ANNELATED 1,5-BENZODIAZEPINES. Part I. THREE, FOUR, AND FIVE MEMBERED RINGS

Alba Chimirri,* Rosaria Gitto, Silvana Grasso, Anna-Maria Monforte, Giovanni Romeo, and Maria Zappalà

Dipartimento Farmaco-Chimico, Università, Viale Annunziata, 98168 Messina, Italy

Abstract - This review describes the synthetic approaches to mono and diannelated 1,5-benzodiazepines with three, four, and five-membered rings fused to different positions of the 1,5-benzodiazepine skeleton.

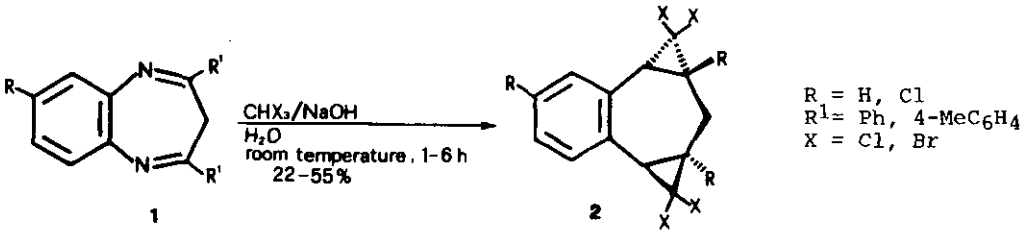
1. INTRODUCTION

The interesting biological activities shown by 1,4- and 1,5-benzodiazepines containing an additional heterocyclic ring fused to the different edges of the heptatomic nucleus have stimulated the exploitation of the chemistry of this class of compounds and an enormous number of papers and patents have appeared in literature.

Although the synthesis of annelated 1,4-benzodiazepines has been previously reviewed,[1] only a partial survey dealing with the chemistry of related 1,5-benzodiazepines has appeared.[2] The present review, dedicated to mono- and diannelated 1,5-benzodiazepines, covers the chemistry and biological activity of this important group of heterocyclic compounds. Derivatives with three, four, five and six-membered rings fused at the different edges of the heptatomic ring are known.

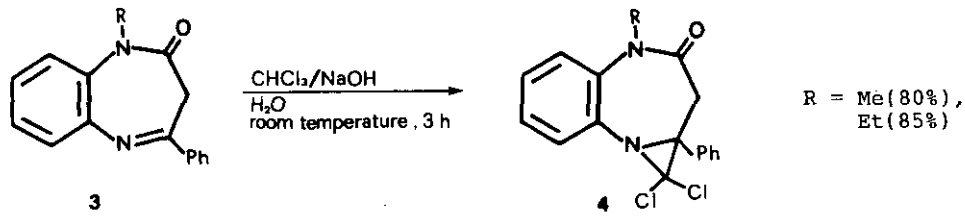
2. Three-membered rings annelated to 1,5-benzodiazepines

Only one example of a synthetic approach to the azirino[1,2-a][1,5]benzodiazepine system was reported.[3,4] The reaction of 3H-1,5-benzodiazepines (1) with dihalocarbenes, generated "in situ" using benzyltriethylammonium chloride in haloform and aqueous sodium hydroxide mixture, gave 1,1a,2a,3-tetrahydro-2H-bisazirino[1,2-a:2',1'-d][1,5]benzodiazepines (2).[3]



1 2

Compounds (4) have similarly been prepared by cycloaddition of dichlorocarbene to 1,5-benzodiazepin-2-ones (3).[4]

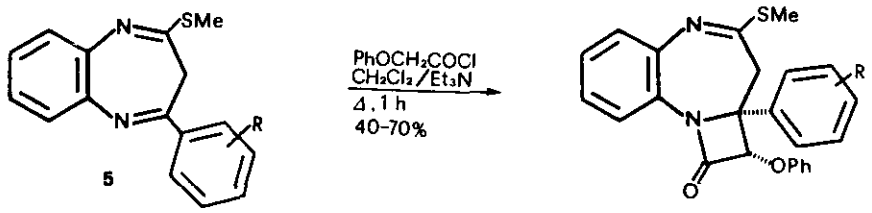


3 4

3. Four-membered rings annelated to 1,5-benzodiazepines

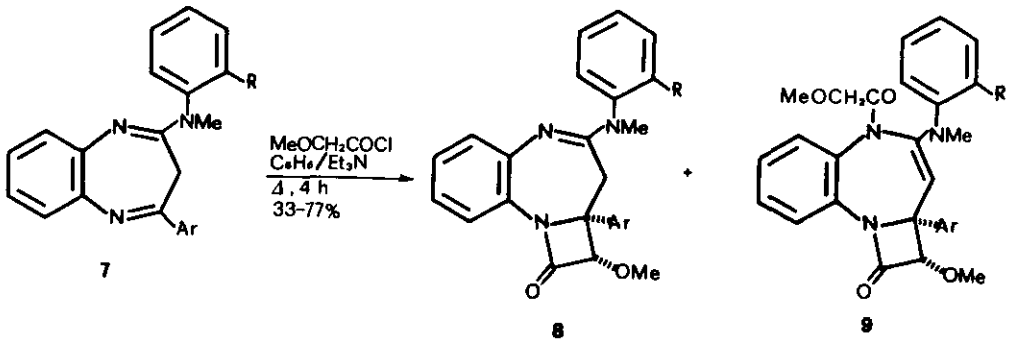
The ß-lactam moiety (6) has been integrated into the benzodiazepine system by regiospecific cycloaddition of phenoxyacetyl chloride to 4-aryl-2-methylthio-3H-1,5-benzodiazepines (5).[5]

The X-ray structure analysis of derivative (6) (R=4-Br) elucidated the stereochemistry of this new ring system.[6] The conformation of the molecule is controlled by steric and electrostatic interactions of the substituents. Owing to steric inhibition caused by the neighbouring oxygen of phenoxy group at C-2 and the sulfur atom of the methylthio substituent at C-4, the 4-bromophenyl ring is rotated by an angle of 85.4(4)° from the mean plane of the heptatomic ring. The diazepine ring adopts a boat conformation, with the four-membered ß-lactam ring planar with phenyl substituents in the eclipsed conformation.



R = H, 3-Br, 4-Br, 4-Cl, 4-F, 4-Me, 4-Et, 4-MeO, 4-NH_2, 4-Ph

Reaction of 1,5-benzodiazepine derivatives (**7**) with methoxyacetyl chloride gave azetodiazepinones (**8**) and (**9**) in an approximately 1:1 ratio.[7-9]



R = H, Me, OMe, Cl, Br
Ar= Ph, 4-MeC_6H_4, 4-ClC_6H_4

The same authors also determined the crystal structure of compound (**9**) (R=H, Ar=4-ClC_6H_4).[9] The seven-membered ring adopts a boat-shaped conformation. The dihedral angles between the best planes through the methoxyacetyl groups and the phenyl ring of the N-methylanilino group at C-4, and between the 4-chlorophenyl ring at C-2a and methoxy groups at C-2 are 128.0(8) and 53.6(8)° respectively, and thus reduce the crowding of these bulky groups on the diazepine ring.

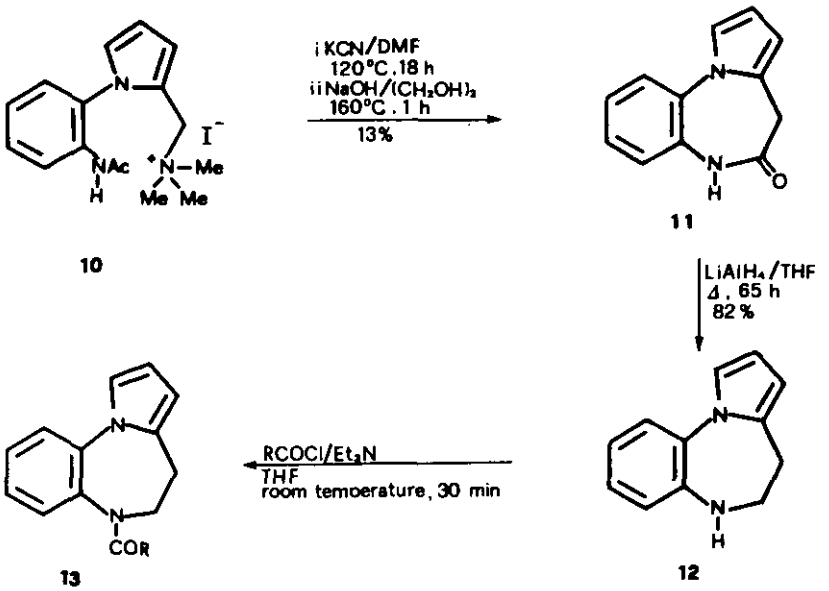
4. Five-membered rings annelated to 1,5-benzodiazepines

Pyrrolo, furo, benzofuro, thieno, pyrazolo, imidazolo, thiazolo, isothiazolo, triazolo, oxadiazolo-1,5-benzodiazepines are known.[10-108]

4.1 Pyrrolo-1,5-benzodiazepines

The synthesis of 4H-pyrrolo[1,2-a][1,5]benzodiazepines related to the antitumoral antibiotic anthramycin, a derivative of 5H-pyrrolo[2,1-c][1,4]-

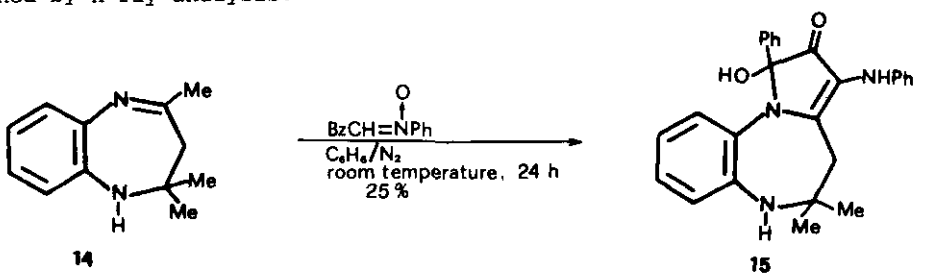
benzodiazepine, was reported.[10] Reaction between 1-(o-acetamidophenyl)-2-dimethylaminomethylpyrrole iodomethylate (**10**) and potassium cyanide afforded 5,6-dihydro-4H-pyrrolo[1,2-a][1,5]benzodiazepin-5-one (**11**), which was reduced with lithium aluminum hydride to 5,6-dihydro-4H-pyrrolo[1,2-a]-[1,5]benzodiazepine (**12**). Some 6-acyl derivatives (**13**) of the latter compound were also described.[10]



10 **11** **12** **13**

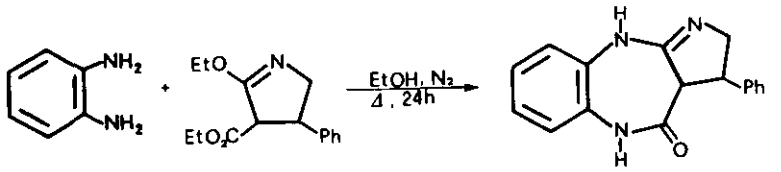
R = Me(81%), CH_2Cl(62%), $CHCl_2$(60%)

Recently, the tetrahydropyrrolobenzodiazepine system has been obtained by reaction of the 1,5-benzodiazepine (**14**) with (Z)-N-(benzoylmethylene)-aniline N-oxide in anhydrous benzene at room temperature; the structure of the obtained cycloadduct 5,6-dihydro-5,5-dimethyl-1-hydroxy-1-phenyl-3-phenylamino-1H-pyrrolo[1,2-a][1,5]benzodiazepin-2(4H)-one (**15**), was established by X-ray analysis.[11]



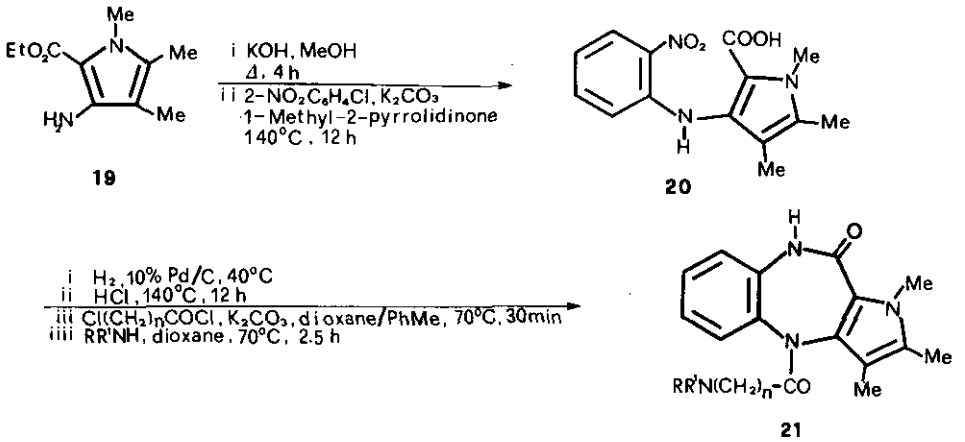
14 **15**

One patent[12] reports the synthesis of the pyrrolo[2,3-b][1,5]benzodiazepine derivative (**18**). This compound, useful as tranquilizer and hypotensive-antihypertensive agent, was prepared by refluxing 2-ethoxy-3-(ethoxycarbonyl)pyrroline (**17**) with o-phenylenediamine (**16**) in ethanol under nitrogen.



