ANNELATED 1,5-BENZODIAZEPINES. Part II[1]. SIX MEMBERED RINGS

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Abstract - This review describes the synthetic approaches to mono and diannelated 1,5-benzodiazepines with six-membered ring fused to different edges of the 1,5-benzodiazepine skeleton.

INTRODUCTION

A number of papers and patents concerning the chemistry and the biological activity of 1,4- and 1,5-benzodiazepines containing an additional heterocyclic ring fused to different positions of the heptatomic nucleus have appeared in literatures.

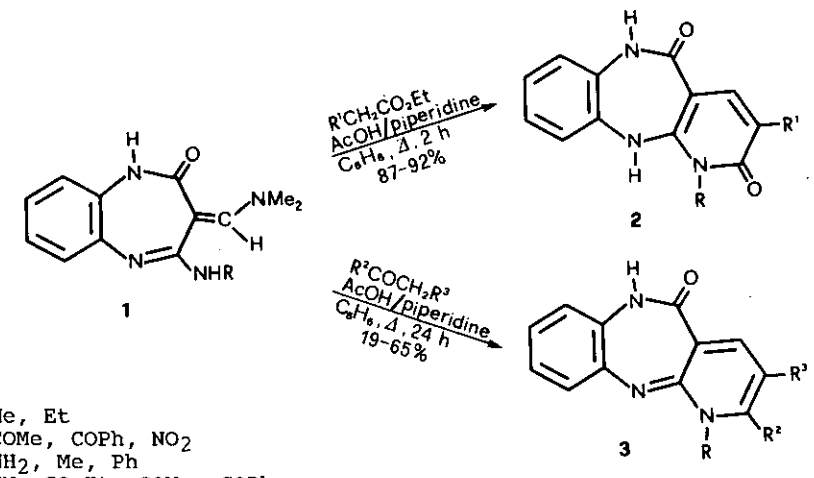
The present review complements our previous review[1] concerning heterocycle fused benzodiazepine ring system and is addressed to mono and diannelated 1,5-benzodiazepines fused to six membered rings.

Pyrido-, quino-, pyrano-, benzopyrano-, pyrimido-, pyrazino- quinoxalino-, and oxazino-1,5-benzodiazepines are reported in literature.

1. Pyrido-1,5-benzodiazepines

Two general synthetic routes towards the pyrido[2,3-b][1,5]benzodiazepine ring system have been exploited, starting from a preformed 1,5-benzodiazepine nucleus or from 1,2-phenylenediamine and nicotinic acid derivatives.

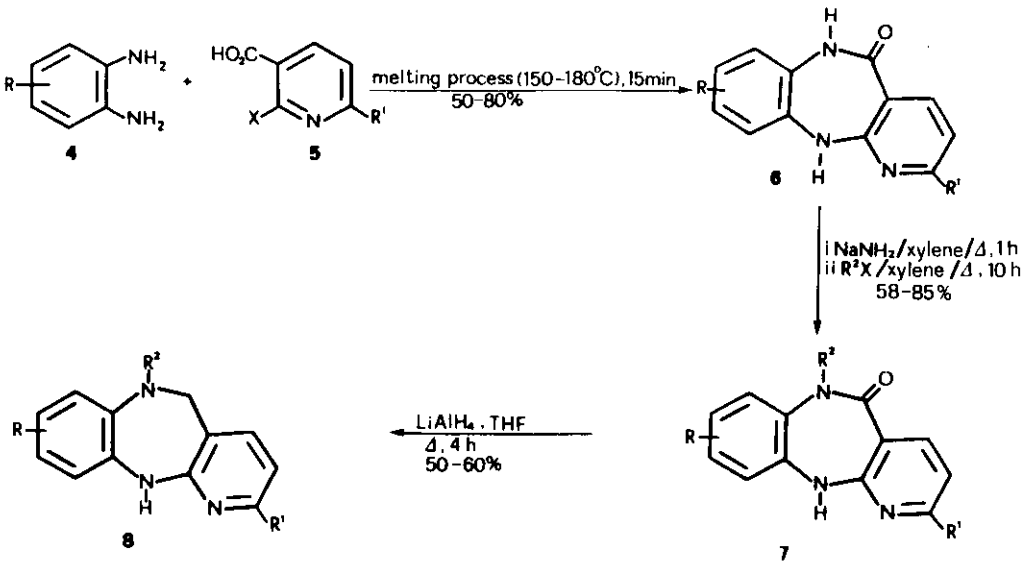
The first approach is based on the reaction of (Z)-4-alkylamino-3-dimethylaminomethylene-1,3-dihydro-2H-1,5-benzodiazepin-2-ones (**1**) with suitable active methylene compounds (e.g. ethyl nitroacetate or acetylacetone). The presence of two electrophilic carbon atoms, bonded to the active methylene group, lead to the isolation of derivatives (**2**) or (**3**) depending on the employed reagent.[2]



R = Me, Et
R^1= COMe, COPh, NO_2
R^2= NH_2, Me, Ph
R^3= CN, CO_2Et, COMe, COPh

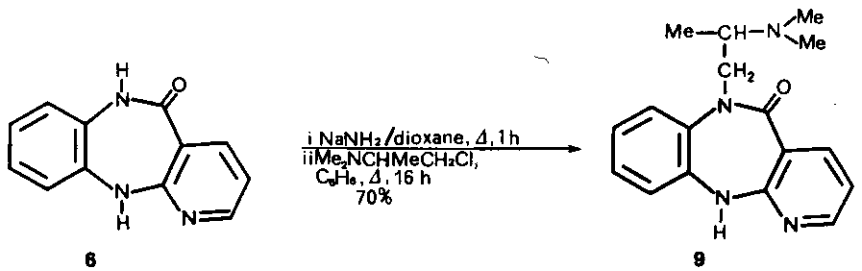
The alternative route involved the condensation of 2-halonicotinic acid (**5**) with 1,2-phenylenediamine derivatives (**4**) to give 6,11-dihydro-5H-pyrido-[2,3-b][1,5]benzodiazepin-5-ones (**6**).[3-9]

Treatment of 6,11-dihydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-ones (**6**) with alkyl halides afforded 6-alkyl derivatives (**7**) which can be reduced to 5,6-dihydro-11H-pyrido[2,3-b][1,5]benzodiazepines (**8**) by the reaction with lithium alluminum hydride; the alkylation can be otained before or after reduction.[4,5,7,10-14] Pharmacological tests showed that pyridobenzodiazepin-5-ones have antidepressive, antihistaminic, thymoanaleptic and antispasmodic properties,[5] while their reduction products exhibit antitussive, antipyretic, antiphlogistic and bronchial secretion activities.[13-14]

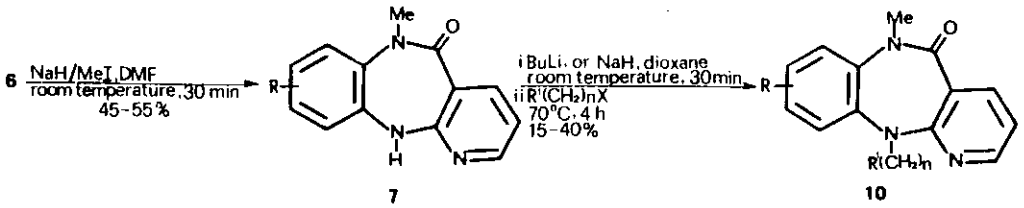


X = Cl, Br, I
R = H, 8-Cl, 8-Me, 8,9-Cl_2, 8,9-Me_2
R^1= H, Me, 3-$NO_2C_6H_4$, 3-piperidinyl
R^2= Me, Et, i-Bu, allyl, $PhCH_2$, 4-$ClC_6H_4CH_2$, 4-$OMeC_6H_4CH_2$, $(CH_2)_nNMe_2$ (n = 1,2,3), 2-morpholinoethyl, piperidinyl

The synthesis and the psychopharmacological profile of 6-(2-dimethylamino-propyl)-6,11-dihydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-one (propizepine) (**9**) as a tricyclic antidepressant were reported.[4,5,15] The quantification in blood of patients suspected of poisoning was determined by gas chromatography and mass spectrometry.[16]

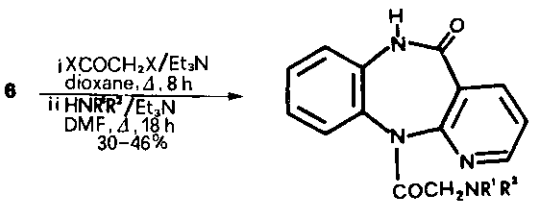


By treatment of 6,11-dihydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-ones (**6**) with NaH and MeI, compounds (**7**) were obtained; subsequent aminoalkylation with alkyl halides and NaH or BuLi afforded 11-aminoalkyl derivatives (**10**) which showed pharmacological properties as cholinergic and muscarinic neurotransmitter antagonists and antiemetics.[12,17,18]



