

RECENT ADVANCES IN THE SYNTHESIS OF ANNELATED 1,4-BENZODIAZEPINES

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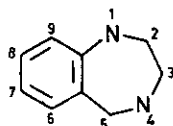
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Abstract — This review describes the recent progress in the syntheses of mono- and di-annelated 1,4-benzodiazepines with three, four, five, six and seven-membered rings fused to different positions of 1,4-benzodiazepine nucleus.

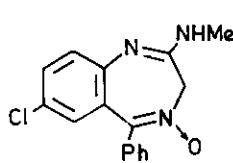
1. Introduction

1,4-Benzodiazepines (1) are bicyclic heterocyclic compounds with two nitrogen atoms at 1 & 4 positions of a seven-membered ring fused to benzene ring.

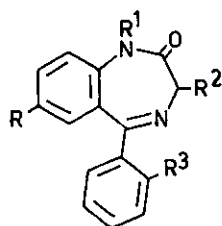


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Several substituted 1,4-benzodiazepines and their oxo derivatives have acquired pharmacological importance as potential tranquilizing, CNS depressant, anti-inflammatory, anti-convulsant, antispasmodic, muscle relaxant, hypnotic and sedative agents¹. This led to the discovery of several drugs, and particular mention



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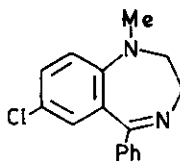


(3) $R = Cl, R^1 = Me, R^2 = R^3 = H$

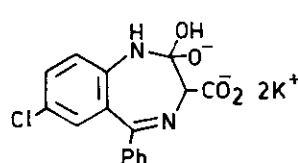
(4) $R = Cl, R^1 = R^3 = H, R^2 = OH$

(5) $R = NO_2, R^1 = R^2 = R^3 = H$

(6) $R = Cl, R^1 = CH_2CH_2NEt_2, R^2 = H, R^3 = F$



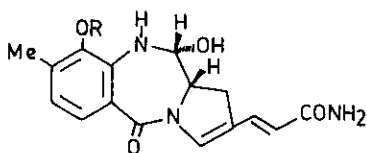
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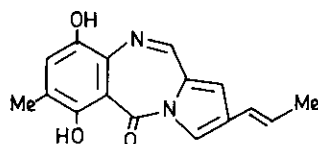
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may be made of the seven drugs marketed under the trade names Librium (chlordiazepoxide, 2), Valium (diazepam, 3), Serax (oxazepam, 4), Mogadan (nitrazepam, 5), Dalmane (flurazepam, 6), Nobrium (medazepam, 7), Tranxene or Tranxilium (chlorazepate, 8), for their extensive and useful psychopharmacological activity.

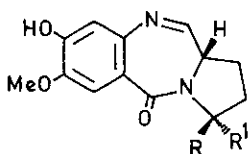
Since the discovery of anthramycin (9)², sibiromycin (10)³, neothramcyin (11a, 11b)⁴, pretomeimycin (11c)⁵ and tomaymycin (11d)⁶ as antibiotics, and oxazolam (12)⁷, cloxazolam (12a)⁷, estazolam (13)^{7a}, alprazolam (14)⁸, triazolam (14a)⁸, ketazolam (15)⁹ as antianxiety agents, a great deal of work has been carried out during the past two decades on various facets of hetero ring annelated 1,4-benzodiazepines.



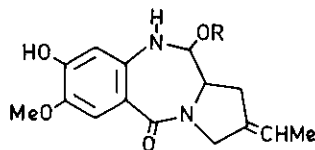
(9) R = H
(9a) R = Me



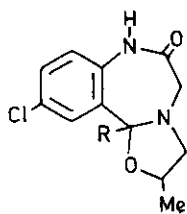
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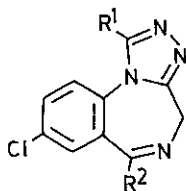
(11a) R = H, R¹ = OH
(11b) R = OH, R¹ = H



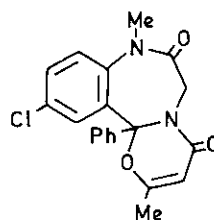
(11c) R = Et
(11d) R = Me



(12) R = C₆H₅
(12a) R = 2-Cl-C₆H₄



(13) R¹ = H, R² = C₆H₅
(14) R¹ = Me, R² = C₆H₅
(14a) R¹ = Me, R² = 2-Cl-C₆H₄

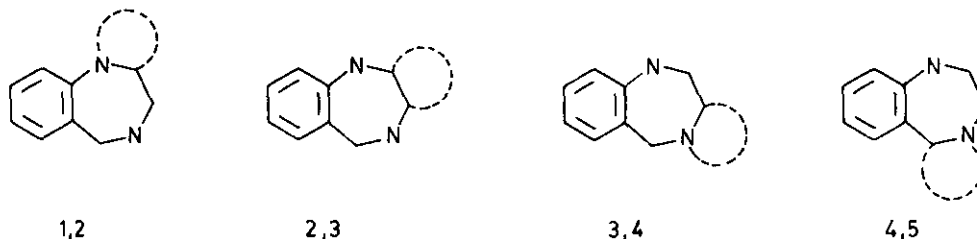


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While the chemistry of 1,4-benzodiazepine derivatives has been comprehensively reviewed by various authors¹⁰⁻¹⁹, no such review on the syntheses of annelated 1,4-benzodiazepines is available except a partial survey along with 1,5-benzodiazepines, 1,3-benzodiazepines and 2,4-benzodiazepines^{19,20}. Diannelated systems based on 1,4-benzodiazepines are not given significant coverage in the latter. As such, the present article, covering all the available literature on mono- and diannelated 1,4-benzodiazepines has been prepared. In view of the voluminous data available on the synthesis, chemistry and pharmacological properties of these derivatives, emphasis has been given to the synthetic methodology in the present review. This review covers, methods reported in literature upto December, 1985.

2. Mono-annelated 1,4-benzodiazepines

Compounds with three, four, five, six and seven-membered rings fused to the different positions of 1,4-benzodiazepine skeleton are known.



3. Three-membered rings annelated to 1,4-benzodiazepines

Only one example of this class - oxazirino[2,3-d][1,4]benzodiazepine (17) is reported²¹⁻²⁵. This is prepared by the photoisomerization of the corresponding substituted 1,3-dihydro-2H-1,4-benzodiazepin-2-one-4-oxides (16) (Scheme 1).

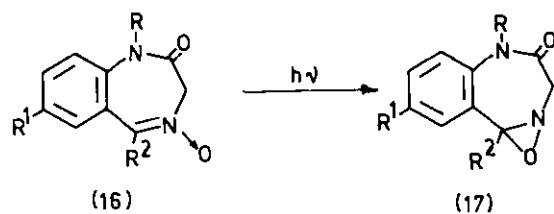
4. Four-membered rings annelated to 1,4-benzodiazepines

Novel azeto[3,4-b][1,4]benzodiazepines (19) were obtained by Shenoy²⁶⁻²⁸ by 40% alkali induced rearrangement of the adduct (18), prepared from chlordiazepoxide (2) and aliphatic aldehydes. The mechanism of the methyl migration into diazepine ring is not clear. Use of 10% sodium hydroxide in this reaction, however, resulted in 1,5-benzodiazocine-5-oxides²⁹. Walter and Emilio³⁰ prepared azetobenzodiazepine-dione (21) by the cyclocondensation of L-2-azetidinecarboxylic acid with 5-chloroisatoic anhydride (20). A simple preparation of azetidino[1,2-d][1,4]benzodiazepine (22) has been reported³¹ by the treatment of diazepam (3) with $\text{EtO}_2\text{CCH}=\text{C}(\text{Me})\text{NHCH}_2\text{CO}_2\text{K}$ in the presence of triethylamine and phosphorus oxychloride (Scheme 2).

