

Química Farmacéutica

AGENTES PSICOTERÁPICOS: ANTIPSICÓTICOS Y ANSIOLÍTICOS

Cap. 11

**“Foye’s Principles of Medicinal Chemistry” 5ª Ed.
D. A. Williams et al.(2002)**

FARMACOS PSICOACTIVOS:

ANTIPSICOTICOS

NEUROLEPTICOS

Fenotiazinas

Tioxantenos

Benzisoxazoles

ANSIOLITICOS

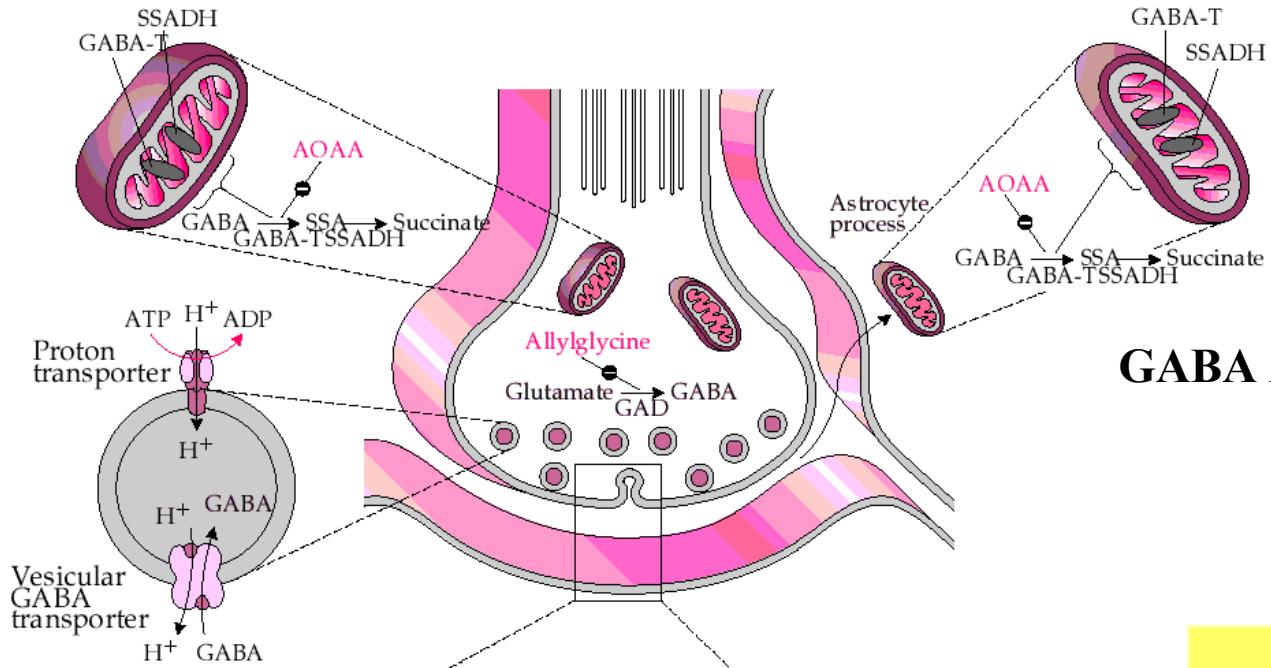
Benzodiazepinas

Otros ansiolíticos

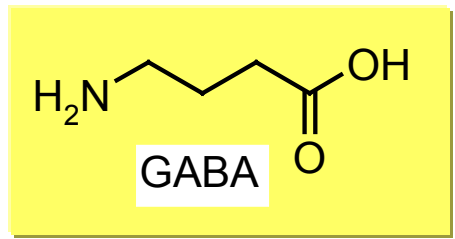
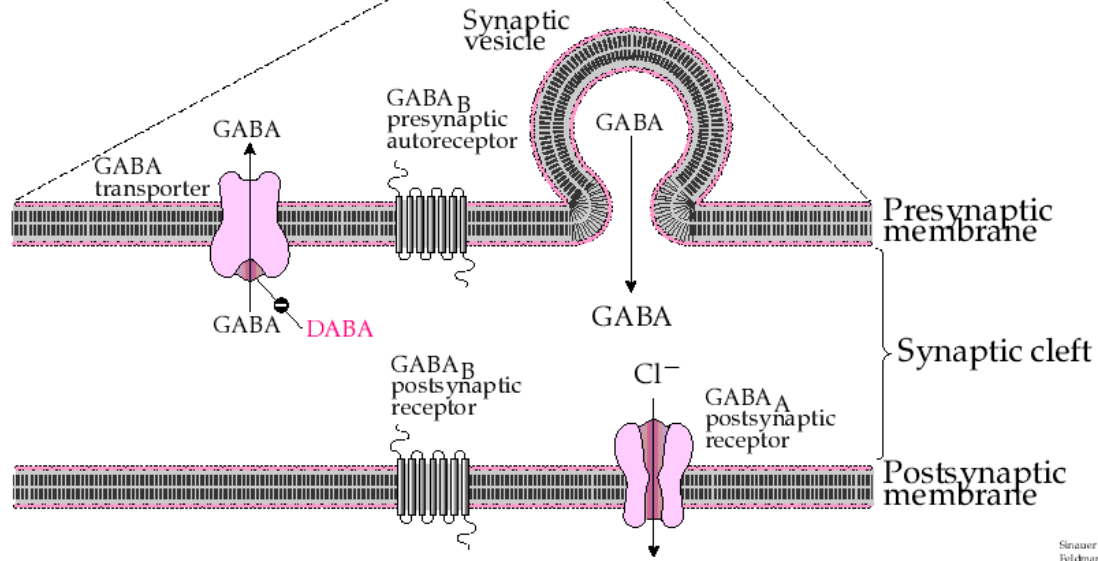
“Foye’s Principles of Medicinal Chemistry” 5ª Ed.