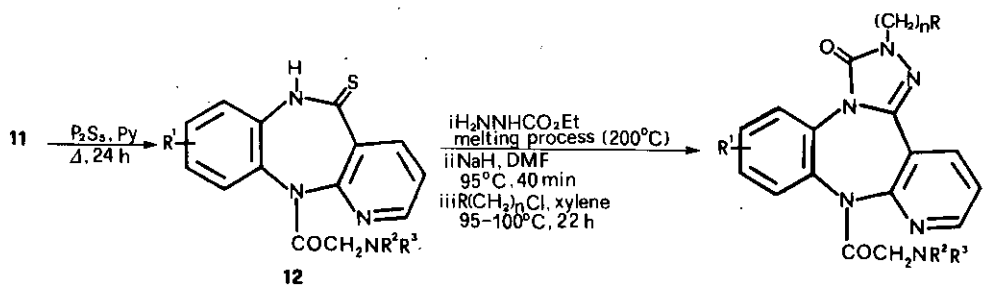
n = 2, 3
X = Cl, Br
R = H, 8,9-Me_2
R^1= Me_2N, Et_2N, morpholinyl, piperazinyl, pyrrolidinyl

The 11-acyl analogues (**11**) were prepared as potential cardiovascular antimuscarinic agents by treatment of 5H-pyrido[2,3-b][1,5]benzodiazepin-5-ones (**6**) with haloacyl halides and subsequent reaction with various amines.[19-26]



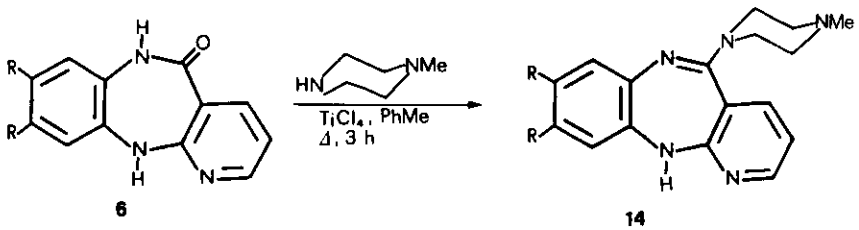
NR^1R^2= morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl

After the thiation of **11**, these compounds were converted into the corresponding pyrido[2,3-b][1,5]benzodiazepine-5-thiones (**12**) whose condensation with $H_2NNHCOOEt$ and subsequent alkylation or aminoalkylation gave 2,9-dihydro-3H-pyrido[3,2-c][1,2,4]triazolo[4,3-a][1,5]benzodiazepin-3-ones (**13**), with potential sedative, tranquilizing, antitussive and muscle relaxant activities.[27]



n = 2, 3
R = H, Me_2N, 1-piperazinyl, 1-piperidinyl, 1-pyrrolidinyl
R^1= H, 8,9-Br_2, 8,9-Cl_2, 8,9-F_2, 8,9-Me_2
NR^2R^3= Me_2N, Et_2N, Pr_2N, piperidinyl, piperazinyl, 4-methylpiperazinyl, 2-hydroxypiperazinyl, pyrrolidinyl

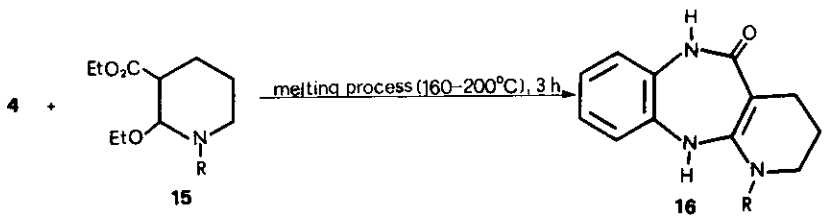
5-Piperazinyl-11H-pyrido[2,3-b][1,5]benzodiazepines (**14**) were prepared from pyridobenzodiazepinones (**6**) by using of N-methylpiperazine and $TiCl_4$.[28]



6 **14**

R = H(90%), Cl(31%)

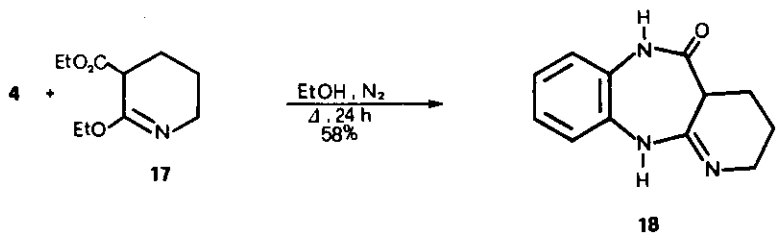
The synthesis of 1,2,3,4,6,11-hexahydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-ones (**16**) was carried out by reaction of 1,2-phenylenediamine (**4**) with 2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (**15**).[29]



15 **16**

R = H(50%), Et(60%)

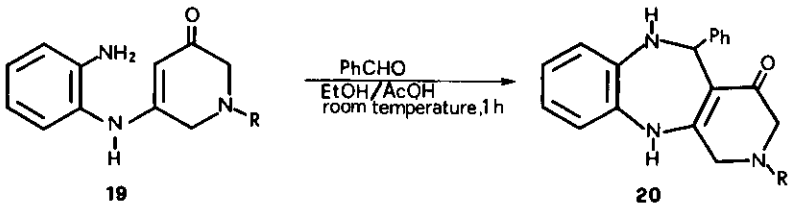
The hexahydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-one (**18**) was similarly prepared starting from 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine (**17**) and 1,2-phenylenediamine (**4**).[30]



17 **18**

The hexahydro-5-phenyl-5H-pyrido[3,4-b][1,5]benzodiazepin-4-ones (**20**) (with potential analgesic, sedative, antipyretic, anticonvulsant, hypoglycemic and antiinflammatory activities) were prepared by enamination of N-

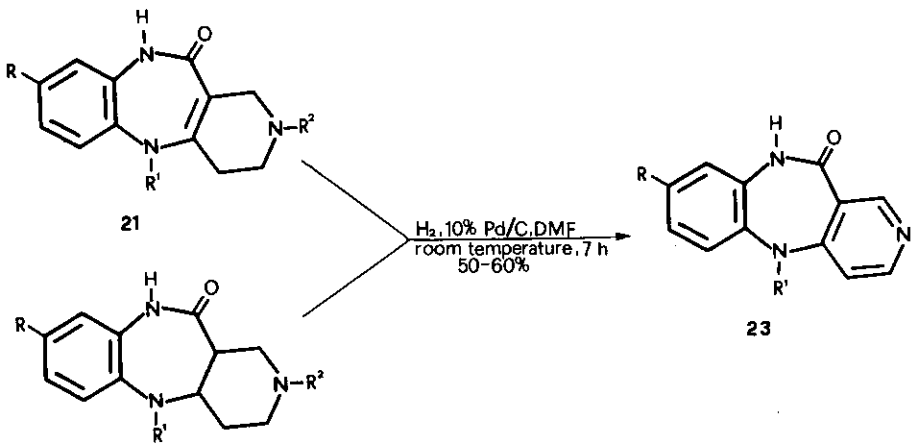
substituted piperidin-3,5-diones with 1,2-phenylenediamine, followed by treatment of the enaminones (**19**) with benzaldehyde in the presence of catalytic amount of acetic acid.[31,32]



19 **20**

R = COMe(16%), CH_2Ph(30%), tosyl(20%), CO_2Et(25%)

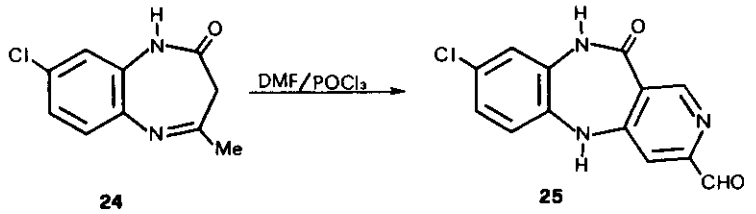
10,11-Dihydro-5H-pyrido[4,3-b][1,5]benzodiazepin-11-ones (**23**) were obtained by dehydrogenation of the corresponding 1,2,3,4,5,10-hexahydro (**21**) or 1,2,3,4,4a,5,10,11a-octahydroderivatives (**22**) with Pd/C in DMF. The compounds (**20**) as well as their octahydroderivatives (**22**) show analgesic, antiinflammatory and psychotropic activity.[33,34]