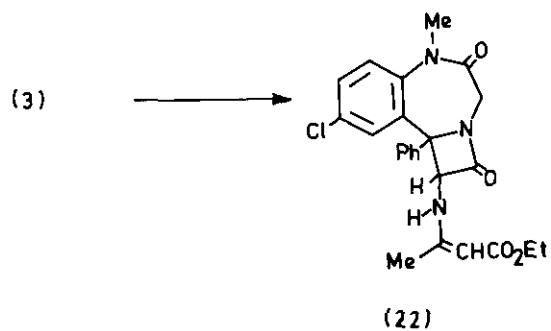
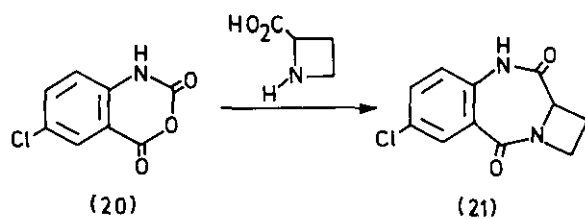
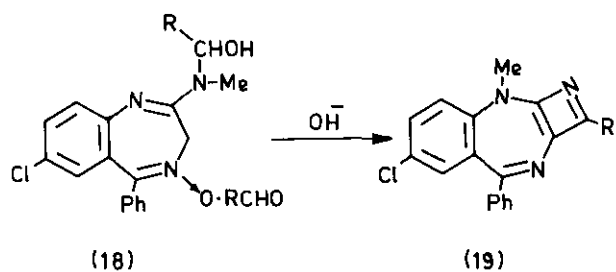
5. Five-membered rings annelated to 1,4-benzodiazepines

Pyrrolo, thieno, oxazolo, isoxazolo, pyrazolo, imidazo, thiazolo, triazolo, oxadiazolo, tetrazolo and thia-triazolo-1,4-benzodiazepines are known in literature.

Scheme 1



Scheme 2



5.1 Pyrrolo-1,4-benzodiazepines

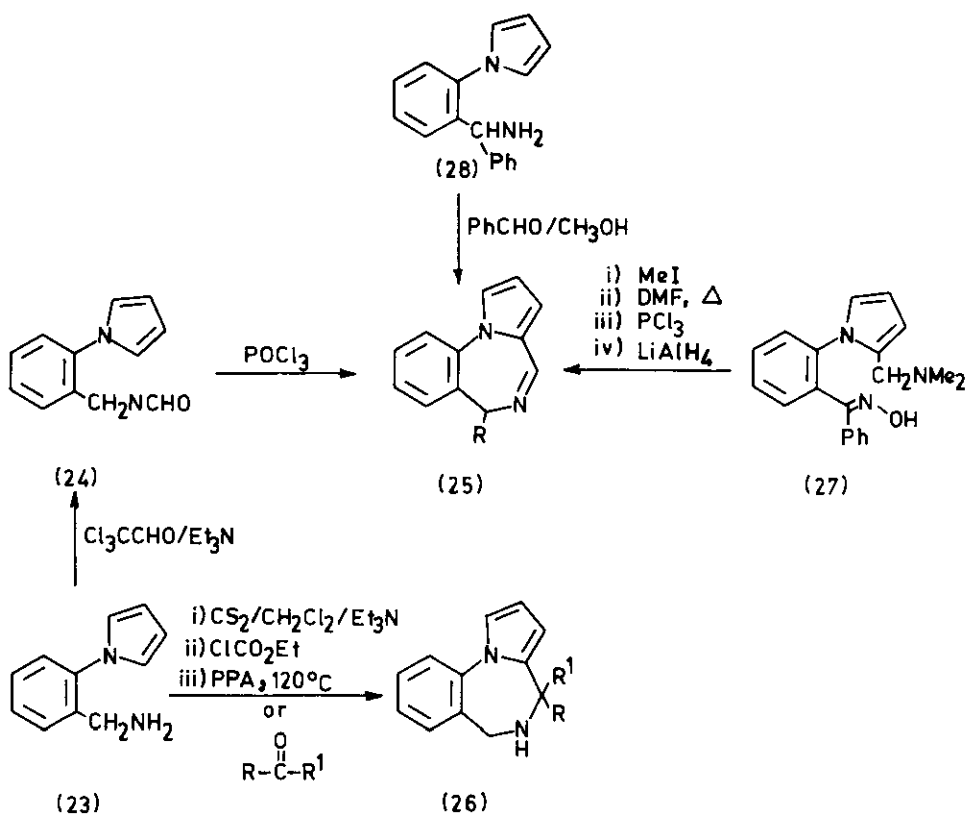
Pyrrolobenzodiazepines are antitumor antibiotics and of the three possible types, 1,4-benzodiazepines fused at 3,4-position are important. The general synthetic methods of the various pyrrolobenzodiazepines are outlined in Scheme 3-8.

6H-Pyrrolo[1,2-a] [1,4] benzodiazepine (25, R=H), prepared by the cyclization^{32,33} of 1-[2-(formylamino-methyl)phenyl]pyrrole (24) with phosphorus oxychloride. The formyl compound (24) was in the turn prepared by the reaction of 1-[2-(aminomethyl)phenyl]pyrrole (23) with chloral hydrate in the presence of triethylamine. Condensation of the hydrochloride of (23) with ketones³⁴ gave, on the other hand, 5,6-dihydro-4H-pyrrolo[1,2-a] [1,4]benzodiazepines (26)³². The isothiocyanation of 23 gave 2-(1-pyrrolidinyl)phenylmethyl isothiocyanate which on heating at 120°C in the presence of polyphosphoric acid³⁵ yielded (26, R=R'=S). The 6-aryl analogs of (25, R=Ph) are also known^{36,37} and were prepared starting from 2-(2-dimethylamino-1-pyrrolyl)benzophenone oxime (27) and 2-(1-pyrrolyl)benzhydramine (28) (Scheme 3). Yasutaka and his coworkers³⁸ obtained 30 in 65% yield by the hydrazinolysis of 2-pyrrolo-1-yl-benzophenones (29) as shown in Scheme 4.

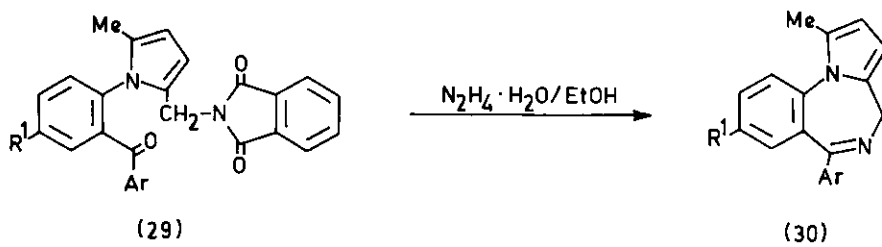
Three principal approaches are known for preparing pyrrolo[2,1-c] [1,4]benzodiazepines. The first one involved the reductive cyclization of 2-substituted 1-(2'-nitrobenzoyl)pyrrole derivatives. Thus, the oxime of 1-(2'-nitrobenzoyl)pyrrole-2-carboxaldehyde (31) on reductive cyclization³⁹ gave 10,11-dihydro-5H-pyrrolo[2,1-c] [1,4]benzodiazepine (32). Compound 33 underwent similar cyclization at room temperature in the presence of hydrogen and Pd/BaSO₄ to give 34. In this reaction, reduction of nitro to amino followed by cyclodehydration and hydrogenolysis of benzyloxy group seems to occur in one-step^{40,41}. Use of 10% Pd-C in a reductive cyclization⁴² of 35 afforded 36. The reductive cyclization⁴³ of benzylmethylaminomethyl 1-(2-nitrobenzyl)-2-pyrrolyl ketone (37) gave 10,11-dihydro-5H-pyrrolo[2,1-c] [1,4]benzodiazepine (38). Massa and his coworkers⁴⁴ reported the synthesis of pyrrolo[2,1-c] [1,4]benzodiazepine-5,11-dione (40) from 1-(2-nitrobenzoyl)pyrrolidine derivative (39). The key intermediate 42, in the total synthesis of anthramycin (9)² was also prepared by this method from 41 by sodium dithionite treatment followed by cyclization using hydrochloric acid. Recently Anand and his coworkers⁴⁵ used catalytic hydrogenation followed by treatment with methanolic hydrochloric acid in a similar reaction (Scheme 5). The second approach uses isatoic anhydride (43) with L-(-)-proline⁴⁶⁻⁵⁰. A facile and new method for the synthesis of dimethyl anhydrosibromycinone⁵¹ which is a pyrrolo[2,1-c] [1,4]benzodiazepine derivative, was reported from sulphinamide anhydride (45) and substituted pyrrole-2-carboxaldehyde, which underwent cyclocondensation to give 67% of dimethyl anhydrosibromycinone (46) (Scheme 6).

