

ANNELATED 1,5-BENZODIAZEPINES. Part II¹. 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

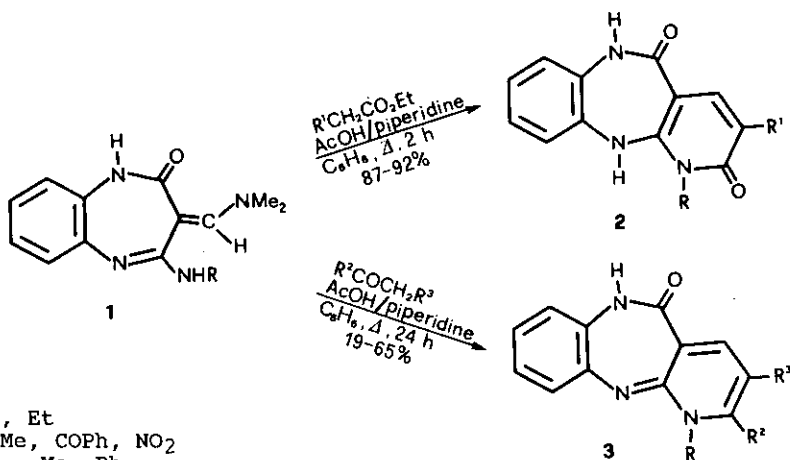
A number of papers and patents concerning the chemistry and the biological activity of 1,4- and 1,5-benzodiazepines containing an additional heterocyclic ring fused to different positions of the heptatomic nucleus have appeared in literatures.

The present review complements our previous review¹ 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

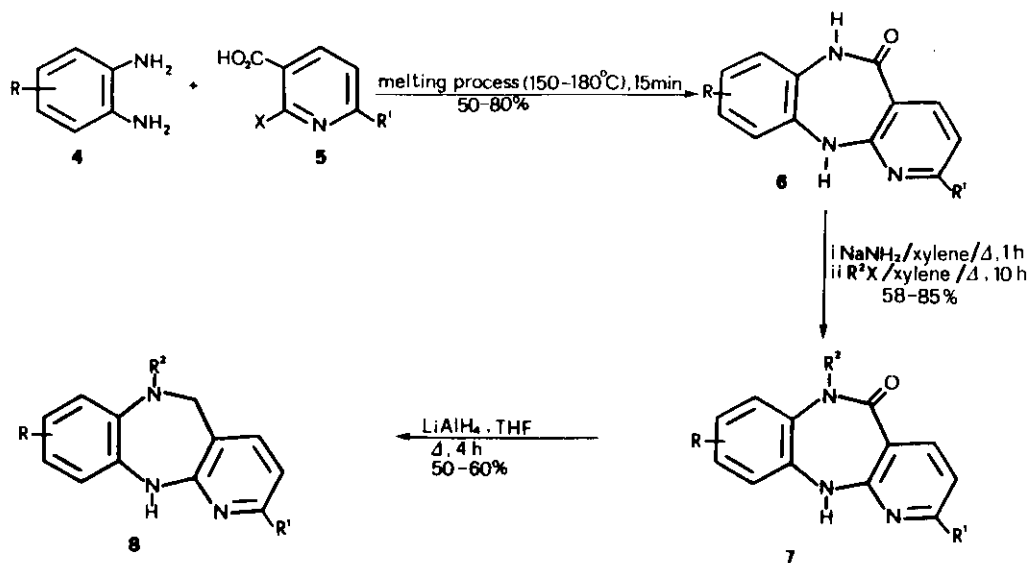
Two general synthetic routes towards the pyrido[2,3-*b*][1,5]benzodiazepine ring system have been exploited, starting from a preformed 1,5-benzodiazepine nucleus or from 1,2-phenylenediamine and nicotinic acid derivatives. The first approach is based on the reaction of (Z)-4-alkylamino-3-dimethylaminomethylene-1,3-dihydro-2H-1,5-benzodiazepin-2-ones (**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
 R¹ = COMe, COPh, NO₂
 R² = NH₂, Me, Ph
 R³ = CN, CO₂Et, 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 aluminum hydride; the alkylation can be obtained 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



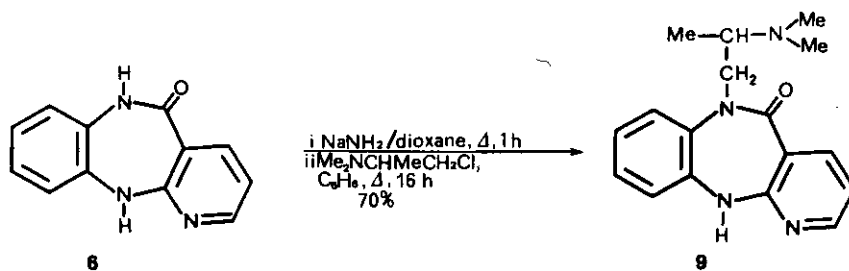
X = Cl, Br, I

R = H, 8-Cl, 8-Me, 8,9-Cl₂, 8,9-Me₂

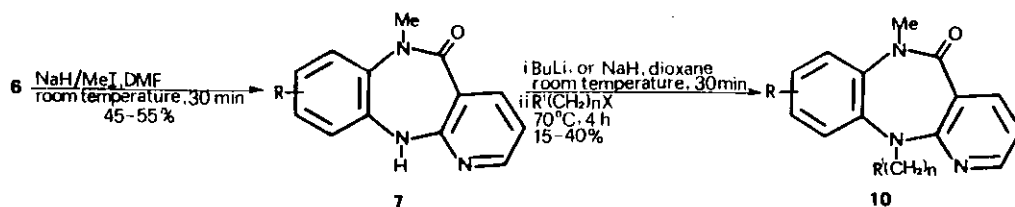
R¹ = H, Me, 3-NO₂C₆H₄, 3-piperidinyl

R² = Me, Et, i-Bu, allyl, PhCH₂, 4-ClC₆H₄CH₂, 4-OMeC₆H₄CH₂, (CH₂)_nNMe₂
(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}



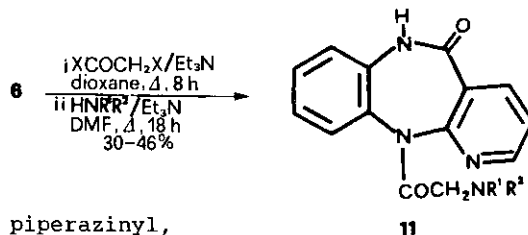
$n = 2, 3$

$X = \text{Cl, Br}$

$R = \text{H, 8,9-Me}_2$

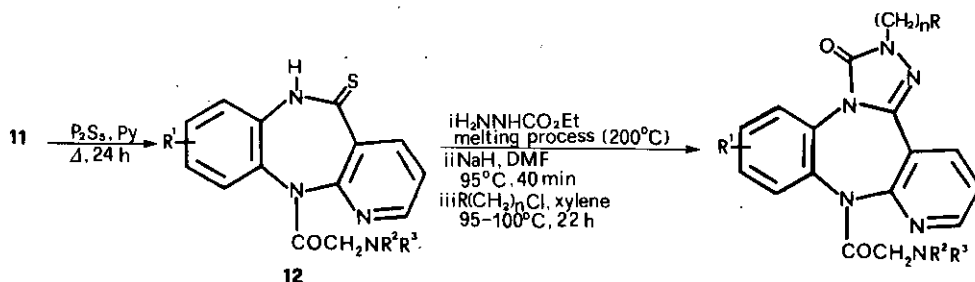
$R^1 = \text{Me}_2\text{N, Et}_2\text{N, morpholinyl, piperazinyl, pyrrolidinyl}$