21 **22** **23**

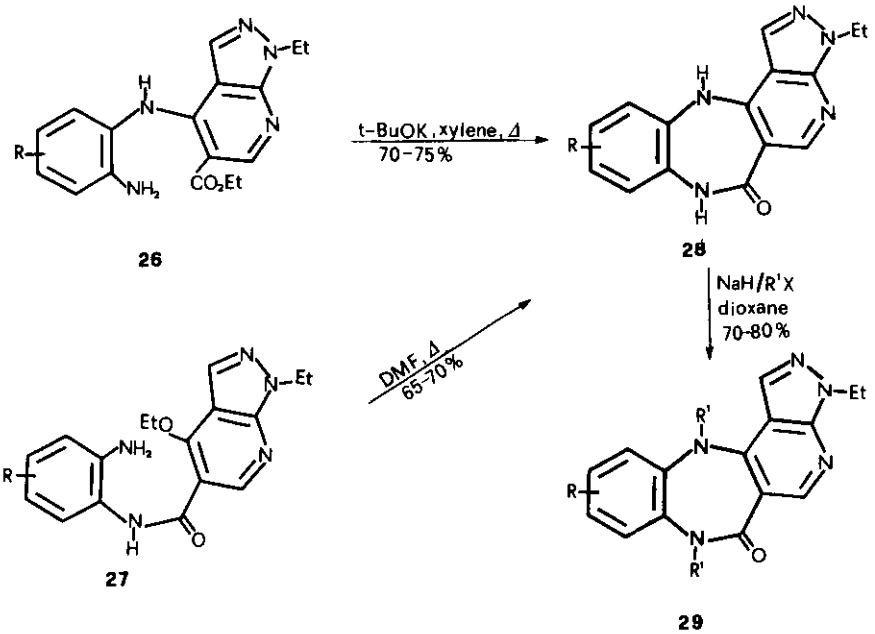
R = H, Cl
R^1= H, $MeCH_2CO$, $ClCH_2CO$
R^2= COMe, $(CH_2)_3CN$, CH_2Ph, 2-phenylethyl, COPh, 4,4-bis(4-fluorophenyl)butyl, (dimethylamino)ethyl, 4-(4-fluorophenyl)-4-oxobutyl, 2-phenoxyethyl,

Treatment of 8-chloro-2,3-dihydro-4-methyl-1H-1,5-benzodiazepin-2-ones (**24**) with Vilsmeier reagent afforded 8-chloro-10,11-dihydro-5H-pyrido[4,3-b]-[1,5]benzodiazepin-11-one 3-carboxaldehydes (**25**).[35]



24 25

Several 7,12-dihydropyrazolo[4',3':5,6]pyrido[4,3-b][1,5]benzodiazepin-6(3H)-ones (**28**) were prepared by refluxing the esters (**26**) or anilides (**27**) in xylene in the presence of potassium t-butoxide or DMF respectively; 7,12-dialkylderivatives (**29**) were also prepared by reaction of **28** with NaH and alkyl halides. These compounds were tested as potential anxiolytics, antiinflammatory and tranquilizing agents.[36,37]



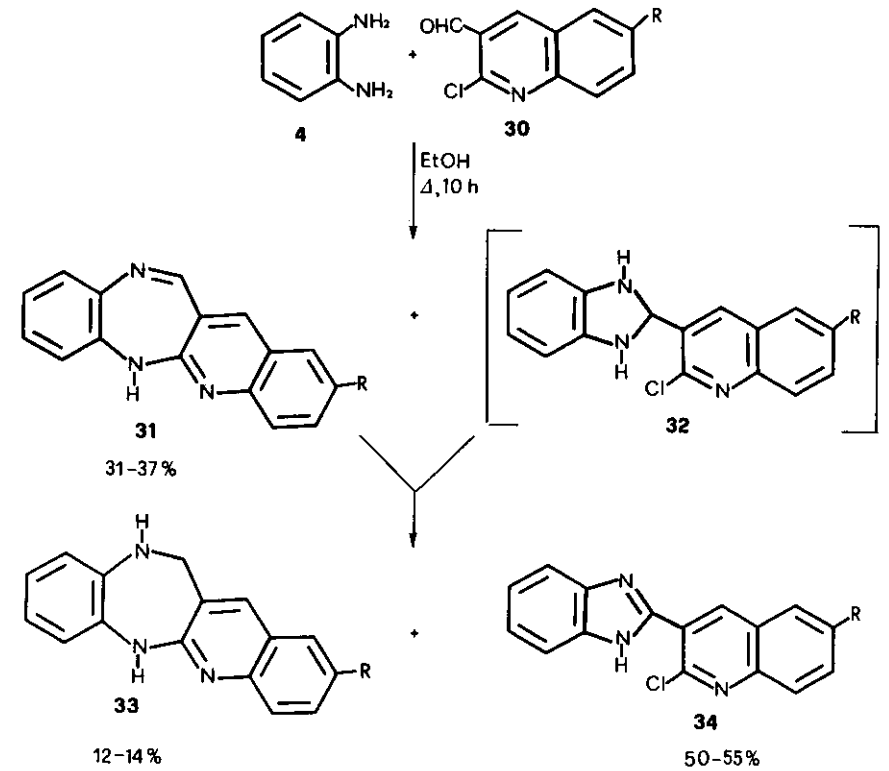
26 28 27 29

R = H, 6-Cl, 7-Cl
R^1= Me, Et, $(CH_2)_2NMe_2$, $(CH_2)_3NMe_2$, $CHMeCH_2NMe_2$, $(CH_2)_2NEt_2$, 3-piperidinopropyl, CH_2Ph

2. Quino-1,5-benzodiazepines

6H-Quino[2,3-b][1,5]benzodiazepines (**31**) were obtained by the reaction of 2-chloroquinoline-3-carboxaldehyde (**30**) with 1,2-phenylenediamine (**4**) together with high yields of a benzimidazolylderivative (**34**) and low yields of 11,12-dihydro-6H-quino[2,3-b][1,5]benzodiazepine (**33**). This latter is

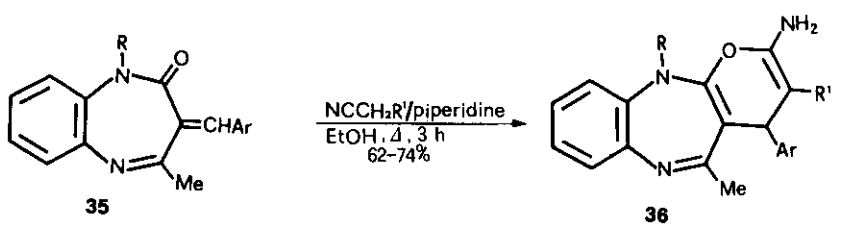
assumed to be formed from (**31**) by reduction with the 2-chloro-3-benzimidazolinyl intermediate (**32**).[38]



R = H, Me, MeO

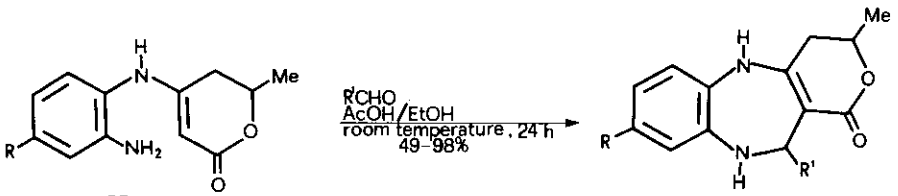
3. **Pyrano-1,5-benzodiazepines**

4,11-Dihydropyrano[2,3-b][1,5]benzodiazepines (**36**) were prepared from (Z/E)-N-alkyl-1,3-dihydro-4-methylbenzodiazepinones (**35**) and malononitrile or ethyl cyanoacetate.[39]



R = H, Me, Et, Bu
R^1= CN, CO_2Et

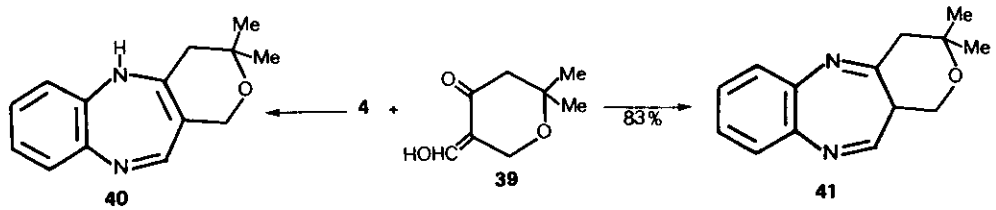
Synthesis of 11-substituted 3-methyl-4,5,10,11-tetrahydropyrano[4,3-b]-[1,5]benzodiazepin-1(3H)-ones (**38**) involved cyclocondensation of enamino-lactones (**37**) with aromatic or heteroaromatic aldehydes.[40] Although it is possible for two isomers to exist regarding the configuration of the substituents at C-3 and C-11 of **38**, single isomers were isolated: however, the stereochemistry of **38** was not determined.