Other methods known for the synthesis of pyrrolo[2,1-c] [1,4]benzodiazepines, viz. [48, 50 (R=OH, NH₂), 11a, 11b, 52] involve the cyclization⁵² of 1-(2-aminobenzyl)pyrrole (47) with methoxy hemiacetal of methyl glyoxylate, either base catalyzed⁵³ or phase transfer reaction⁵⁴ of 1-(2-aminobenzyl)-2-cyanopyrrole (49), refluxing 1-(2-arylaminobenzyl)-2-cyanopyrrole (51) with phosphorus oxychloride⁵⁵ and thermal cycliza-

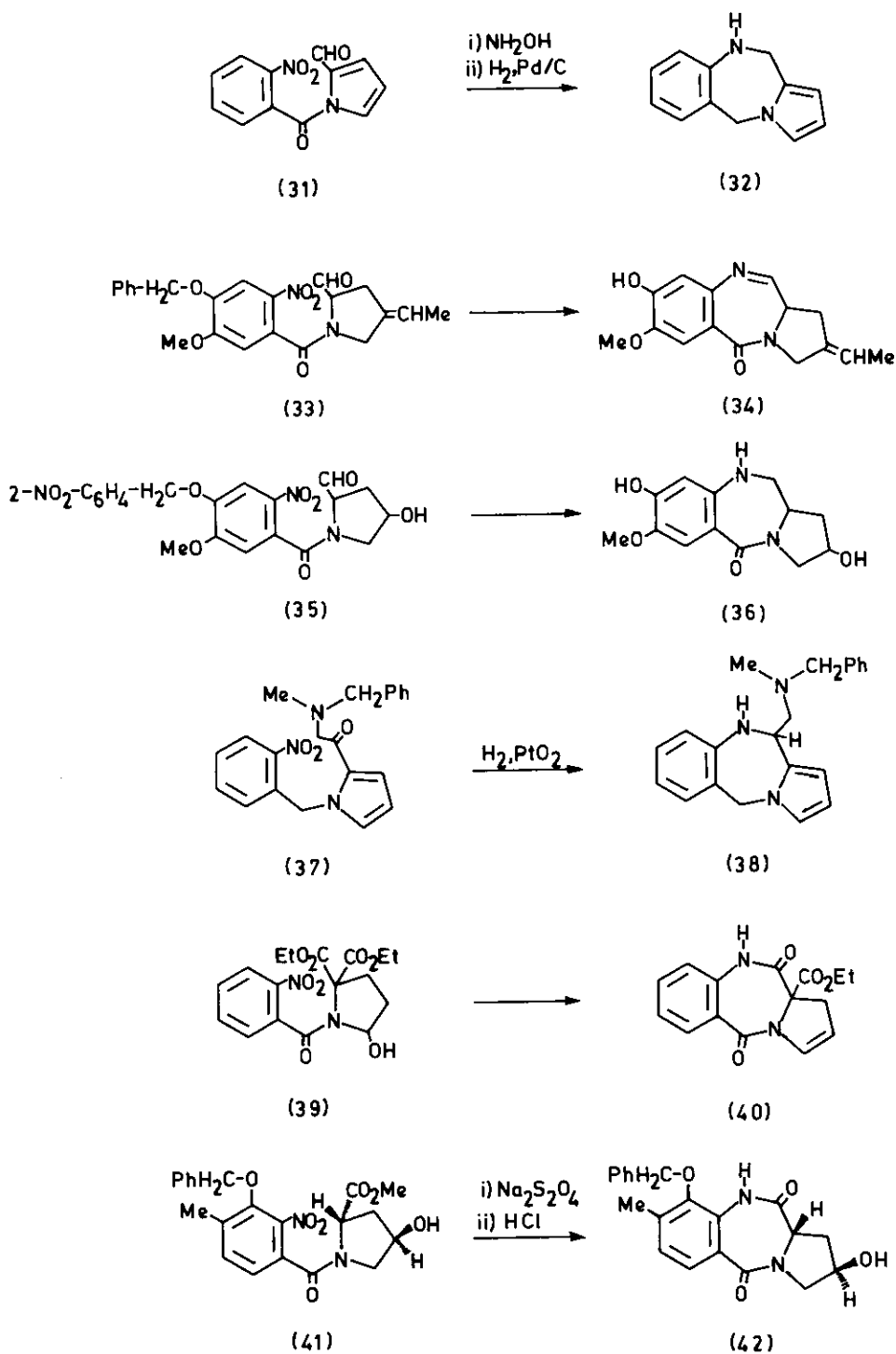
Scheme 3



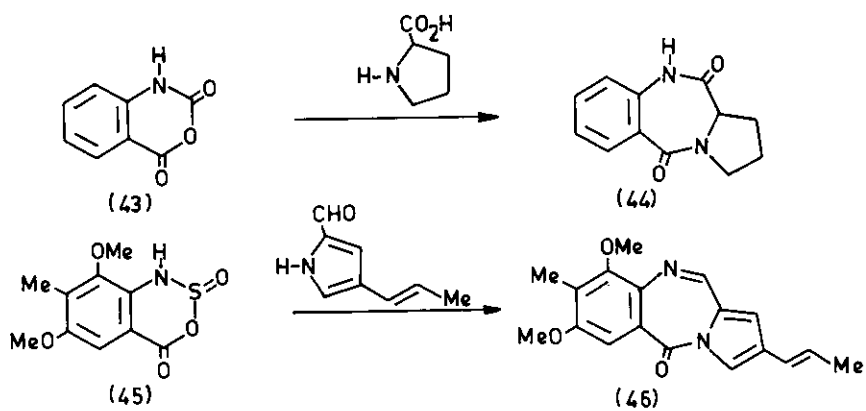
Scheme 4



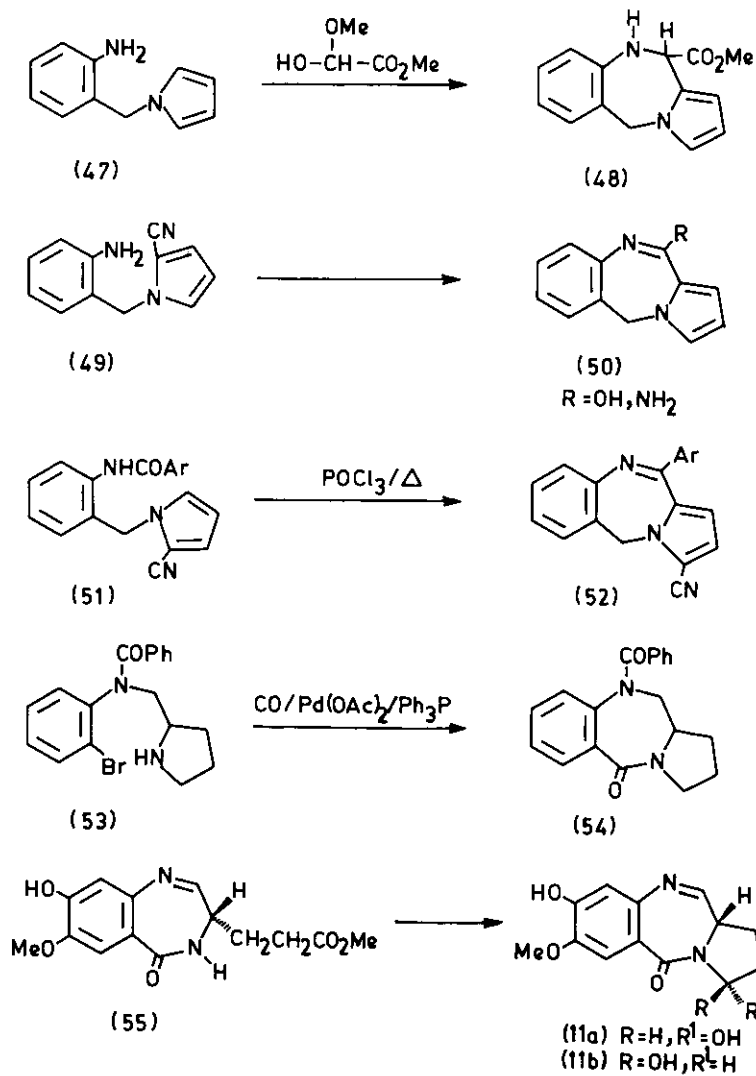
Scheme 5



Scheme 6



Scheme 7



tion^{4,56} of 3-substituted 1,4-benzodiazepin-5-one (55). Recently, a new pyrrolo-1,4-benzodiazepine (54) was synthesised by the insertion of CO with 2-bromopropylaniline (53) in the presence of palladium (II) acetate and triphenyl phosphine⁵⁷. In this palladium-catalyzed carbonylation reaction, the use of $(\text{Me}_2\text{N})_3\text{PO}$ as solvent and high pressure of carbon monoxide (5 atm.) increased the yield of 54 (Scheme 7).