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



$\text{NR}^1\text{R}^2 = \text{morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl}$

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 $\text{H}_2\text{NNHCO}_2\text{Et}$ 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



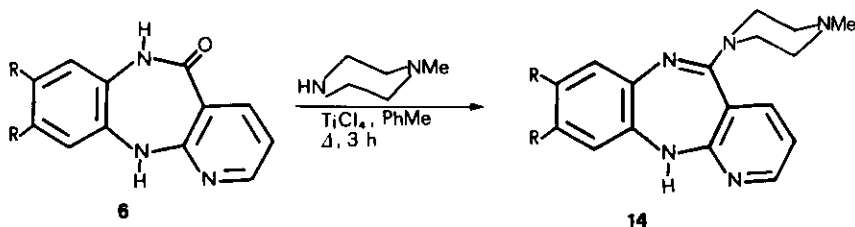
$n = 2, 3$

$R = \text{H, Me}_2\text{N, 1-piperazinyl, 1-piperidinyl, 1-pyrrolidinyl}$

$R^1 = \text{H, 8,9-Br}_2, 8,9\text{-Cl}_2, 8,9\text{-F}_2, 8,9\text{-Me}_2$

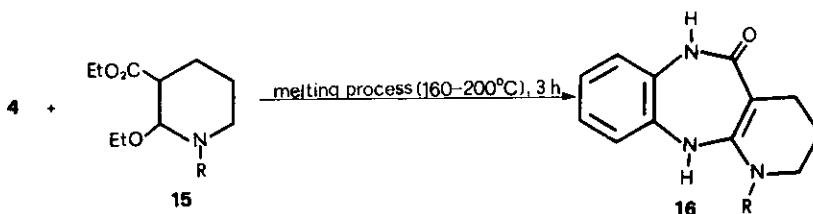
$\text{NR}^2\text{R}^3 = \text{Me}_2\text{N, Et}_2\text{N, Pr}_2\text{N, piperidinyl, piperazinyl, 4-methylpiperazinyl, 2-hydroxypiperazinyl, pyrrolidinyl}$

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



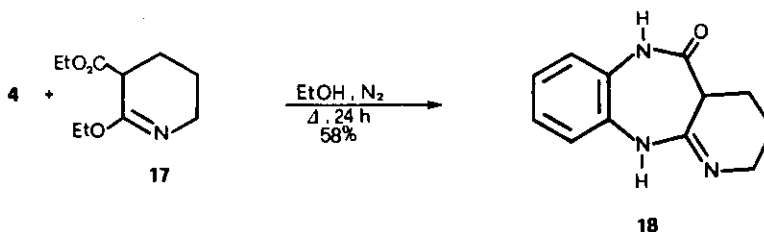
R = H(90%), Cl(31%)

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



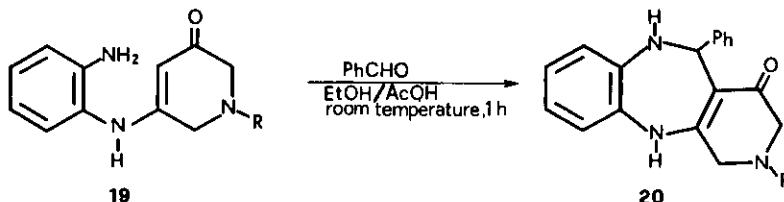
R = H(50%), Et(60%)

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



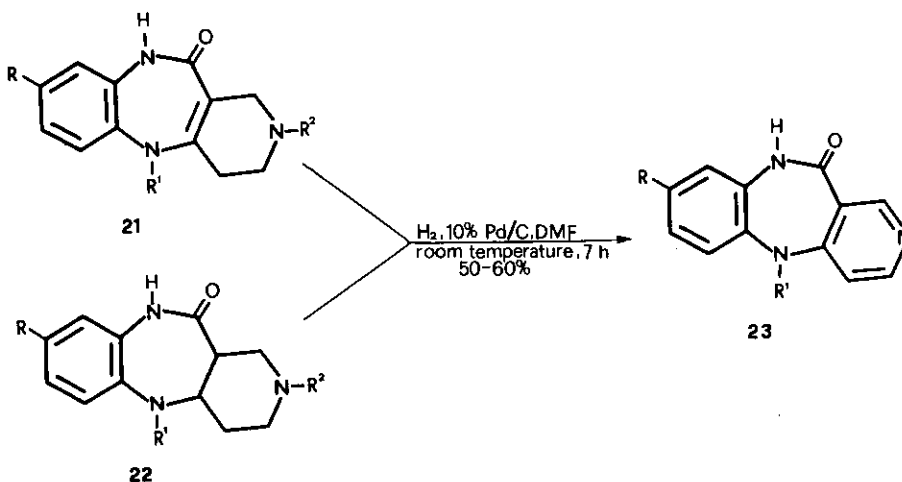
The hexahydro-5-phenyl-5H-pyrido[3,4-b][1,5]benzodiazepin-4-ones (**20**) (with potential analgesic, sedative, antipyretic, anticonvulsant, hypoglycemic and antiinflammatory activities) were prepared by enamination of *N*-

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}



R = COMe(16%), CH₂Ph(30%), tosyl(20%), CO₂Et(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}

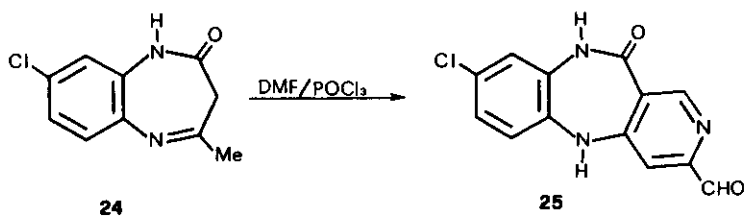


R = H, Cl

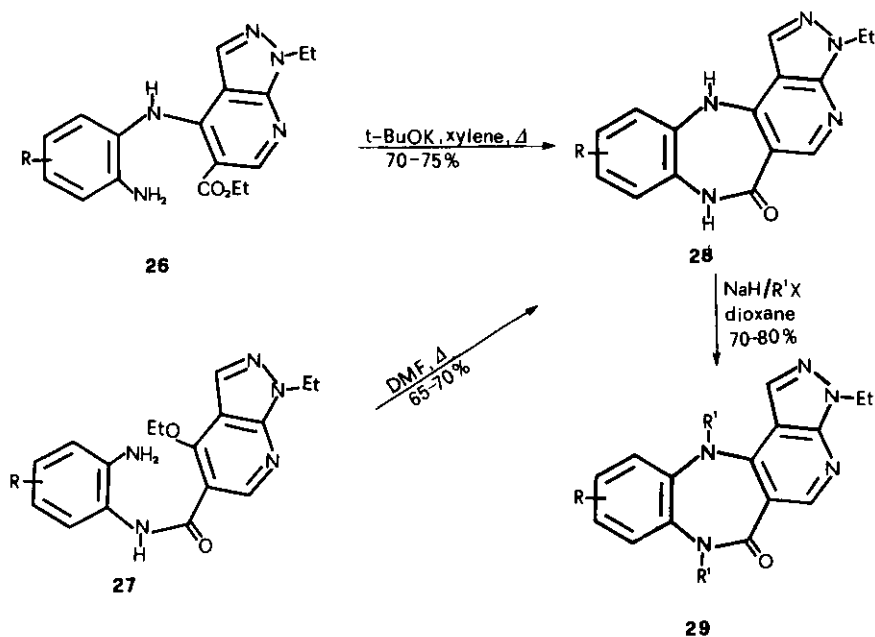
R¹ = H, MeCH₂CO, ClCH₂CO

R² = COMe, (CH₂)₃CN, CH₂Ph, 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