16 **17** **18**

Pyrrolo[3,2-b][1,5]benzodiazepin-10(1H)-ones (**21**) have shown interesting biological properties as antiulcer agents: compounds (**21**) were obtained starting from ethyl 3-amino-1,4,5-trimethylpyrrole-2-carboxylate (**19**), which was saponified, nitrophenylated with 2-cloronitrobenzene to **20**, and successively reduced, cyclized, acylated and further aminated to give **21**.[13]



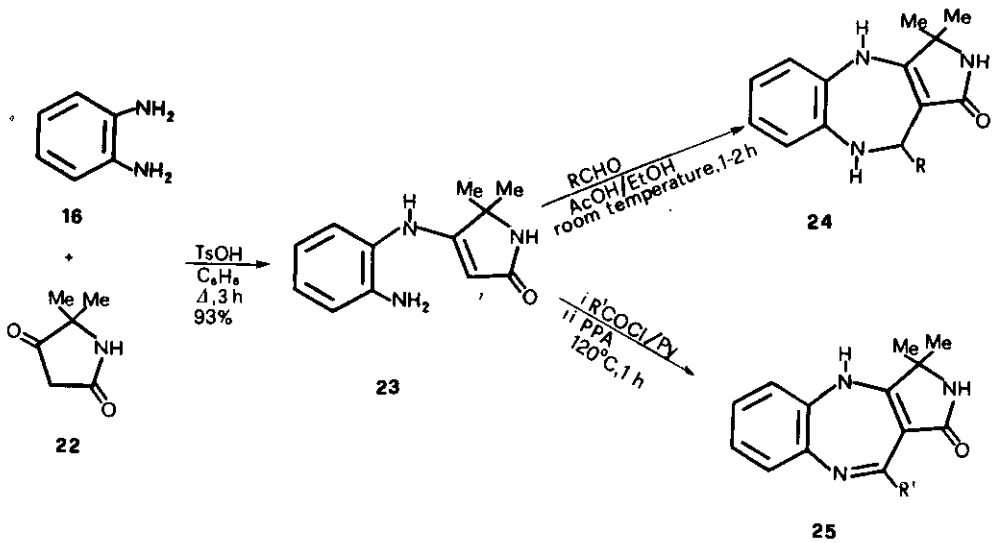
19 **20** **21**

n = 0-2
NRR^1= Me_2N, Et_2N, Pr_2N, EtNH, $Me_2NCH_2CH_2NH$, 4-morpholinyl, 1-piperazinyl, 4-methyl-1-piperazinyl, 1-piperidinyl, 1-pyrrolidinyl

A series of N-acyl derivatives of **21**, their enantiomers, diastereoisomers and physiologically acceptable salts were also prepared; these compounds show a favorable effect on heart frequency as vagal pacemakers, or as

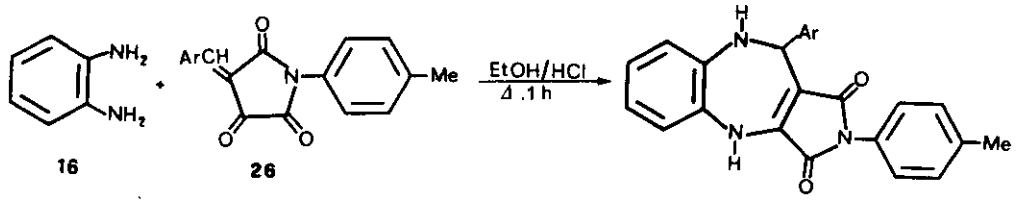
cardioselective antimuscarinic agents useful for treatment of heart disorders such as bradycardia and arrhythmia.[14-16]

The pyrrolo[3,4-b][1,5]benzodiazepin-1(2H)-one system has been also reported;[17-19] pyrrolo[3,4-b][1,5]benzodiazepin-1(2H)-ones (**24**) and (**25**) have been synthesized from appropriate enamino lactam (**23**), obtained by the reaction of 5,5-dimethyltetramic acid (**22**) with o-phenylenediamine (**16**) in the presence of a catalytic amount of p-toluenesulfonic acid.[17,18] The Mannich-type cyclization or the acylation with RCOCl and subsequent cyclization with polyphosphoric acid afforded **24** and **25** respectively.



R = Et(95%),1-propenyl(67%), Ph(71%), 2-ClC_6H_4(89%), 2-$NO_2C_6H_4$(84%), 3,4-$(MeO)_2C_6H_3$(78%), 2-(5-NO_2)-furyl(95%), 2-thienyl(84%), styryl(96%)
R^1= Ph(57%), 2-ClC_6H_4(55%), 2-$NO_2C_6H_4$(50%)

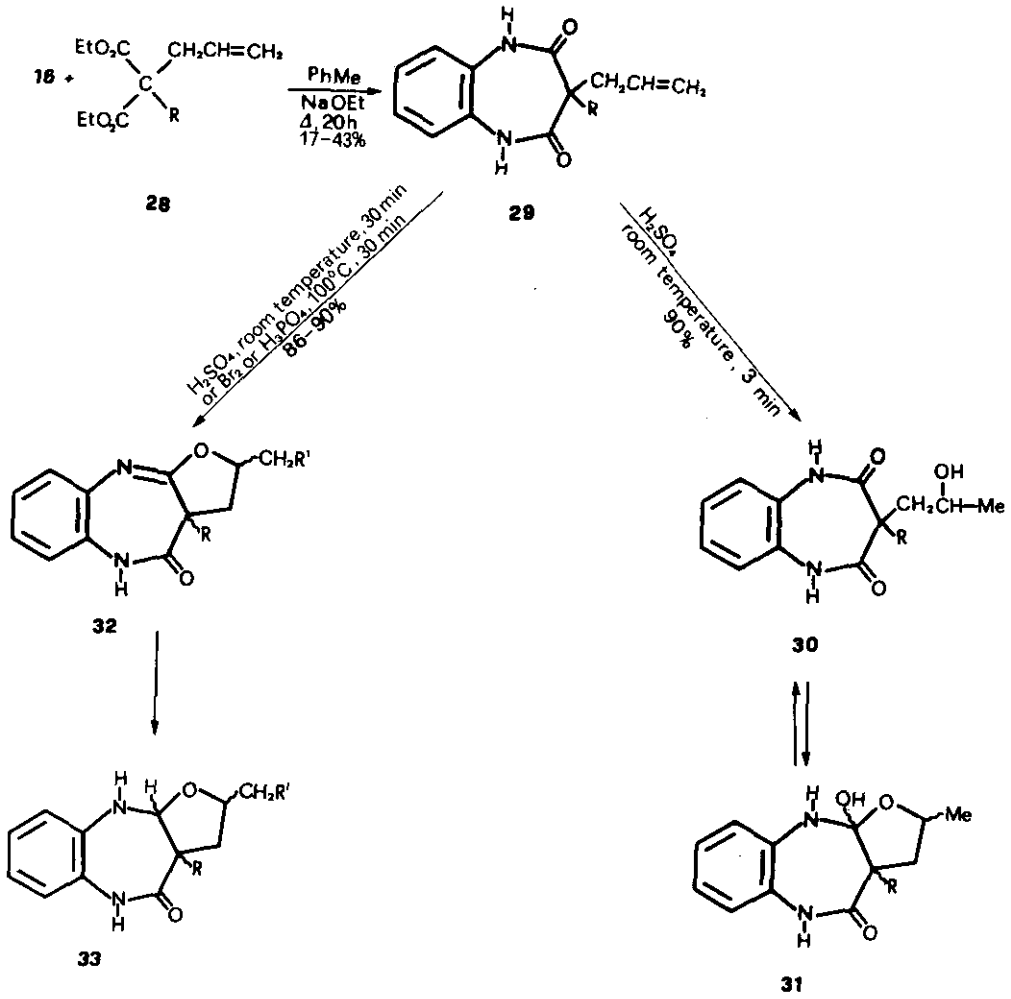
Analogously, pyrrolo[3,4-b][1,5]benzodiazepine-1,3(2H,4H)-diones (**27**) were easily prepared by cyclocondensation of (Z/E)-1-arylmethylenepyrrolidine-2,3,5-triones (**26**) with o-phenylenediamine (**16**) in ethanol.[19]



Ar = Ph(27%), 4-ClC_6H_4(25%), 3-$NO_2C_6H_4$(69%)

4.2 **Furo-1,5-benzodiazepines**

Furo[2,3-b][1,5]benzodiazepines were synthesized starting from 3,3'-allylalkyl-1,5-benzodiazepine-2,4-diones (**29**), obtained by refluxing o-phenylenediamine (**16**) and allylalkylmalonic esters (**28**) in toluene in the presence of sodium ethoxide.[20,21] It has been suggested that hydration of benzodiazepinediones (**29**) affords the corresponding 6ß-hydroxypropyl derivatives (**30**) in equilibrium between two hemiketal forms cis and trans (**31**).[20] Treatment of **29** with concentrated H_2SO_4[21-22] or hot 85% H_3PO_4[21] or

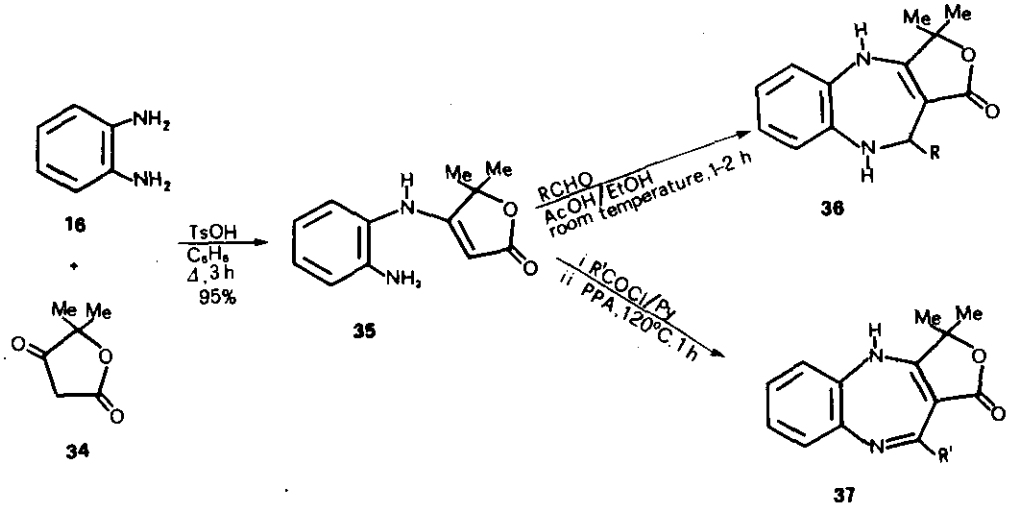


R = Me, Et, i-Pr, allyl, Bu, $CH_2CH_2CHMe_2$, $CH_2CH_2NEt_2$, cyclohexyl, Ph
R^1= H, Br

bromine[23] gave the furobenzodiazepines (**32**) which were also reduced to give 10,10a-dihydro derivatives (**33**).[22] The stereochemistry of the asymmetric centers has not been reported.

The results of biological tests[24] indicated that several furo[2,3-b][1,5]-benzodiazepines (**32**) seem to be particularly interesting owing to their ataractic properties, low toxicity, no or weak hypnotic action and negligible disturbance of the motor coordination.

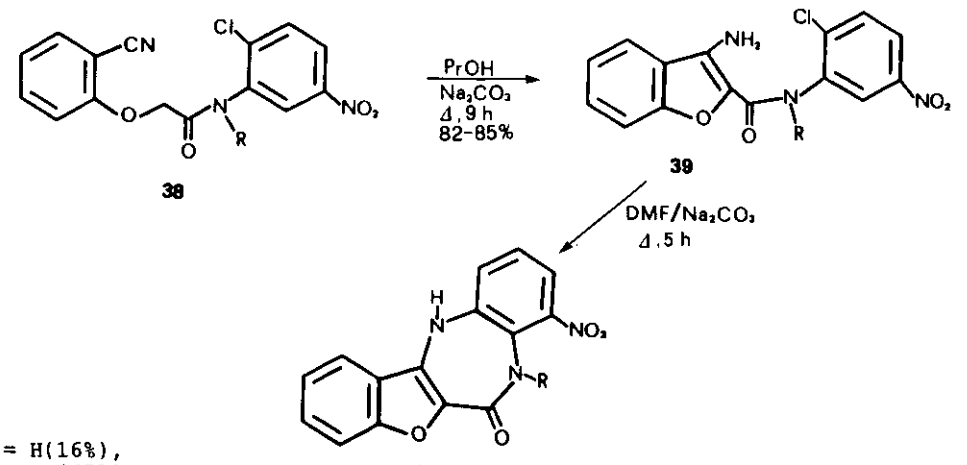
The synthesis of furo[3,4-b][1,5]benzodiazepine system was carried out by condensation of 1,2-phenylenediamine (**16**) with 5,5-dimethyltetronic acid (**34**) in the presence of a catalytic amount of p-toluenesulfonic acid to give the enamino lactone (**35**); treatment of the latter compound with various aldehydes in ethanol in the presence of small amounts of acetic acid gave 10-substituted 3,3-dimethyl-3,4,9,10-tetrahydro-1H-furo[3,4-b]-[1,5]benzodiazepin-1-ones (**36**).[17] 3,4-Dihydrofuro[3,4-b][1,5]benzodiazepin-1-ones (**37**) were also prepared by acylation of amine (**35**) with acyl chlorides followed by cyclization with polyphosphoric acid.[18]



R = 1-propenyl(87%), Ph(98%), 2-ClC_6H_4(92%), 2-FC_6H_4(94%), 4-$MeOC_6H_4$(96%), 4-$NO_2C_6H_4$(89%), 2-pyridyl(98%), 2-thienyl(85%), styryl(99%)
R^1= Ph(52%), 2-ClC_6H_4(85%), 4-$NO_2C_6H_4$(83%), 2-pyridyl(16%)

4.2.1. **Benzofuro-1,5-benzodiazepines**

5,6-Dihydro-12H-benzofuro[3,2-b][1,5]benzodiazepin-6-ones (**40**) have been prepared by cyclization of N-(2-chloro-5-nitrophenyl)-3-amino-2-benzofurancarboxamides (**39**) obtained from N-(2-chloro-5-nitrophenyl)-2-(2-cyanophenoxy)acetamides (**38**).[25]



38 **39** **40**

4.3 **Thieno-1,5-benzodiazepines**

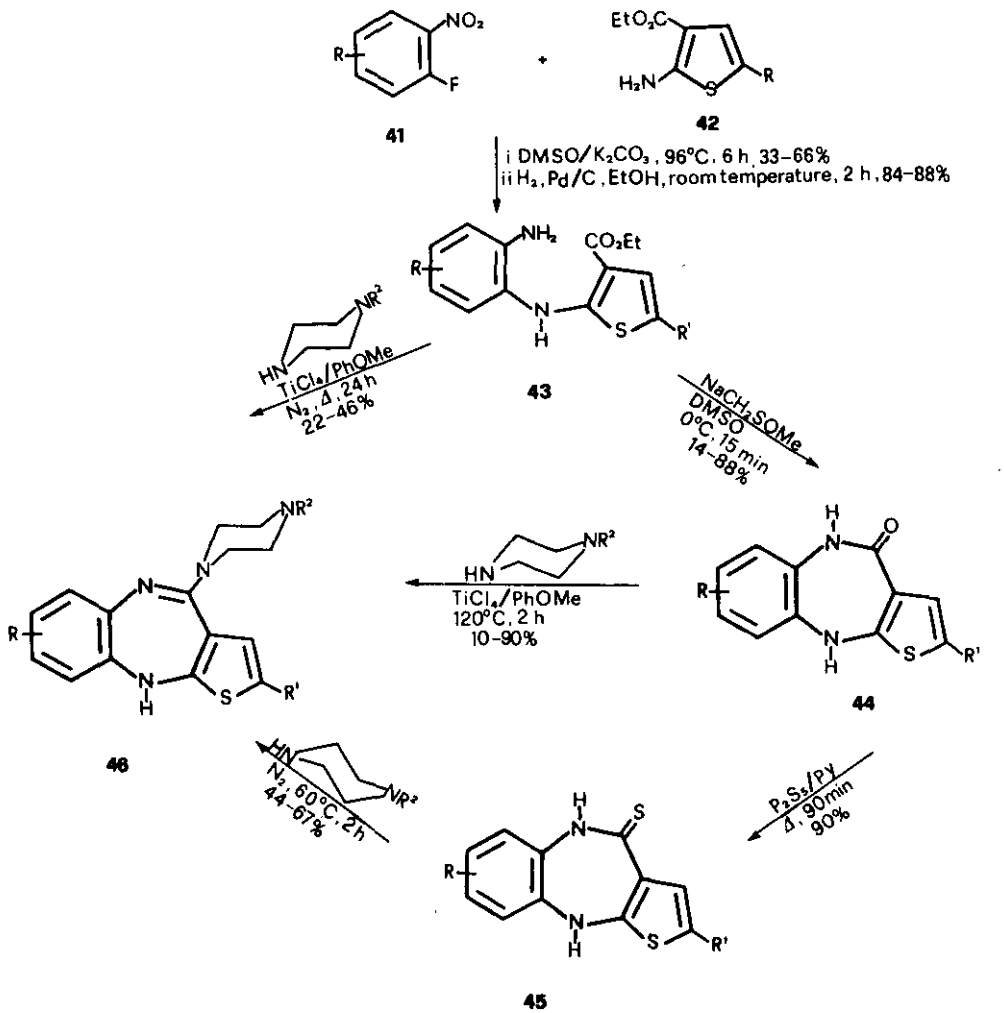
Three different ring systems are reported, according to the various fusions of the pentatomic ring to the benzodiazepine nucleus.