Pyrrolo[1,2-d] [1,4]benzodiazepine (57) was prepared by Aiello and his coworkers⁵⁸ from the reductive cyclization of the corresponding pyrrol-1-yl-acetic acid (56) in Pd-C/EtOH. The compound 57 was also prepared⁵⁹ by the reaction of 2-methyl-3-acetyl-5-(2'-aminophenyl)pyrrole (58) with bromoacetyl bromide in triethylamine (Scheme 8).

DL-Benzoylkynurenylglycine (59) was heated above its melting point in vacuum to give 2-benzamido-2,7-dihydro-5H-pyrrolo[1,2-d] [1,4]benzodiazepin-3,6-dione (60) in 72% yield^{60,61}. Formation of 60 is explained through thermal intramolecular cyclocondensation to a pyrrolinone intermediate followed by lactimization (Scheme 9).

The benzo analogs of pyrrolobenzodiazepines viz. indolobenzodiazepines are known to possess antidepressant and anticonvulsive properties⁶²⁻⁶⁵. Three isomeric systems [3,2-b], [2,1-c] and [1,2-d] (61, 62, 63) have so far been reported and their methods of synthesis generally are the same as of the corresponding pyrrolobenzodiazepines (Scheme 10).

5.2 Thieno-1,4-benzodiazepines

Three types of thienobenzodiazepines are known so far. Safir and his coworkers^{66,67} prepared 4H-thieno-[3,4-b] [1,4]benzodiazepin-9-(10H)-one (65, X=H, Cl, F) by heating the respective amides (64) at 115-118°C in polyphosphoric acid.

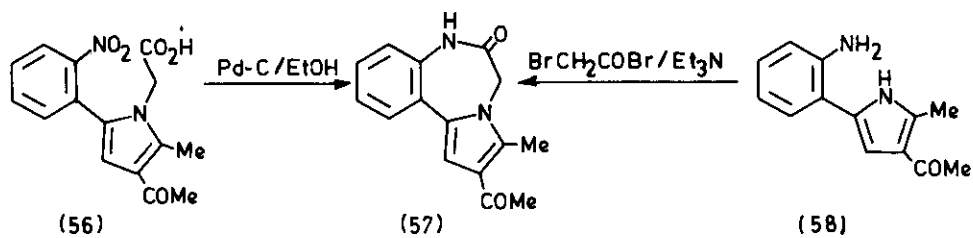
Chakrabarti and Tupper⁶⁸ reported the synthesis of the other type, 4H-thieno [2,3-b] [1,4]benzodiazepin-9-one (67) by the treatment of 5-acetyl-3-amino-2-(2'-methoxycarbonylanilino)thiophene (66) with dimethyl sodium in dimethyl sulphoxide. Thieno[3,2-b] [1,4]benzodiazepin (69) was prepared from the nitro acid (68) by the treatment of $\text{EtOCOCl}/\text{Et}_3\text{N}$ followed by hydrogenation in Pd-C⁶⁹. Compound 68 after esterification, catalytic reduction and cyclisation under basic conditions⁷⁰ afforded 69 (Scheme 11).

5.3 Oxazolo-1,4-benzodiazepines

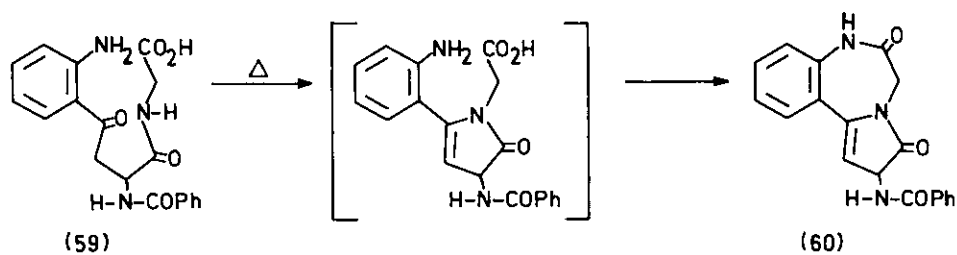
Three types of oxazolobenzodiazepines are known. In all the cases, the oxazole ring is built on 1,4-benzodiazepine derivatives using suitable reagents. Thus, 6-aryl-1,2-dihydrooxazolo[3,2-a] [1,4]benzodiazepines (71) were conveniently prepared by reacting the benzodiazepinone (70) with ethylene dibromide in the presence of a base⁷¹. On the other hand, oxazolo[4,5-b] [1,4]benzodiazepine derivatives (73) were prepared by treating 7-chloro-2-amino-3-hydroxy-5-phenyl-3H-1,4-benzodiazepine (72) with ethyl oxalyl chloride⁷². Chlordiazepoxide (2) also gave (73) under similar experimental conditions.

The N-oxide of 7-chloro-2-amino-5-phenyl-3H-1,4-benzodiazepine (74) on heating with acetic anhydride yielded (75), involving a Polovonski rearrangement in the process⁷².