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}



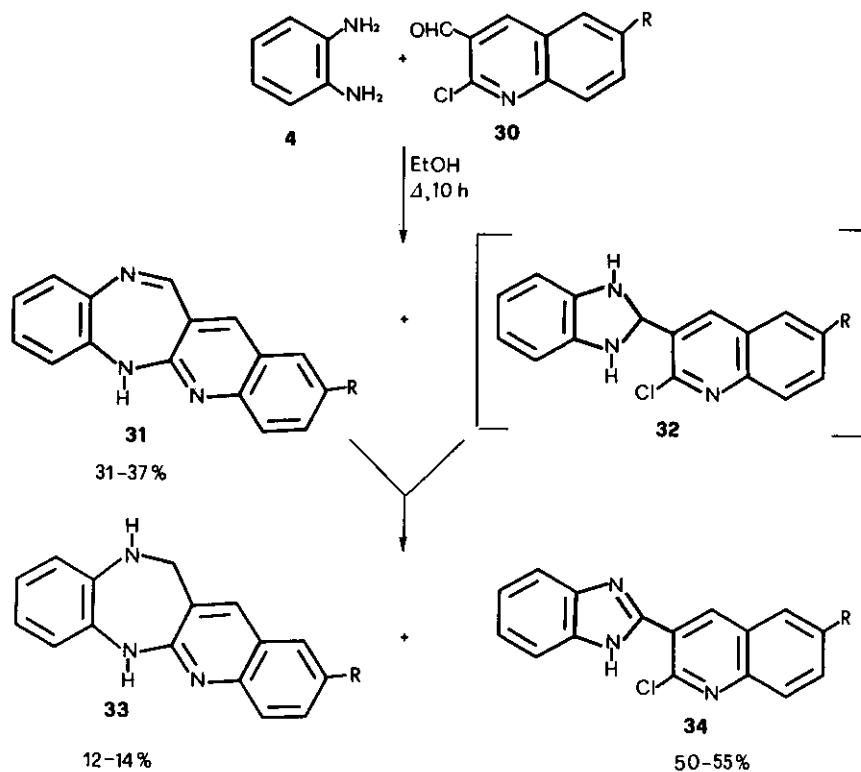
R = H, 6-Cl, 7-Cl

R¹ = Me, Et, (CH₂)₂NMe₂, (CH₂)₃NMe₂, CHMeCH₂NMe₂, (CH₂)₂NEt₂, 3-piperidino-propyl, CH₂Ph

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 benzimidazolyl derivative (34) and low yields of 11,12-dihydro-6H-quinol[2,3-b][1,5]benzodiazepine (33). This latter is

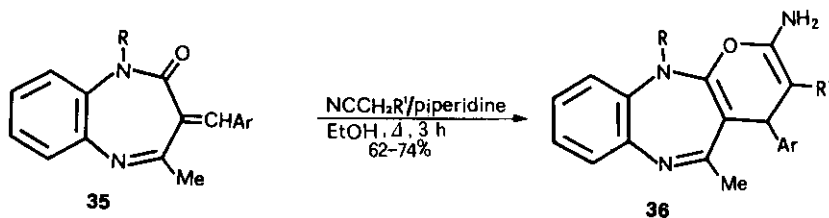
assumed to be formed from (31) by reduction with the 2-chloro-3-benzimidazolinylnyl intermediate (32).³⁸



R = H, Me, MeO

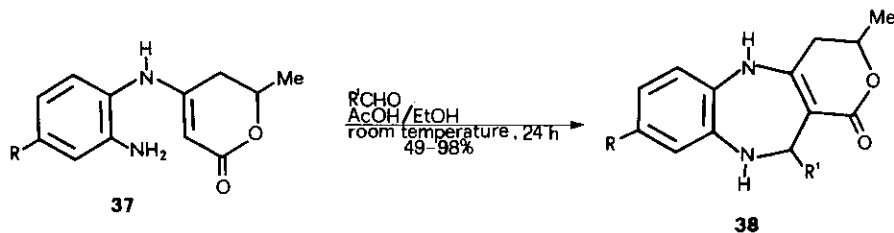
3. Pyrano-1,5-benzodiazepines

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
R¹ = CN, CO₂Et

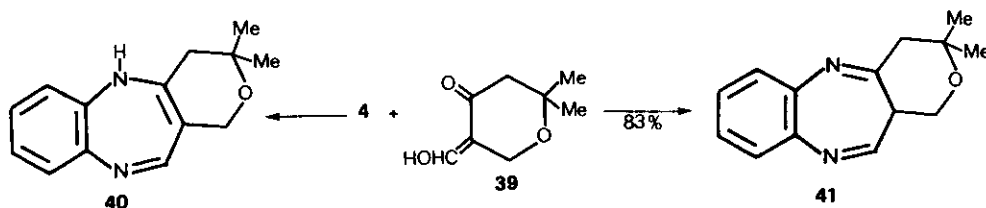
Synthesis of 11-substituted 3-methyl-4,5,10,11-tetrahydropyrano[4,3-b]-[1,5]benzodiazepin-1(3H)-ones (**38**) involved cyclocondensation of enamino-lactones (**37**) with aromatic or heteroaromatic aldehydes.⁴⁰ Although it is possible for two isomers to exist regarding the configuration of the substituents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



R = H, Cl

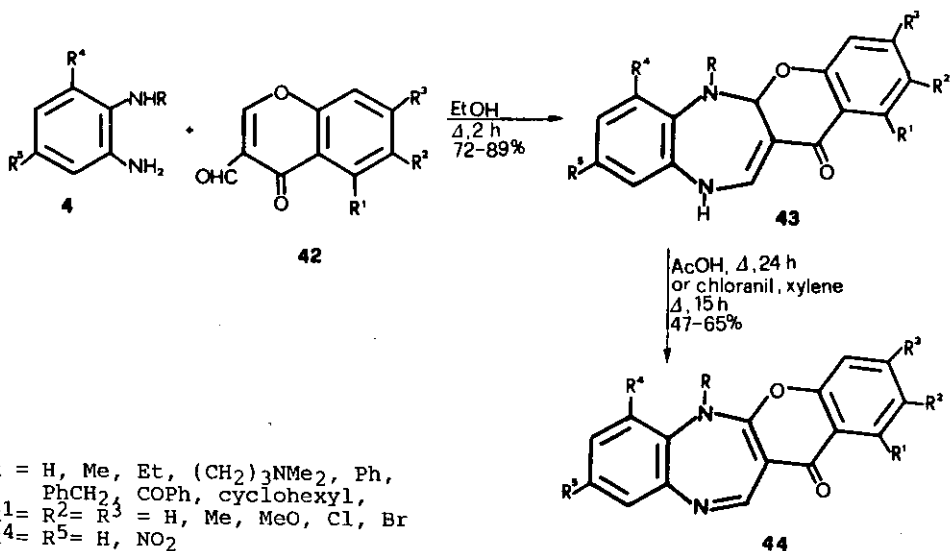
R¹ = Ph, 2-ClC₆H₄, 3-MeC₆H₄, 2-NO₂C₆H₄, 2-pyridyl, 2-thienyl, 5-nitro-2-furyl