A general synthetic route to the thieno[2,3-b]-, [3,2-b]- and [3,4-b][1,5]-benzodiazepine ring systems has been developed.[26,27] The approach is based on the reaction of suitably substituted aminothiophenecarboxylates with variously substituted 2-fluoronitrobenzenes to give nitroesters, which by sequential catalytic reduction and cyclization of the resulting diaminoesters affords the corresponding thieno-1,5-benzodiazepines.

Thus, the reaction of ethyl 2-aminothiophene-3-carboxylates (**42**) with 2-fluoronitrobenzenes (**41**), in the presence of DMSO and K_2CO_3, led to the nitro esters, which by reduction to amino esters (**43**) and subsequent cyclization, promoted by 3 equivalents of sodium methylsulphinyl methanide, gave the 10H-thieno[2,3-b][1,5]benzodiazepin-4(5H)-ones (**44**).[26-28]

A series of 4-piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepines (**46**), useful as anxiolitics and tranquilizers, have been also prepared by

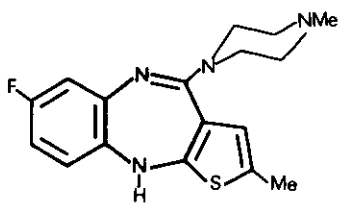
reaction of thienodiazepinones (**44**) with the appropriate piperazine in the presence of $TiCl_4$ and anisole.[26,29,30] Alternatively, the amidino derivatives (**46**) have been obtained through the conversion of thienodiazepinones (**44**) into thienodiazepinethiones (**45**) by reaction with P_2S_5, and successive treatment with amines. Furthermore, it was also shown that the diamino esters (**43**) can be directly converted into derivatives (**46**) by reaction with N-methylpiperazine, $TiCl_4$ and anisole at higher temperatures.[29,30]



R = H, 7-F, 8-F, 6,8-F_2, 7,8-F_2, 7-Cl, 8-Me, 7-MeS, 7-NH_2, 7-NO_2
R^1= H, Et, Me, t-Bu, 2-hydroxyethyl, i-Pr, n-C_6H_{13}, COMe, Ph
R^2= Me, Et, Pr, CH_2Ph, Ph, 4-$ClC_6H_4CH_2$, 3-ClC_6H_4, 3-$CF_3C_6H_4$

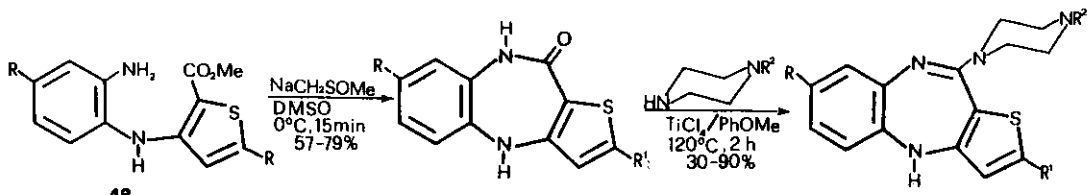
Several derivatives (**46**) showed potent neuroleptic activity, higher than clozapine.[29] A Free-Wilson study of substituent contributions to antidopaminergic activity was also reported.[31] The structure-activity relationship indicates the importance of the disposition of the distal piperazine nitrogen with respect to the tricyclic system on the levels of antidopaminergic and anticholinergic activity.[30]

Among the tested compounds, flumezapine, 7-fluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (**47**) was the most interesting as antagonist of central dopamine and serotonine receptors.[32] It was demonstrated that 5-hydroxytriptamine antagonism is not involved in the lack of synergism of flumezapine with amfonelic acid.[33] A study on in vitro metabolism of **47** was also reported.[34]



47

Several 4H-thieno[3,2-b][1,5]benzodiazepines (**49**)[26-28,35] and (**50**)[26,35] have been prepared using the above reported synthetic strategy, starting from amino esters (**48**).

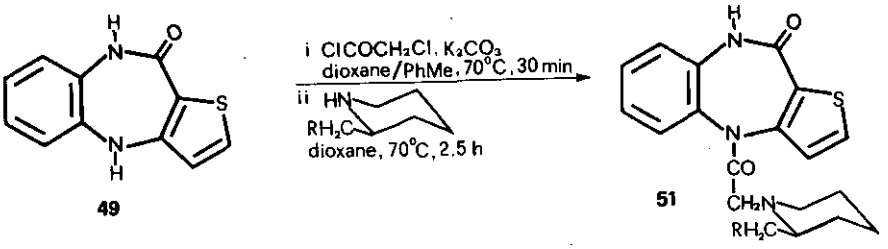


48 **49** **50**

R = H, F, Cl
R^1= H, Me
R^2= H, Me, $(CH_2)_2OH$, $(CH_2)_3OH$, CO_2Et, CH_2Ph

The activity of 10-piperazinyl-4H-thieno[3,2-b]benzodiazepines (**50**) as neuroleptics has been evaluated and some of them demonstrate a greater potency than clozapine.[35]

9,10-Dihydro-4H-thieno[3,2-b][1,5]benzodiazepin-10(9H)-one (**49**) was chloroacetylated by treatment with chloroacetyl chloride, and successively aminated to give derivatives (**51**).[14]



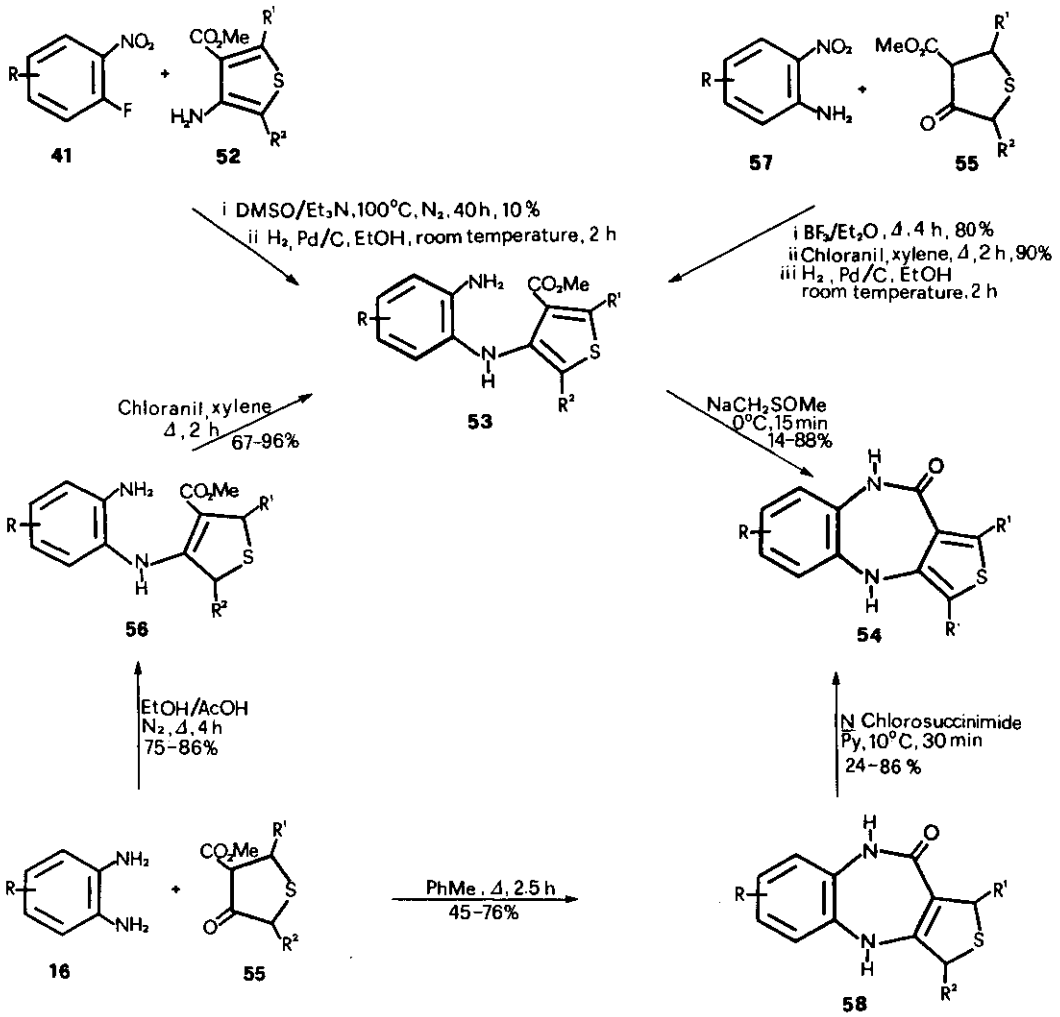
R = Me_2N, 4-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl

Many reports describe the synthesis of the 4H-thieno[3,4-b][1,5]benzodiazepine system. The most general synthetic approach to diazepinone (**54**) is based on the cyclization of the corresponding amino esters (**53**), obtained from the reaction of 2-fluoronitrobenzenes (**41**) with methyl 4-aminothiophene-3-carboxylates (**52**) and successive reduction.[27,35]

The amino esters (**53**) were also derived from the condensation of 4-(carboxymethyl)tetrahydrothiophen-3-one (**55**) with an appropriate 1,2-phenylenediamine derivative (**16**) and aromatization of the resulting dihydrothiophene (**56**) by chloranil in boiling toluene or xylene.[35,36] Similar reaction of the above keto ester (**55**) with o-nitroanilines (**57**) produced nitro esters, which on subsequent aromatization and catalytic reduction gave the amino ester (**53**).

When 1,2-phenylenediamine (**16**) was condensed with 4-(carboxymethyl)-tetrahydrothiophen-3-one (**55**) in boiling toluene 4H-1,3-dihydrothieno-[3,4-b][1,5]benzodiazepin-10(9H)-one (**58**) was obtained, which by aromatization gave (**54**).[35,37-42]

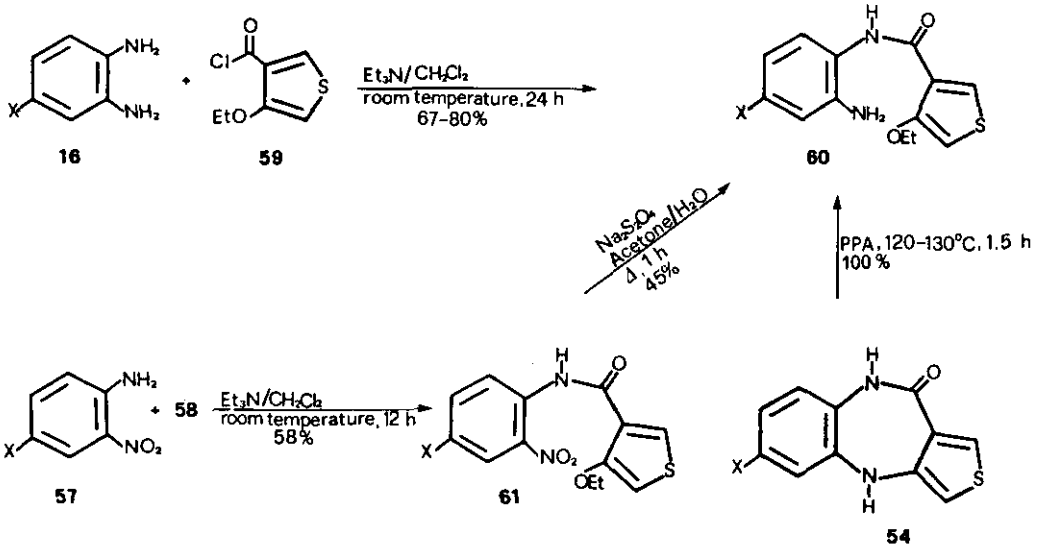
Thienodiazepinones (**54**) have been 4,9-diaminoalkylated[36-41] or 4-amino-acylated[16,41,43-46] by treatment with chloroacetylchloride or phosgene and successively with amines.



R = H, 6-CF_3, 7-CF_3, 6-Cl, 7-Cl, 6,7-Cl_2, 7-F, 6-Me, 6,7-Me_2, 6-Et, 6-MeO, 7-MeO, 7-MeS
R^1= H, R^2= H, Me
R^1= Me, R^2= H

A selective, high yield synthesis[47] of thieno[3,4-b][1,5]benzodiazepinones (**54**) (X = Cl or F) involved the condensation of 4-ethoxy-3-thiophenecarbonyl chloride (**59**) with 4-chloro- or 4-fluoro-1,2-phenylenediamine (**16**) which gives the amino amides (**60**) exclusively. Presumably, the mesomeric influence of the halo substituent sufficiently enhances the nucleophilicity

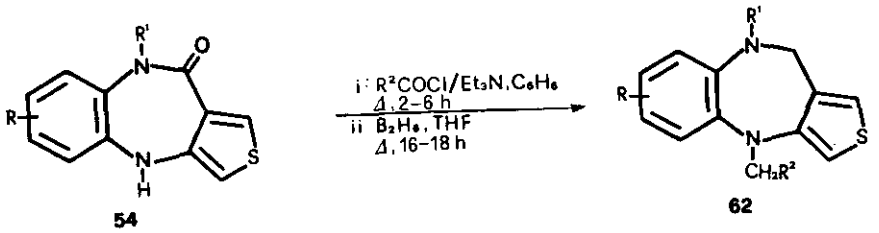
of the 1-amino group to give rise to observed regiospecific reaction. The latter compounds were cyclized to **54** by treatment with polyphosphoric acid. The intermediate amino amide (**60**) can be also obtained starting from 4-chloro-2-nitroaniline (**57**) (X = Cl) and **59** after reduction of the nitro group of the intermediate (**61**) with sodium hydrosulfite.