37 **38**

R = H, Cl
R^1= Ph, 2-ClC_6H_4, 3-MeC_6H_4, 2-$NO_2C_6H_4$, 2-pyridyl, 2-thienyl, 5-nitro-2-furyl

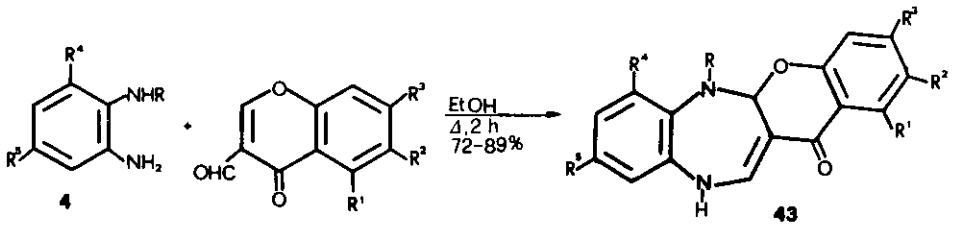
Cyclocondensation of 2,2-dimethyl-5-hydroxymethylenetetrahydropyran-4-ones (**39**) with 1,2-phenylenediamine (**4**) gave isomeric 1,3,4,5-tetrahydro- (**40**) and 1,3,4,11a-tetrahydropyrano[4,3-b][1,5]benzodiazepines (**41**).[41,42]

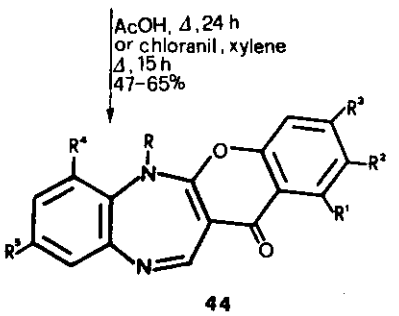


40 **39** **41**

4. Benzopyrano-1,5-benzodiazepines

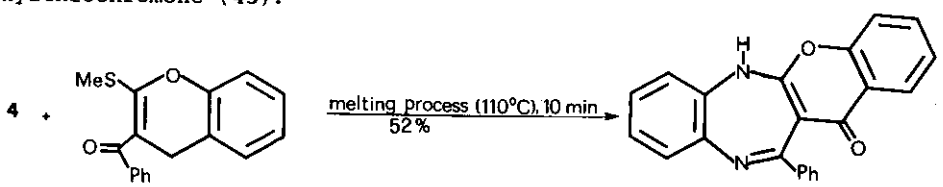
Cyclocondensation of 3-formylchromones (**42**) (or the corresponding acetal) with 1,2-phenylenediamine derivatives (**4**) afforded 5a,11-dihydroderivatives (**43**), which were dehydrogenated by prolonged heating, or treatment with chloranil, air oxidation or digestion in acetic acid to give [1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-ones (**44**) which showed anti-convulsant, analgesic and antiinflammatory activities. 6-Substituted derivatives were also prepared starting from N-substituted 1,2-phenylene-diamines or by alkylation or acylation of the corresponding benzopyrano-benzodiazepinones.[43-51]



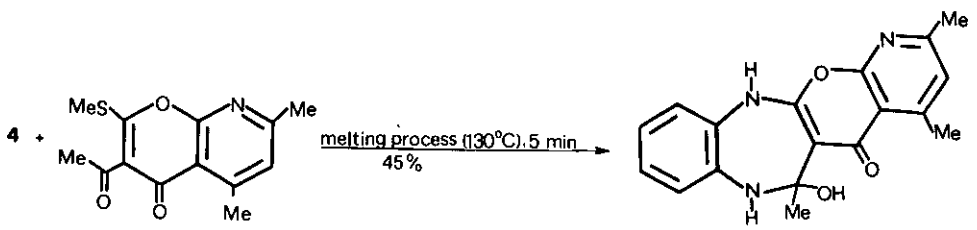


R = H, Me, Et, $(CH_2)_3NMe_2$, Ph, $PhCH_2$, COPh, cyclohexyl,
R^1= R^2= R^3 = H, Me, MeO, Cl, Br
R^4= R^5= H, NO_2

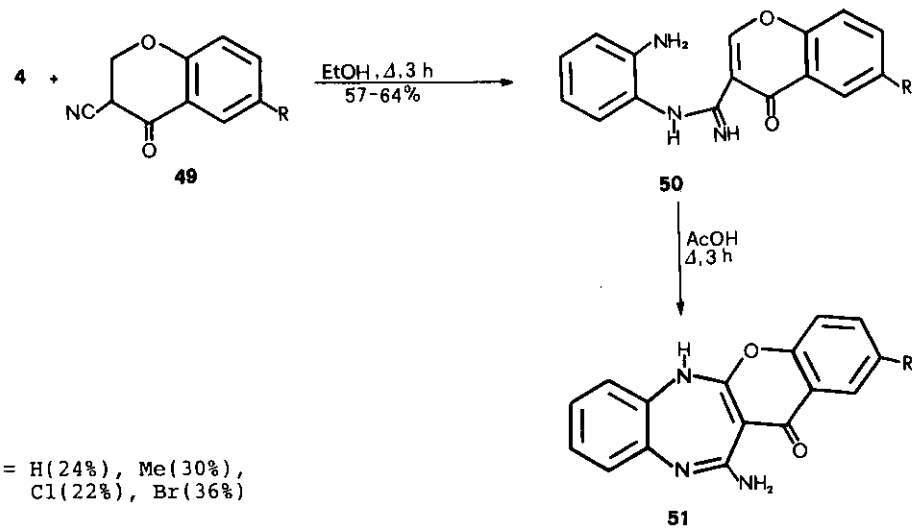
12-Phenyl[1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-one (**46**) was similarly prepared by reaction of 1,2-phenylenediamine (**4**) and 3-benzoyl-2-methylthiochromone (**45**).[52]



The same authors reported the reaction of 3-acetyl-2-methylthioazachromone (**47**) with 1,2-phenylenediamine (**4**) which afforded 7,12-dihydro-6-hydroxy-2,4,6-trimethylpyrido[3',2':5,6]pyrano[2,3-b][1,5]benzodiazepin-5(6H)-one (**48**).[53]



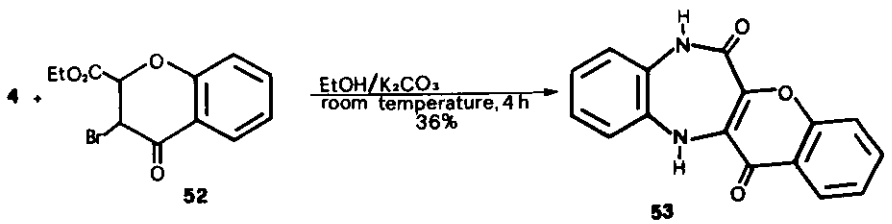
12-Amino substituted derivatives (**51**) were also synthesized starting from 4-oxo-4H-[1]benzopyran-3-carbonitriles (**49**). The 1,2-addition of 1,2-phenylenediamine (**4**) to the nitrile function gave the intermediate amidines (**50**) which on cyclization and subsequent air oxidation afforded **51**.[54]



49 **50** **51**

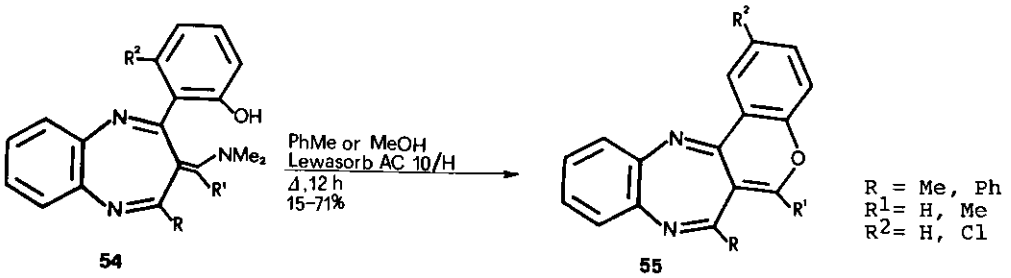
R = H(24%), Me(30%), Cl(22%), Br(36%)

The reaction of ethyl 3-bromochromone-2-carboxylate (**52**) with 1,2-phenylenediamine (**4**) in the presence of anhydrous potassium carbonate afforded 7,12-dihydro[1]benzopyrano[3,2-b][1,5]benzodiazepin-6,13-dione (**52**).[55]



