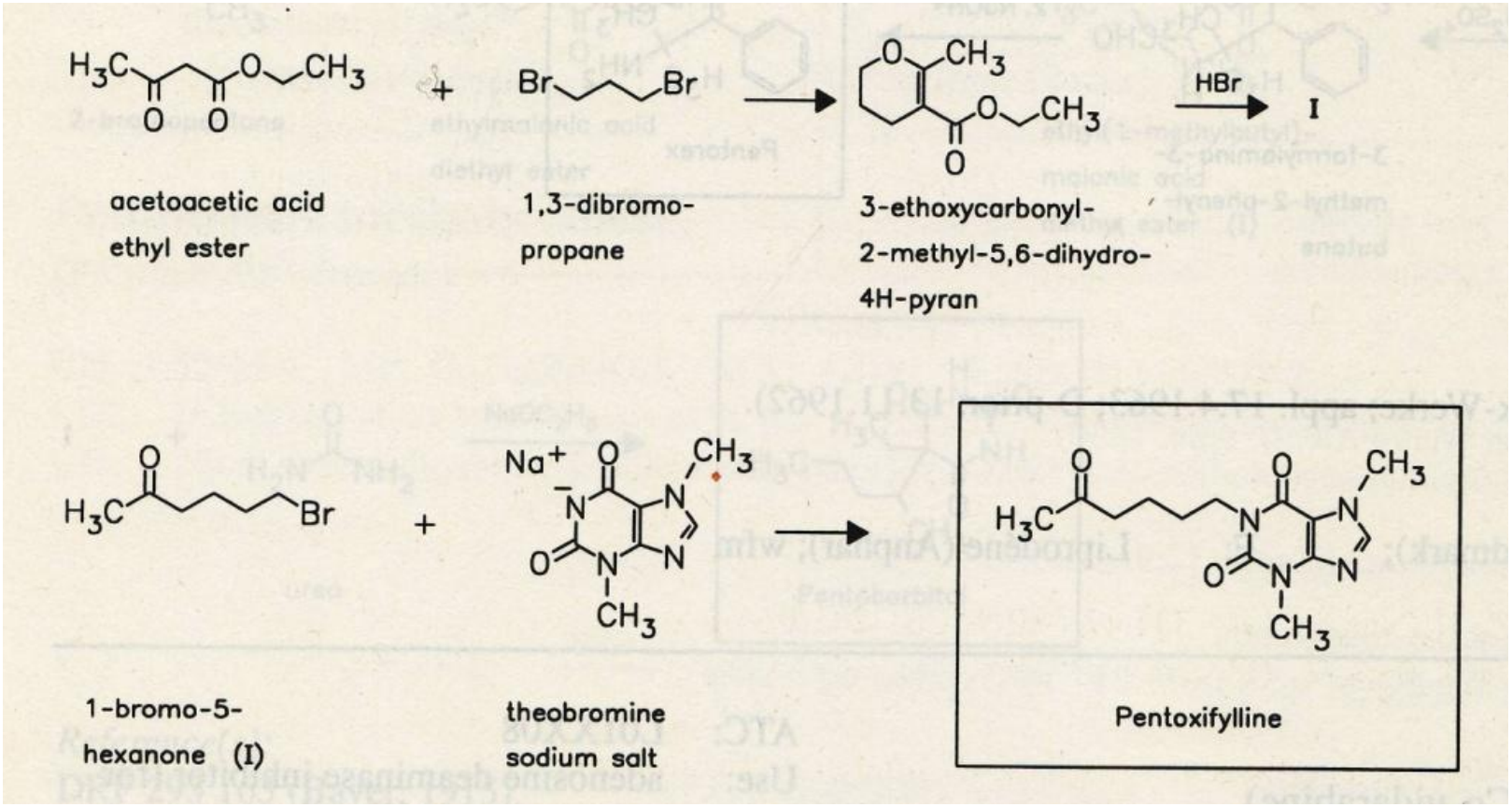


Trapidil

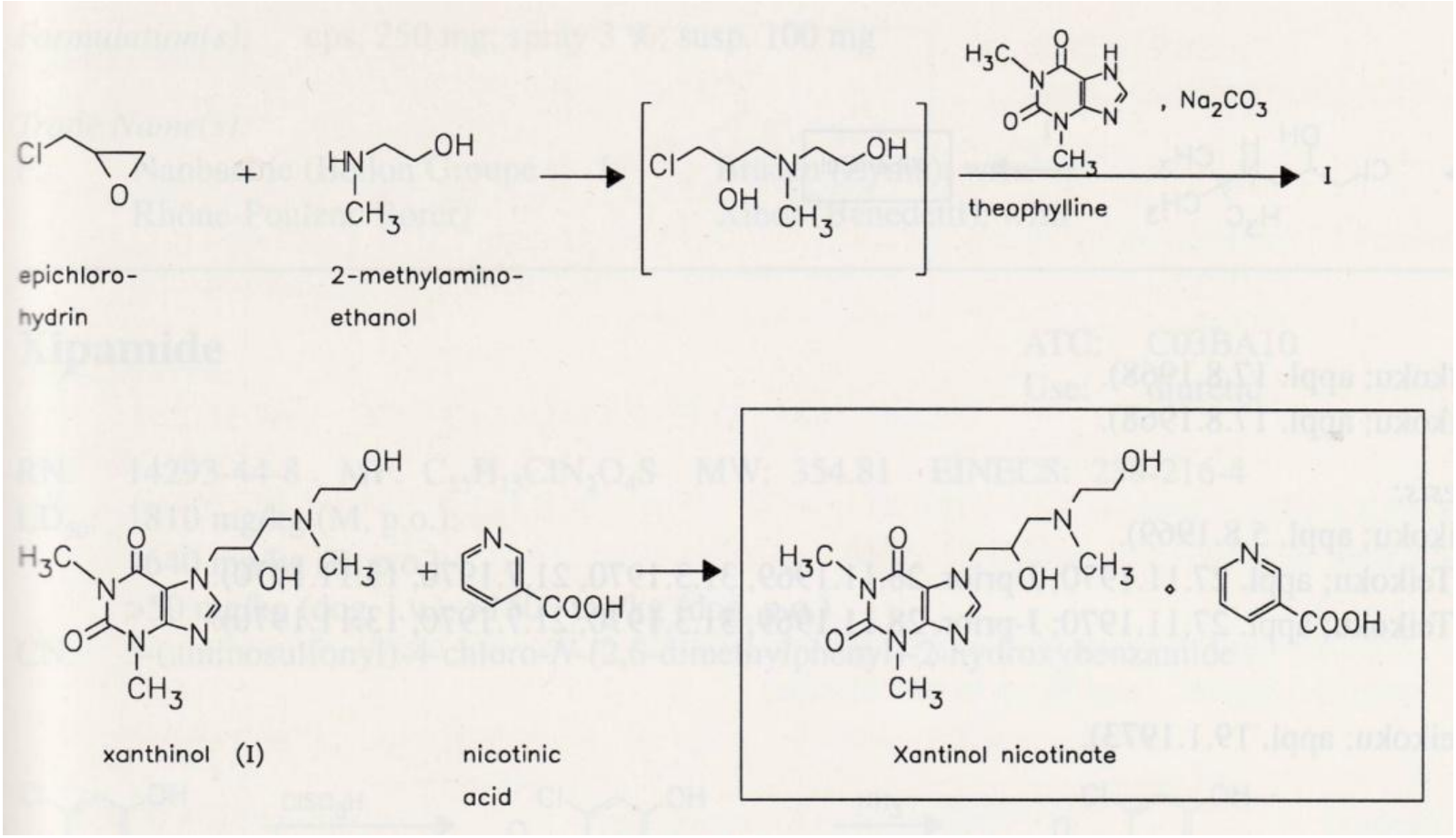


Xanthinol

Pentoxifylline



Xanthinol

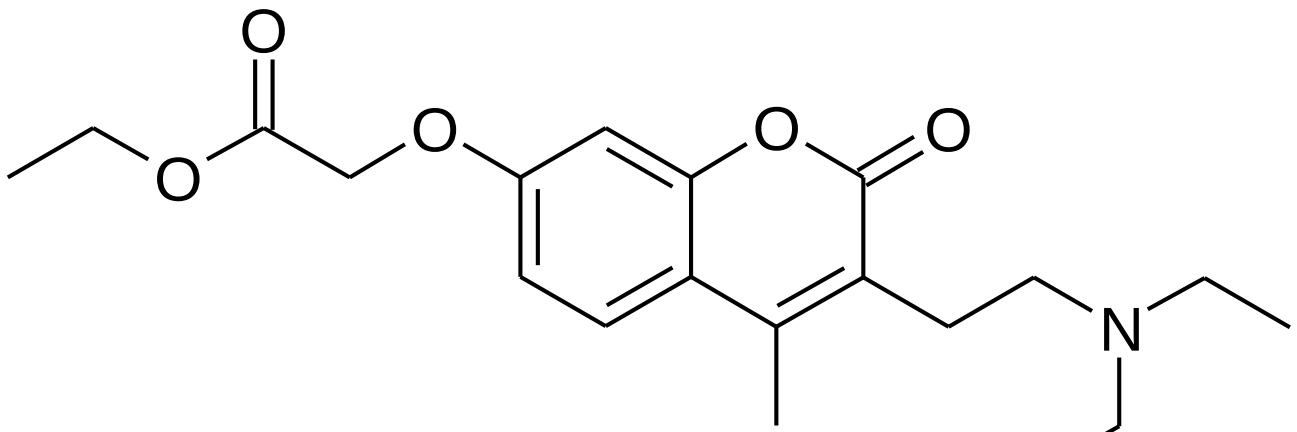

epichloro-
hydrin
2-methylamino-
ethanol
theophylline
, Na_2CO_3
I
xanthinol (I)
nicotinic
acid
Xantinol nicotinate

Nicotinic acid

- low dosis – vasodilating effect on upper part of body
- higher dosis – antihyperlipidemic effect