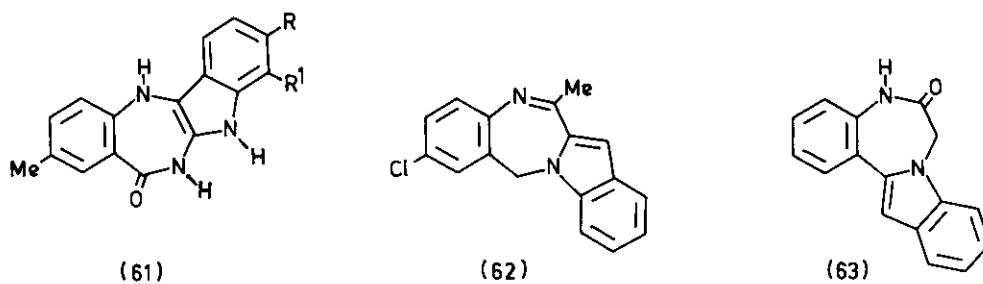
Scheme 8



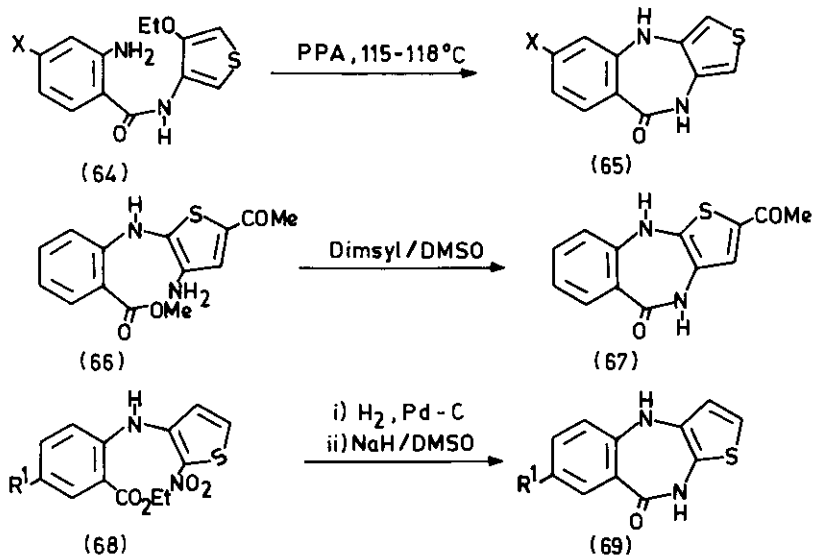
Scheme 9



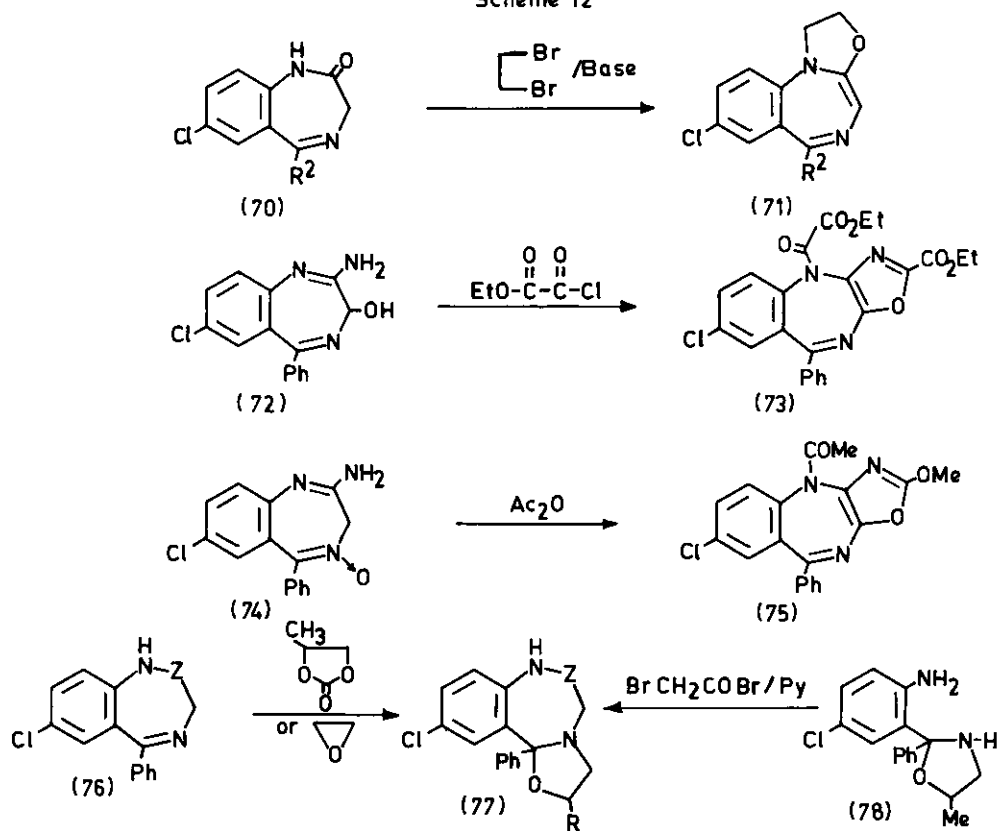
Scheme 10



Scheme 11



Scheme 12



Masuko⁷³ prepared oxazol[3,2-d] [1,4]benzodiazepine (77, Z=CH₂, R=Me) by heating dihydro-1,4-benzodiazepine (76, Z=CH₂) with 1,2-propylene carbonate. The oxo derivative (77, Z=CO, R=Me), also known as oxazolam (12), however, was conveniently prepared by cyclizing the substituted oxazolidine (78) with bromoacetyl bromide in pyridine⁷⁴. 5-Chloro-2-(bromoacetamido)benzophenone on treatment with aziridine⁷⁵ or ethanolamine⁷⁶ gave 77 (Z=CO, R=H). Acid catalyzed addition of ethylene oxide⁷⁷⁻⁸¹ to 4,5-double bond of benzodiazepinone 76 (Z=CO) afforded 77 (Z=CO), (Scheme 12).

5.4 Isoxazolo-1,4-benzodiazepines

Takashima and his coworkers⁸² reported the synthesis of a large number of isoxazolo[2,3-d] [1,4]benzodiazepines (79) from suitably substituted 1,4-benzodiazepin-2-one-4-oxides (16) and alkynes. The mechanism of this reaction is explained through an intermolecular 1,3-dipolar [$\pi 4s + \pi 2s$] cycloaddition of the nitron (16) to alkyne⁸²⁻⁸⁴. The regiospecificity of this 1,3-dipolar cycloaddition⁸⁵ has been established by the reaction of acrylic ester with diazepam-4-oxide (16, R=Me, R¹=Cl, R²=Ph) to give tetrahydro-isoxazolo[2,3-d] [1,4]benzodiazepinone (80, R=Me, R¹=Cl, R²=Ph, R³=R⁴=H, R⁵=CO₂Et), (Scheme 13).

5.5 Pyrazolo-1,4-benzodiazepines

These compounds are prepared by the cyclization of suitably substituted pyrazolyl derivatives. Thus, pyrazolo[1,5-a] [1,4]benzodiazepine (82) was prepared from 81 by heating with a mixture of Zn/AcOH/HCl⁸⁶. Dattolo and his coworkers⁸⁷ recently prepared a new type of pyrazolo[1,5-d] [1,4]benzodiazepine derivative (84) by the hydrogenative cyclization of the pyrazol-1-yl-acetic acid (83) over 10% Pd-C catalyst. Adopting this method, 5H-pyrazolo[5,1-c] [1,4]benzodiazepine (85) was also prepared^{88,89}.

The benzo analogs of pyrazolobenzodiazepines are also known. Thus, the 3-(2'-aminophenyl)indazole derivative (86, R=Cl, Br, Me; R¹=H, Br; R²=SO₂NH₂), on reaction with chloroacetyl chloride, gave the corresponding indazolo[2,3-c]quinazolines (87), which on alkali treatment underwent ring expansion to give 5,7-dihydro-6-oxo-6H-indazolo[2,3-d] [1,4]benzodiazepines (88)⁹⁰ (Scheme 14).

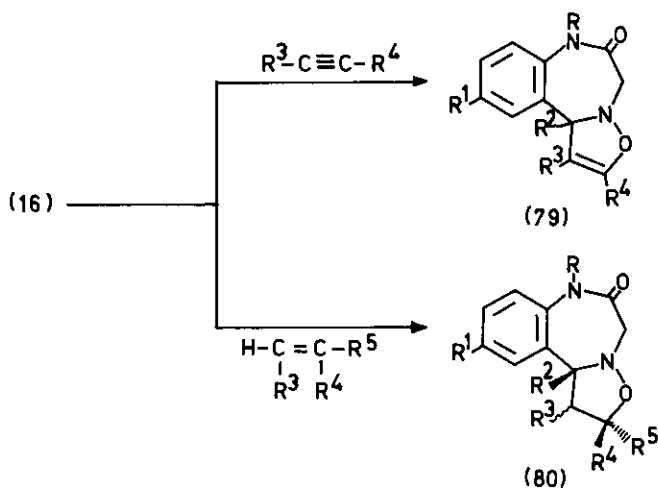
5.6 Imidazo-1,4-benzodiazepines

Six types of fused imidazobenzodiazepines are known and the synthetic methods vary with the type of fusion and generally fall under two categories - a) reactions leading to imidazole ring on preformed benzodiazepines and b) cyclizations of suitably functionalized imidazolyl derivatives.