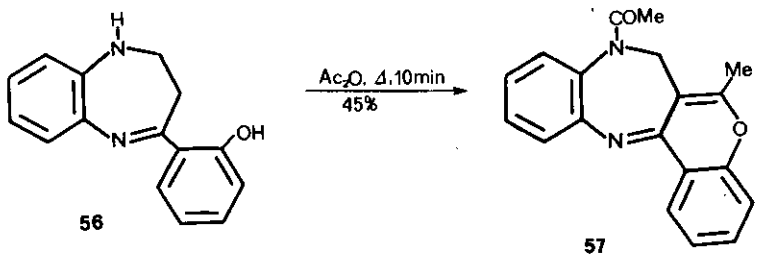
52 **53**

[1]Benzopyrano[4,3-b][1,5]benzodiazepines (**55**) useful as sedatives, antihypertensives, analgesics, anticonvulsants and sympatholytics, were prepared by cyclizing (Z)-3-dimethylaminomethylidene-1,5-benzodiazepines (**54**), under reflux in toluene or methanol containing an acid ion exchanger (Lewasorb AC 10/H).[56-58]



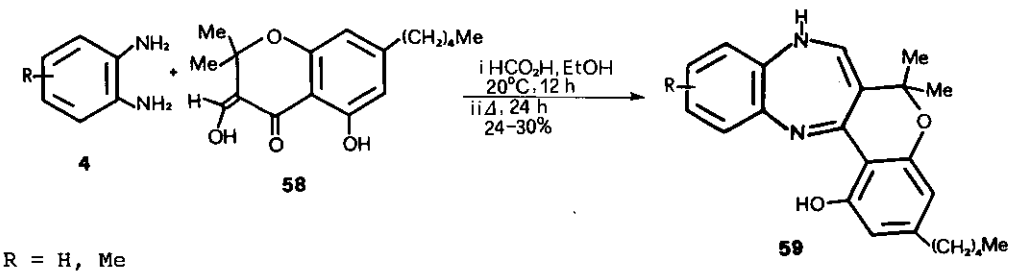
54 55

Similarly, 2,3-dihydro-4-(2-hydroxyphenyl)-1H-1,5-benzodiazepine (**56**) was reacted with acetic anhydride to achieve the ring closure to 7,8-dihydro[1]benzopyrano[4,3-b][1,5]benzodiazepine (**57**).[59]



56 57

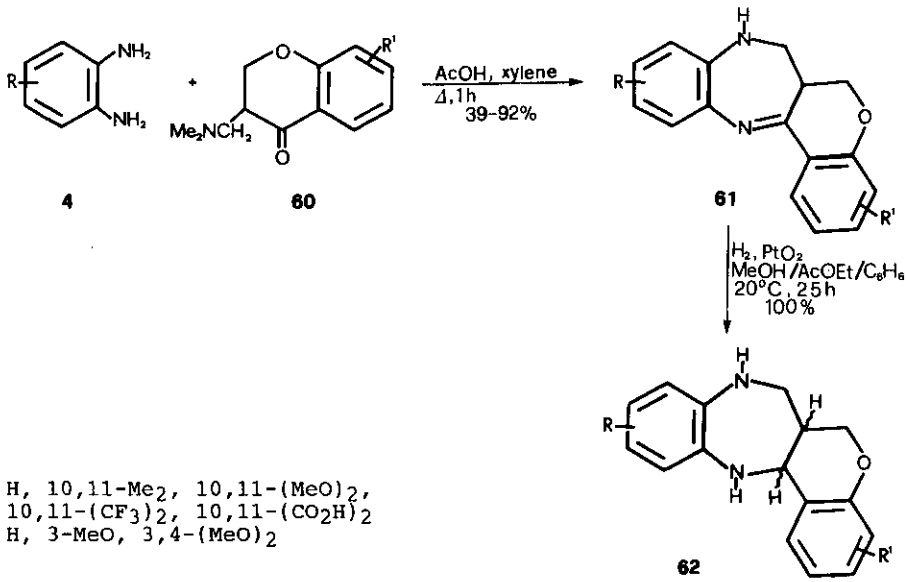
The azacannabinols, 6,8-dihydro[1]benzopyrano[4,3-b][1,5]benzodiazepin-1-ole derivatives (**59**), were prepared by treatment of benzopyranone (**58**) with a suitable 1,2-phenylenediamine (**4**) and cyclization by heating in vacuum.[60]



4 58 59

R = H, Me

Some 6,6a,7,8,13,13a-hexahydro[1]benzopyrano[4,3-b][1,5]benzodiazepine derivatives (**62**) show antileukemic and adenylate cyclase system stimulating activity. These compounds were prepared by cyclocondensation of 1,2-phenylenediamine (**4**) with 3-dimethylaminomethyl-4-chromanone derivatives (**60**) in the presence of acetic acid, followed by hydrogenation of **61** to give a mixture of cis and trans forms of **62**.[61-63]

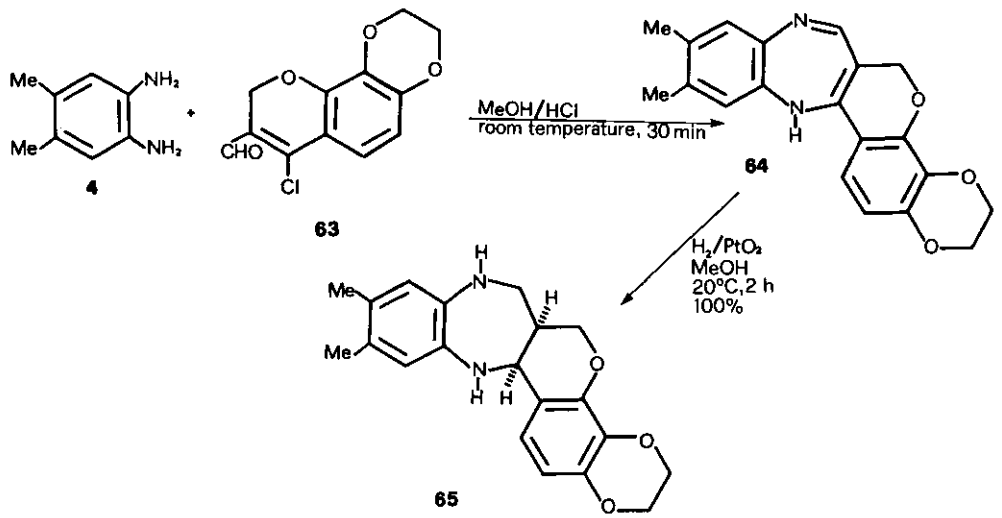


4 60 61 62

R = H, 10,11-Me_2, 10,11-$(MeO)_2$,
10,11-$(CF_3)_2$, 10,11-$(CO_2H)_2$
R^1= H, 3-MeO, 3,4-$(MeO)_2$

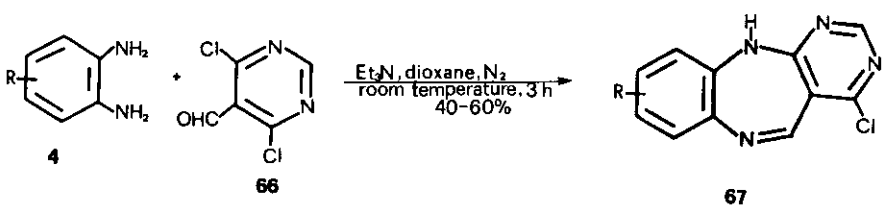
The separation of the mixture into the antileukemic cis-form and the inefficacious trans-form is reported;[62] optically active antipodes were also resolved with (+)-ß-binaphthylphosphoric acid.[64,65] The absolute configurations of the HBr salts were assigned by X-ray analysis.[65,66] Contrary to the high biological activity of (+)-enantiomer against leukemia its (-)-antipode was completely inactive. The antitumor mechanism was studied.[67-69] For (+)- and (±)- compounds binding studies, using phosphatidylcholine and phosphatidylcholine-chlolesterole liposomes as models of biological membranes, were also effected.[70]

Recently [1]benzopyrano[4,3-b][1,5]benzodiazepines were synthesized as antileukemics and intermediates for psychotropic drugs and antineoplastic agents; the synthesis involved cyclocondensation of 3,4-dimethyl-1,2-phenylenediamine (**4**) with 4-chloro-3-formyl-7,8-ethanediyldioxy-2H-chromene (**63**) in methanol containing HCl, to give unsatured benzodiazepine derivatives (**64**) which were hydrogenated over PtO_2 to give, after resolution, the corresponding 6,6a,7,8,13,13a-hexahydro[1]benzopyrano-[4,3-b][1,5]benzodiazepine (**65**) which showed antileukemic activity.[71]