16 59 60 57 58 61 54

X = Cl, F

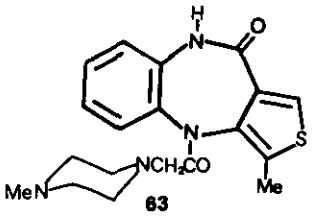
9-Alkyl derivatives of **54** were acylated at the 4-position and the products were reduced (B_2H_6-THF) to yield 9,10-dihydro-4H-thieno[3,4-b][1,5]benzodiazepines (**62**).[48]



54 62

R = H, 6,7-Cl_2, 6,7-Me_2, 6-NO_2
R^1= H, Me, Et, Pr, 2-propenyl, 2-methyl-2-propenyl, 2-cyclohexen-1-yl
R^2= Me, Et, cyclopropyl, pentyl, CH_2Ph

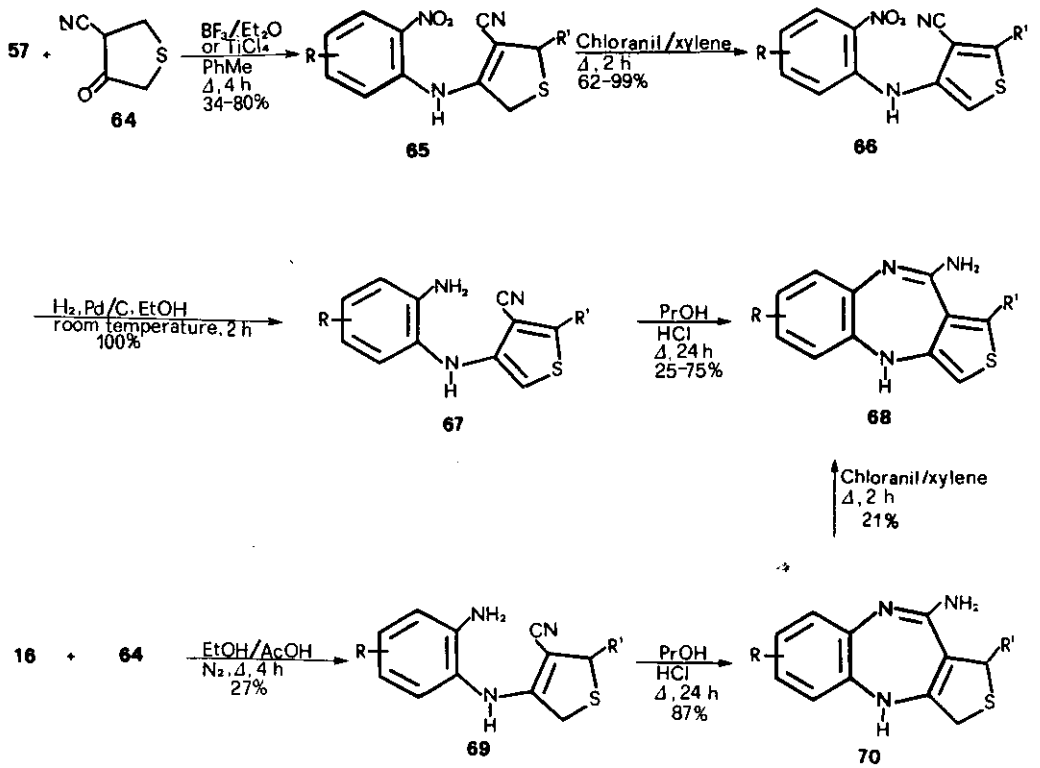
Several 4-(1-piperazinyl)acetyl derivatives of **54** showed marked gastric antisecretory properties which might be of potential value in the treatment of peptic ulcer disease.[43,44] One of the most promising compounds of this series was telenzepine (3-methyl-4-[(4-methyl-1-piperazinyl)acetyl]-4H-thieno[3,4-b][1,5]benzodiazepin-10(9H)-one) (**63**).[49-51] Telenzepine shows a selective activity as inhibitor of muscarinic M1 receptors,[52-61] has a 10-fold higher affinity than pirenzepine at these receptors and is equipotent with atropine.[52] It was also found[62] that telenzepine enantiomers block muscarinic M1 receptors with opposite kinetics. Intestinal permeation of telenzepine with respect to pirenzepine was also evaluated.[63]



63

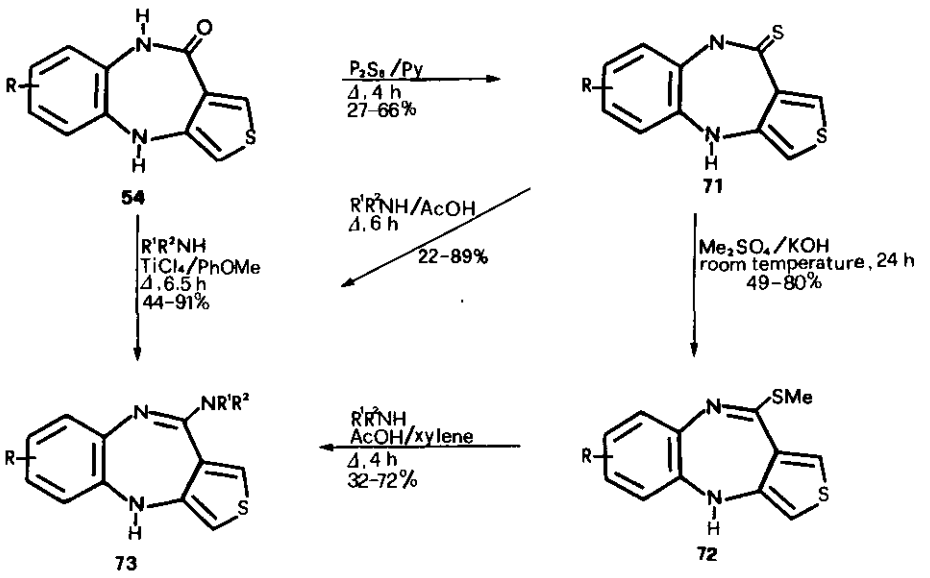
4H-Thieno[3,4-b][1,5]benzodiazepin-10-amines have been intensively studied and several synthetic routes have appeared in literature.

The earliest approach[26,28,35] started from the readily available 4-cyano-tetrahydrothiophen-3-one (**64**) with a suitably substituted 2-nitroaniline (**57**) in the presence of a catalytic amount of BF_3-Et_2O or $TiCl_4$ to give nitro enamines (**65**) which underwent aromatization with chloranil to produce 4-cyano-3-(2-nitroanilino)thiophenes (**66**) in excellent yields. Catalytic hydrogenation of the nitro group afforded the corresponding amino nitriles (**67**) which, without further purification, were subjected to acid-catalyzed ring closure towards amidines (**68**). Similarly, the condensation of 1,2-phenylenediamines (**16**) with 4-cyanotetrahydrothiophen-3-one (**64**) afforded dihydrothiophene derivatives (**69**) which on acid cyclization produced amidine salts (**70**). Conversion to the free base and aromatization gave the required amidines (**68**).[35]



R = H, 7-Cl, 7-F, 6-CF_3, 7-CF_3, 7-MeO, 7-MeS
R^1= H, Me

The same synthetic procedures reported for thieno[2,3-b]- (**46**) and [3,2-b]-[1,5]benzodiazepines (**50**) were employed for thieno[3,4-b][1,5]benzodiazepine derivatives (**73**). In the principal method[39,40,64,65] the lactam (**54**) was converted to the corresponding thiolactam (**71**) by the action of P_2S_5 in pyridine. Alkylation of **71** gave the methyl thioether (**72**) which reacted smoothly with a variety of amines to give the desired (**73**). Alternatively[39], reaction of thiolactam directly with the appropriate amine gave **73** in moderate yield. A more useful procedure[35,39,40] utilizes $TiCl_4$ to catalyze the condensation of lactam (**54**) with amines to give **73**.



R = H, 6-CF_3, 7-CF_3, 6-Cl, 7-Cl, 6-F, 6-Me, 7-Me, 6-Et, 6-MeO, 6-MeS, 6-NO_2
NR^1R^2= NH_2, NMe_2, 4-methylpiperazinyl, 4-(1-hydroxyethyl)piperazinyl, 4-ethylpiperazinyl, 4-propylpiperazinyl, pyrrolidinyl

Basic hydrolysis of amidines (**73**) gave the corresponding diazepinones (**54**).[35]

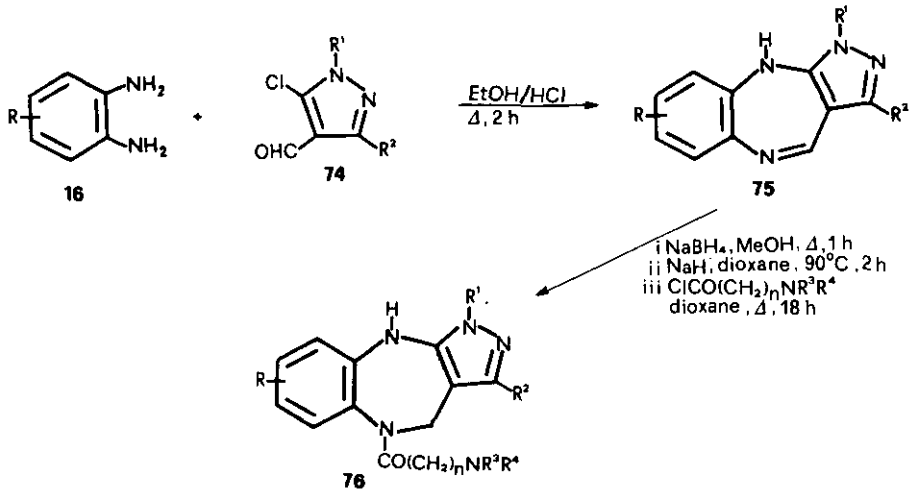
Several [3,4-b][1,5]benzodiazepines (**73**) were found to be potent neuroleptic agents and to exhibit additional antidepressant activity.[35]

4.4 Pyrazolo-1,5-benzodiazepines

Fusion of the pyrazole ring to the 1,5-benzodiazepine system has been reported and involves only the facet "b" of the heptatomic nucleus.

The two isomeric pyrazolo[3,4-b]- and pyrazolo[4,3-b][1,5]benzodiazepine systems can be further subdivided into two isomeric classes, depending on which of the pyrazole nitrogen atom is substituted.

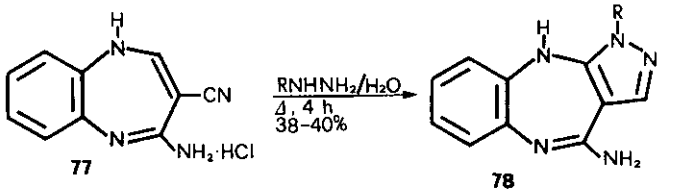
1,10-Dihydropyrazolo[3,4-b][1,5]benzodiazepines (**75**) have been prepared by cyclization of 1,2-phenylenediamine derivatives (**16**) with 1,3-disubstituted 5-chloro-4-pyrazolecarboxaldehydes (**74**);[66] reduction of **75** with $NaBH_4$ and successive aminoacylation gave 1,4,5,10-tetrahydropyrazolo[3,4-b][1,5]-benzodiazepines (**76**).



16 74 75 76

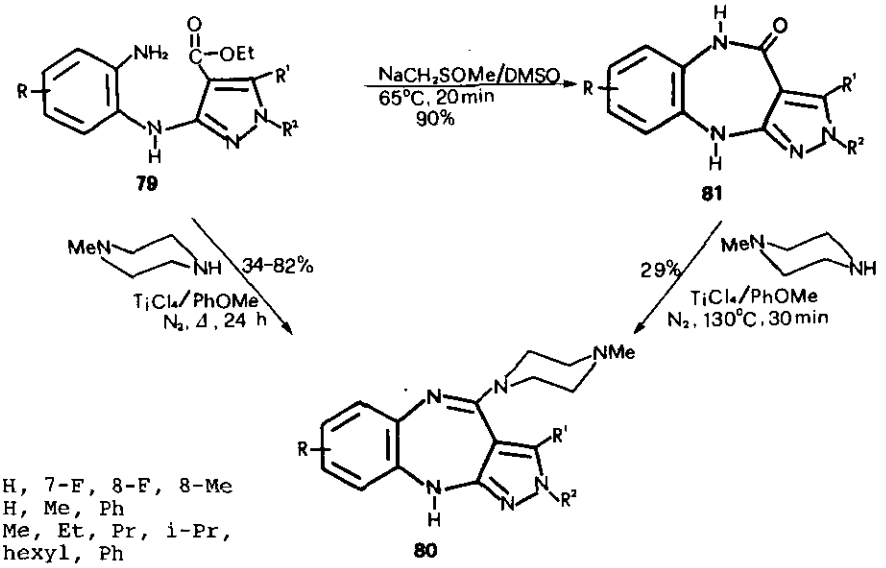
R = H, 7-Cl, 8-Cl, 7-Me, 8-Me, 7-OMe, 8-OMe, 7-CO_2Me, 8-CO_2Me
R^1= Et, cyclohexyl, Ph, CH_2Ph
R^2= Me, Et, i-Pr; n= 0, 1
NR^3R^4= NH_2, $NHNH_2$, NHNHCOMe, Me_2N, $Et_2N(CH_2)_2N$, 4-(2-hydroxyethyl)piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, morpholinyl, 2-(4-morpholinyl)ethylamino, 2-(4-morpholinyl)propylamino, piperidinyl

1,10-Dihydropyrazolo[3,4-b][1,5]benzodiazepine-4-amine derivatives (**78**) were obtained by cyclocondensation of **77** with hydrazine derivatives.[67]



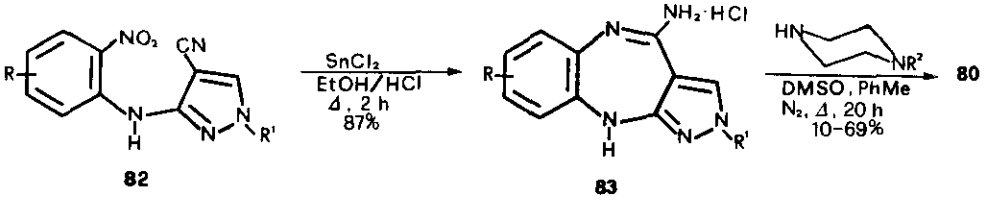
77 78 R = H, Me, Ph

A series of amidino derivatives (**80**) was synthesized by reacting an anisole solution of ethyl 3-(2-aminoanilino)pyrazole-4-carboxylates (**79**) with N-methylpiperazine in the presence of $TiCl_4$, under nitrogen;[68,69] an alternative approach[69] relies on the cyclization of ethyl 3-(2-aminoanilino)pyrazole-4-carboxylate (**79**) with sodium (methylsulfinyl)-methanide to give pyrazolo[3,4-b][1,5]benzodiazepin-4-ones (**81**), which readily reacted with N-methylpiperazine and $TiCl_4$ in anisole to give **80**.