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}

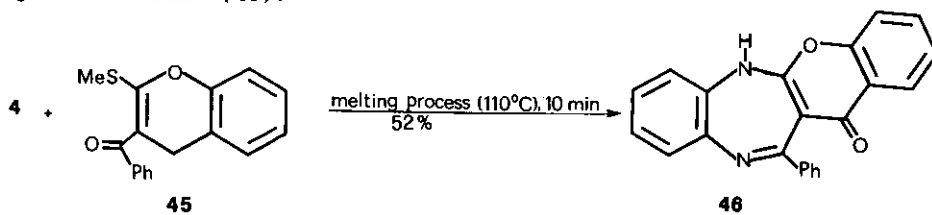


4. Benzopyrano-1,5-benzodiazepines

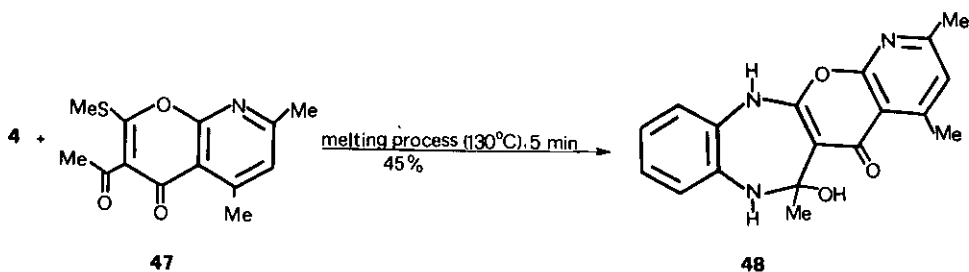
Cyclocondensation of 3-formylchromones (**42**) (or the corresponding acetal) with 1,2-phenylenediamine derivatives (**4**) afforded 5a,11-dihydroderivatives (**43**), which were dehydrogenated by prolonged heating, or treatment with chloranil, air oxidation or digestion in acetic acid to give [1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-ones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



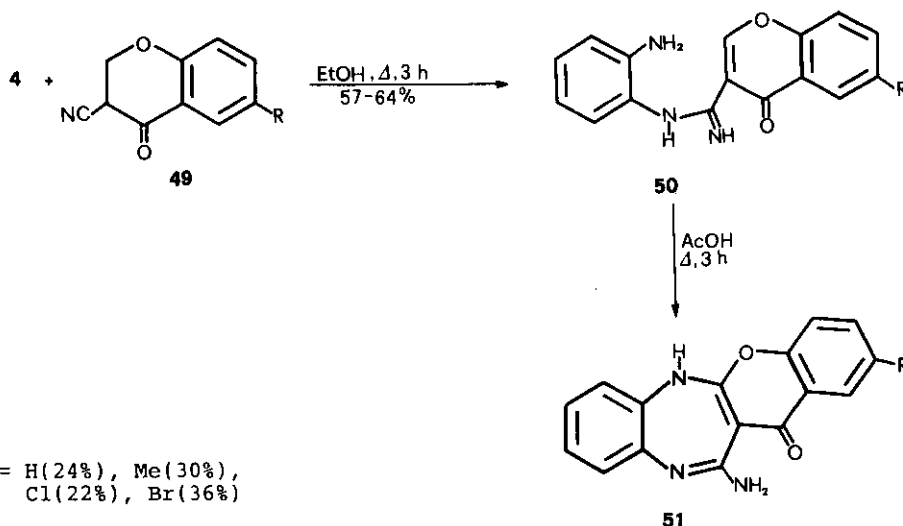
12-Phenyl[1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-one (46) was similarly prepared by reaction of 1,2-phenylenediamine (4) and 3-benzoyl-2-methylthiochromone (45).⁵²



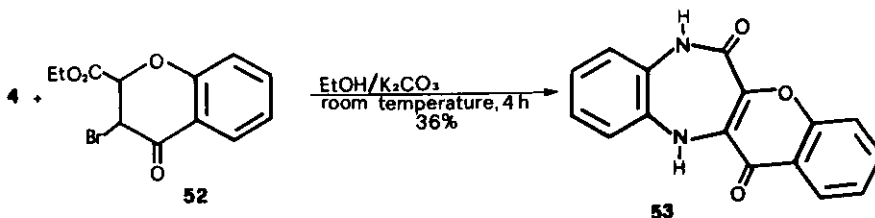
The same authors reported the reaction of 3-acetyl-2-methylthioazachromone (47) with 1,2-phenylenediamine (4) which afforded 7,12-dihydro-6-hydroxy-2,4,6-trimethylpyrido[3',2':5,6]pyrano[2,3-b][1,5]benzodiazepin-5(6H)-one (48).⁵³



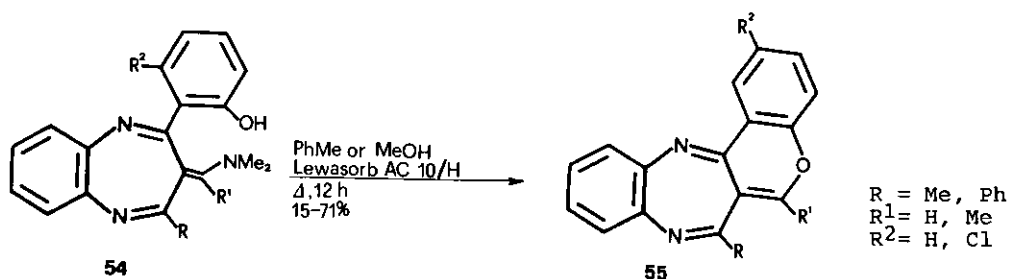
1,2-Amino substituted derivatives (51) were also synthesized starting from 4-oxo-4H-[1]benzopyran-3-carbonitriles (49). The 1,2-addition of 1,2-phenylenediamine (4) to the nitrile function gave the intermediate amidines (50) which on cyclization and subsequent air oxidation afforded 51.⁵⁴



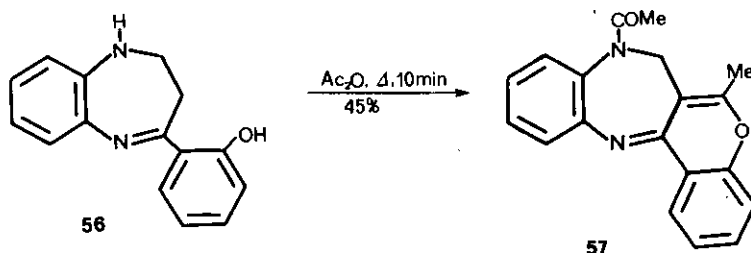
The reaction of ethyl 3-bromochromone-2-carboxylate (52) with 1,2-phenylenediamine (4) in the presence of anhydrous potassium carbonate afforded 7,12-dihydro[1]benzopyrano[3,2-b][1,5]benzodiazepin-6,13-dione (53).⁵⁵