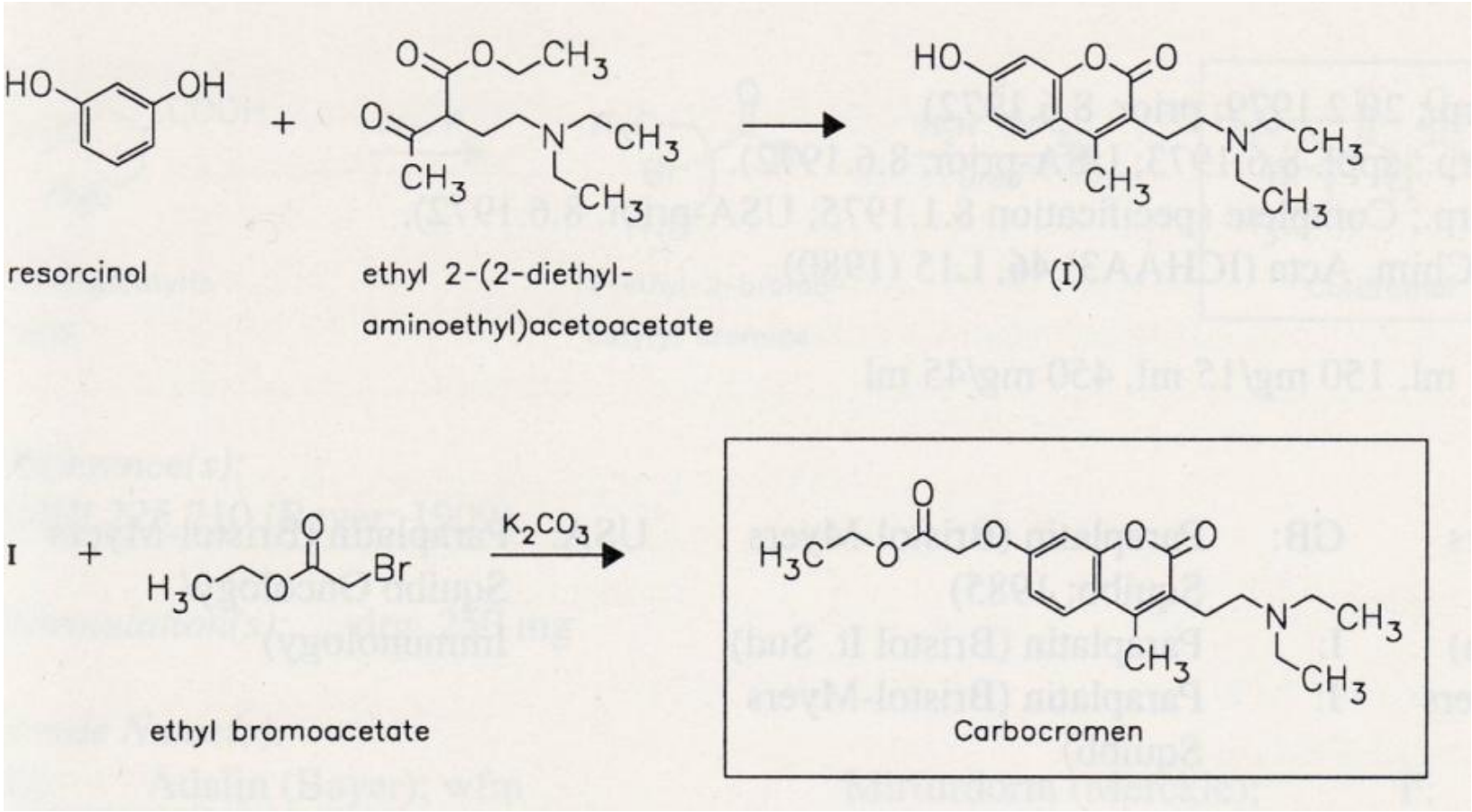
Cromone derivatives

- PDE inhibitor, enhances anaerobic glycolysis
- 2X increased coronary flow without affecting blood pressure