R = H, 7-F, 8-F, 8-Me
R^1= H, Me, Ph
R^2= Me, Et, Pr, i-Pr, hexyl, Ph

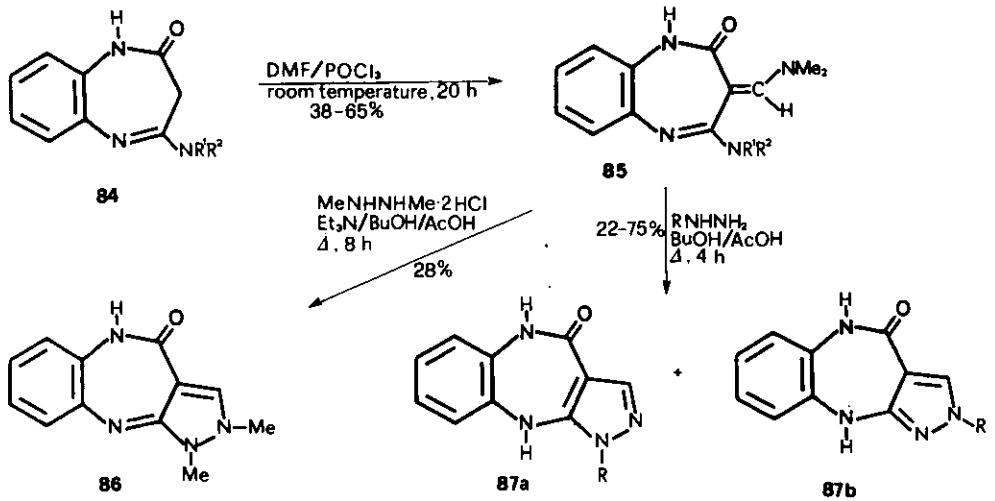
Furthermore, reduction of 3-(2-nitroanilino)pyrazole-4-carbonitrile (**82**) with anhydrous $SnCl_2$ in aqueous ethanolic HCl led directly to pyrazolo-[3,4-b][1,5]benzodiazepine-4-amine (**83**) as hydrochloride. Transamination of **83** with an appropriate amine gave amidine derivatives **80**.[68,69] Pharmacological activity evaluation is also reported:[69] some of the 4-piperazinyl-2,10-dihydropyrazolo[3,4-b][1,5]benzodiazepines (**95**) demonstrated potent anxiolytic activity, higher than clordiazepoxide.



R = 7-F, 7,8-F_2, 7-Cl, 8-Cl, 7,8-Cl_2, 7-Br, 7-I, 7-CF_3, 7-COPh, 7-SO_2Me
R^1= Me, Et, i-Bu, cyclopentyl, n-decyl, CH_2Ph
R^2= H, Me, CH_2CH_2OH, CO_2Et

A synthetic route which leads to isomeric pyrazolo[3,4-b][1,5]benzodiazepine systems is based on the reaction of 4-dialkylamino-1,3-dihydro-2H-1,5-benzodiazepin-2-ones (**84**) with Vilsmeier reagent at room temperature. The obtained (Z)-4-dialkylamino-3-dimethylaminomethylene-1,3-dihydro-2H-1,5-benzodiazepin-2-ones (**85**), were then made to react with

substituted hydrazines to afford pyrazolo[3,4-b][1,5]benzodiazepine derivatives (**86-87**) mono- or disubstituted according to the hydrazino-derivative employed.[70,71]



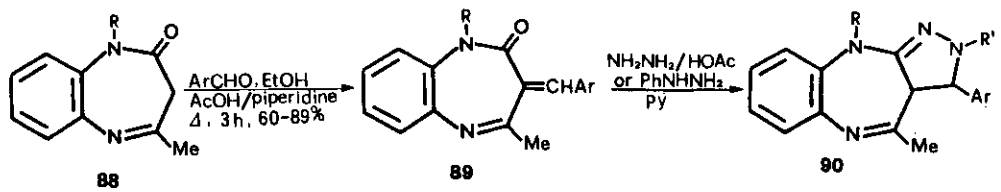
84 **85** **86** **87a** **87b**

NR^1R^2= Me_2N, Et_2N, pyrrolidinyl

R = Me(22%), H(75%), Ph(62%)

R = Me(23%)

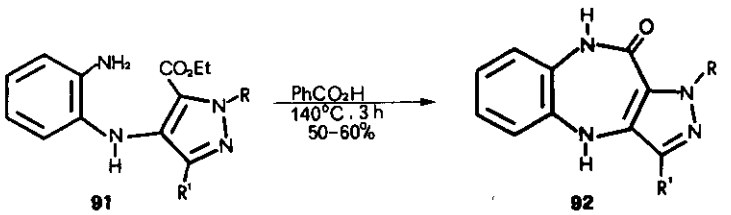
Analogously, condensation of 2,3-dihydro-4-methyl-1H-1,5-benzodiazepin-2-one derivatives (**88**) with aromatic aldehydes gave (Z/E)-3-arylidene derivatives (**89**), which by successive treatment with NH_2NH_2-HOAc or $PhNHNH_2$ in pyridine gave 4-methyl-2,3,3a,10-tetrahydropyrazolo[3,4-b][1,5]-benzodiazepines (**90**).[72]



88 **89** **90**

R = H, Me, Et
R^1= Ac, Ph
Ar= 2-HOC_6H_4, 4-HOC_6H_4, 4-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$, 2-thienyl

Pyrazolo[4,3-b][1,5]benzodiazepin-10(1H)-ones (**92**) were obtained by cyclization of an appropriate aminopyrazolecarboxylic acid derivative (**91**). The obtained compounds (**92**) were also 4-acylated and aminated to give **93**.[73,74]



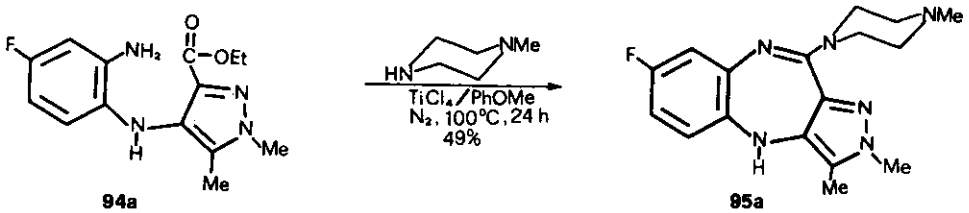
91 92

i $ClCO(CH_2)_nCl$, K_2CO_3, dioxane/PhMe, 70°C, 2 h, 80–95%
ii R^2R^3NH, dioxane, 80°C, 1 h, 70–90%

n = 2, 3
R = Me, Et
R^1 = H, Me, Et
R^2 = R^3 = Me, Et, i-Pr
NR^2R^3 = morpholinyl, piperidinyl, pyrrolidinyl, 4-methylpiperazinyl, 4-phenylmethylpiperazinyl

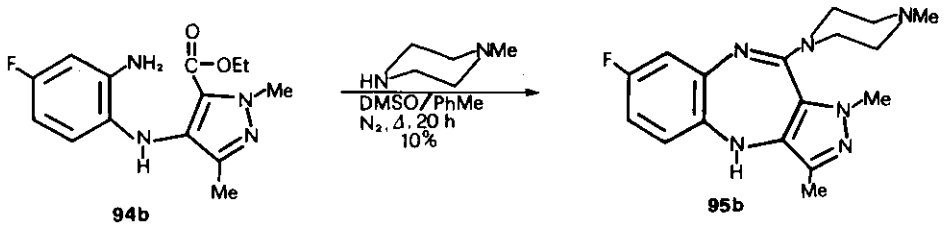
93

Cyclization of ethyl 4-(2-aminoanilino)pyrazole-3-carboxylates (**94a**) with N-methylpiperazine in the presence of $TiCl_4$ and anisole afforded amidino derivatives (**95a**).[69]



94a 95a

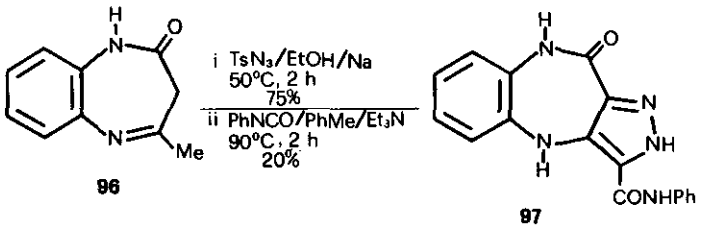
Similarly, 1,3-dimethyl isomer (**95b**) was obtained in lower yield by reaction of **94b** with N-methylpiperazine in different experimental conditions.



94b 95b

2,10-Dihydropyrazolo[4,3-b][1,5]benzodiazepin-4(5H)-one (**97**) has been synthesized from 1,5-benzodiazepin-2-one (**96**): reaction with tosyl azide

occurs at the cyclic methylene group to afford a 3-diazo derivative, which, by reaction with phenyl isocyanate, gave compound (**97**).[75]

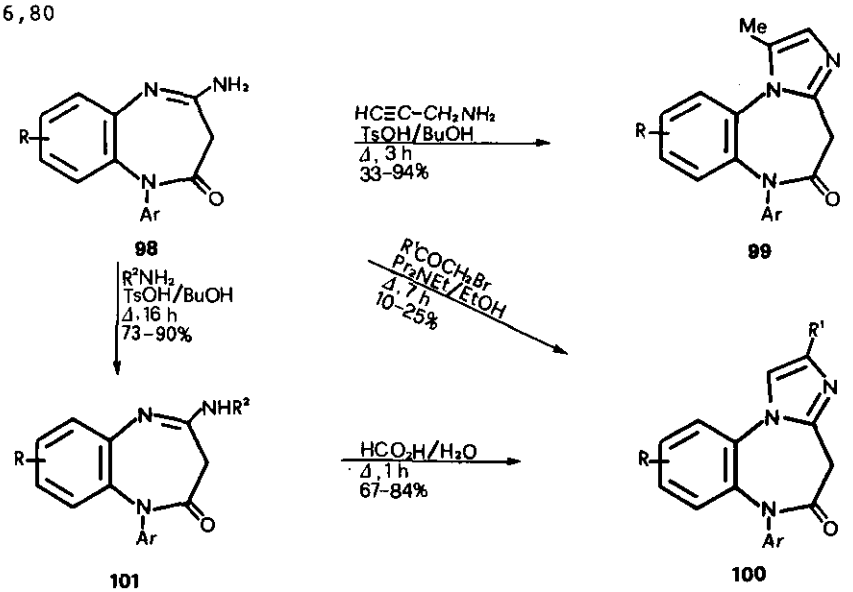


96 **97**

4.5 **Imidazo-1,5-benzodiazepines**

A series of 6-phenyl-4H-imidazo[1,2-a][1,5]benzodiazepin-5(6H)-ones were synthesized and evaluated for CNS activity.[76-80]

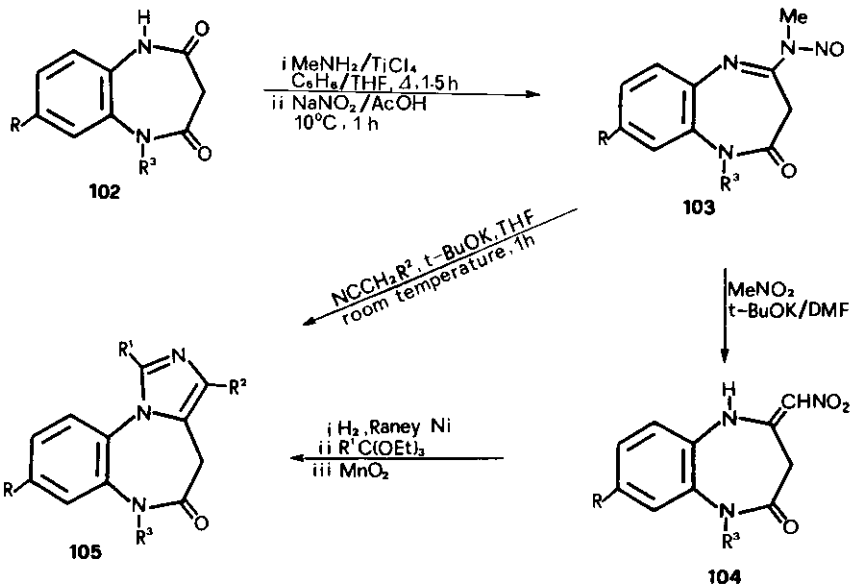
Treatment of 4-amino-1,3-dihydro-1-phenyl-2H-1,5-benzodiazepin-2-ones (**98**) with propargylamine[76-78] in the presence of p-toluenesulfonic acid or with α-bromo ketone[77,79] gave **99** and **100** respectively. The latter compounds were also synthesized by treatment of **98** with α-amino aldehyde acetal, to give the amidine derivatives (**101**), followed by their cyclization in formic acid.[76,80]



98 **99** **101** **100**

R= H, 8-Cl, 8-CF_3, 9-CF_3
R^1= H, Me, Et, Pr
R^2= $CH_2CH(OMe)_2$, $MeC(OEt)_2$, $MeCH_2CH(OEt)_2$
Ar= Ph, 2-FC_6H_4

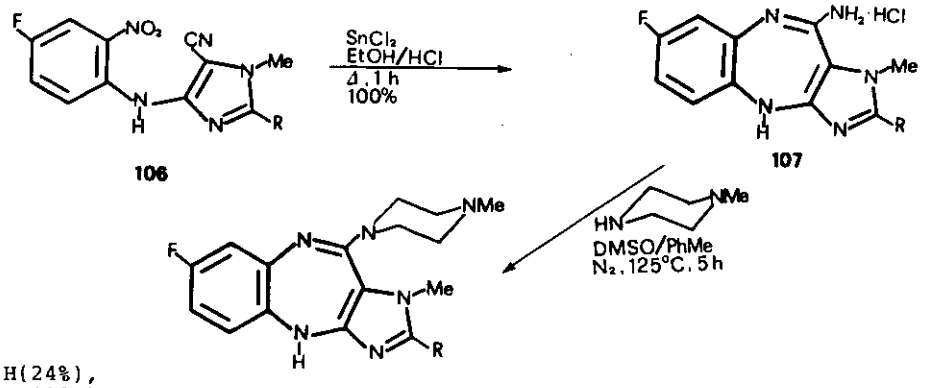
Imidazo[1,5-a][1,5]benzodiazepin-5(6H)-ones (**105**) and their 3,3a-dihydro-derivatives, useful as anxiolytics, anticonvulsants, muscle relaxants and sedatives, were prepared by amination of benzodiazepinedione (**102**) with methylamine in presence of $TiCl_4$ and following nitrosation to give nitroso-amines (**103**).[81] Compounds (**103**), treated with $MeNO_2$ and potassium t-butoxide gave (Z/E)-nitromethylene derivatives (**104**) which were hydrogenated (H_2, Raney Ni), cyclized with $RC(OEt)_3$ and dehydrogenated with MnO_2 to afford imidazo[1,5-a][1,5]benzodiazepin-5(6H)-ones (**105**), also prepared by reaction of **103** with $CNCH_2R^2$ in the presence of potassium t-butoxide.[82,83]



102 **103** **104** **105**

R = H, Cl, Br, I, NO_2
R^1= H, Me
R^2= H, CO_2Me, CO_2Et, $CONMe_2$
R^3= Ph, 2-ClC_6H_4, 2-FC_6H_4, 2-pyridyl

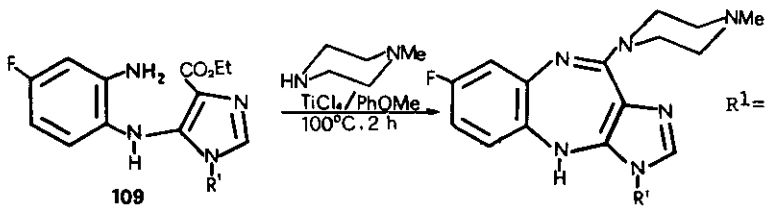
Two isomeric 4H-imidazo[4,5-b][1,5]benzodiazepine series have been synthesized:[84] compounds (**108**), 1-methyl and 1,2-dimethyl substituted, were prepared from the appropriate 4-(2-nitroanilino)imidazole-5-carbonitrile (**106**), by reduction and cyclization to the cyclic amidines (**107**) and successive transamination with N-methylpiperazine.