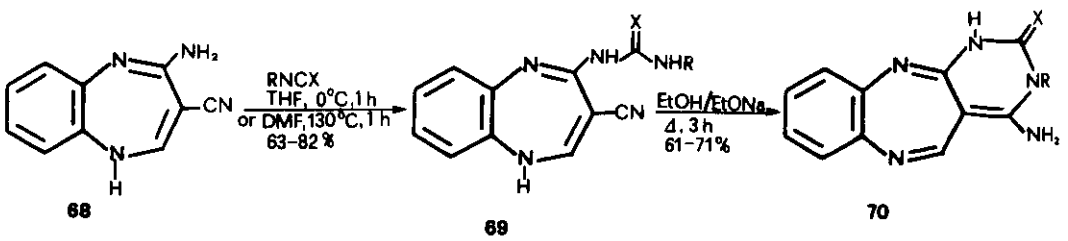
5. **Pyrimido-1,5-benzodiazepines**

Only one synthetic approach to pyrimido[4,5-b][1,5]benzodiazepines (**67**) has been reported, which involves the cyclocondensation of 4,6-dichloro-5-pyrimidinecarboxaldehyde (**66**) with 1,2-phenylenediamines (**4**) in triethylamine and dioxane.[72,73]



R = H, 8-Me, 9-Me, 8,9-Me_2, 8,9-$(MeO)_2$, 8-CO_2H, 8-CO_2Me, 8-CF_3, 8,9-Cl_2, 8-NO_2

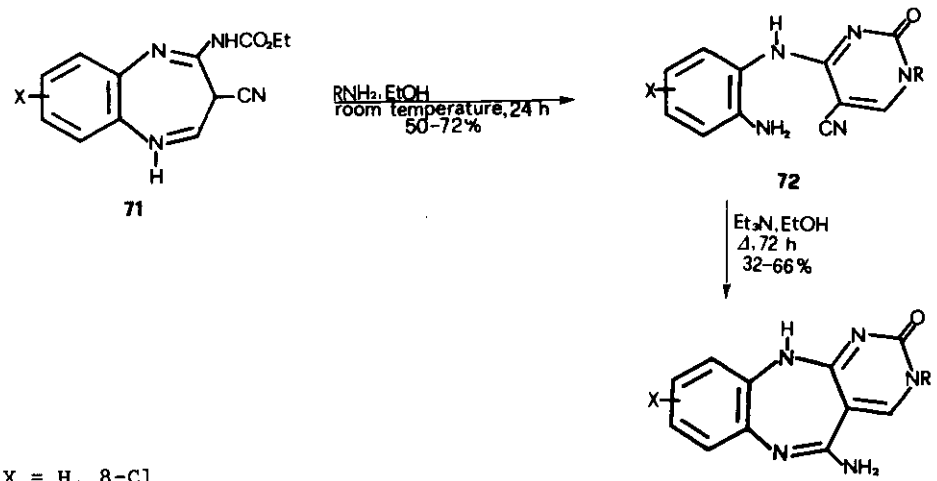
Pyrimido[4,5-b][1,5]benzodiazepin-2-one and 2-thione derivatives (**70**) were synthesized by intramolecular cyclization of N-(3-cyano-1H-1,5-benzodiazepin-4-yl)-N'-alkylureas and N'-phenylthioureas (**69**), which were obtained by reaction of 4-amino-1H-1,5-benzodiazepine-3-carbonitrile (**68**) with alkylisocyanates and phenylisothiocyanates respectively.[74]



68 69 70

R = Me, Et, Ph
X = O, S

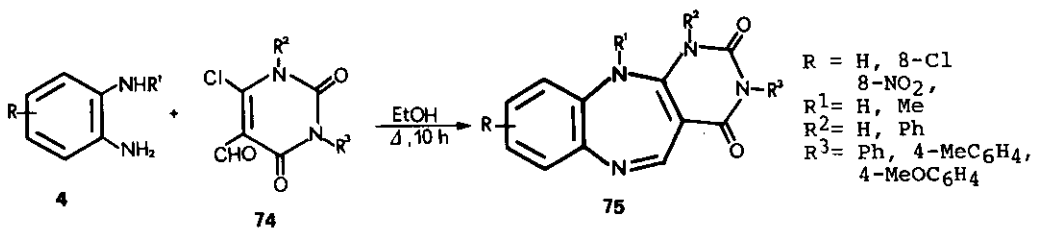
On the other hand, reaction of 1-(ethoxycarbonylamino)-1H-1,5-benzodiazepine-3-carbonitrile (**71**) with amines gave (aminoanilino)pyrimidinocarbonitriles (**72**), which, upon treatment with Et_3N, cyclized to 11H-pyrimido[4,5-b][1,5]benzodiazepin-2-ones (**73**).[75-77]



71 72 73

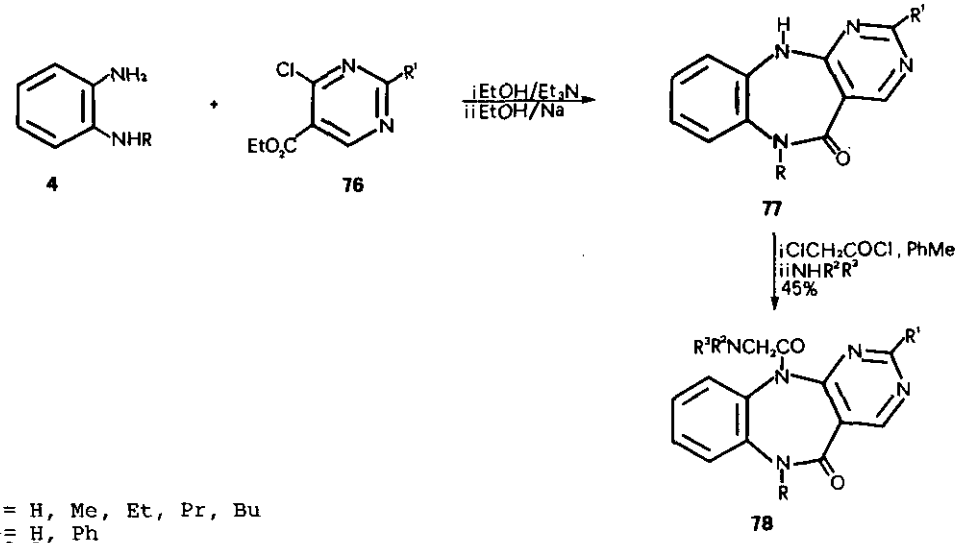
X = H, 8-Cl
R = Me, Et, Pr, i-Pr, Bu, pentyl, dodecyl, cyclohexyl, allyl, hydroxyethyl, CH_2Ph, diethylaminoethyl, 2-(4-morpholinoethyl)

1,3-Dihydro-11H-pyrimido[4,5-b][1,5]benzodiazepine-2,4-diones (**75**) were prepared by boiling 1,2-phenylenediamine (**4**) with **74** in ethanol.[78]



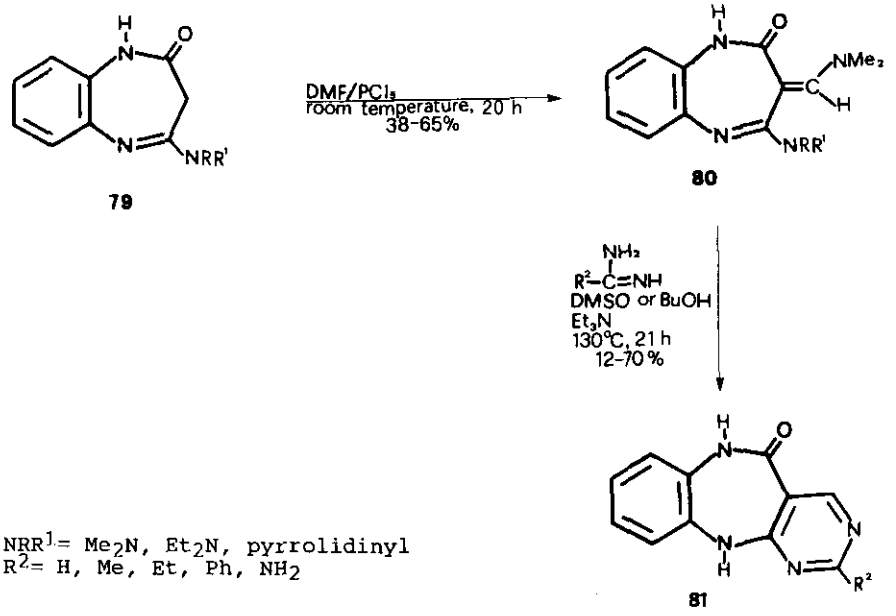
4 74 75

Different synthetic approaches have been envisaged for the 6,11-dihydro-5H-pyrimido[4,5-b][1,5]benzodiazepin-5-one system. One method involved the condensation of 1,2-phenylenediamine (**4**) with 4-chloro-5-carbethoxy-pyrimidine derivatives (**76**) in ethanol to give pyrimidobenzodiazepinones (**77**). These compounds were N-acylated with chloroacetyl chloride and successively aminated. The obtained compounds (**78**) have been shown to be useful as inhibitors of stomach and intestinal ulcer and of gastric secretion.[79]