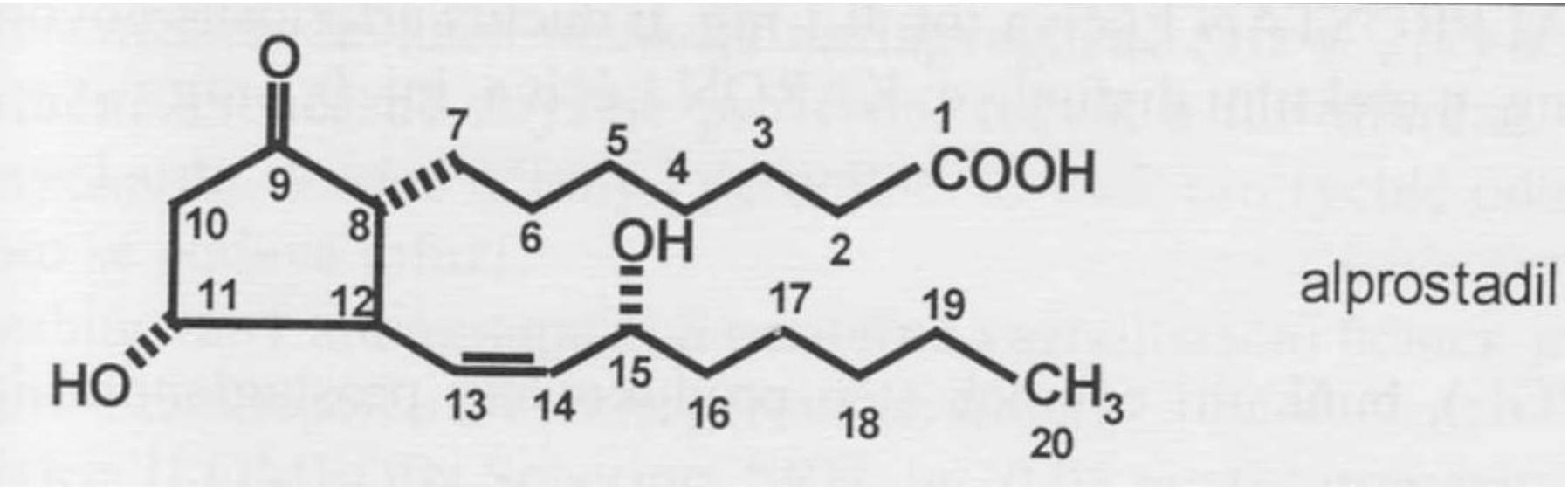
Carbocromen

Carbocromen



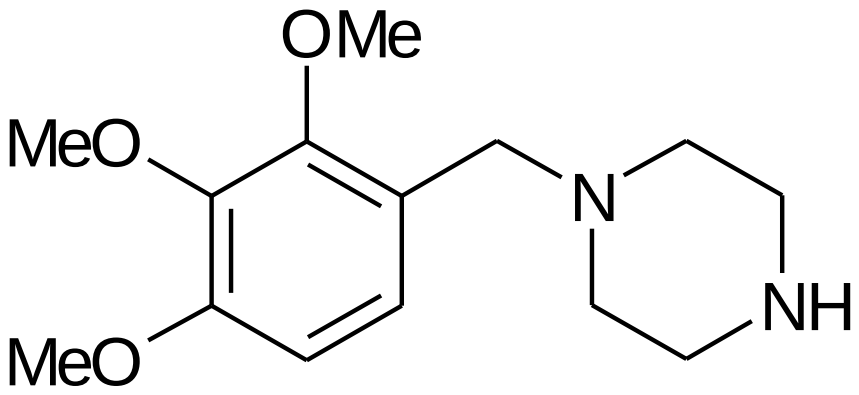
Prostaglandines

- various prostaglandines has vasodilating effect
- Alprostadil is used in some heart insufficiencies