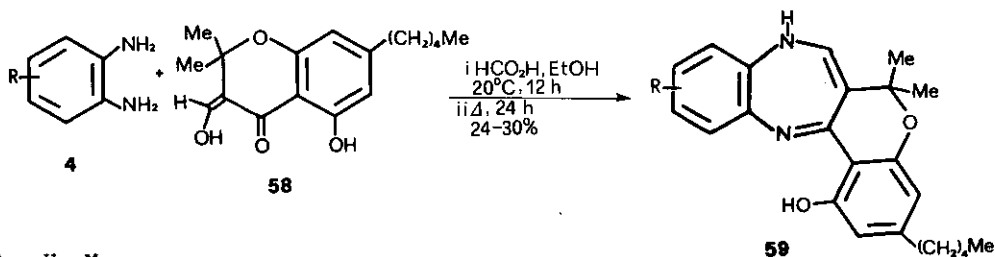
[1]Benzopyrano[4,3-b][1,5]benzodiazepines (55) useful as sedatives, anti-hypertensives, analgesics, anticonvulsants and sympatholytics, were prepared by cyclizing (Z)-3-dimethylaminomethylidene-1,5-benzodiazepines (54), under reflux in toluene or methanol containing an acid ion exchanger (Lewasorb AC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



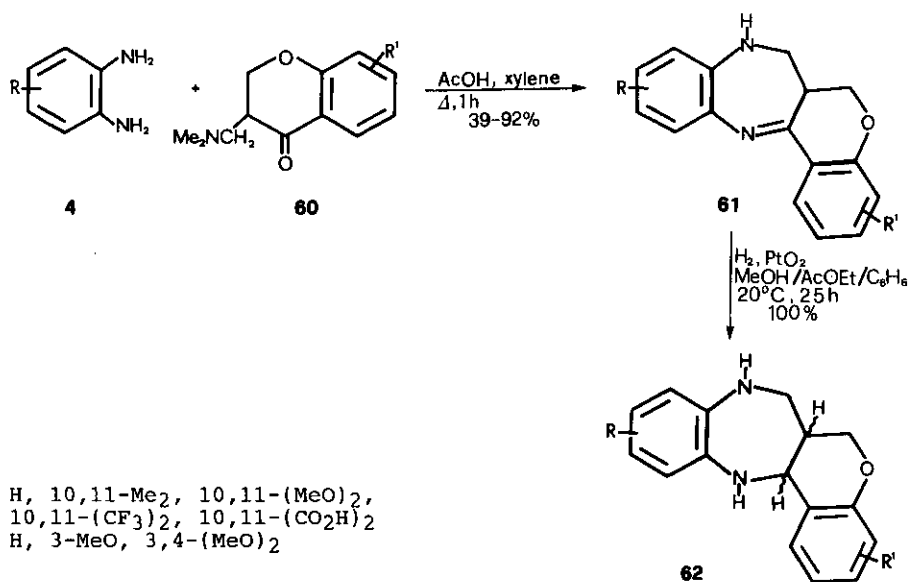
Similarly, 2,3-dihydro-4-(2-hydroxyphenyl)-1H-1,5-benzodiazepine (56) was reacted with acetic anhydride to achieve the ring closure to 7,8-dihydro[1]benzopyrano[4,3-b][1,5]benzodiazepine (57).⁵⁹



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

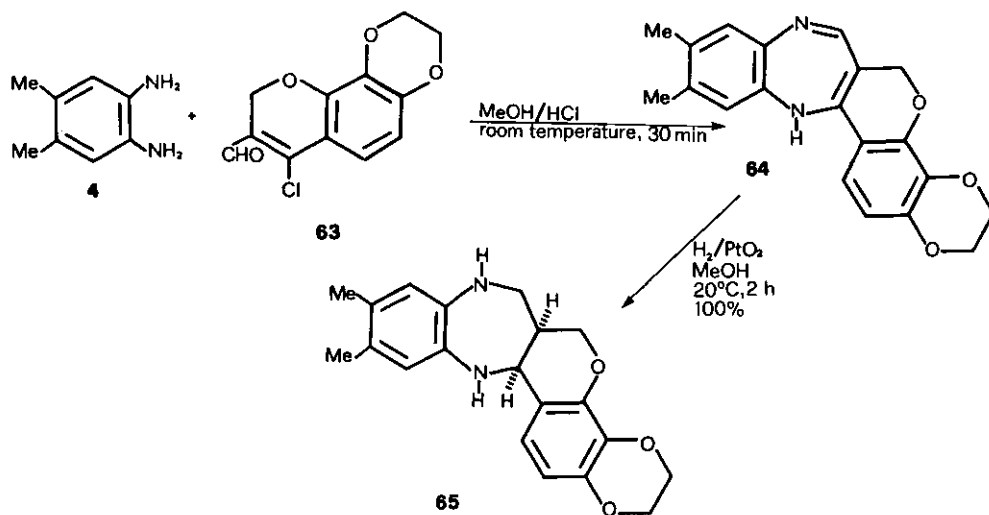


Some 6,6a,7,8,13,13a-hexahydro[1]benzopyrano[4,3-b][1,5]benzodiazepine derivatives (62) show antileukemic and adenylate cyclase system stimulating activity. These compounds were prepared by cyclocondensation of 1,2-phenylenediamine (4) with 3-dimethylaminomethyl-4-chromanone derivatives (60) in the presence of acetic acid, followed by hydrogenation of 61 to give a mixture of cis and trans forms of 62.⁶¹⁻⁶³



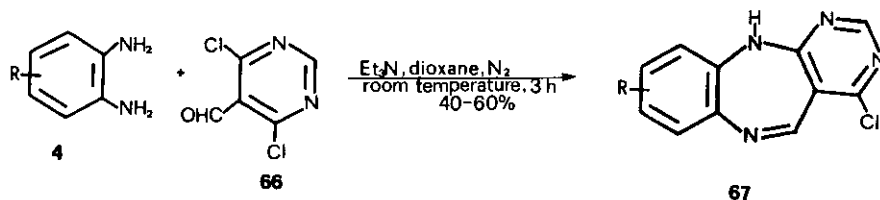
The separation of the mixture into the antileukemic *cis*-form and the inefficacious *trans*-form is reported;⁶² optically active antipodes were also resolved with (+)- β -binaphthylphosphoric acid.^{64,65} The absolute configurations of the HBr salts were assigned by X-ray analysis.^{65,66} Contrary to the high biological activity of (+)-enantiomer against leukemia its (-)-antipode was completely inactive. The antitumor mechanism was studied.⁶⁷⁻⁶⁹ For (+)- and (\pm)- compounds binding studies, using phosphatidylcholine and phosphatidylcholine-cholesterole 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-ethanedioldioxy-2H-chromene (63) in methanol containing HCl, to give unsaturated benzodiazepine derivatives (64) which were hydrogenated over PtO₂ 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



