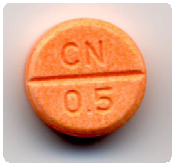
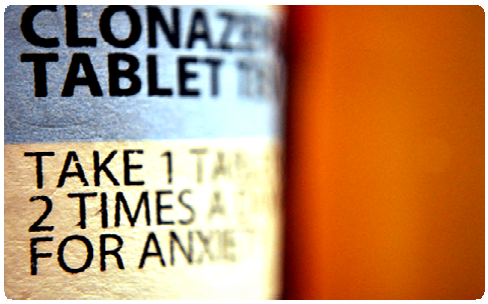
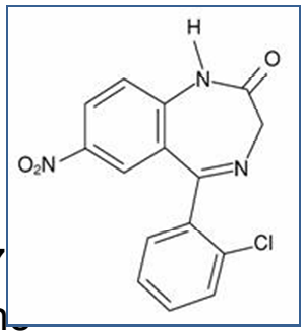




Clonazepam

Clonazepam

→relieve panic attacks



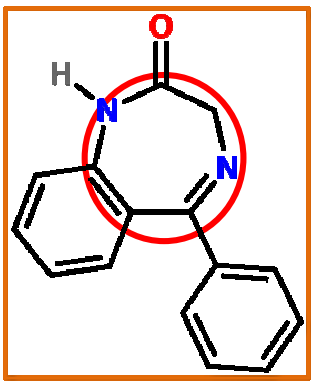
IUPAC Name:
5-(2-chlorophenyl)-1,3-dihydro-7
nitro-2H-1,4- benzodiazepin-2-on

Molecular weight: 315.72

Appearance: light yellow crystalline powder

lead compound discovery

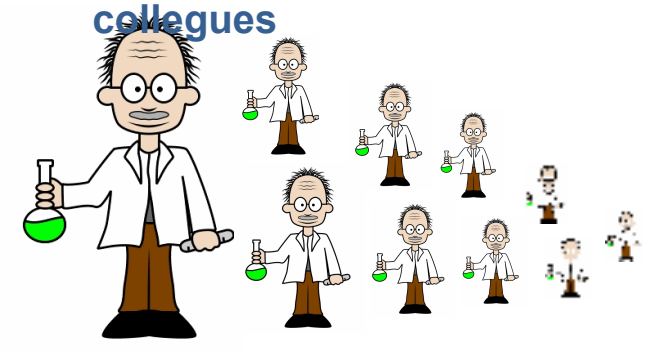
- **Nitrazepam** --a type of benzodiazepine



The core structure of benzodiazepine

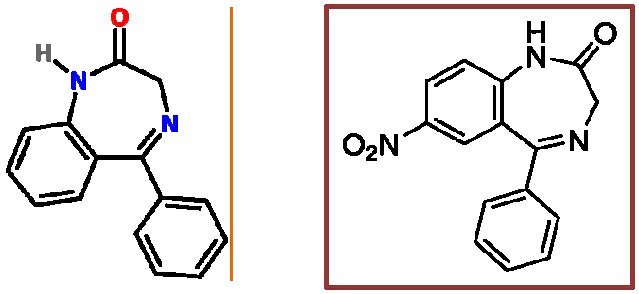
There was a group of scientists :

Sternbach and his collegues



They tried to modify benzodiazepine , one of which is the introduction of nitro group

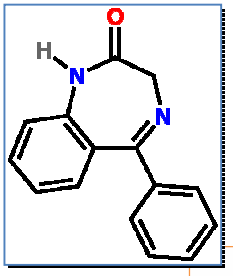
several nitro compounds were prepared and **nitrazepam** is one of the successful products



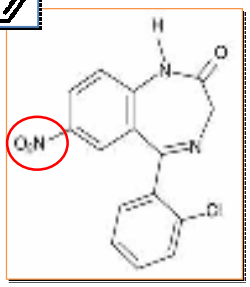
much more potent than chlordiazepoxide in both mice and cats.

Molecular modification

- a chloro-nitrobenzodiazepine (a chlorinated derivative of nitrazepam)
- differs from nitrazepam with the substitution of a chlorine atom



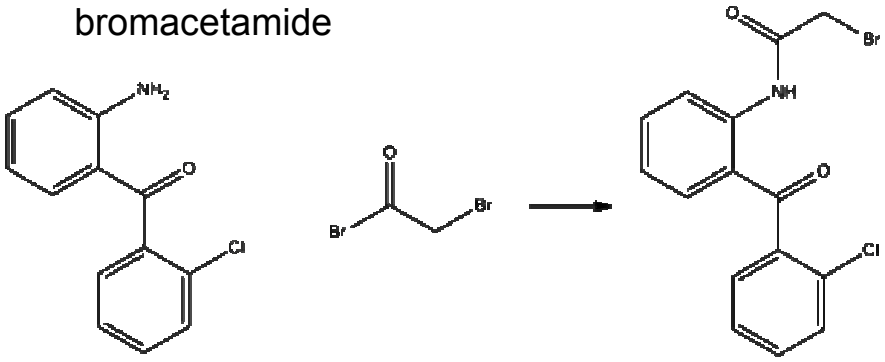
nitrazepam



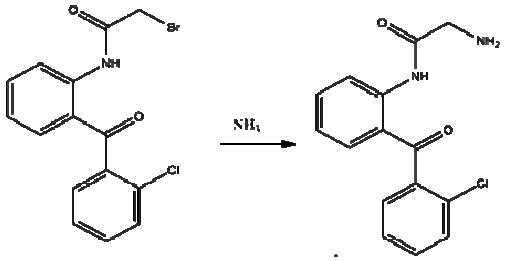
Clonazepam

- IUPAC: 5-(2-chlorphenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-2-one
- synthesized by derivatives of 1,4-benzodiazepines
- the acceptor nitro group (NO_2) or C7 of the benzodiazepine syst is introduced at the last stage of synthesis