D. A. Williams et al., Cap. 17 (2002)

BENZODIAZEPINAS



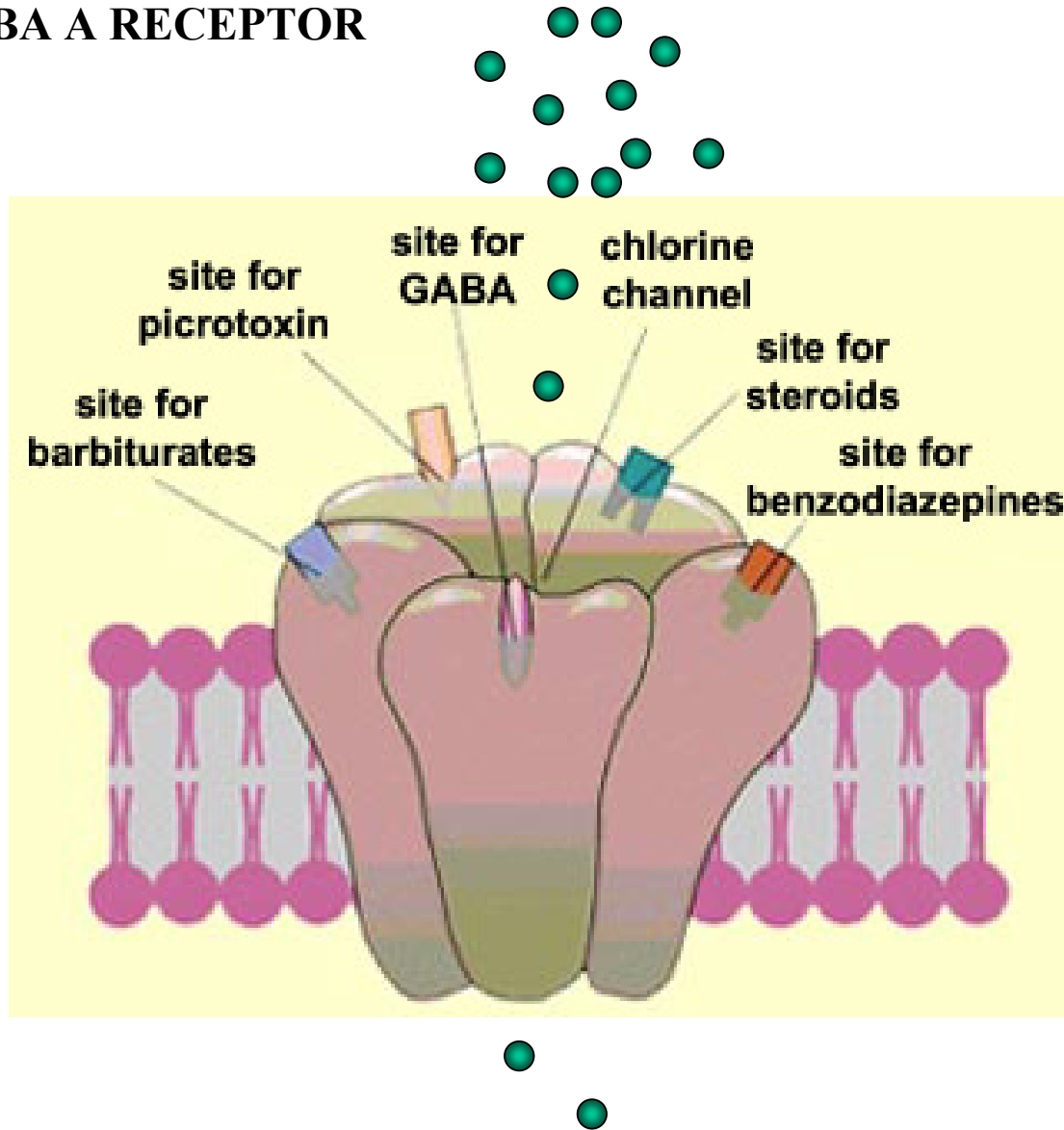
GABA A RECEPTOR



BENZODIAZEPINAS

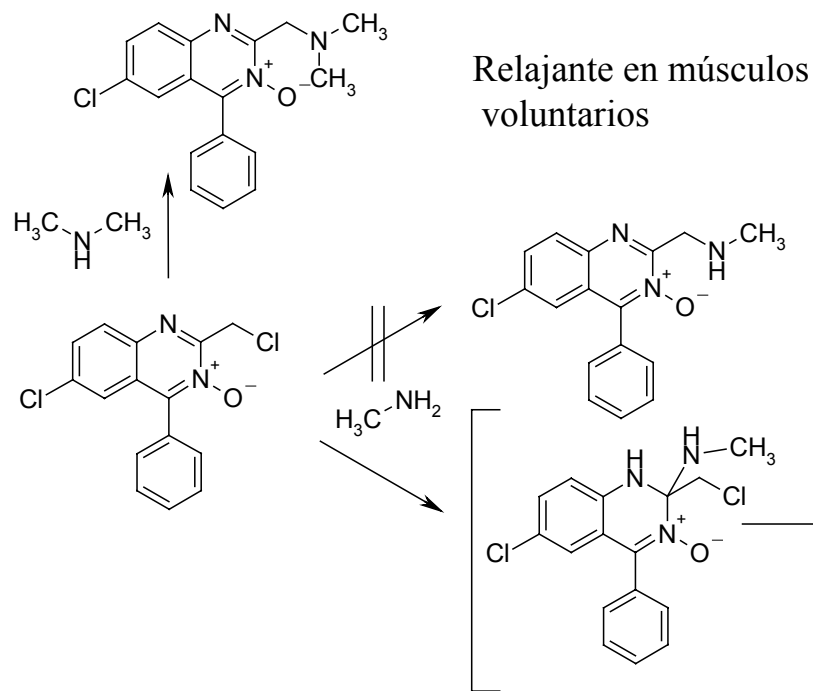
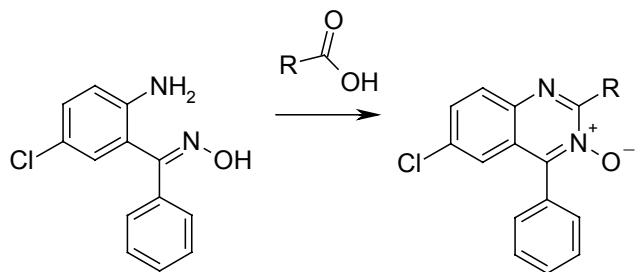
GABA A RECEPTOR