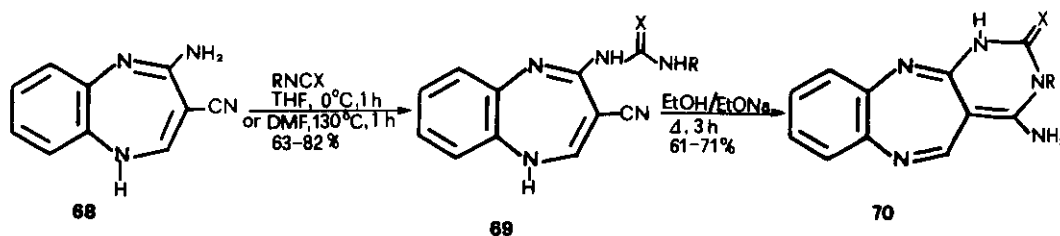
5. Pyrimido-1,5-benzodiazepines

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}



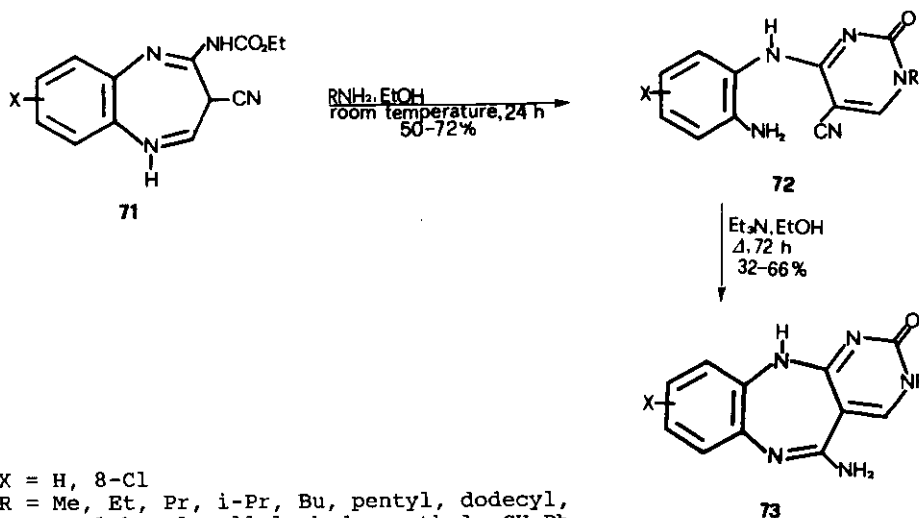
R = H, 8-Me, 9-Me, 8,9-Me₂, 8,9-(MeO)₂, 8-CO₂H, 8-CO₂Me, 8-CF₃, 8,9-Cl₂, 8-NO₂

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



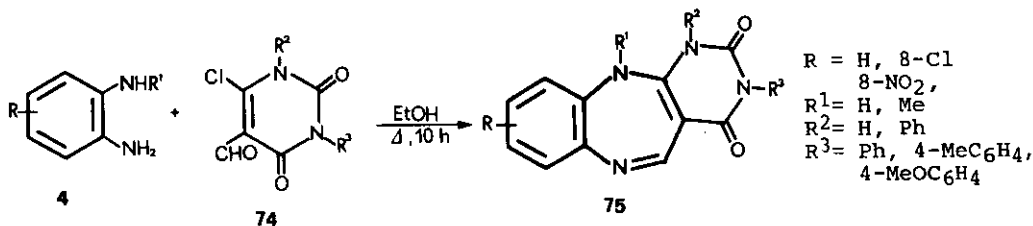
R = Me, Et, Ph
X = O, S

On the other hand, reaction of 1-(ethoxycarbonylamino)-1H-1,5-benzodiazepine-3-carbonitrile (71) with amines gave (aminoanilino)pyrimidocarbonitriles (72), which, upon treatment with Et₃N, cyclized to 11H-pyrimido[4,5-b][1,5]benzodiazepin-2-ones (73).⁷⁵⁻⁷⁷

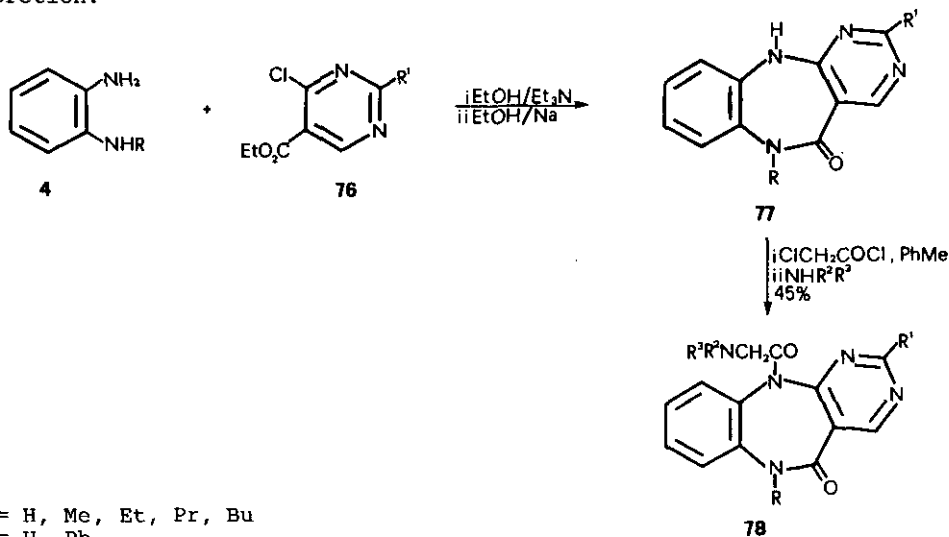


X = H, 8-Cl
R = Me, Et, Pr, i-Pr, Bu, pentyl, dodecyl, cyclohexyl, allyl, hydroxyethyl, CH₂Ph, diethylaminoethyl, 2-(4-morpholinoethyl)

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



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-carbomethoxy-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

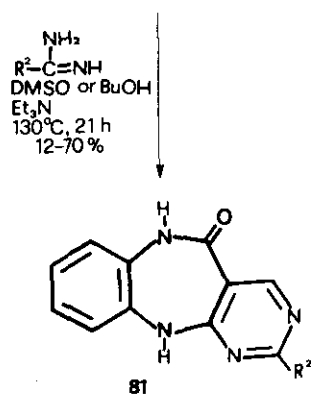
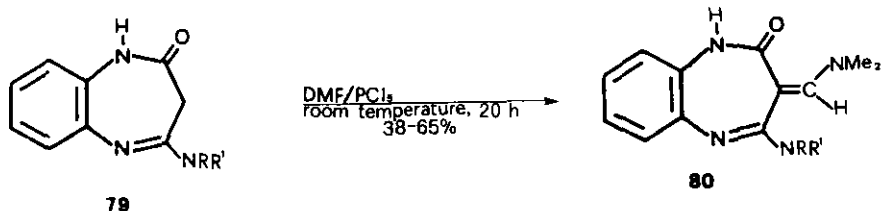