106 107 108

R = H(24%), Me(12%)

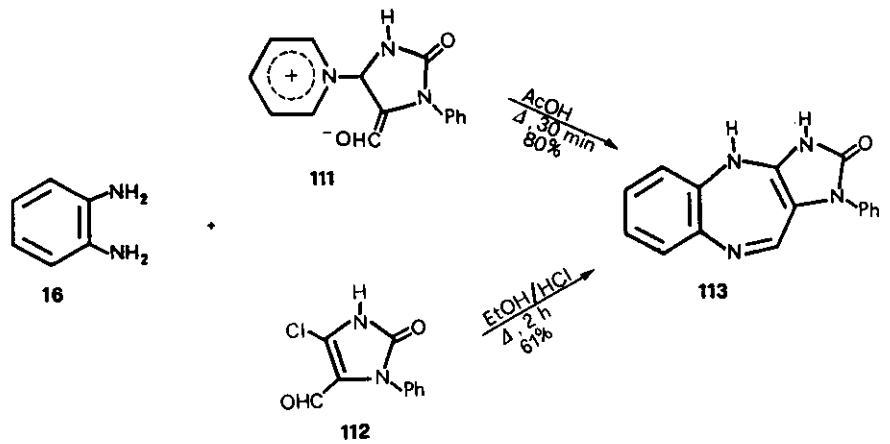
Similarly, 3-alkyl substituted imidazo[4,5-b][1,5]benzodiazepines (**110**) were prepared from the appropriate ethyl 4-(2-aminoanilino)imidazole-5-carboxylate (**109**) with an excess of N-methylpiperazine and $TiCl_4$ in refluxing anisole. The antidopaminergic and anticholinergic activites of imidazobenzodiazepine derivatives have been also examined but no compound showed reproducible activity.[84]



109 110

R^1= Me(83%), Et(30%), cyclohexyl(52%)

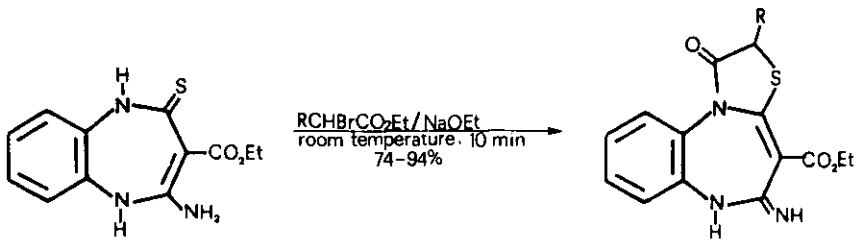
Imidazo[4,5-b][1,5]benzodiazepin-2(1H)-one (**113**) was obtained by treatment of o-phenylenediamine (**16**) with betaine (**111**) or with 5-chloro-2-oxo-3-phenylimidazoline-4-carboxaldehyde (**112**).[85]



16 111 112 113

4.6 **Thiazolo-1,5-benzodiazepines**

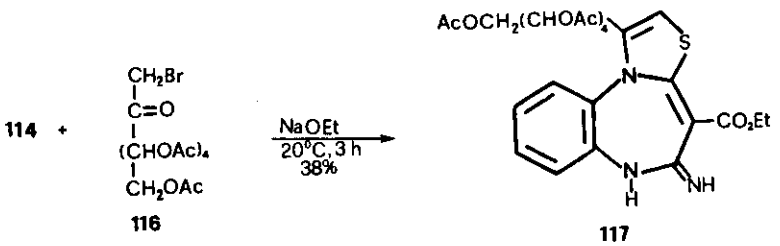
5-Imino-1-oxo-1,2,5,6-tetrahydrothiazolo[3,2-a][1,5]benzodiazepine-4-carboxylates (**115**) were prepared by cyclization of 2-amino-4,5-dihydro-4-thioxo-1,5-benzodiazepin-3-carboxylates (**114**) with α-halo esters.[86,87]



114 **115**

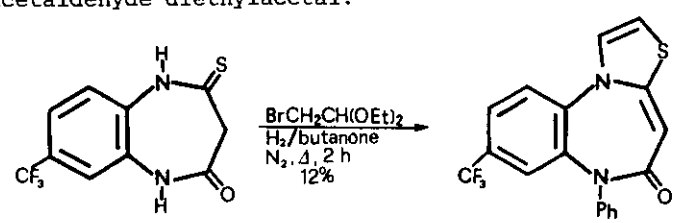
R = H, Me, Et

The cyclocondensation of **114** with 3,4,5,6,7-penta-O-acetyl-1-bromo-1-deoxy-D-galactoheptulose (**116**) afforded the 5,6-dihydrothiazolo[3,2-a][1,5]benzodiazepine-4-carboxylate (**117**).[88]



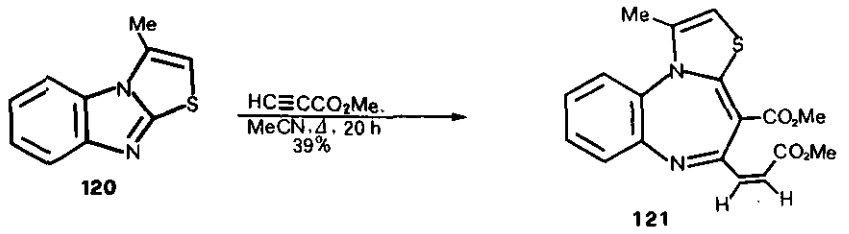
116 **117**

Similarly, 5,6-dihydrothiazolo[3,2-a][1,5]benzodiazepin-5-one (**119**) was prepared from the corresponding thioxobenzodiazepinone (**118**) by reaction with bromoacetaldehyde diethylacetal.[76]



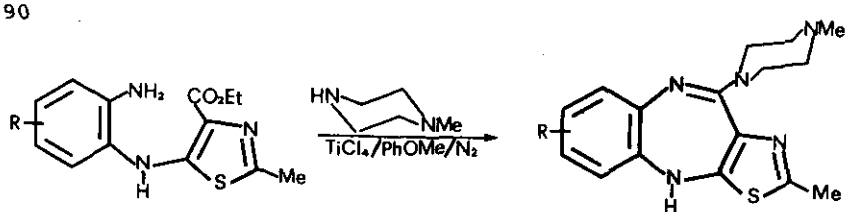
118 **119**

A different approach involved the cycloaddition of 3-methylthiazolo[3,2-a]-benzimidazole (**120**) with methyl propiolate in refluxing MeCN to give the Z-isomer of thiazolo[3,2-a][1,5]benzodiazepine (**121**).[89]



120 121

4H-Thiazolo[5,4-b][1,5]benzodiazepines were synthesized, as potential central nervous system agents, by reacting amino esters (122) with a mixture of $TiCl_4$, N-methylpiperazine and anisole under nitrogen to give 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thiazolo[5,4-b][1,5]benzodiazepines (123).[90]

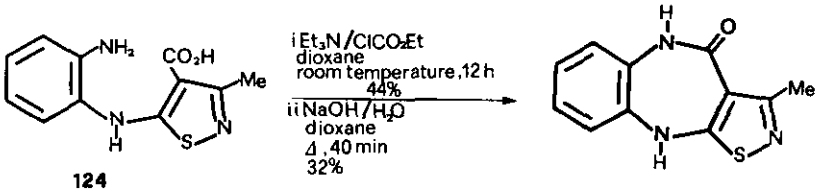


122 123

R = H, 7-Cl, 6-F, 7-F

4.7 Isothiazolo-1,5-benzodiazepines

Only one example of this class of annelated 1,5-benzodiazepines is reported.[91] Isothiazolo[5,4-b][1,5]benzodiazepine (125) was prepared by cyclization of 5-(2-aminoanilino)-3-methylisothiazole-4-carboxylic acid (124).

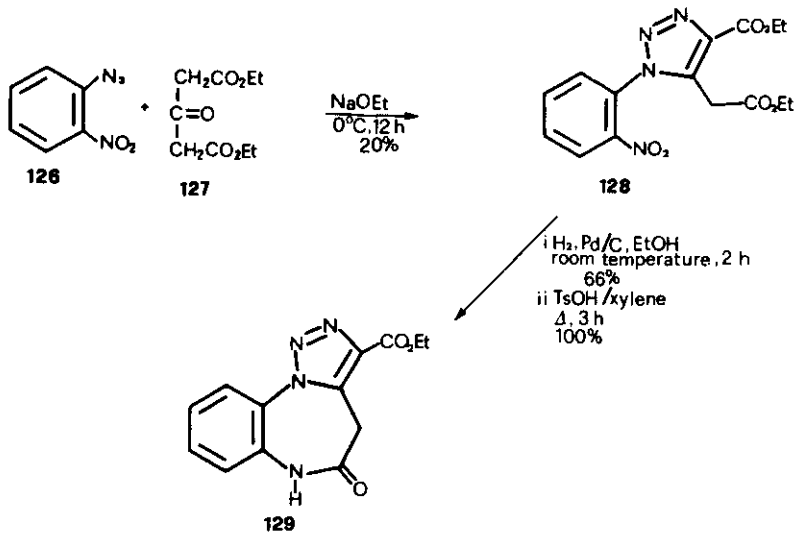


124 125

4.8 Triazolo-1,5-benzodiazepines

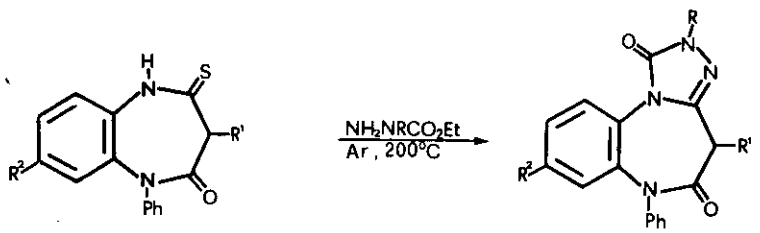
5,6-Dihydro-4H-[1,2,3]triazolo[1,5-a][1,5]benzodiazepin-5-one (129) was prepared by reaction of acetone dicarboxylate (127) with 2-nitrophenyl-azide (126) in the presence of sodium ethoxide to give ethyl 4-(ethoxy-carbonyl)-1-(2-nitrophenyl)-1,2,3-triazole-5-acetate (128). Catalytic hydrogenation furnished the corresponding amine, which on heating in the

presence of a catalytic amount of p-toluenesulfonic acid, underwent cyclization to [1,2,3]triazolo[1,5-a][1,5]benzodiazepinone (**129**).[92]



126 **127** **128** **129**

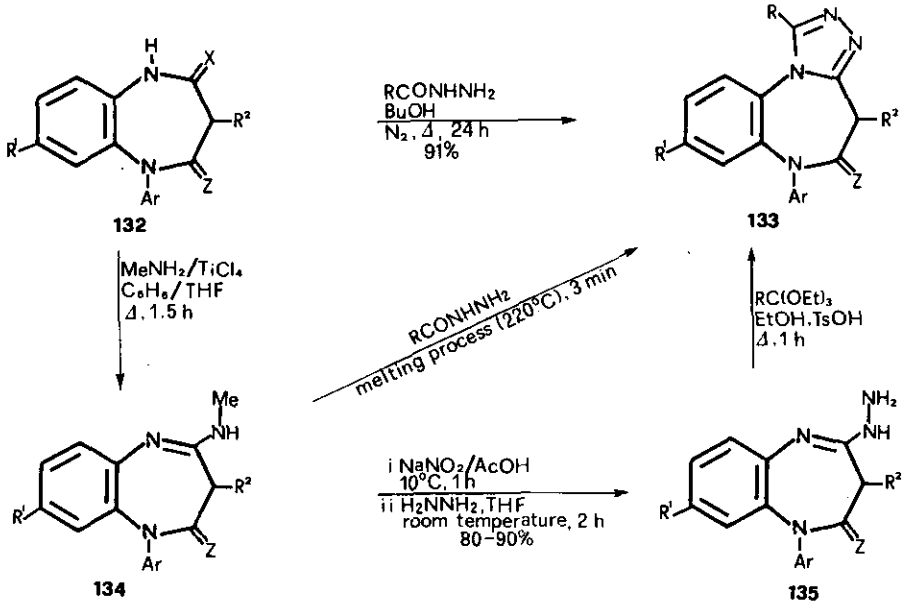
2,4-Dihydro-1H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-1,5(6H)-diones (**131**), useful as a tranquilizing, muscle relaxant, were prepared heating under argon benzodiazepine-2-thione derivatives **130** with NH_2NRCO_2Et.[93]