Cl⁻ ●



BENZODIAZEPINAS

DESCUBRIMIENTO DEL CABEZA DE SERIE *Serendipia*



Relajante en músculos voluntarios



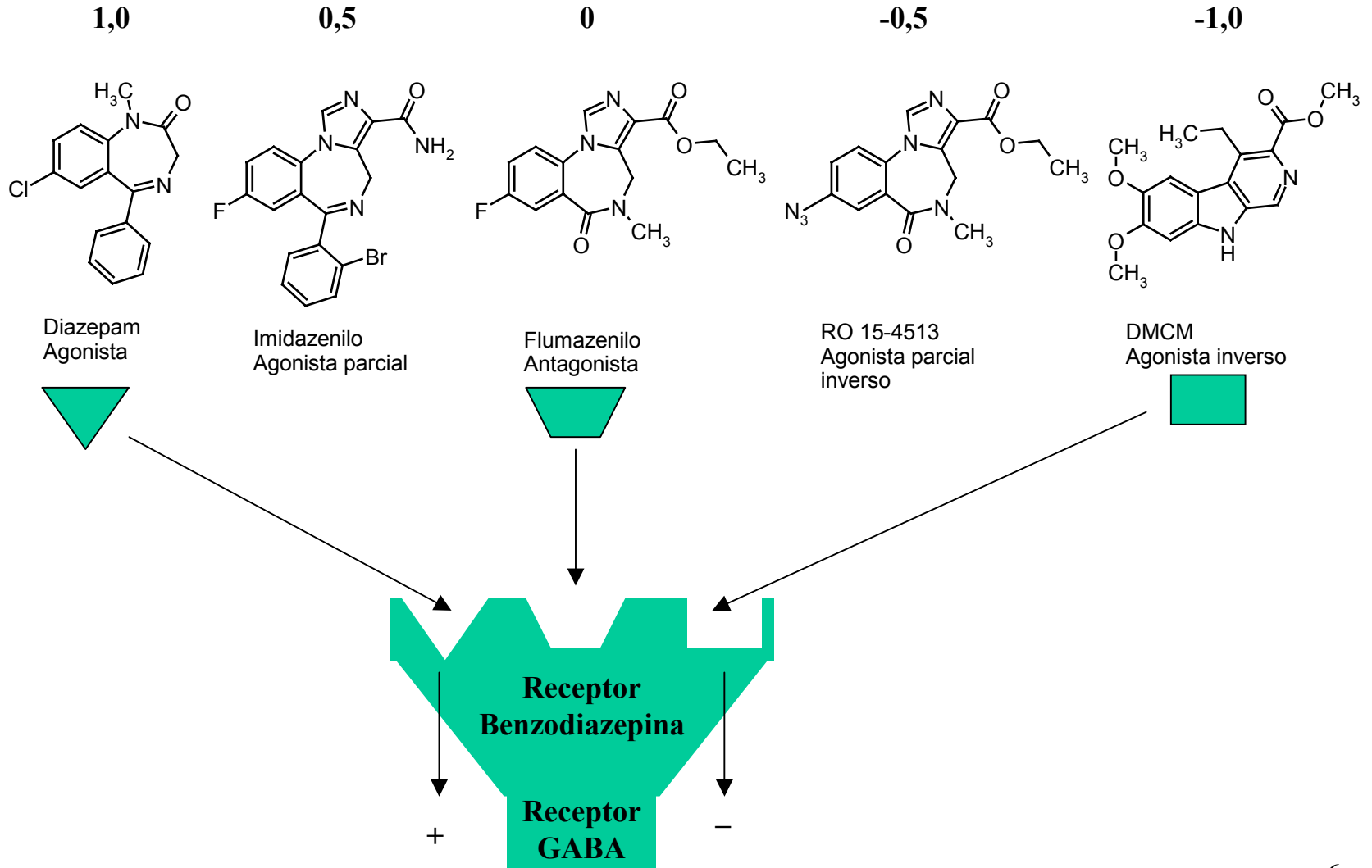
Leo H. Sternbach

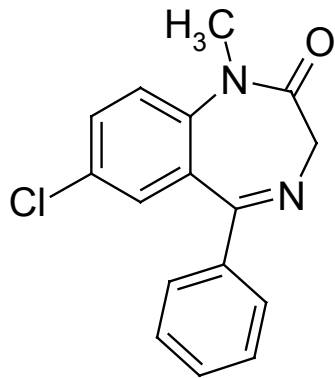
Clordiazepóxido
(ansiolítico)

L. H. Sternbach y E. Reeder (1957)

BENZODIAZEPINAS

ACTIVIDAD INTRINSECA





ACTIVIDAD BIOLÓGICA

1) Efecto antiansiedad

2) Efectos secundarios sobre SNC

2a) Relajación muscular

2b) Efecto anticonvulsivante

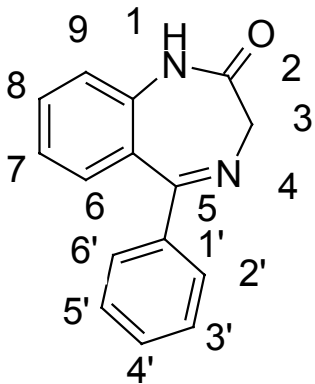
FARMACOCINETICA

Se absorben bien por vía oral

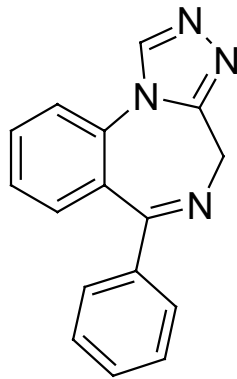
Tienen semividas largas (6-50 h.)