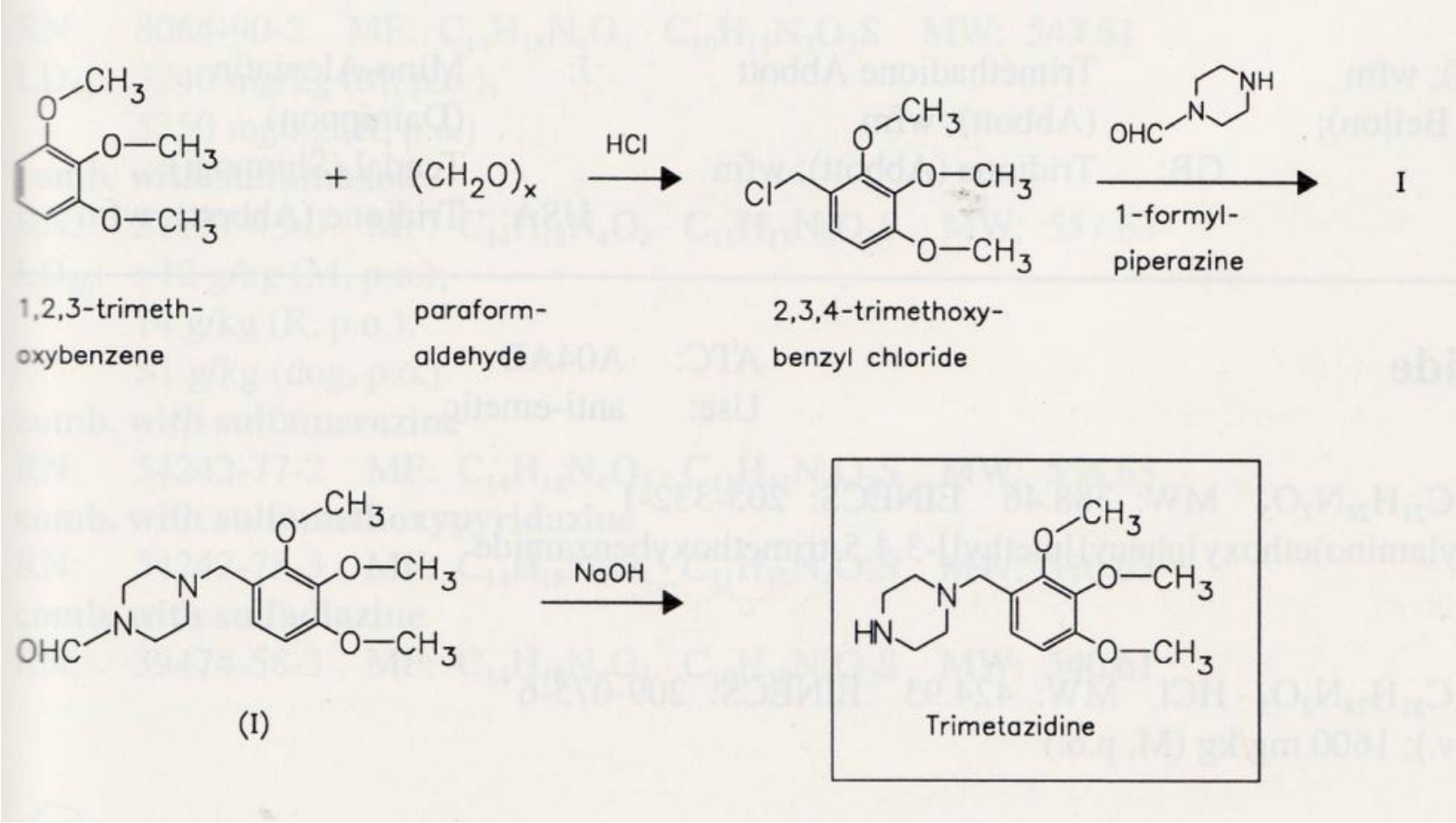


Trimetazidine

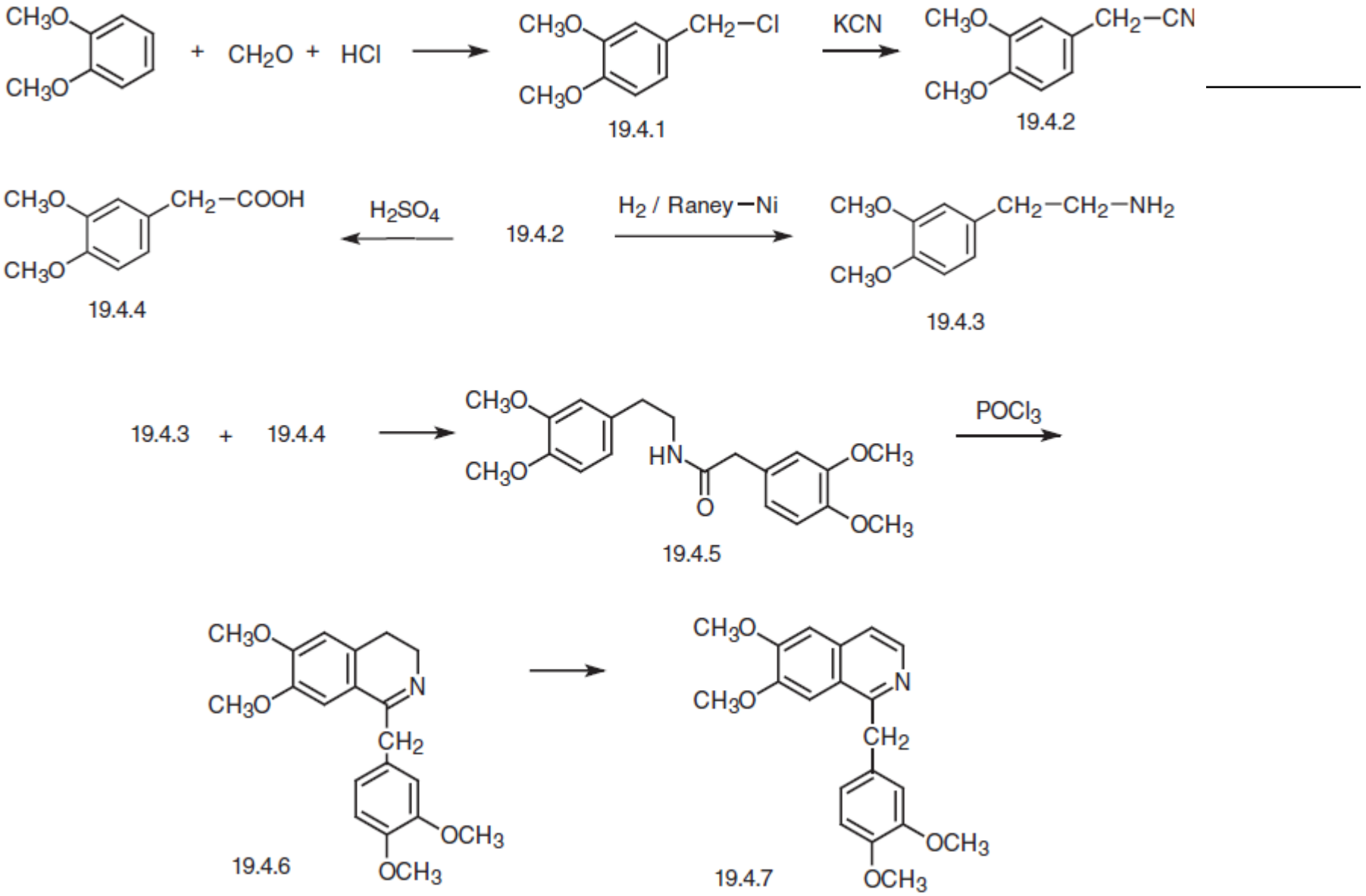
- decreases intracelular ATP



Trimetazidine synthesis



Papaverine


CH3O
CH3O
+ CH2O + HCl
CH2–Cl
19.4.1
KCN
CH2–CN
19.4.2
CH2–COOH
19.4.4
H2SO4
19.4.2
H2 / Raney–Ni
CH2–CH2–NH2