R = H, Me, Et, Pr, Bu

R¹ = H, Ph

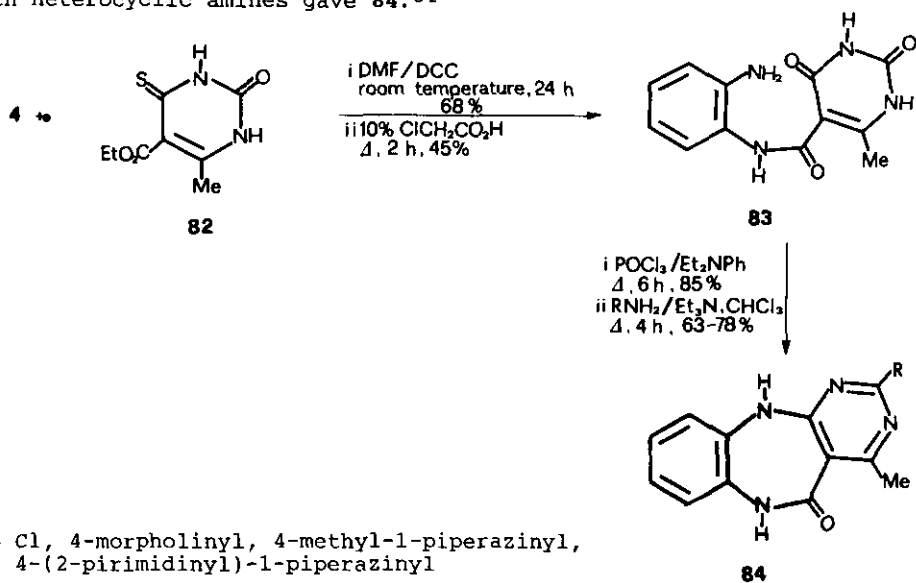
NR²R³ = Me₂N, Et₂N, Bu₂N, morpholinyl,
piperazinyl, pyrrolidinyl

Alternatively, the reaction of 4-dialkylamino-1,3-dihydro-2H-1,5-benzodiazepin-2-one (79) with DMF in the presence of PCl₅ 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

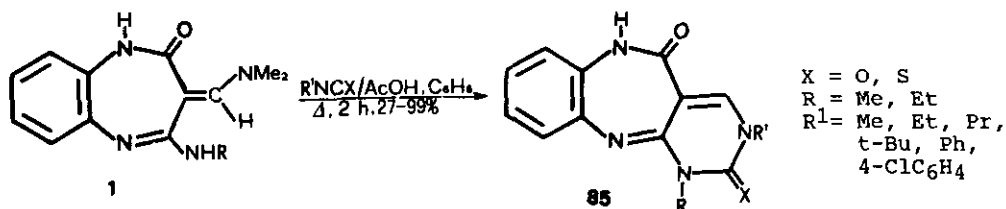


$\text{NRR}^1 = \text{Me}_2\text{N, Et}_2\text{N, pyrrolidinyl}$
 $\text{R}^2 = \text{H, Me, Et, Ph, NH}_2$

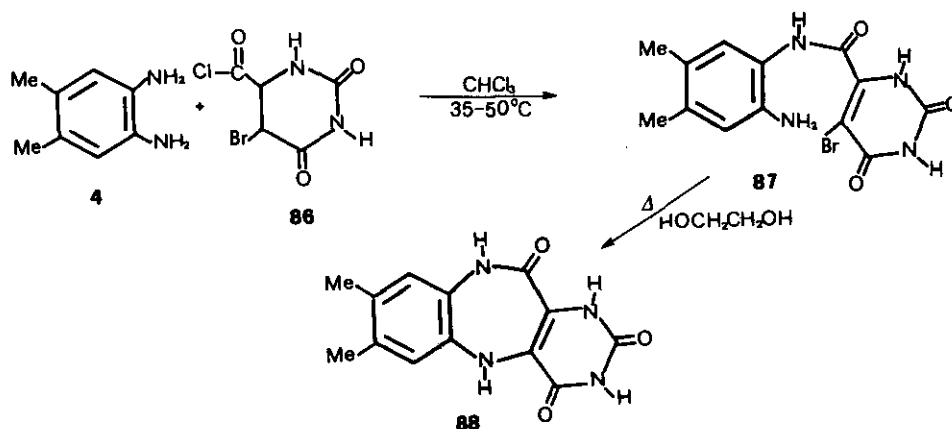
6,11-Dihydro-5H-pyrimido[4,5-b][1,5]benzodiazepin-5-ones (84) were also prepared in several steps from ethyl 6-methyl-1,2,3,4-tetrahydro-2-oxo-4-thioxopyrimidin-5-carboxylate (82). Reaction of 82 with 1,2-phenylenediamine (4), followed by conversion to the dioxo derivative (83), chlorination with POCl_3 using Et_2NPh as catalyst and successive amination with heterocyclic amines gave 84.⁸¹



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

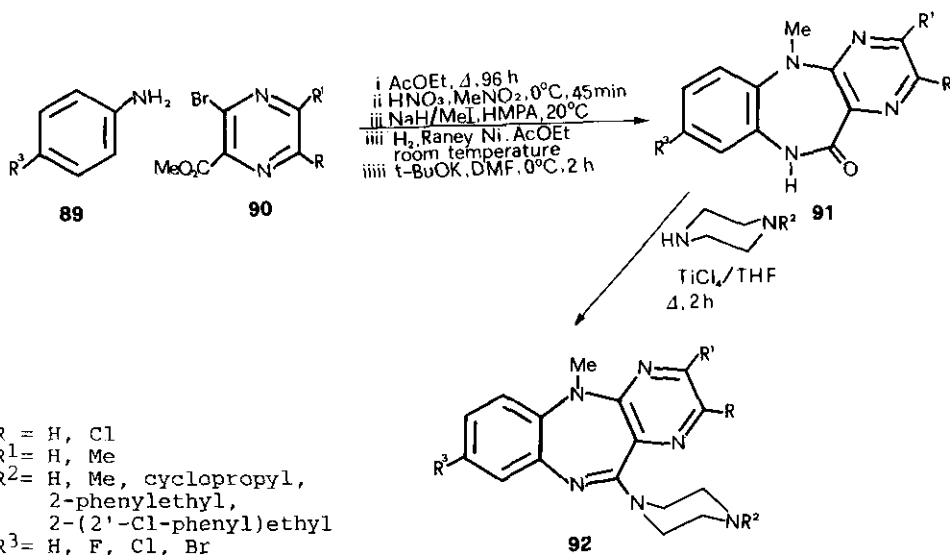


Pyrimido[5,4-b][1,5]benzodiazepines (88) were prepared by reacting 4,5-dimethylphenylenediamine (4) with 5-bromoorotic chloride (86) in $CHCl_3$ at 35-50°C. The resulting 1-N-(5-bromo-4'-orotyl)-4,5-dimethylphenylenediamine amide (87) was cyclized in ethylene glycol.⁸³