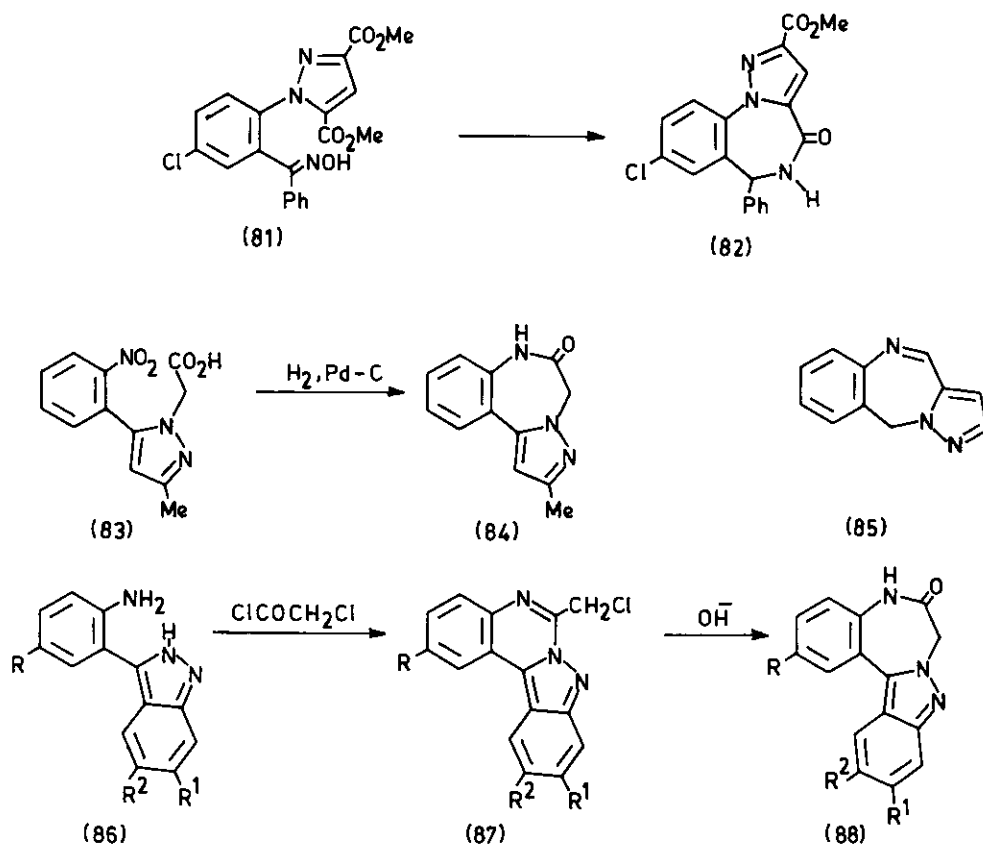
Imidazo[1,2-a] [1,4]benzodiazepine-1,2-diones (90) are prepared by heating chlordiazepoxide (2) with oxalyl chloride in benzene⁷². Compound 90 are also obtained in the condensation reactions of (89, R=NH₂) with oxalyl chloride⁷². Benzodiazepines (89, R=SH, SMe, SO₂Et) on condensation with propargylamine in p-toluenesulphonic acid gave 35% of 4H-imidazo[1,2-a] [1,4]benzodiazepines (91)⁹¹. The cyclocondensation of glycine with 89, (R=SH) afforded 92⁹².

The second method of synthesis starts from imidazolylbenzophenone derivatives. Thus, 94 is prepared from 93 by reacting with hexamine/EtOH⁹³, (Scheme 15).

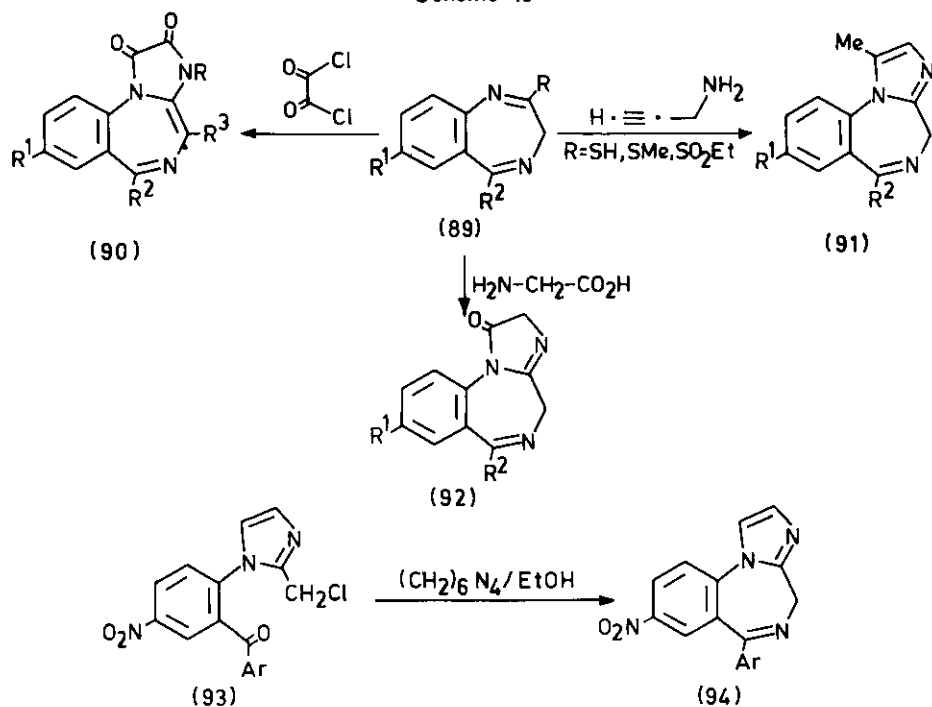
Scheme 13



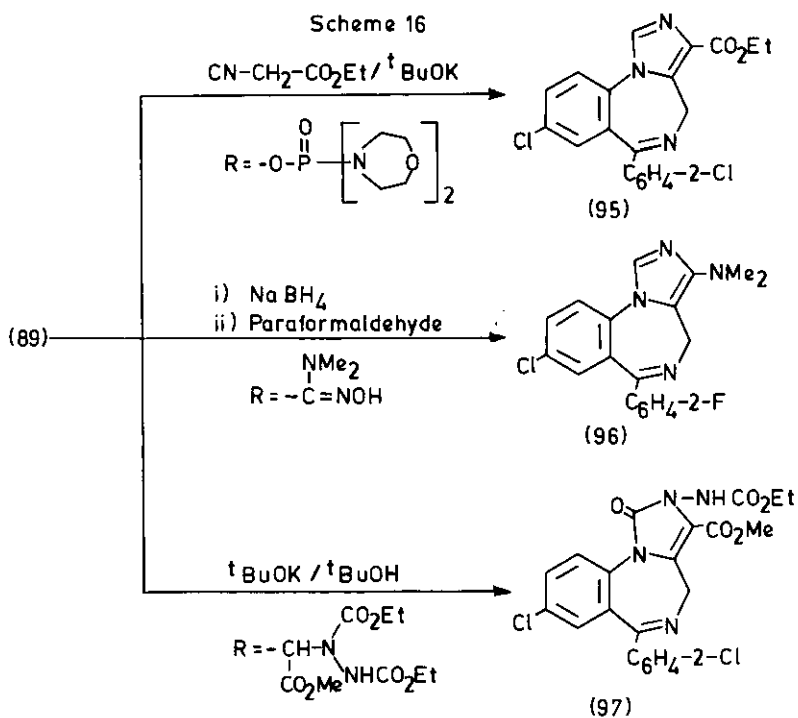
Scheme 14



Scheme 15



Scheme 16



Imidazo[1,5-a] [1,4]benzodiazepines (95, 96, 97) are prepared by the reaction of 2-substituted benzodiazepines (89) with various reagents under different conditions⁹⁴⁻⁹⁷ described under Scheme 16.

Reductive cyclization of imidazolylbenzophenone derivatives such as 98 also yielded imidazo[1,5-a] [1,4]benzodiazepines (99)⁸⁶. 3H-1,4-Benzodiazepine-2,5-dione (100) on treatment with ethyl isocyanoacetate gave imidazobenzodiazepine (101)⁹⁸, (Scheme 17).

An interesting ring transformation of (102), with the loss of carbon dioxide and methylamine in the presence of 2-propanol, led to the formation of imidazo[4,5-b] [1,4]benzodiazepine (103)⁹⁹. This appears to be the only example of its kind in literature.

Only one example (105) of imidazo[5,1-c] [1,4]benzodiazepine derivatives is available. It was prepared by the reaction of 3-carbamoylbenzodiazepinone (104) with oxalyl chloride and nucleophiles¹⁰⁰, (Scheme 18). Recently, Walther and his coworkers¹⁰¹ obtained 5H-imidazo[2,1-c] [1,4]benzodiazepine (107) by heating ethyl 1-(2'-aminobenzyl)imidazole-2-carboxylate (106) in acetic acid.

Reactions of 2-aminophenyl imidazolines (108) with α -chloro phenacetyl chloride or dimethyl acetylenedicarboxylate results in imidazo[1,2-d] [1,4]benzodiazepines (109, 110)^{102,103}.

A large number of imidazo[1,5-d] [1,4]benzodiazepine derivatives (112) were prepared by the dehydrative cyclization of the corresponding formylbenzodiazepinones (111) with phosphorus oxychloride¹⁰⁴, (Scheme 19). Bogatskii and his coworkers¹⁰⁵ reported the synthesis of benzimidazo[2,1-c] [1,4]benzodiazepines (114) by the cyclization of 1-(2'-aminobenzyl)-2-acylbenzimidazoles (113). Benzimidazo[1,2-d] [1,4]benzodiazepine-2-one (116) was obtained by heating 2-(2'-chloroacetamidophenyl)benzimidazole (115) in diethylbenzene^{65,106}, (Scheme 20). The two benzimidazobenzodiazepines (114 & 116) were tested for anticonvulsive and antidepressant activity.