19.4.3
19.4.3 + 19.4.4
HN
O
OCH3
19.4.5
POCl3
N
CH2
19.4.6
19.4.7

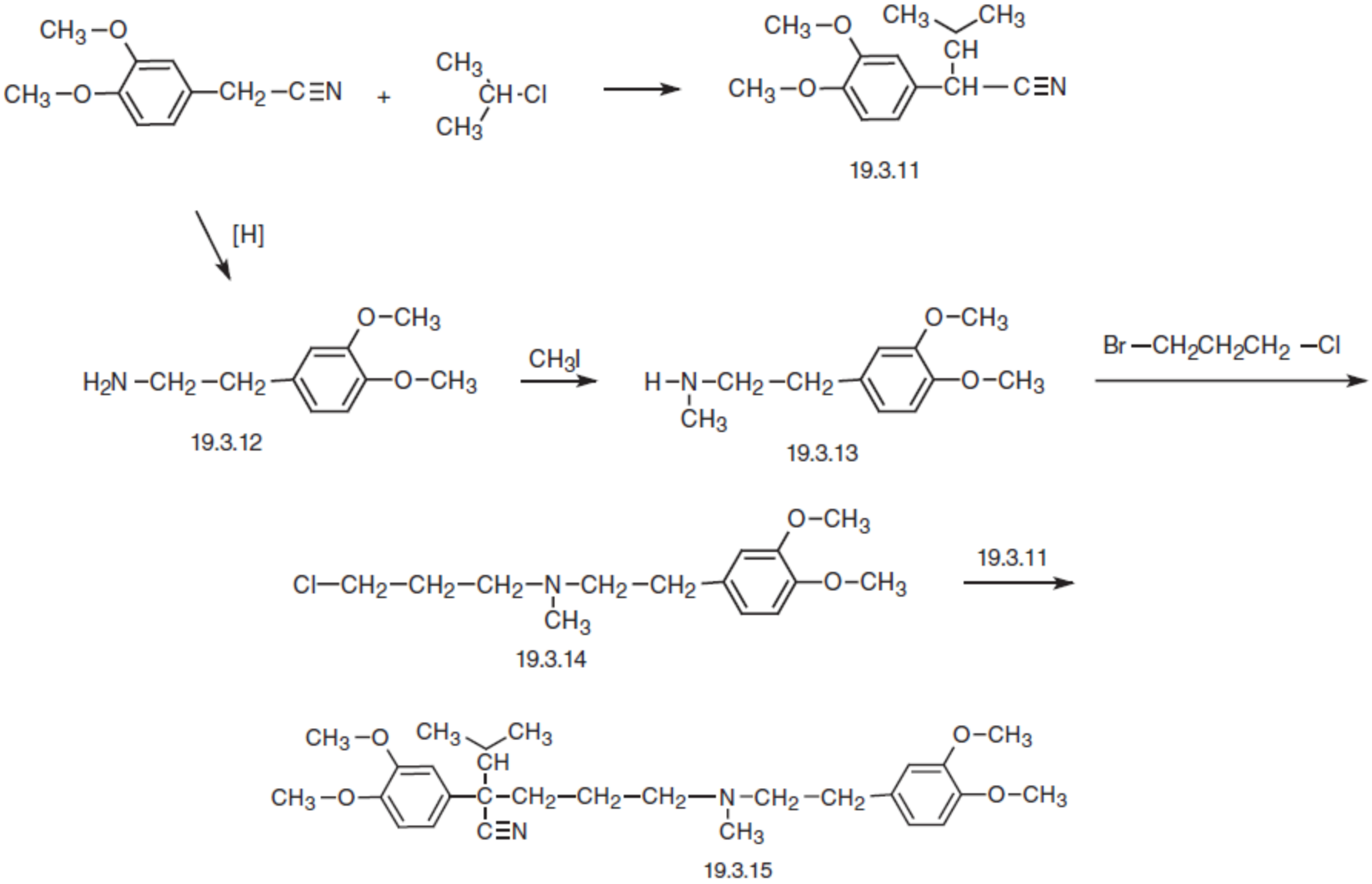
β-adrenergic receptor antagonists

- in lower dosis decrease myocardium need for oxygen
- Propranolol, Metoprolol, Acebutolol, Atenolol, Nadolol – see adrenergic antagonists