BENZODIAZEPINAS

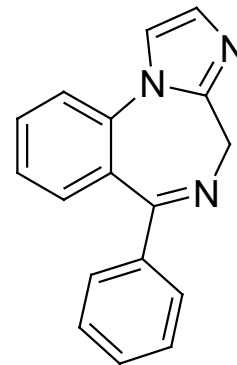
NOMENCLATURA



5-Fenil-1,4-benzodiazepin-2-ona

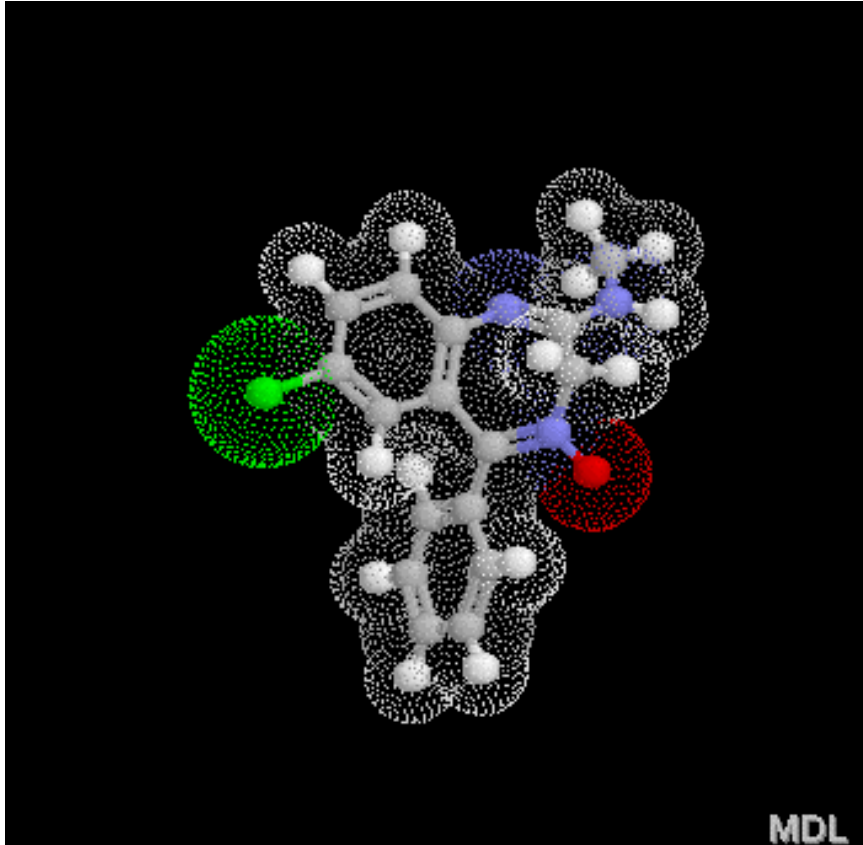


s-Triazolo[4,3a][1,4]benzodiazepina

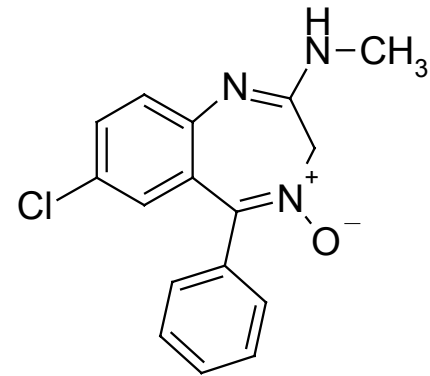


Imidazolo[1,5a][1,4]benzodiazepina

BENZODIAZEPINAS



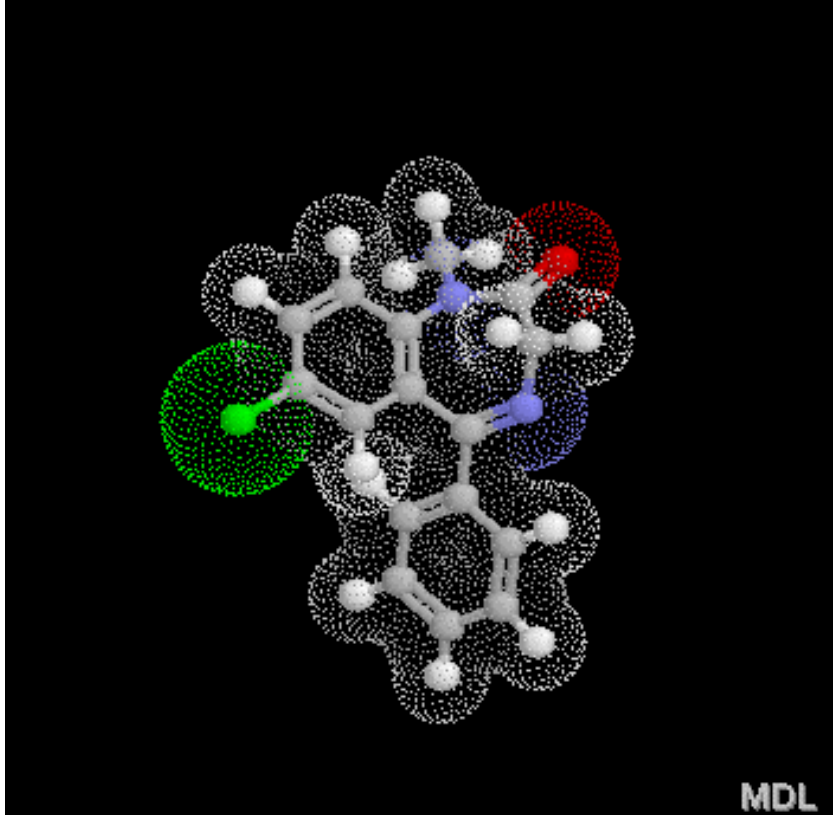
CLORDIAZEPOXIDO



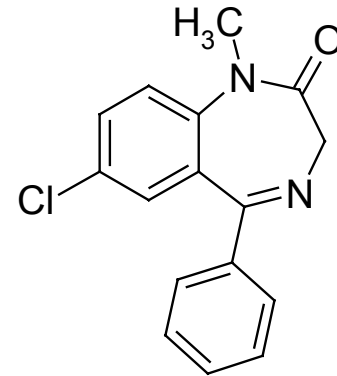
CLogP = 4.15

7 - chloro - 2 - metilamino - 5 - phenil - 3H - 1, 4 - benzodiazepin 4 - oxide

BENZODIAZEPINAS



DIAZEPAM

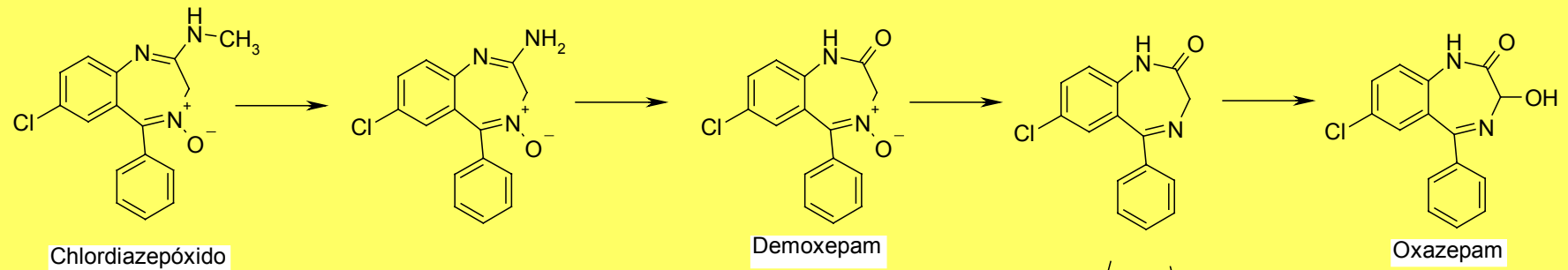
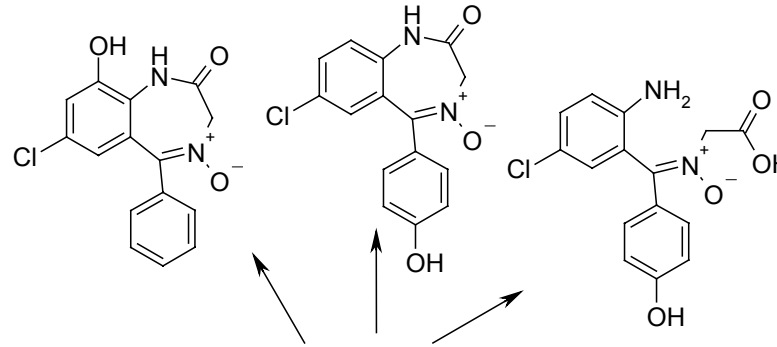


CLogP = 3.21

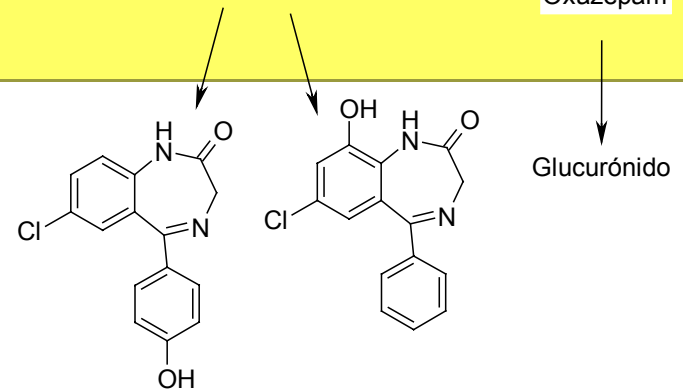
7 - chloro - 1, 3 - dihydro - 1 - methyl - 5 - phenyl - 2H - 1, 4 - benzodiazepin - 2 - one