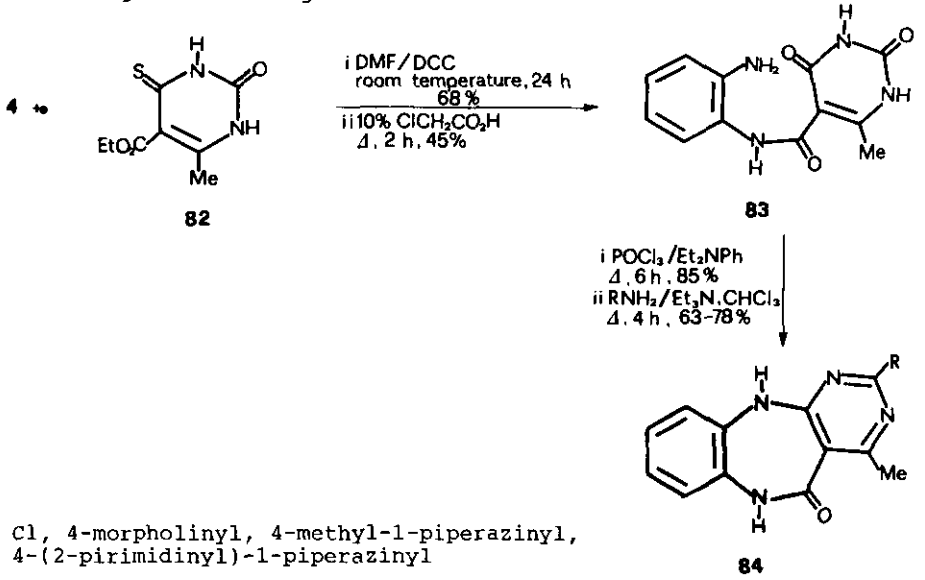
R = H, Me, Et, Pr, Bu
R^1 = H, Ph
NR^2R^3 = Me_2N, Et_2N, Bu_2N, morpholinyl, piperazinyl, pyrrolidinyl

Alternatively, the reaction of 4-dialkylamino-1,3-dihydro-2H-1,5-benzodiazepin-2-one (**79**) with DMF in the presence of PCl_5 at room temperature gave rise to the formation of (Z)-4-dialkylamino-3-dimethylaminomethylene-1,3-dihydro-2H-1,5-benzodiazepin-2-ones (**80**). By treatment with hydrazines pyrazolo[3,4-b][1,5]benzodiazepines have been obtained, whereas reaction with amidines afforded 5H-pyrimido[4,5-b][1,5]benzodiazepin-5-ones (**81**).[80]



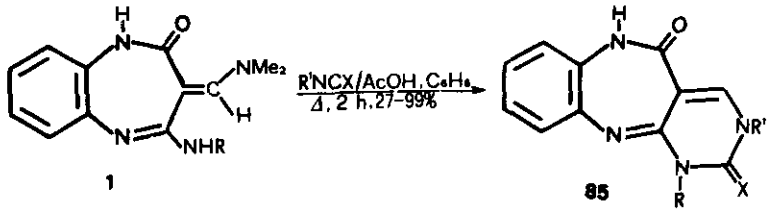
NRR^1= Me_2N, Et_2N, pyrrolidinyl
R^2= H, Me, Et, Ph, NH_2

6,11-Dihydro-5H-pyrimido[4,5-b][1,5]benzodiazepin-5-ones (**84**) were also prepared in several steps from ethyl 6-methyl-1,2,3,4-tetrahydro-2-oxo-4-thioxopyrimidin-5-carboxylate (**82**). Reaction of **82** with 1,2-phenylenediamine (**4**), followed by conversion to the dioxo derivative (**83**), chlorination with $POCl_3$ using Et_2NPh as catalyst and successive amination with heterocyclic amines gave **84**.[81]



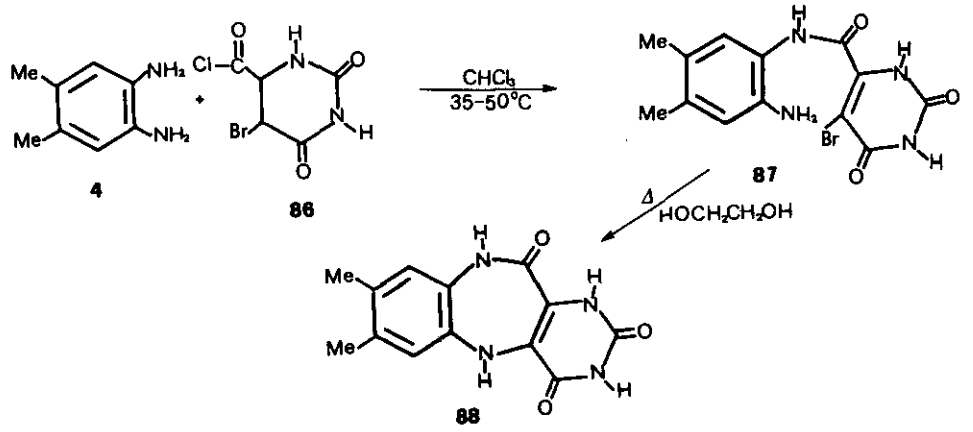
R = Cl, 4-morpholinyl, 4-methyl-1-piperazinyl, 4-(2-pirimidinyl)-1-piperazinyl

1H-Pyrimido[4,5-b][1,5]benzodiazepine-2,5-diones or thiones (**85**) were obtained by reaction of 1,5-benzodiazepines (**1**) with alkyl or phenyl isocyanates or with phenyl or 4-chlorophenyl isothiocyanates using acetic acid as catalyst.[82]



1 **85**

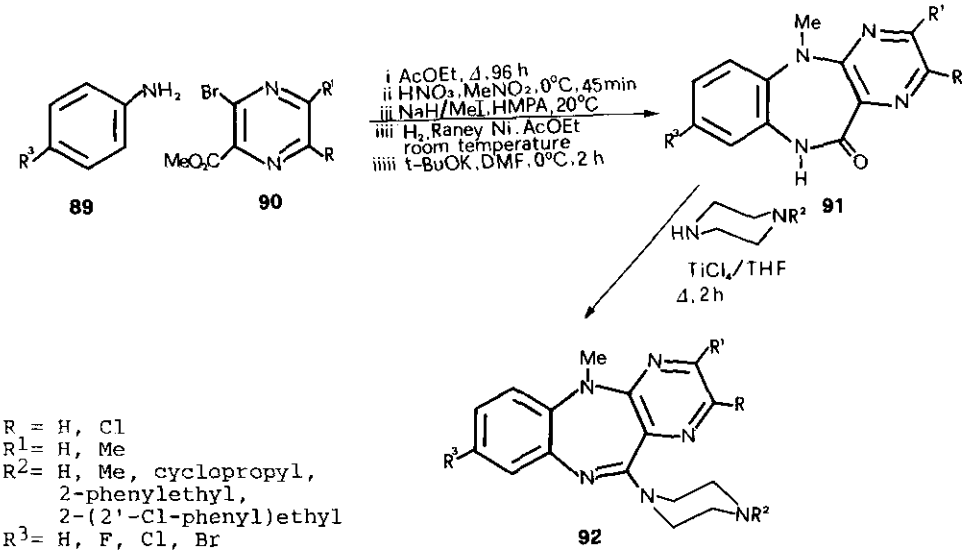
Pyrimido[5,4-b][1,5]benzodiazepines (**88**) were prepared by reacting 4,5-dimethylphenylenediamine (**4**) with 5-bromoorotic chloride (**86**) in $CHCl_3$ at 35-50°C. The resulting 1-N-(5-bromo-4'-orotyl)-4,5-dimethylphenylenediamine amide (**87**) was cyclized in ethylene glycol.[83]



4 **86** **87** **88**

6. Pyrazino-1,5-benzodiazepines

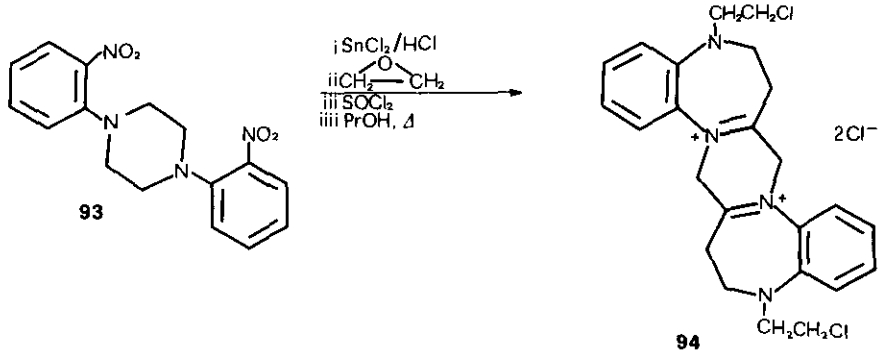
The reaction of substituted methyl 3-bromopyrazine-2-carboxylates (**90**) with substituted anilines (**89**), followed by nitration, alkylation and alkenylation, reduction of the nitro group and cyclization with potassium t-butoxide, gave 5H-pyrazino[2,3-b][1,5]benzodiazepin-11(10H)-one derivatives (**91**), which reacted with N-substituted piperazines and $TiCl_4$ in THF to give 11-piperazinyl derivatives (**92**) tested as potential neuroleptics, antidepressant and sedatives.[84]