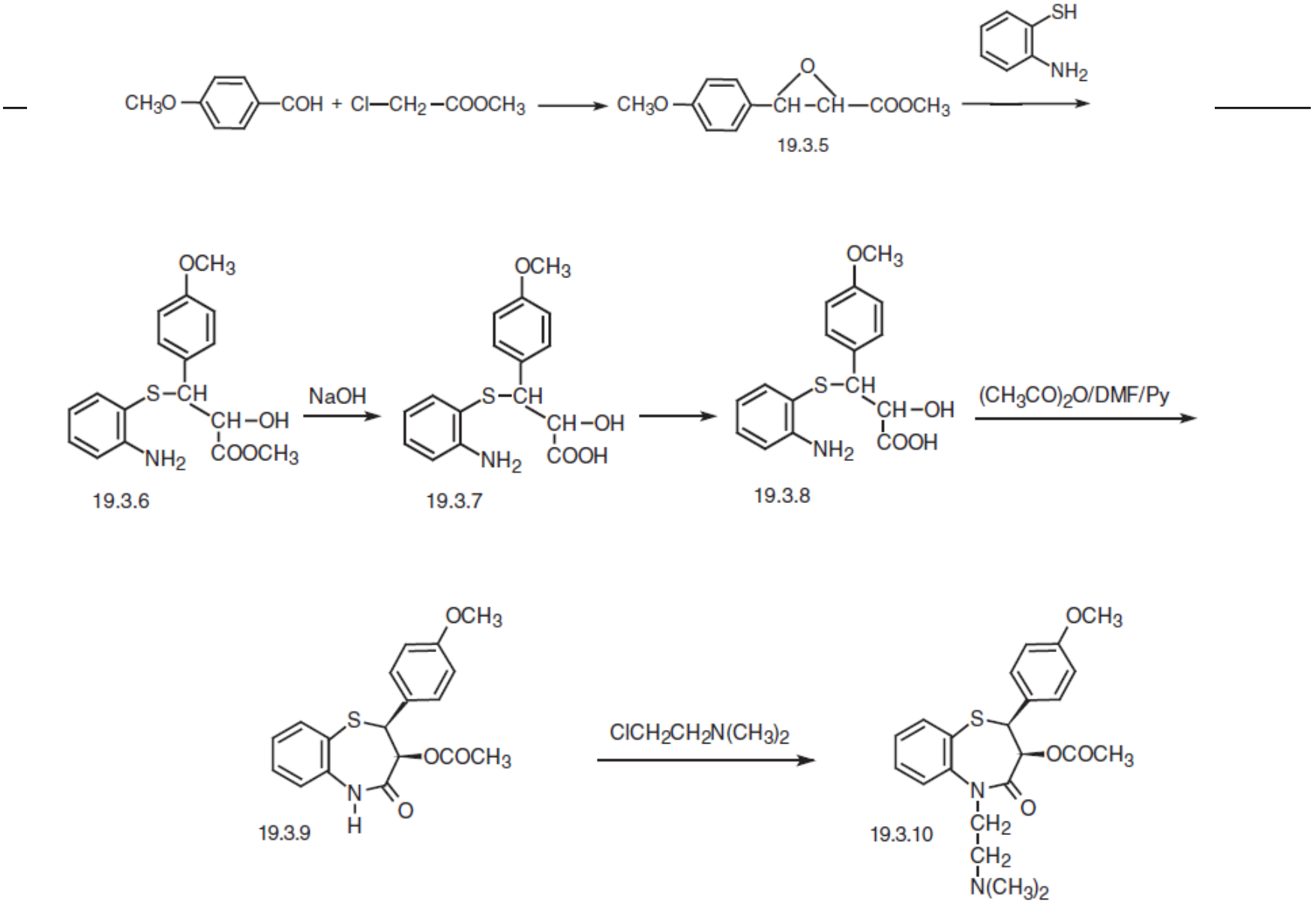
Calcium channel blockers

- reduction of calcium ions decrease strength of heart contraction = decrease need for oxygen
- Verapamil
- Diltiazem
- Dihydropyridines