130 **131**

R = H, Me, $(CH_2)_3NH_2$, $CH_2CHMeNHMe$, Ph
R^1= H, OH, OAc
R^2= Cl, MeSO, $MeSO_2$, NH_2, NHAc, NO_2

The condensation of various benzodiazepinediones or thiones (**132**) with hydrazides gave [1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5-ones or thiones (**133**).[76,94-96] Alternatively, compounds (**133**) were obtained from **132** by treatment with methylamine to give compound (**134**), which was nitrosated, treated with hydrazine to give **135** and cyclized with $RC(OEt)_3$ to give **133**. Furthermore, treatment of **134** with $RCONHNH_2$ gave **133** directly.[97]

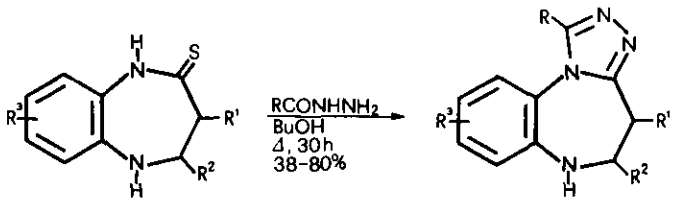


132 133 134 135

X = Z = O, S
R = H, Me, Et, i-Pr, CH_2OH, CH_2Cl, cyclohexyl, Ph
R^1= H, Cl, Br, CF_3, Me, MeO, NO_2, NH_2
R^2= H, Me
Ar = Ph, 2-ClC_6H_4, 2-FC_6H_4, 2-$CF_3C_6H_4$

Two derivatives (**133**) (X=O, R=H, R^1=Cl, CF_3, Ar=2-ClC_6H_4) showed anticonvulsant activity without clinical toxicity.[98] Several derivatives of this class of benzodiazepines were evaluated as platelet activating-factor (PAF) antagonists.[99]

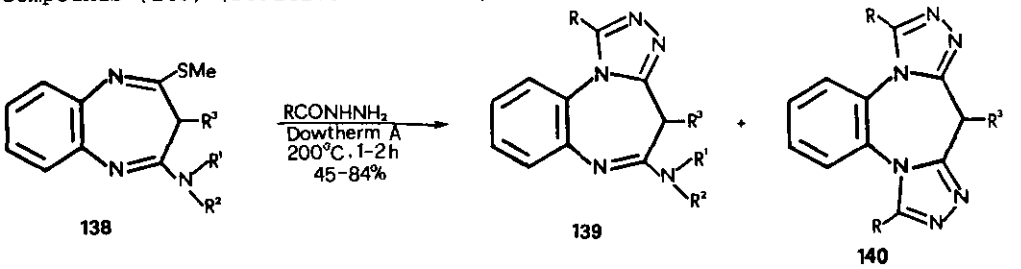
The same synthetic procedure was employed to obtain 5,6-dihydro-4H-[1,2,4]-triazolo[4,3-a][1,5]benzodiazepines (**137**) by reaction of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-thiones (**136**) with hydrazides.[100-102]



136 137

R = Ph, 3-Py, 4-Py, 4-ClC_6H_4, 2-$MeOC_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl
R^1= H, R^2= Me
R^1= Me, R^2= H
R^3= H, 8-Cl, 9-Cl, 8,9-Cl_2, 9-MeO

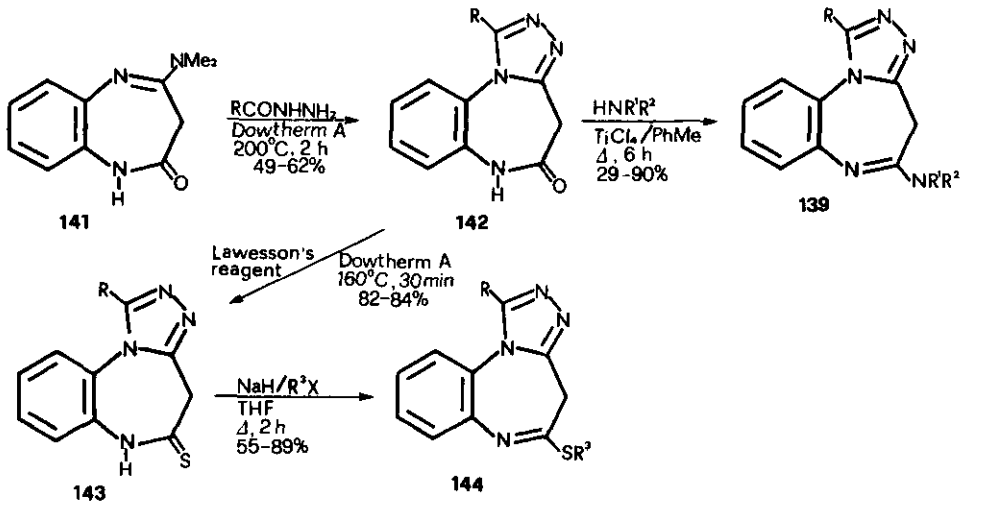
Another pathway to N,N-disubstituted 4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5-amines (**139**) has been described.[103] The reaction of N,N-disubstituted 4-methylthio-3H-1,5-benzodiazepin-2-amines (**138**) with hydrazides afforded derivatives (**139**) along with lower amounts of tetracyclic compounds (**140**) (relative ratio 3:1).



138 **139** **140**

R = H, Me, Ph
NR^1R^2= Me_2N, Et_2N, pyrrolidinyl
R^3 = H, Me

Benzodiazepines (**139**) were also obtained in a two step synthetic route by cyclocondensation of 1,2-dihydro-3H-4-dimethylamino-1,5-benzodiazepin-2-one (**141**) with hydrazides to give triazolobenzodiazepinones (**142**), which were in turn reacted with suitable primary or secondary amines, in the presence of $TiCl_4$, to give the desired 5-amino derivatives (**139**).[104]

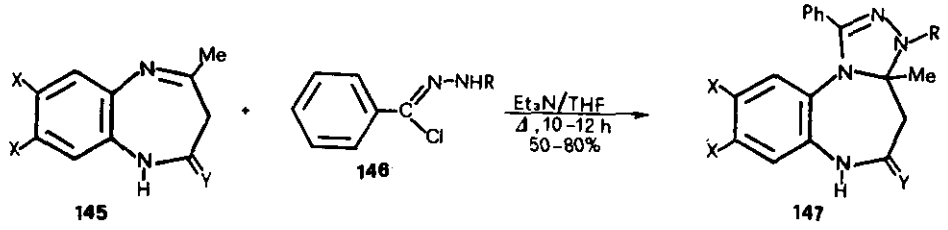


141 **142** **139** **143** **144**

R = H, Me, Ph
NR^1R^2= NHMe, NHEt, NHcyclopropyl, NPr_2, NBu_2, N(allyl)$_2$, morpholinyl, piperidinyl, 4-phenylpiperidinyl, 4-methylpiperazinyl, 4-carbethoxypiperazinyl
R^3= Me, Pr, CH_2CO_2Et

When compounds (**142**) were treated with Lawesson's reagent thiolactams (**143**) were obtained, which then reacted with NaH and proper alkyl halides to yield the 5-alkylthio derivatives (**144**).[104] A number of compounds (**139**) and (**140**) and 5-alkylthioderivatives (**144**) were tested for their analgesic, antinflammatory[103] and anticonvulsant[104] properties and some of them showed significant activity.

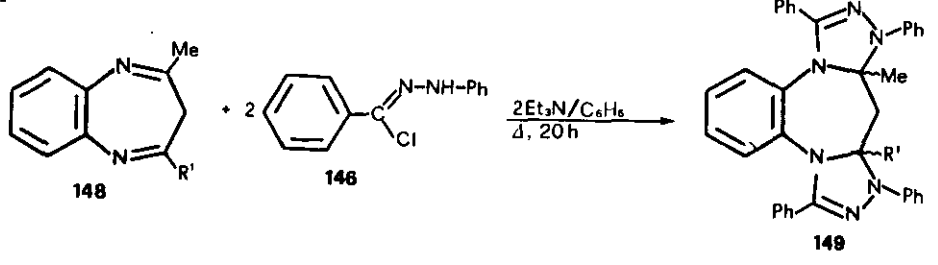
The reaction of 2,3-dihydro-1H-1,5-benzodiazepines (**145**) with benzonitrile N-phenyl- or N-ethoxycarbonylimine, generated *in situ* from the hydrazonic chlorides (**146**), afforded 3a,4,5,6-tetrahydro-3H-[1,2,4]triazolo[4,3-a]-[1,5]benzodiazepines (**147**).[105]



145 **146** **147**

X = H, Cl
Y = O, 2xMe
R = Ph, CO_2Et

Analogously, 3a,4,4a,5-tetrahydro-3H-bis[1,2,4]triazolo[4,3-a:3',4'-d][1,5] benzodiazepines (**149**) were prepared from 3H-1,5-benzodiazepines (**148**) and benzonitrile N-phenylimine, obtained *in situ* from hydrazonic chloride (**146**).[105] The stereochemistry of the asymmetric centers has not been reported.

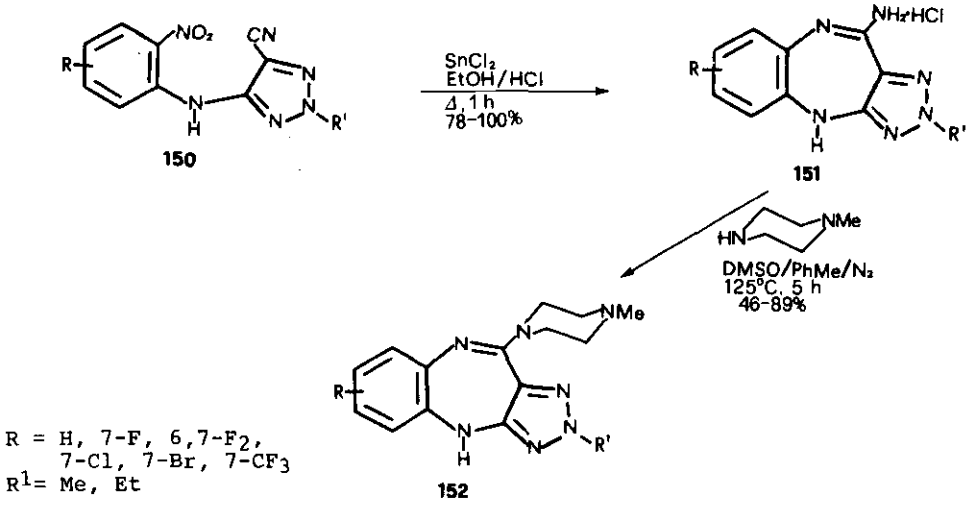


148 **146** **149**

R^1= Me(65%), Ph(70%)

Two series of 4H-1,2,3-triazolo[4,5-b][1,5]benzodiazepin-10-amines (**151**), 2-alkyl and/or 3-alkyl substituted, are known. The synthesis of these compounds was carried out by reducing and cyclizing 4-(2-nitroanilino)-2H-

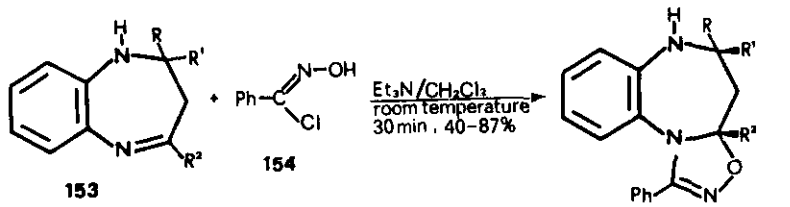
[1,2,3]triazolo-5-carbonitrile (**150**) with $SnCl_2$ in the presence of hydrochloric acid.[84,106] Transamination of the obtained amidines (**151**) with N-methylpiperazine gave the corresponding 10-piperazinyl-4H-[1,2,3]triazolo [4,5-b][1,5]benzodiazepines (**152**), some of which show antipsychotic activity.



R = H, 7-F, 6,7-F_2, 7-Cl, 7-Br, 7-CF_3
R^1= Me, Et

4.9 Oxadiazolo-1,5-benzodiazepines

A one-pot synthetic approach to the novel [1,2,4]oxadiazolo[4,5-a][1,5]-benzodiazepine system has been reported.[107] 1,3-Dipolar cycloaddition of benzonitrile oxides, generated in situ from benzohydroxamoyl chloride (**154**) and triethylamine, to 1,5-benzodiazepines (**153**) gave 3a,4,5,6-tetrahydro-1,2,4-oxadiazolo[4,5-a][1,5]benzodiazepines (**155**) in good yields.



R+R^1=O, R^2=Me
R+R^1=O, R^2=Ph
R=R^1=R^2=Me
R=H, R^1=Ph, R^2=Me
R=Ph, R^1=H, R^2=Me

The anticonvulsant activity and the potency of various 1,5-benzodiazepine and oxadiazolo[4,5-a][1,5]benzodiazepine derivatives to inhibit [^{3}H]-flunitrazepam binding was evaluated.[108]

REFERENCES

1. M. Ghulam, S. R. Padala, A. Khalil, and V. R. Chengalva, Heterocycles, 1986, **24**, 3489.
2. J. W. H. Watthey and J. L. Stanton, Chemistry of Heterocyclic Compounds, ed. by A. Weissberger and E.C. Taylor, Wiley, New York, 1984, **43**, 1.
3. M. Takahashi, T. Takada, and T. Sakagami, J. Heterocycl. Chem., 1987, **24**, 797.
4. R. Achour, E. M. Essassi, M. Salem, and R. Zniber, Bull. Soc. Chim. Belg., 1989, **98**, 405.
5. E. Cortes and R. Martinez, J. Heterocycl. Chem., 1983, **20**, 161.
6. M. Soriano-Garcia, R. A. Toscano, E. Cortes, and R. Martinez, Acta Crystallogr., Sect. C: Cryst. Struct. Commun., 1984, **C40**, 1460.
7. E. Cortes, R. Martinez, and I. Ceballos, J. Heterocycl. Chem., 1989, **26**, 119.
8. E. Cortes, R. Martinez, and R. Hernandez, Org. Mass Spectrom., 1989, **24**, 276.
9. M. Soriano-Garcia, R. A. Toscano, E. Cortes, M. C. Romero and I. Ceballos, Acta Crystallogr., Sect. C: Cryst. Struct. Commun., 1987, **C43**, 269.
10. F. Chimenti, S. Vomero, R. Giuliano, and M. Artico, Il Farmaco, Ed.Sc., 1977, **32**, 339.
11. M. C. Aversa, P. Giannetto, A. Ferlazzo, and G. Bruno, J. Chem. Soc., Perkin Trans. 2, 1986, 1533.
12. M. K. Eberle and W. J. Houlihan, Ger. Offen. 2,050,344 (1971) (Chem. Abstr., 1971, **75**, 49157).
13. J. Senn-Bilfinger, R. Riedel, H. Schaefer, and K. Klemm, Eur. Pat. Appl. EP 57,428 (1982) (Chem. Abstr., 1982, **97**, 216248).
14. W. Engel, G. Trummlitz, W. Eberlein, G. Mihm, G. Schmidt, R. Hammer, and A. Giachetti, Ger Offen DE 3,409,237 (1985) (Chem. Abstr., 1986, **104**, 129934).
15. W. Engel, W. Eberlein, G. Mihm, G. Trummlitz, N. Mayer, and A. De Jonge, Ger Offen DE 3,643,666 (1988) (Chem. Abstr., 1989, **110**, 39029).