BENZODIAZEPINAS

METABOLISMO DE CLORDIAZEPOXIDO

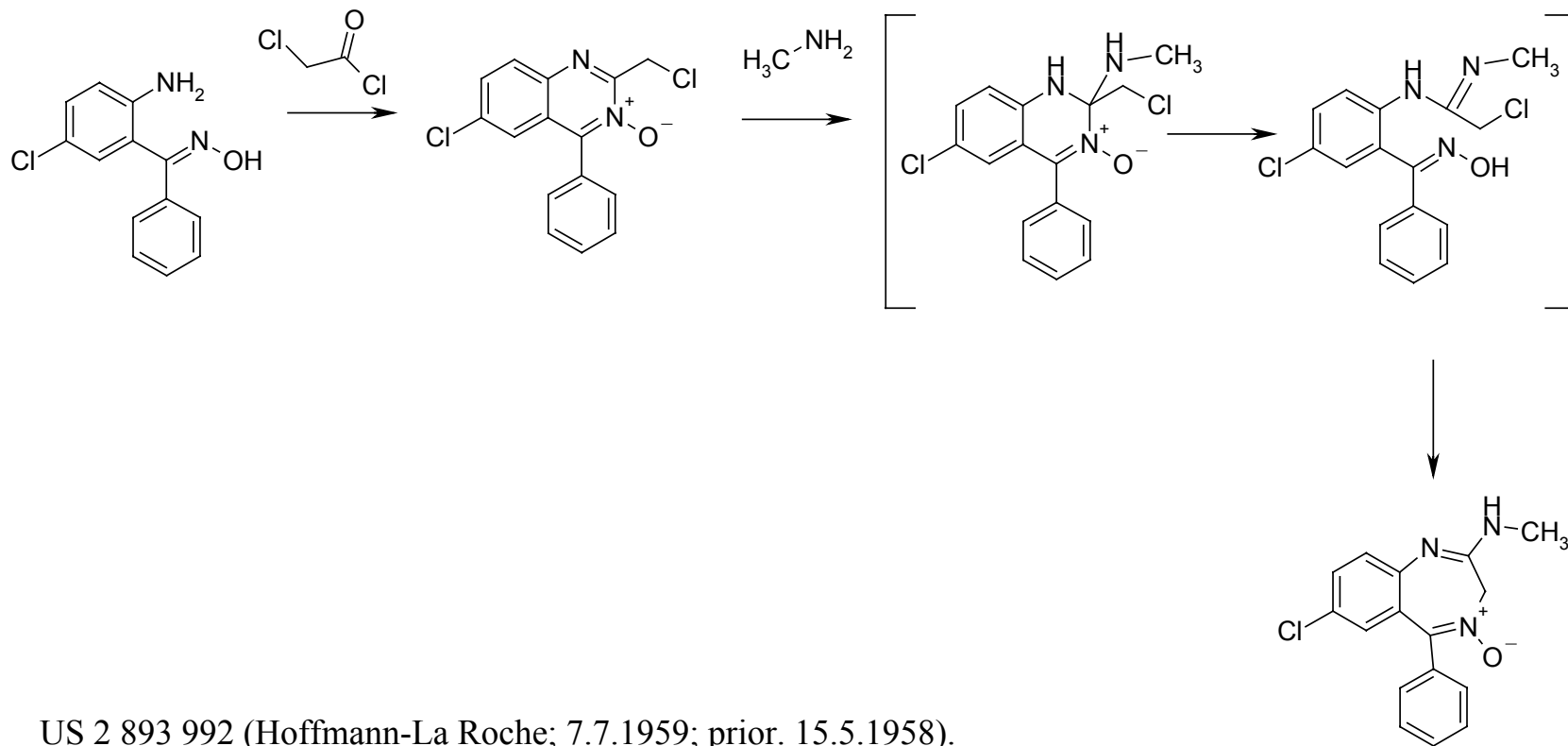


Clordiazepóxido y metabolitos activos



BENZODIAZEPINAS

SINTESIS INICIAL



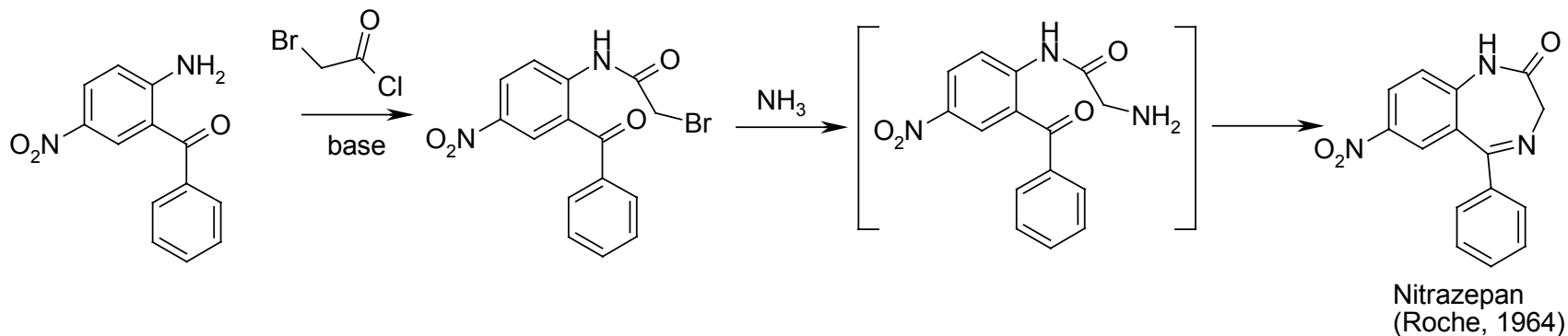
US 2 893 992 (Hoffmann-La Roche; 7.7.1959; prior. 15.5.1958).

DE 1 096 363 (Hoffmann-La Roche; appl. 24.4.1959; USA-prior. 15.5.1958).

Sternbach, L.H. et al.: J. Org. Chem. (JOCEAH) 26, 1111 (1961).

Clordiazepóxido

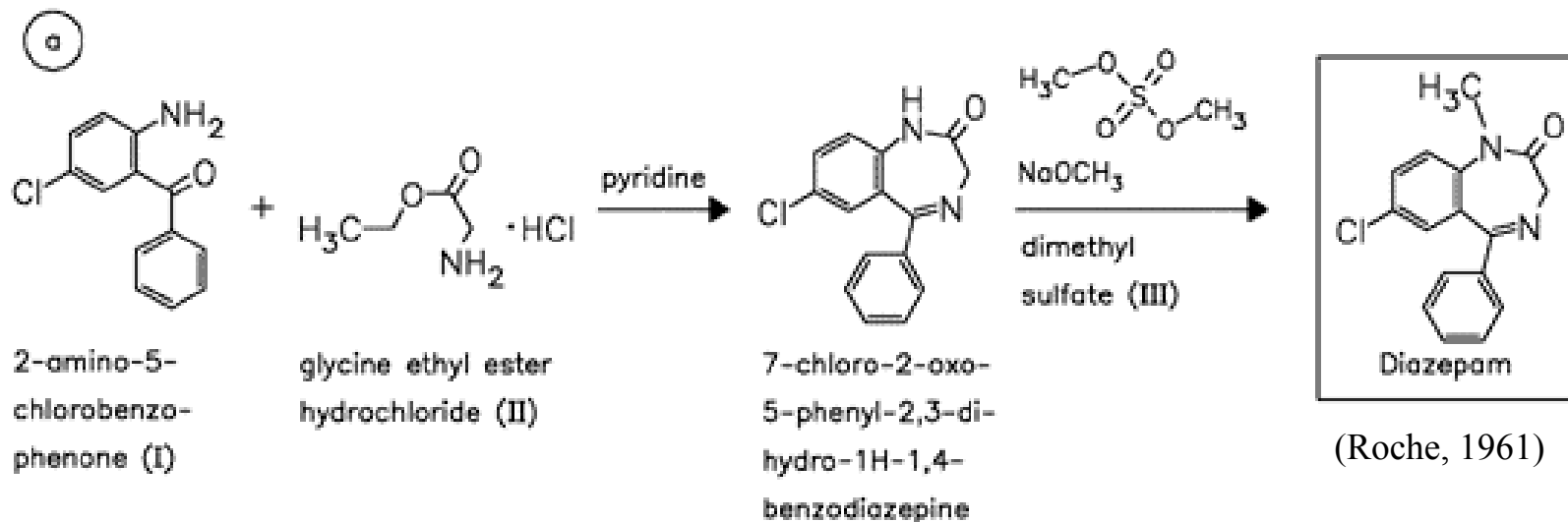
SINTESIS NITRAZEPAM



L. H. Sternbach et al. J. Med. Chem. 6, 261 (1963)

BENZODIAZEPINAS

SINTESIS DE DIAZEPAM



US 3 109 843 (Hoffmann-La Roche; 5.11.1963; appl. 21.6.1962; prior. 28.7.1961).

US 3 136 815 (Hoffmann-La Roche; 9.6.1964; USA-prior. 10.12.1959).