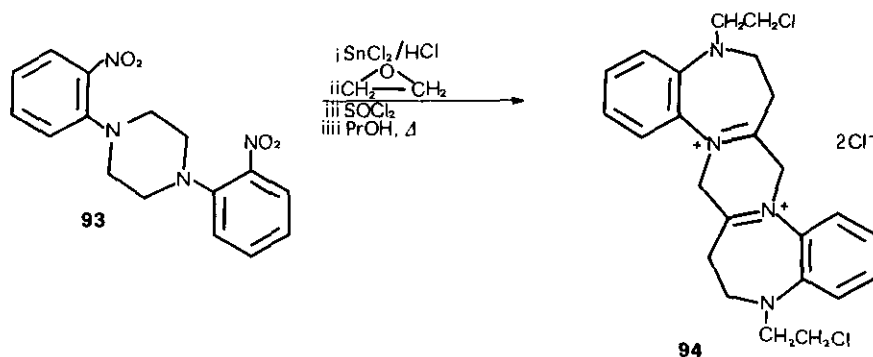


6. Pyrazino-1,5-benzodiazepines

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

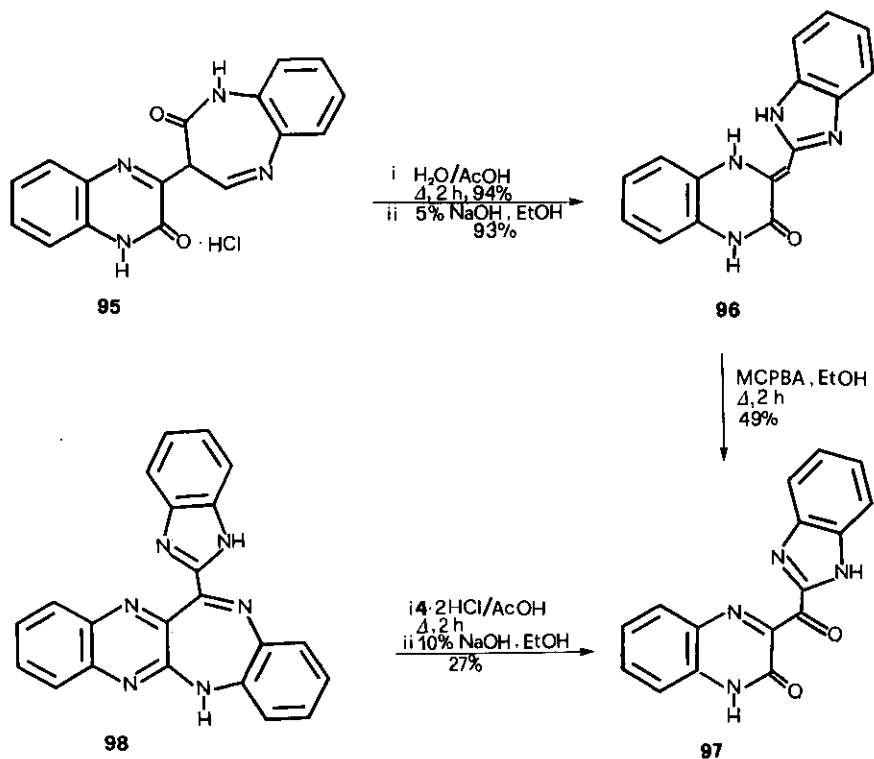


The bis-quaternary salt of pyrazino[1,2-a:4,5-a']bis[1,5]benzodiazepine (94) was prepared from compound (93) by successive reduction, hydroxy-ethylation, treatment with thionyl chloride and heating in propanole.⁸⁵

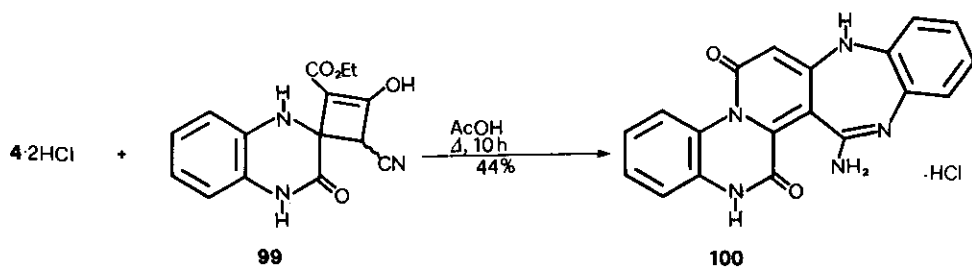


7. Quinoxalino-1,5-benzodiazepines

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}

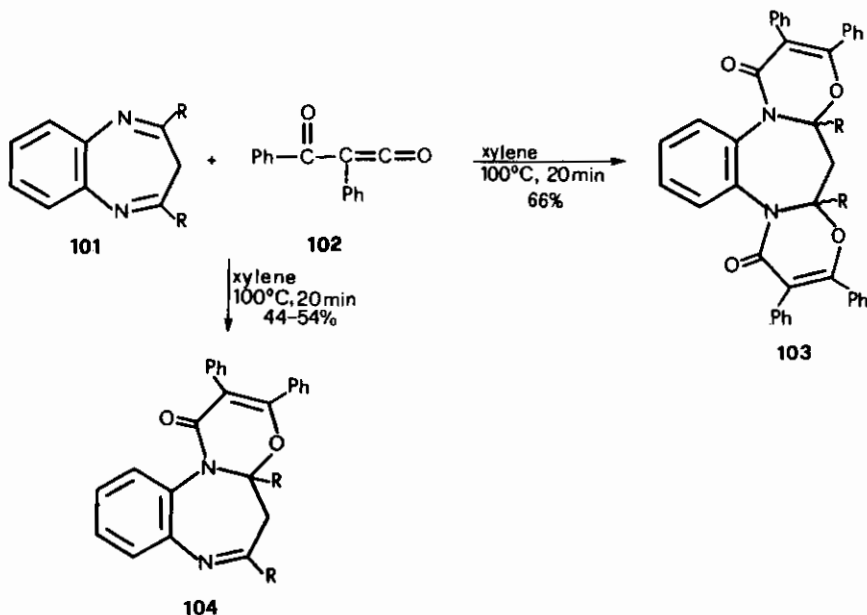


Analogously, the same authors reported the ring transformation of ethoxycarbonylspiro[2-cyclobutene-1,2'(1H)-quinoxaline] (99) to 14-aminoquinoxalino[1',2':1,2]pyrido[4,3-b][1,5]benzodiazepine-6,15(8H,16H)-dione hydrochloride (100) by reaction with *o*-phenylenediamine dihydrochloride (4) in acetic acid.^{88,89}



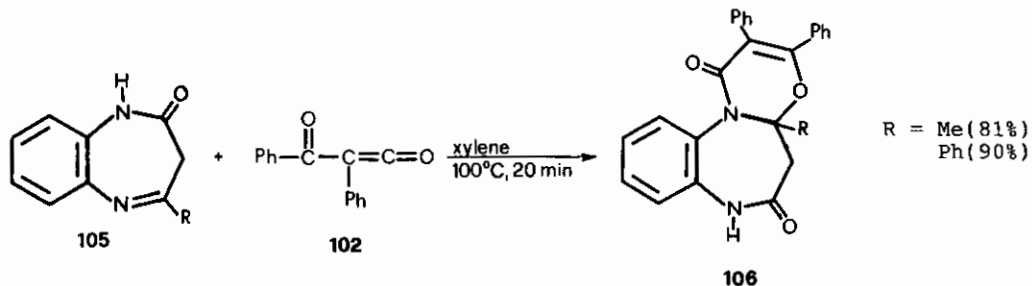
8. Oxazino-1,5-benzodiazepines

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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