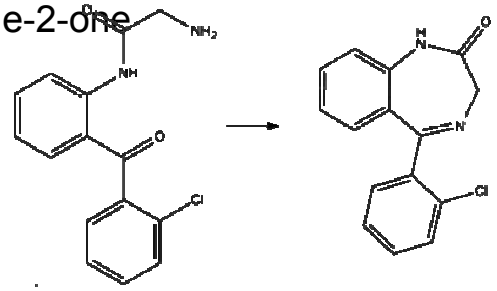
1. 2-chloro-2'-nitrobenzophenone → is reduced to 2-chloro-2'-aminobenzophenone by hydrogen over Raney nickel
2. amidated by 2-bromoacetyl bromide to give the bromacetamide



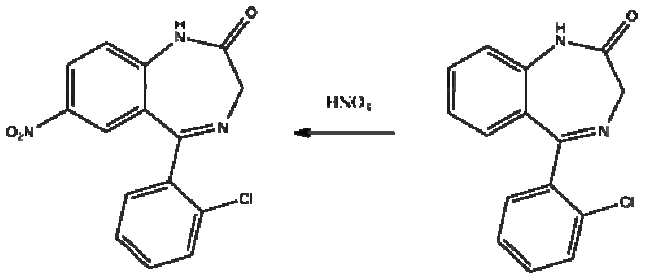
3. converted into aminoacetamide upon reaction with ammonia



4. cycled into 5-(2-chlorophenyl)-2,3-dihydro-1H-1,4- benzodiazepine-2-one



5. nitration of the resulting product in mild conditions (potassium nitrate in sulfuric acid)



DONE!

Clonazepam *VS* Nitrazepam

Clonazepam

- longer half-life: 18–50 hours
- No carcinogenicity studies have been conducted
- faster onset of action and higher effectiveness rate: maximum plasma concentrations are reached within 1 to 4 hours after oral administration

Nitrazepam

- half-life :15-38 hours
- Long-term use will increase the risk of developing cancer.
- maximum plasma concentrations are reached within 3hours after oral administration

Formulation development

- available as tablets, orally disintegrating tablets (wafers), oral solution (drops), solution for injection or intravenous infusion

- inactive ingredients of Clonazepam tablet :
  - anhydrous lactose
  - colloidal silicon dioxide
  - magnesium stearate
  - microcrystalline cellulose
  - pregelatinized starch
  - sodium lauryl
  - colourings

(IV)Safety tests and human trials

- **(i) Aim: To study the deficiency diseases caused by the use of clonazepam during pregnancy**
- **(ii)Aim: To test the effectiveness of clonazepam in treating p**

Clonazepam was administered orally to pregnant rabbits

0.2 mg/kg/day

1.5 mg/kg/day

10 mg/kg/day

Result 1

- ALL babies show malformations :
  cleft palate, open eyelid, fused sternebrae or limbs

Fused legs

Result 2

- dosages of **5 & 10 mg/kg/day** :
  reductions in maternal weight gain

- dosage of **10 mg/kg/day** :
  reduction in embryo-fetal growth

Conclusion

fixed-dose study	flexible-dose study
• 9-week & 4 phases : • 1-week placebo lead-in • 3-week upward titration, • 6-week fixed dose • 7-week discontinuance phase. • doses of 0.5, 1, 2, 3 or 4 mg/day or placebo	• 6-week & 3 phases • 1-week placebo lead-in • 6-week optimal-dose • 6-week discontinuance phase. • doses range of 0.5 to 4 mg/day or placebo • mean clonazepam dose during the optimal dosing period was 2.3 mg/day.

Result : fixed-dose study

- **1 mg/day** group shows the most significant effect

→**74%** free of full panic attacks

→placebo-treated patients : **56%**

Result: flexible-dose study

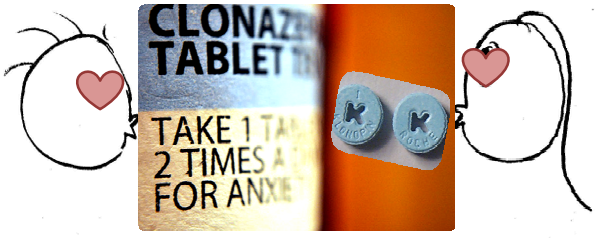
Patients receiving clonazepam

→ **62%** of patients : **free of full panic attacks**

→ of placebo-treated patients : **37%**

Conclusion:

- Clonazepam is significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency.



(V)Approval for marketing:

August 3, 2005,