5.7 Thiazolo-1,4-benzodiazepines

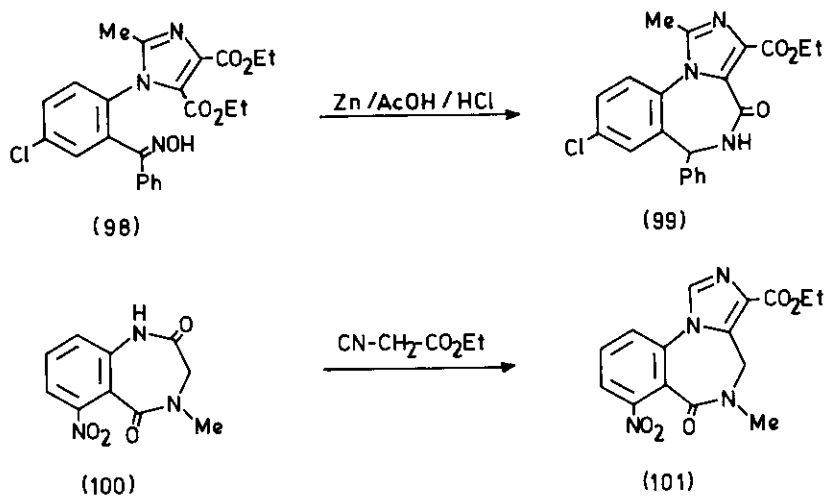
Three types of thiazolobenzodiazepines are known. 6-Aryl-1,2-dihydrothiazolo[3,2-a] [1,4]benzodiazepine (117, $Z = CH_2$; $R^1 = Cl, I$; $R^2 = \text{phenyl, halophenyl}$)⁷¹ were prepared by the ring closure of 1,4-benzodiazepine-2-thiol (89, $R = SH$, $R^1 = Cl, I$; $R^2 = \text{phenyl, halophenyl}$) with ethylene dibromide in a base. In an alternate approach, 89, ($R = SH$) was converted to benzodiazepinyl-2-thioacetic acid (89, $R = -SCH_2CO_2H$) with α -bromoacetic acid, followed by cyclisation using acetic anhydride-triethylamine mixture to 117, ($Z = CO$)¹⁰⁷. The reaction of 2-nitrobenzoyl chloride and methyl 4-thiazolidinecarboxylate gave the intermediate (118), which on reductive cyclization by iron in acetic acid led to the formation of thiazolo[4,3-c] [1,4]benzodiazepine (119)^{46,47,108}.

A large number of thiazolo[3,2-d] [1,4]benzodiazepines (121, $Z = CH_2, CO, CS$) have also been prepared from the respective benzodiazepines (120) and thioglycolic acid¹⁰⁹, (Scheme 21).

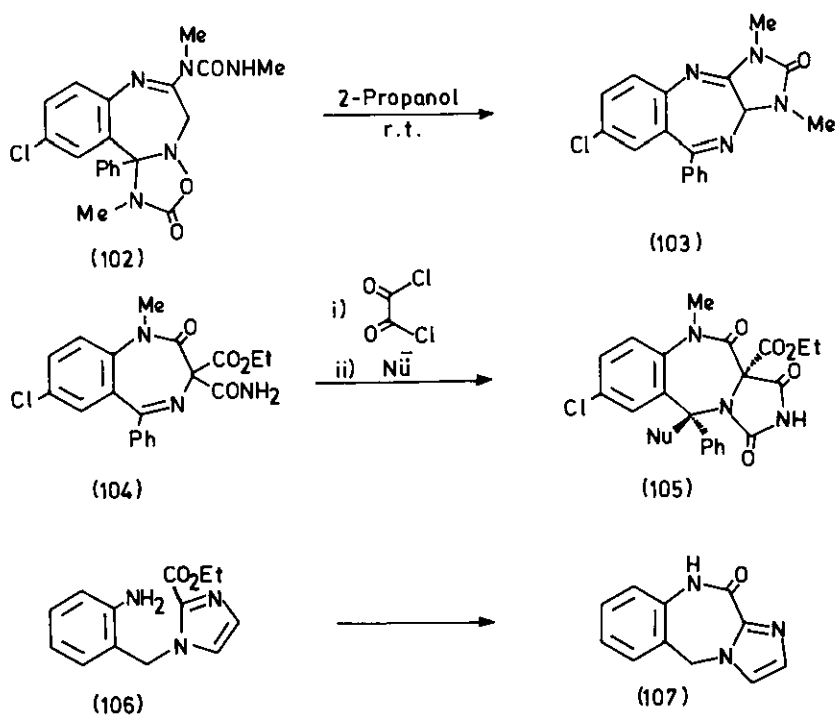
5.8 Triazolo-1,4-benzodiazepines

The drugs estazolam (13), alprazolam (14) and triazolam (14a), useful as antianxiety agents have a triazolo-benzodiazepine structure. Hence, a large amount of synthetic work has been carried out on this tricyclic

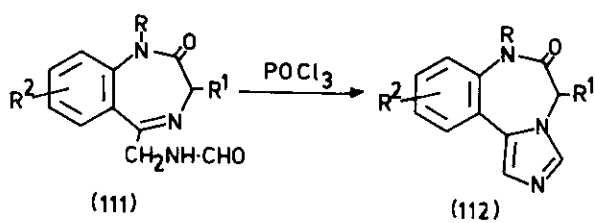
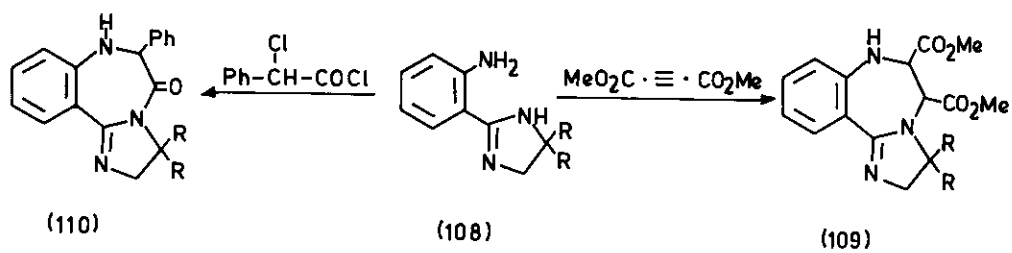
Scheme 17



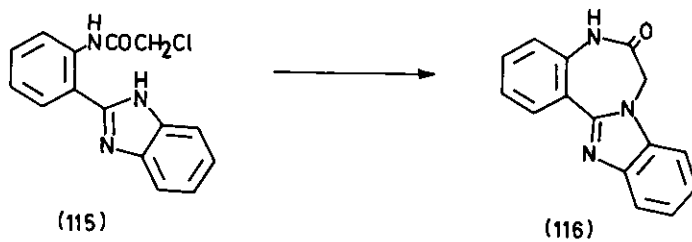
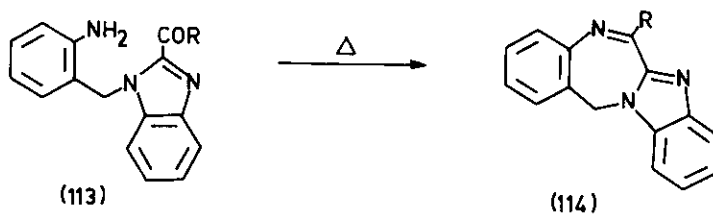
Scheme 18



Scheme 19



Scheme 20



system. Five different systems are known in this category, of which s-triazolo[4,3-a][1,4]benzodiazepine (122) are most important. These were prepared by the reaction of 2-mercapto-^{110,111}, 2-hydrazino-^{112,113}, and 2-hydrazono-¹¹⁴ substituted 1,4-benzodiazepines (89) with aroyl hydrazides^{110,111,115}, acids, acid chlorides, esters^{112,113}, and acetals¹¹⁴ respectively. s-Triazolobenzodiazepines (122) are also obtained by the hydrazinolysis of the corresponding triazolyl benzophenones (125, Y = phthalimidomethyl)^{116,117} or by acidic hydrolysis of 125 (Y = carbobenzyloxy)¹¹⁸ or by ammonolysis of 125 (Y = CH₂Cl¹¹⁹, Y=SO₂Me)¹²⁰, (Scheme 22).