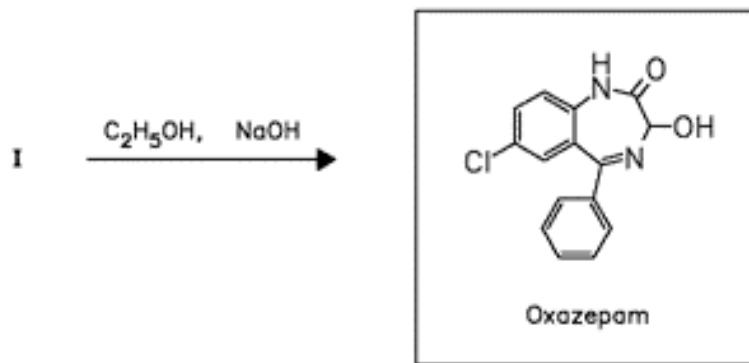
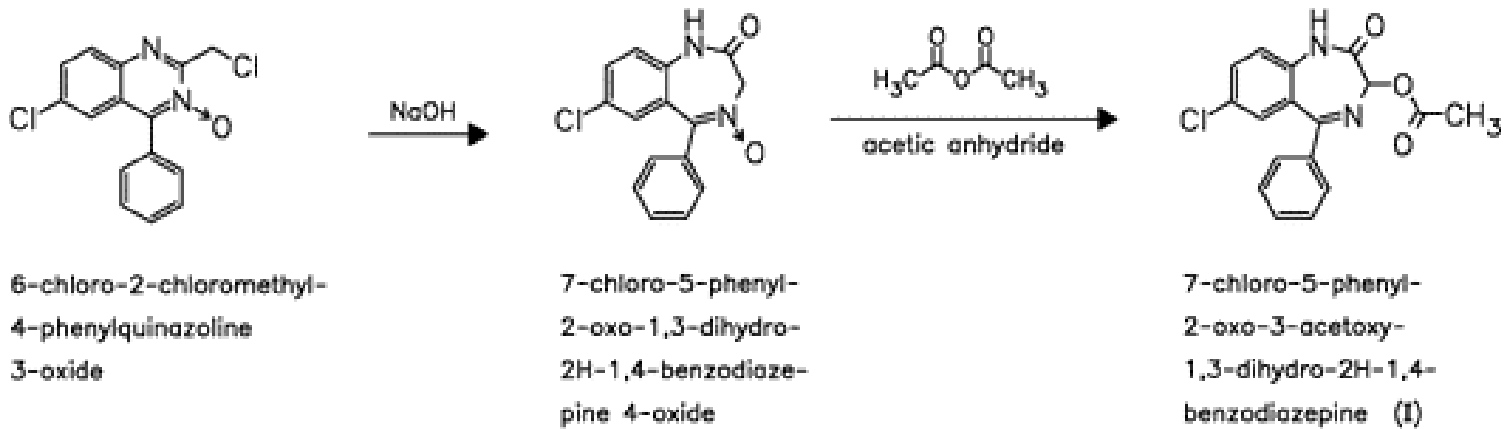
DE 1 136 709 (Hoffmann-La Roche; appl. 7.12.1960; USA-prior. 10.12.1959, 26.4.1960, 27.6.1960).

DE 1 145 626 (Hoffmann-La Roche; appl. 7.12.1960; USA Prior. 10.12.1959, 15.1.1960, 26.4.1960, 27.6.1960).

US 3 371 085 (Roche; 27.2.1968; CH-prior. 2.10.1960).

BENZODIAZEPINAS

SINTESIS DE OXAZEPAM



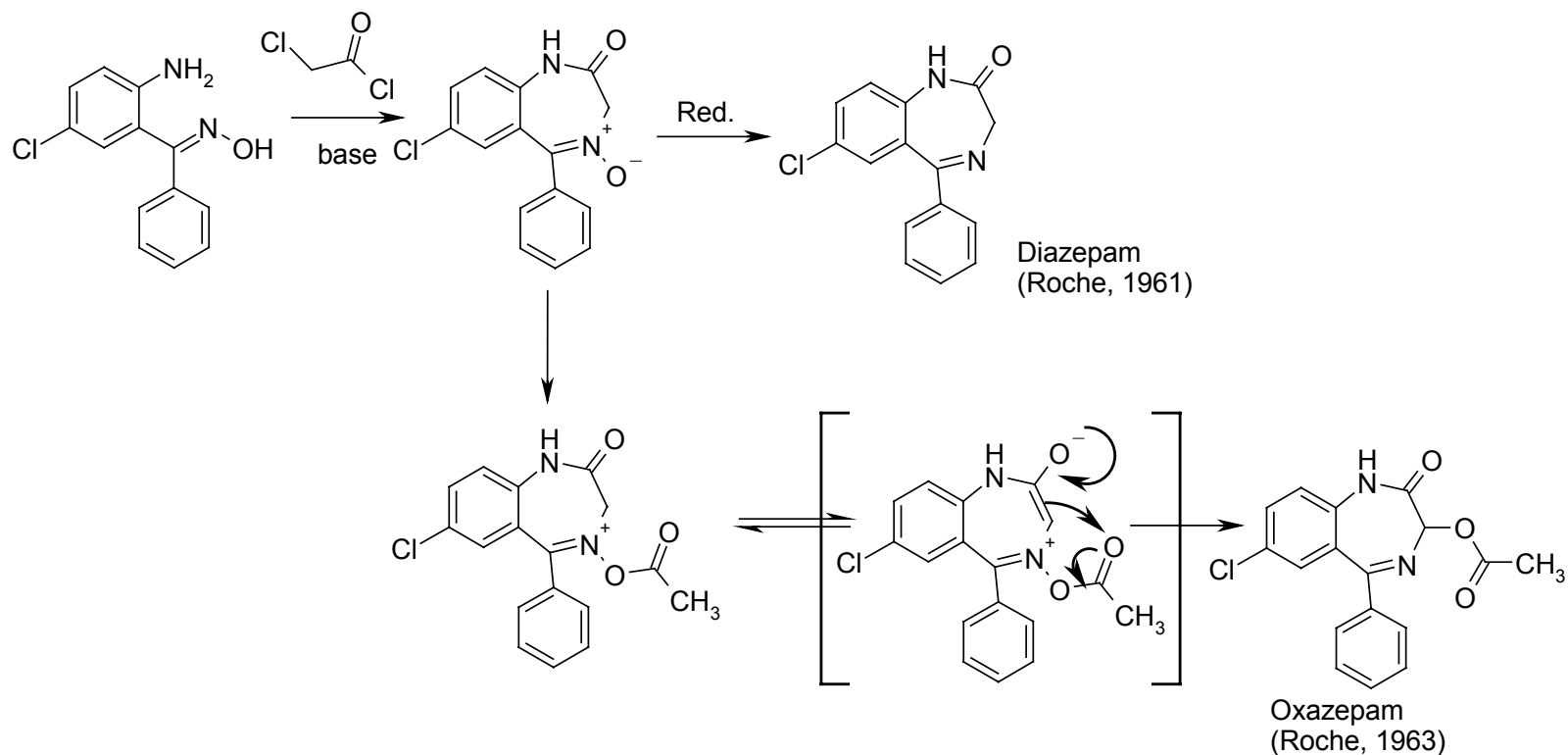
US 3 176 009 (American Home Products; 30.3.1965; prior. 5.3.1962).

US 3 296 249 (American Home Products; 3.1.1967; appl. 4.6.1963; prior. 29.8.1961, 5.3.1962).

DE 1 445 412 (American Home Products; appl. 17.8.1962; USA-prior. 29.8.1961, 5.3.1962).