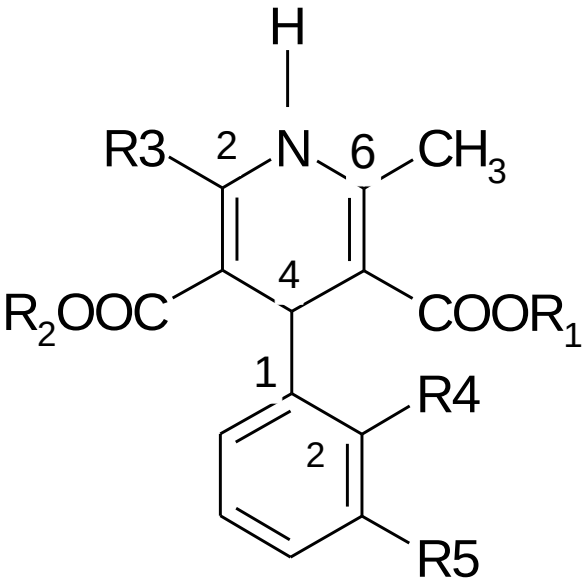
Verapamil


CH3–O
CH3–O
CH2–C≡N
+
CH3
CH·Cl
CH3
CH3–O
CH3–O
CH3
CH3
CH
CH
CH–C≡N
19.3.11
[H]
H2N–CH2–CH2
O–CH3
O–CH3
19.3.12
CH3I
H–N–CH2–CH2
CH3
O–CH3
O–CH3
19.3.13
Br–CH2CH2CH2–Cl
Cl–CH2–CH2–CH2–N–CH2–CH2
CH3
O–CH3
O–CH3
19.3.14
19.3.11
CH3–O
CH3–O
CH3
CH3
CH
C
CH2–CH2–CH2–N–CH2–CH2
C≡N
CH3
O–CH3
O–CH3
19.3.15

Diltiazem


CH3O
COH + Cl—CH2—COOCH3
CH3O
CH—CH—COOCH3
O
SH
NH2
19.3.5
OCH3
S—CH
CH—OH
COOCH3
NH2
19.3.6
NaOH
COOH
19.3.7
19.3.8
(CH3CO)2O/DMF/Py
N
H
O
OCOCH3
19.3.9
ClCH2CH2N(CH3)2
CH2
N(CH3)2
19.3.10

Dihydropyridines



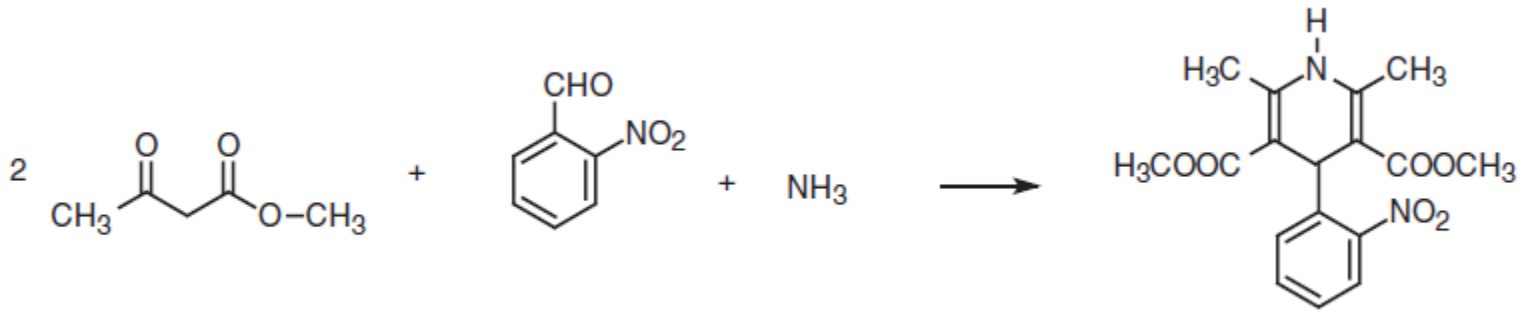
DIHYDROPYRIDINES

R_1, R_2 – aliphatic ester, branched aliphatic chain

R4 or R5 nitro group or halogen

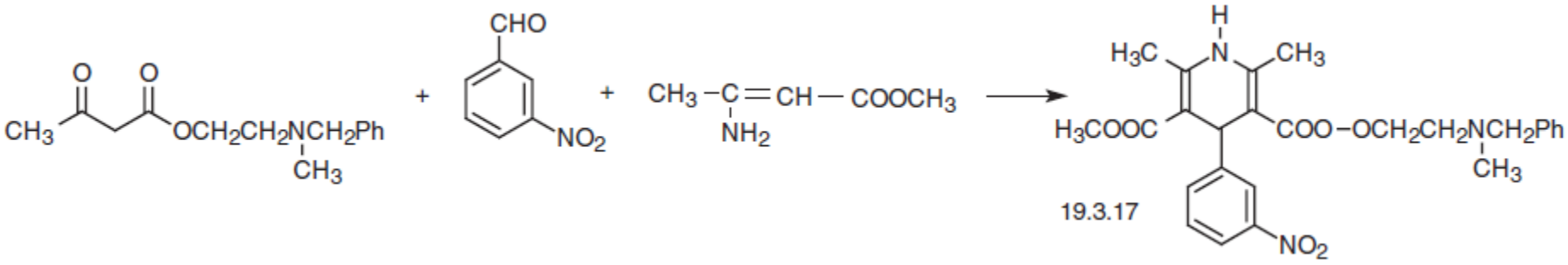
R3 methyl or substituted alkyl

Nifedipine



19.3.16

Nicardipine



Dipyridamole

- potentiates adenosine activity
- blocks phosphodiesterase, improves microcirculation
- inhibits thrombocyte formation and aggregation – see antithrombotics