89 90 91 92

R = H, Cl
R^1= H, Me
R^2= H, Me, cyclopropyl, 2-phenylethyl, 2-(2'-Cl-phenyl)ethyl
R^3= H, F, Cl, Br

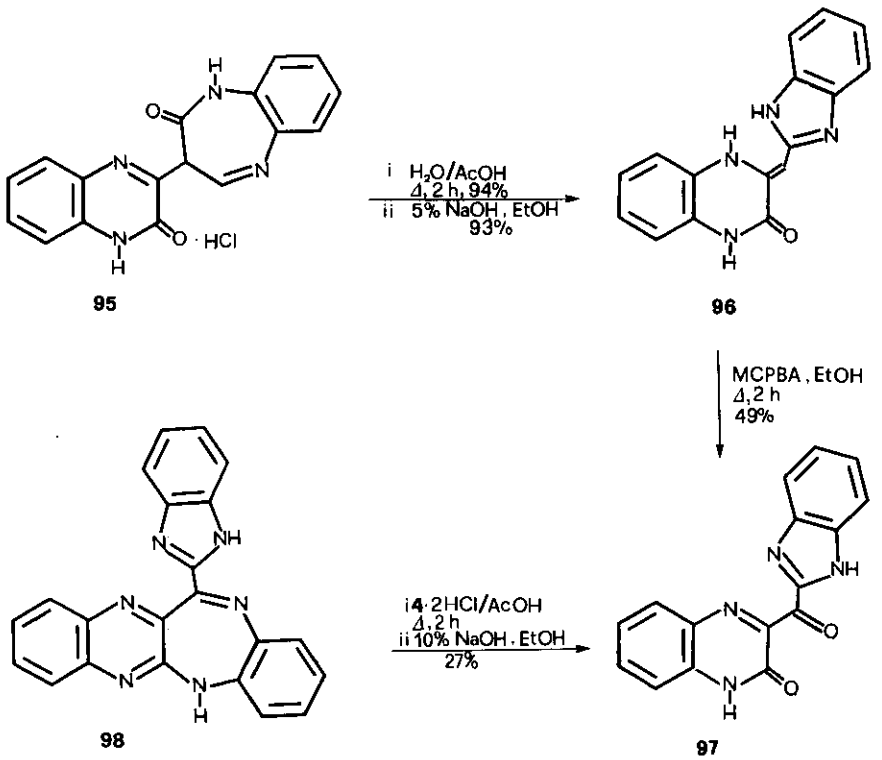
The bis-quaternary salt of pyrazino[1,2-a:4,5-a']bis[1,5]benzodiazepine (**94**) was prepared from compound (**93**) by successive reduction, hydroxyethylation, treatment with thionyl chloride and heating in propanole.[85]



93 94

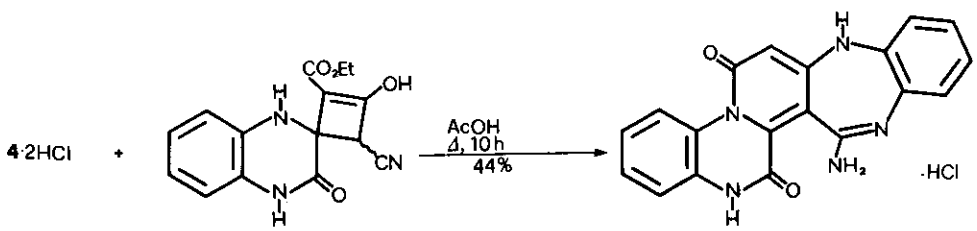
7. Quinoxalino-1,5-benzodiazepines

The ring transformation of a quinoxalinylidenebenzodiazepine hydrochloride (**95**) provided 3-benzimidazol-2-ylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**96**). Oxidation of **96** with m-chloroperbenzoic acid produced 3-benzimidazolyl-2-carbonyl-2-oxo-1,2-dihydroquinoxaline (**97**). Refluxing of **97** with 1,2-phenylenediamine dihydrochloride (**4**) followed by treatment with 10% NaOH afforded 12-benzimidazol-2-yl-6H-quinoxalino[2,3-b][1,5]benzodiazepine (**98**).[86,87]



95 96 98 97

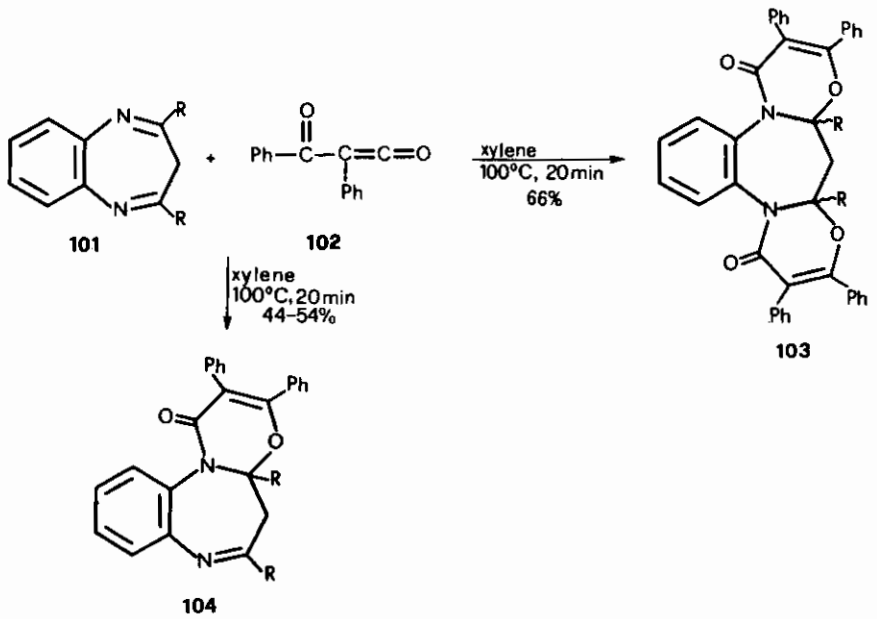
Analogously, the same authors reported the ring transformation of ethoxycarbonylspiro[2-cyclobutene-1,2'(1H)-quinoxaline] (**99**) to 14-aminoquinoxalino[1',2':1,2]pyrido[4,3-b][1,5]benzodiazepine-6,15(8H,16H)-dione hydrochloride (**100**) by reaction with o-phenylenediamine dihydrochloride (**4**) in acetic acid.[88,89]



99 100

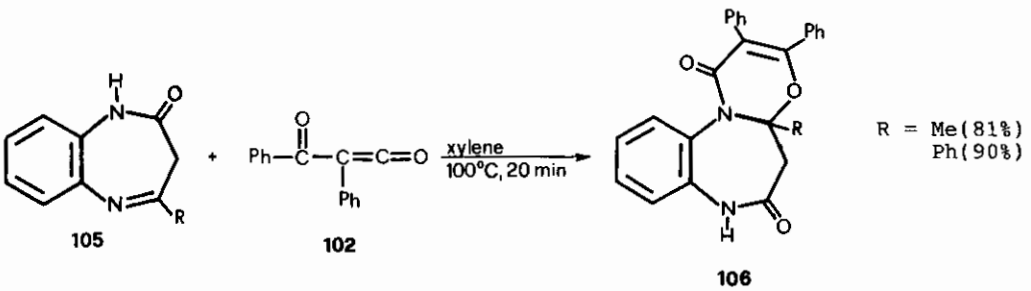
8. Oxazino-1,5-benzodiazepines

6,9a-Dihydro-14H-bis[1,3]oxazino[3,2-a:2',3'-d][1,5]benzodiazepine-6,4-diones (**103**) and 1H-[1,3]oxazino[3,2-a][1,5]benzodiazepin-1-ones (**104**) were prepared by addition to the azomethine bond of the 3H-1,5-benzodiazepines (**101**), of a double or an equimolar amount of benzoyl phenyl ketene (**102**).[90]



R = Me, Ph

Analogously, 1H-[1,3]oxazino[3,2-a][1,5]benzodiazepine-1,6(7H)-diones (**106**) were obtained from 1,5-benzodiazepin-2-ones (**105**).[90]



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