16. W. Eberlein, W. Engel, G. Trummlitz, G. Mohm, N. Mayer, and H. Doods, Eur. Pat. Appl. EP 312,895 (1989) (Chem. Abstr., 1989, **111**, 214513).
17. K. Matsuo and K. Tanaka, Chem. Pharm Bull., 1984, **32**, 3724.
18. K. Matsuo, S. Takada, J. Thoue, and K. Tanaka, Yakugaku Zasshi, 1986, **106**, 715.
19. M. Augustin and P. Jeschke, Synthesis, 1987, 937.
20. B. Bobranski, W. Roman, and E. Wagner, Il Farmaco, Ed.Sc., 1971, **26**, 3.
21. E. Wagner, Rocz. Chem., 1974, **48**, 1289.
22. E. Wagner, Pol. J. Chem., 1982, **56**, 131.
23. E. Wagner, Pol. J. Chem., 1982, **56**, 1027.
24. Z. Kleinrok, K. Kolasa, and G. Szursga, Pol. J. Pharmacol. Pharm., 1980, **32**, 247.
25. G. Viti, D. Giannotti, R. Nannicini, R. Renzo, and V. Pestellini, J. Heterocycl. Chem., 1990, **27**, 1369.
26. J. K. Chakrabarti and D. E. Tupper, Ger. Offen. 2,552,403 (1976) (Chem. Abstr., 1977, **86**, 29893).
27. J. K. Chakrabarti, T. A. Hicks, T. M. Hotten, and D. E. Tupper, J. Chem. Soc., Perkin Trans. 1, 1978, 937.
28. Lilly Industries Ltd., Brit. 1,533,236, (1978), (Chem. Abstr., 1979, **91**, 57065).
29. J. K. Chakrabarti, L. Horsman, T. M. Hotten, A. I. Pullar, D. E. Tupper, and F. C. Wright, J. Med. Chem., 1980, **23**, 878.
30. J. K. Chakrabarti, T. M. Hotten, S. E. Morgan, A. I. Pullar, D. M. Rackham, F. C. Risius, S. Wedley, M. O. Chaney, and N. D. Jones, J. Med. Chem., 1982, **25**, 1133.
31. H. G. Schauzu and P. P. Mager, Pharmazie, 1983, **38**, 562.
32. R. W. Fuller and N. R. Mason, Res. Commun. Chem. Pathol. Pharmacol., 1986, **54**, 23.
33. R. W. Fuller and H. D. Snoddy, J. Pharm. Pharmacol., 1985, **37**, 755.
34. H. R. Sullivan and R. B. Franklin, Drug Metab. Dispos., 1985, **13**, 276.
35. J. K. Chakrabarti, J. Fairhurst, N. J. A. Gutteridge, L. Horsman, A.I. Pullar, C. W. Smith, D. J. Steggles, D. E. Tupper, and F. C. Wright, J. Med. Chem., 1980, **23**, 884.

36. O. Hromatka, D. Binder and K. Eichinger, Monatsh. Chem., 1975, **106**, 375.

37. S. R. Safir, U.S. 3,953,430 (1976) (Chem. Abstr., 1976, **85**, 33101).

38. S. R. Safir, U.S. 4,007,272 (1977) (Chem. Abstr., 1977, **86**, 190031).

39. American Cyanamid Co., Neth. Appl. 76 01,766 (1976) (Chem. Abstr., 1977, **87**, 23344).

40. J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E.N. Greenblatt, and S. R. Safir, J. Med.Chem., 1979, **22**, 725.

41. V. Figala, R. Riedel, G. Rainer, and K. Klemm, Eur. Pat. Appl. EP 39,519 (1981) (Chem. Abstr., 1982, **96**, 104288).

42. V. Figala and M. Ecker, Ger. Offen. DE 3,833,521 (1989) (Chem. Abstr., 1989, **111**, 97295).

43. G. Schmidt, W. Eberlein, W. Engel, G. Trummlitz, R. Hammer, and P. Del Soldato, Ger. Offen. 3,204,153 (1983) (Chem. Abstr., 1983, **99**, 175814).

44. W. Engel, G. Schmidt, W. Eberlein, G. Trummlitz, R. Hammer, and P. Del Soldato, Ger. Offen. 3,204,169 (1983) (Chem. Abstr., 1983, **99**, 175817).

45. W. Engel, G. Trummlitz, W. Eberlein, G. Mihm, N. Mayer, A. De Jonge and K. Rudolf, Ger. Offen. 3,726,908 (1989) (Chem. Abstr., 1989, **111** 214512).

46. G. Mihm, W. Eberlein, W. Engel, G. Trummlitz, N. Mayer, A. De Jonge and H. Doods, Ger. Offen. 3,820,346 (1989) (Chem. Abstr., 1990, **113**, 40739).

47. J. B. Press, C. M. Hofmann, and S. R. Safir, J. Heterocycl. Chem., 1980, **17**, 1361.

48. H. J. Brabander, J. W. Epstein, and L. S. Crawley, U.S. 4,168,269 (1979) (Chem. Abstr., 1980, **92**, 42002).

49. M. Eltze, S. Goenne, R. Riedel, B. Schlotke, C. Schudt, and W. A. Simon, Eur. J. Pharmacol., 1985, **112**, 211.

50. P. Muller, H. Dammann, and B. Simon, Z. Gastroenterol., 1986, **24**, 152.

51. W. Londong, V. Londong, A. Meierl, and U. Voderholzer, Gut, 1987, **28**, 888. (Chem. Abstr., 1988, **108**, 31699).

52. C. Schudt, C. Auriga, B. Kinder, and N. J. M. Birdsall, Eur. J. Pharmacol., 1988, **145**, 87.

53. H. N. Doods, D. Davidesko, A. De Jonge, and P. A. Van Zwieten, Cell.

Mol. Basis. Cholinergic Funct., ed. by M. J. Dowdall and J. N. Hawthorne, Horwood, Chichester, UK, 1987, p. 79.

54. W. Eberlein, W. Engel, G. Trummlitz, G. Schmidt, and R. Hammer, J. Med. Chem., 1988, **31**, 1169.
55. W. Kromer, E. Baron, M. Beinborn, R. Boer, and M. Eltze, Naunyn-Schmiedeberg's Arch. Pharmacol., 1990, **341**, 165.
56. C. Forray and E. El-Fakahany, Mol. Pharmacol., 1990, **37**, 893.
57. W. Kromer, S. Goenne, R. Riedel, and S. Postius, Pharmacology, 1990, **41**, 333.
58. W. Kromer, E. Baron, R. Boer, and M. Eltze, Naunyn-Schmiedeberg's Arch. Pharmacol., 1991, **343**, 7.
59. R. Feifel, J. R. de Miranda, C. Strohmann, R. Tacke, A. Assen, E. Mutschler, and G. Lambrecht, Eur. J. Pharmacol., 1991, **195**, 115.
60. F. Christofi, J. Palmer, and J. Wood, Eur. J. Pharmacol., 1991, **195** 333.
61. A. M. Laties and A. R. Stone, PCT Int. Appl. WO 90 15,604 (1990) (Chem. Abstr., 1991, **114**, 240640).
62. M. Eltze, Eur. J. Pharmacol., 1990, **180**, 161.
63. F. Lauterbach, J. Pharmacol. Exp. Ther., 1987, **243**, 1121.
64. S. R. Safir, U.S. 3,951,981 (1976) (Chem. Abstr., 1976, **85**, 21498).
65. S. R. Safir, U.S. 4,087,421 (1978) (Chem. Abstr., 1978, **89**, 109615).
66. R. Lattrell, W. Bartmann, C. Jochum, J. Musil, and E. Granzer, Ger. Offen. 2,707,270 (1978) (Chem. Abstr., 1979, **90**, 54993).
67. Zeria Shinyaku Kogyo K.K., Jpn. Kokai Tokkyo Koho JP 58,103,389 (1983) (Chem. Abstr., 1983, **99**, 122499).
68. J. K. Chakrabarti and T. M. Hotten, Eur. Pat. Appl. 27,390 (1981) (Chem. Abstr., 1981, **95**, 169232).
69. J. K. Chakrabarti, T. M. Hotten, A. Pullar, and N. C. Tye, J. Med. Chem., 1989, **32**, 2573.
70. G. Roma, A. Balbi, A. Ermili, and E. Vigevani, Il Farmaco, Ed. Sci., 1983, **38**, 546.
71. V. N. Proshkina, Z. F. Solomko, and N. Y. Bozhanova, Khim. Geterotsikl. Soedin., 1988, 1288.

72. A. K. El-Shafei, H. S. El-Kashef, and A. M. El-Khawaga, Indian J. Chem., Sect. B, 1982, **21**, 655.

73. G. Rainer, R. Riedel, K. Klemm, and M. Eltze, Ger. Offen. 3,029,281 (1981) (Chem. Abstr., 1981, **95**, 43186).

74. Byk-Gulden Lomberg Chemische Fabrik G.m.b.H., Ger. Offen. DE 3,113,222 (1982) (Chem. Abstr., 1982, **97**, 216167).

75. L. Capuano and K. Gaertner, J. Heterocycl. Chem., 1981, **18**, 1351.

76. A.Chow, R. Gyurik, and R. Parish, J. Heterocycl. Chem., 1976, **13**, 163.

77. T. Hara, H. Fujimori, Y. Kayama, T. Mori, K. Ito, and Y. Hashimoto, Chem. Pharm. Bull., 1977, **25**, 2584.

78. T. Hara, Y. Kayama, H. Fujimori, K. Ito, T. Mori, T. Suminami, and Y. Hashimoto, Japan Kokai 77 93,795 (1977) (Chem. Abstr. 1978, **88**, 22992).

79. T. Hara, K. Ito, Y. Kayama, H. Fujimori, T. Mori, T. Kakunan, and Y. Ichikawa, Japan Kokai 77,128,397 (1977) (Chem. Abstr. 1978, **88**, 89726).

80. T. Hara, Y. Kayama, H. Fujimori, and T. Kadonami, Japan Kokai 78 73,600 (1978) (Chem. Abstr., 1978, **89**, 197615).

81. A. Walser and R. I. Fryer, U.S. 4,080,233 (1978) (Chem. Abstr., 1978, **89**, 59906).

82. A. Walser, Ger. Offen. 2,813,549 (1978) (Chem. Abstr., 1979, **90**, 23054).

83. F. Hoffmann-La Roche and Co., Neth. Appl. 78 03,585 (1978) (Chem. Abstr., 1979, **90**, 152254).

84. J. K. Chakrabarti, T. M. Hotten, A. I. Pullar, and D. J. Steggles, J. Med. Chem., 1989, **32**, 2375.

85. R. O. Kochkanyan, A. N. Zaritovskii, A. B. Kruglova, and N. A. Klyuev, Khim. Geterotsikl. Soedin., 1986, 233.

86. K. Peseke, Ger. (East) 105,235 (1974) (Chem. Abstr., 1974, **81**, 169568).

87. K. Peseke, Tetrahedron, 1976, **32**, 483.

88. K. Peseke, I. Farkas, and A. Kerber, Pharmazie, 1986, **41**, 548.

89. N. Abe and T. Nishiwaki, Heterocycles, 1981, **16**, 537.

90. J. K. Chakrabarti and T. M. Hotten, Eur. Pat. Appl. EP 354,871 (1990) (Chem. Abstr., 1990, **113**, 115344).

91. S. Rajappa and R. Sreenivasan, Indian J. Chem., Sect. B, 1976, **14**, 394.

92. R. K. Smalley and M. Teguiche, Synthesis, 1990, 654.

93. B. Vogt, Ger. Offen. 2,447,731 (1975) (Chem. Abstr., 1975, **83**, 43397).

94. A. Bauer, K. H. Weber, P. Danneberg, and F. Kuhn, Ger. Offen. 2,813,673 (1974) (Chem. Abstr., 1975, **82**, 57747).

95. R. B. Moffett and B. V. Kamdar, Ger. Offen. 2,444,755 (1975) (Chem. Abstr., 1975, **83**, 58896).

96. R. B. Moffett and B. V. Kamdar, and P. F. Von Voigtlander, J. Med. Chem. 1976, **19**, 192.

97. R. I. Fryer, L. H. Sternbach, and A. Walser, U.S. 4,111,934 (1978) (Chem. Abstr., 1979, **90**, 152253).

98. B. Meldrum and R. Horton, Psichopharmacology (Berlin), 1979, **60**, 277.

99. J. Casals-Stenzel, K. Weber, G. Walther, A. Harreus, and G. Muacevic, Ger. Offen. DE 3,435,972 (1986) (Chem. Abstr., 1986, **105**, 120760).

100. E. Szarvasi, M. Grand, J. C. Depin, and A. Betbeder-Matibet, Eur. J. Med. Chem., 1978, **13**, 113.

101. E. Szarvasi, Ger.Offen. 2,409,308 (1974) (Chem. Abstr., 1975, **82**, 4328).

102. A. Nawojski, W. Nawrocka, M. Wilimowski, K. Orzechowska-Juzwenko, J. Barczynska, L. Kedzierska, W. Wojewodzki, E. Przybylska, and J. Felsztynska, Pol. J. Pharmacol. Pharm., 1979, **31**, 615.

103. M. Di Braccio, G. Roma, G. C. Grossi, M. Ghia, and E. Mereto, Eur. J. Med. Chem., 1990, **25**, 681.

104. M. Di Braccio, G. Roma, G. Grossi, M. Ghia, and F. Mattioli, Eur. J. Med. Chem., 1991, **26**, 489.

105. M. C. Aversa, A. Ferlazzo, P. Giannetto, and F. H. Kohnke, Synthesis, 1986, 230.

106. J. K. Chakrabarti, T. M. Hotten, and D. J. Steggles, Eur. Pat. Appl. EP 54,416 (1982) (Chem. Abstr., 1982, **97**, 182468).

107. A. Chimirri, S. Grasso, R. Ottanà, G. Romeo, and M. Zappalà, J. Heterocycl. Chem., 1990, **27**, 371.

108. G. B. De Sarro, M. Zappalà, S. Grasso, A. Chimirri, C. Spagnolo, and A. De Sarro, Molecular Neuropharmacology, 1992, **1**, 195.

Received, 3rd April, 1992