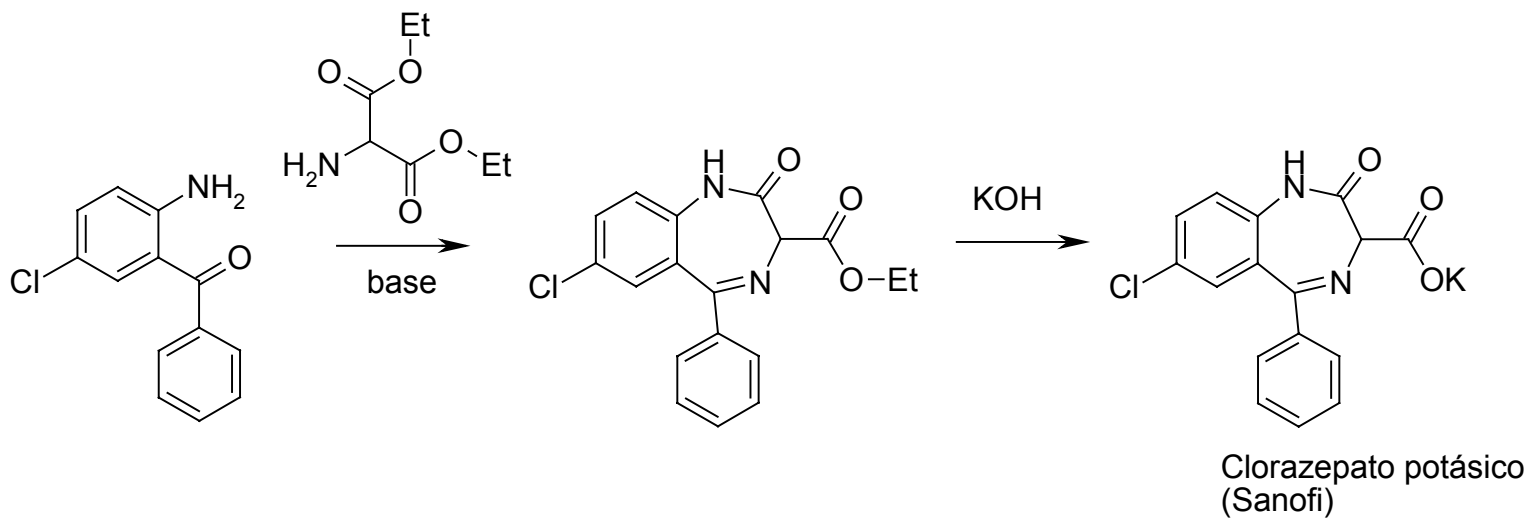
DE 1 795 509 (American Home Products; appl. 17.8.1962; USA-prior. 29.8.1961, 5.3.1962).

SINTESIS DE OXAZEPAM



L. H. Sternbach et al. J. Org. Chem. 26, 4936 (1961)
S. C. Bell et al. J. Org. Chem. 27, 1691(1962)

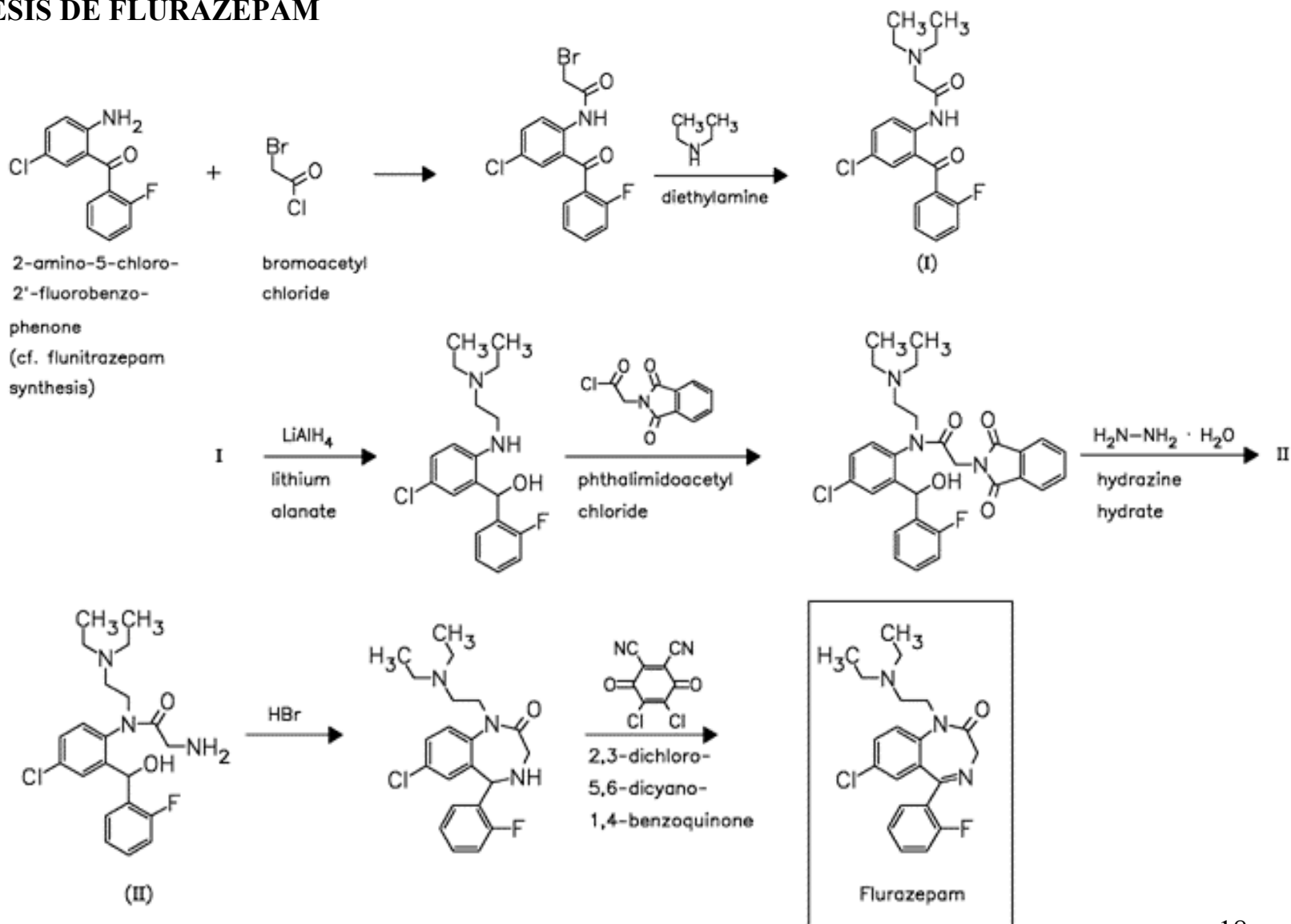
SINTESIS DE CLORAZEPATO



S. C. Bell et al. J. Org. Chem. 33, 216 (1968)

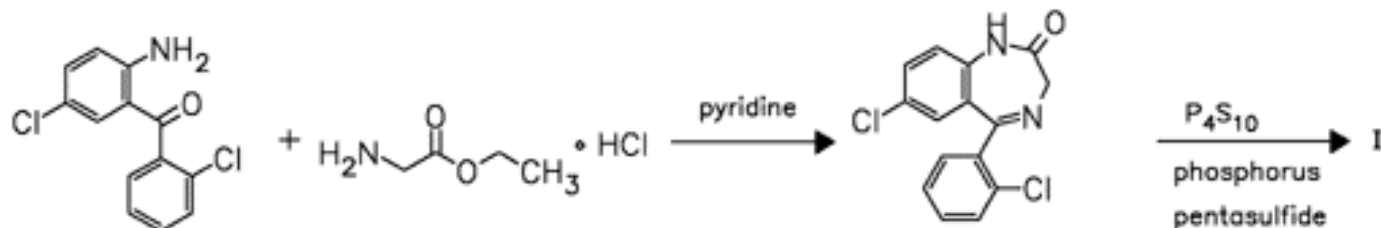
BENZODIAZEPINAS

SINTESIS DE FLURAZEPAM



BENZODIAZEPINAS

SINTESIS DE TRIAZOLAM

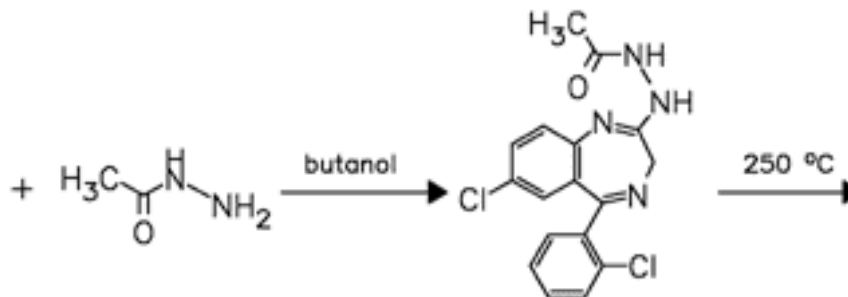


2-amino-2',5-dichlorobenzophenone

glycine ethyl ester hydrochloride

7-chloro-5-(2-chlorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepine

7-chloro-5-(2-chlorophenyl)-2-thioxo-2,3-dihydro-1H-1,4-benzodiazepine (I)



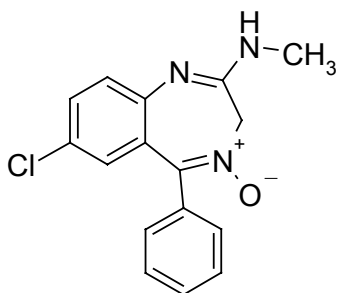
acetylhydrazine

Triazolam

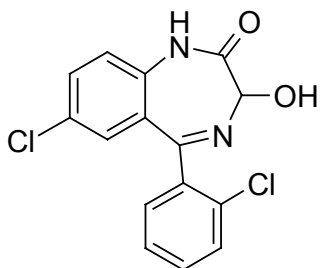
DOS 2 012 190 (Upjohn; appl. 14.3.1970; USA-prior. 17.3.1969, 29.10.1969).
US 3 987 052 (Upjohn; 19.10.1976; prior. 17.3.1969, 29.10.1969).

BENZODIAZEPINAS

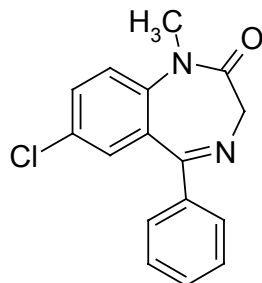
ALGUNOS EJEMPLOS DE USO CLINICO



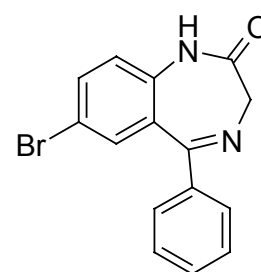
Clordiazepóxido
(Roche, 1959)



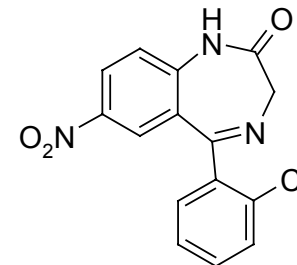
Lorazepam
American Home
Products,
1963)



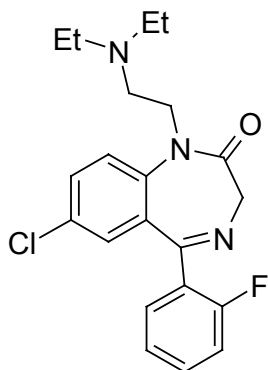
Diazepam
(Roche, 1963)



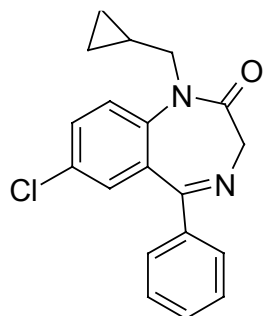
Bromazepam
(Roche, 1965)



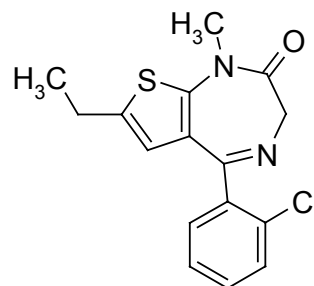
Clonazepam
(Roche, 1967)
Anticonvulsivante



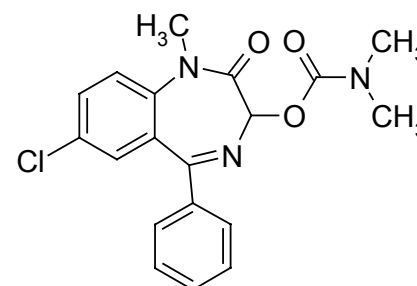
Flurazepam
(Roche, 1964)
Hipnótico-S.



Prazepam
(Warner-Lambert,
1965)



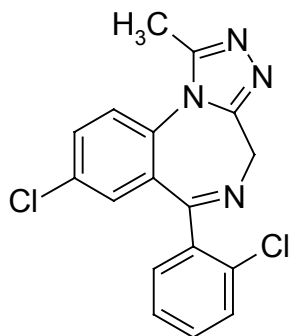
Clotiazepam
(Yoshitomi, 1971)



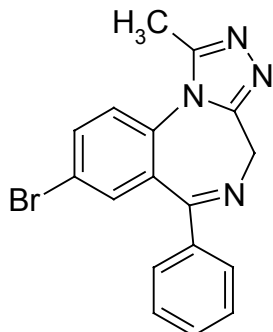
Camazepam
(Siphar, 1972)

BENZODIAZEPINAS

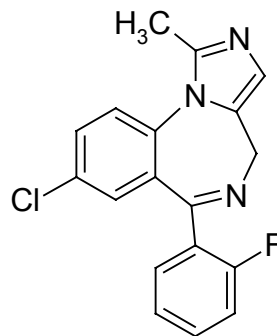
SISTEMAS FUSIONADOS



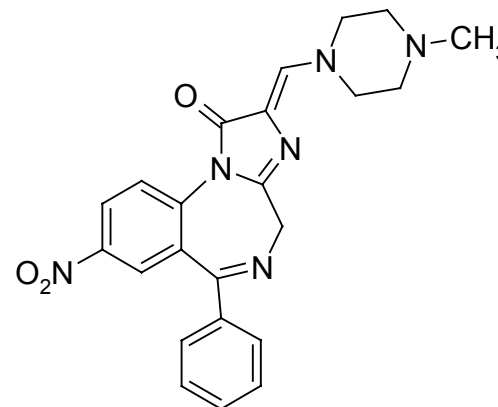
Triazolam
(Upjohn, 1970)
Hipnótico-s.



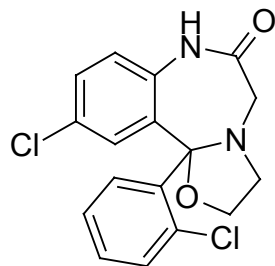
Alprazolam
(Upjohn, 1970)



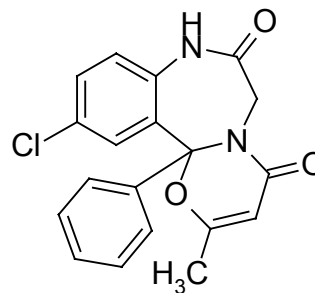
Midazolam
(Roche, 1976)
Anestésico



Loprazolam
(Roussel-UCLAF, 1976)
Hipnótico-s



Cloxazolam
(Sankyo, 1971)



Ketazolam
(Upjohn, 1971)