6-(2'-Chlorophenyl)-4H-s-triazolo[4,3-a][1,4]benzodiazepines (124, R = Me; p-OMe-C₆H₄) were prepared by treatment of the respective 1,5-tetrazoles with the imidoyl chloride (123) in refluxing pyridine¹²¹. In basic conditions, the intermolecular dehydrochlorination leads to the unisolable tetrazolylbenzodiazepines, which loses molecular nitrogen under thermal conditions to generate a nitrile imine in situ, that undergoes 1,5-dipolar electrocycloaddition to 124, (Scheme 23).

The isomeric s-triazolo[1,5-a][1,4]benzodiazepines (126) were obtained by the oxidative cyclization of 2-aminobenzodiazepines (89, R = -N = C(R)-NH₂)^{122,123}. In another approach, 126 was also obtained by the cyclization of triazolyl benzophenones (127, Y = Cl) with NH₄OH-KI-HCl¹²⁴ or hexamine¹²⁵ or NH₃¹²⁶. However, in 127 (Y = N₃) triphenylphosphine¹²⁷ brought about the cyclization, (Scheme 24). Gagneux and his coworkers¹²⁸ prepared 6-aryl-v-triazolo[1,5-a][1,4]benzodiazepine derivatives (129) in one-step by the condensation of propargyl amines with 2-azidobenzophenones (128). Formation of 129 is explained through an intermediate Schiff's base which undergoes an intramolecular [$\pi 4s + \pi 2s$] cycloaddition, (Scheme 25).

The condensation of acid hydrazides with substituted benzodiazepines (120, Z = CO, -CH₂; R² = Cl, OEt) gave s-triazolo[4,3-d][1,4]benzodiazepines (130)¹²⁹⁻¹³².

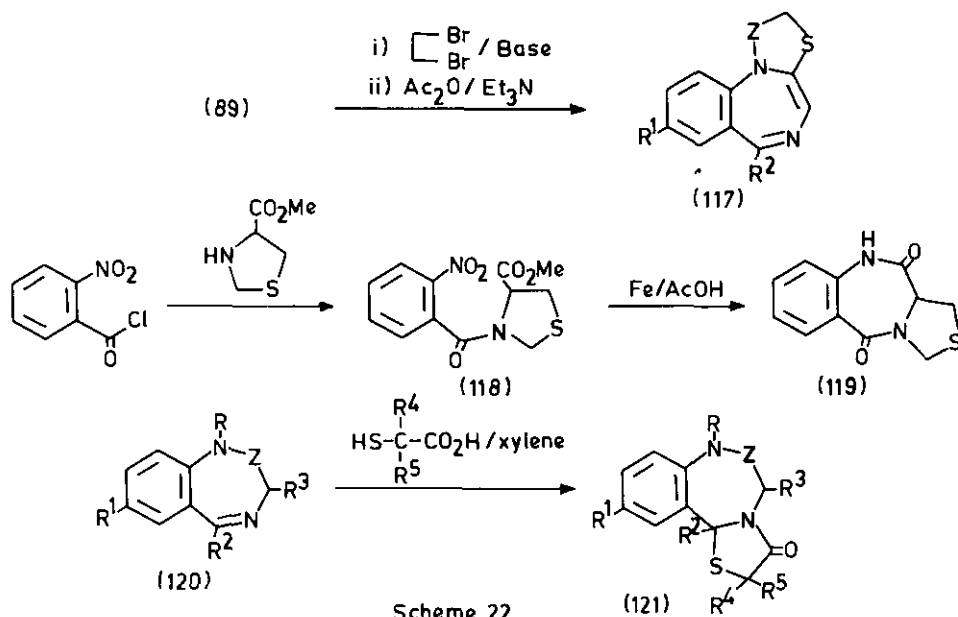
1,3-Dipolar cycloaddition of nitrile imines (prepared in situ by the action of Et₃N on PhC(Cl) = NNHPh) with C = N dipolarophile viz., 1,4-benzodiazepines (120, Z = CH₂, CO, R = H, Me, R¹ = Cl, R² = Ph, R³ = H) gave tetrahydro-1H-s-triazolo[4,3-d][1,4]benzodiazepine (131)¹³³. Further, it is also shown that the newly formed triazole ring dramatically reduced the conformational mobility of the diazepine ring. Kathawala¹³⁴ prepared s-triazolo[1,5-d][1,4]benzodiazepin-6(7H)-one (133) by the cyclization of 5-(2'-bromoacetamido)phenyl-s-triazole (132) in sodium ethoxide/ethanol, (Scheme 26).

5.9 Oxadiazolo-1,4-benzodiazepines

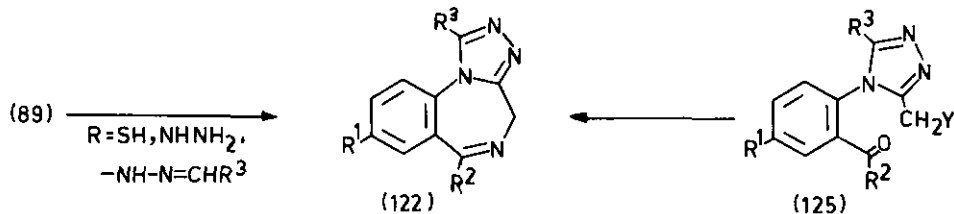
8-Chloro-6-phenyl-1H,4H-[1,2,4]oxadiazolo[4,3-a][1,4]benzodiazepin-1-one (134) was prepared by cyclizing the 2-hydroxylamino-5-phenyl-7-chloro benzodiazepine (89, R = NHOH; R¹ = Cl; R² = Ph) with phosgene¹³⁵. 1,2,5-Oxadiazolo[2,3-d][1,4]benzodiazepines (135, 136)⁹⁹ have been prepared by the treatment of chlorodiazepoxide (2) with methyl isocyanate through a cycloaddition reaction.

Hester and his coworkers prepared [1,2,4]oxadiazolo[4,3-d][1,4]benzodiazepine (137) by condensing 5-hydroxyaminobenzodiazepine (120, R = Me, R¹ = Cl, R² = NHOH, R³ = H, Z = CH₂) with 1,1'-carbonyldiimidazole

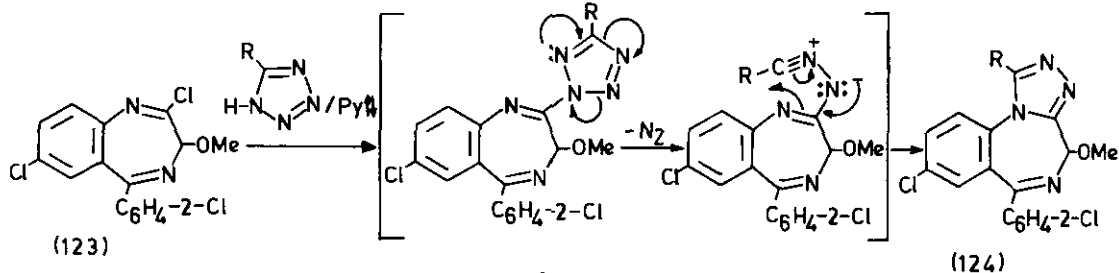
Scheme 21



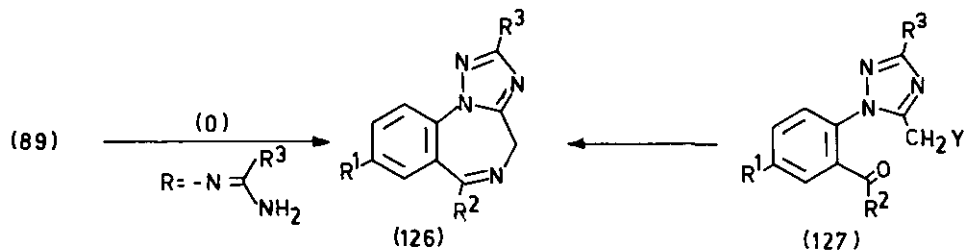
Scheme 22



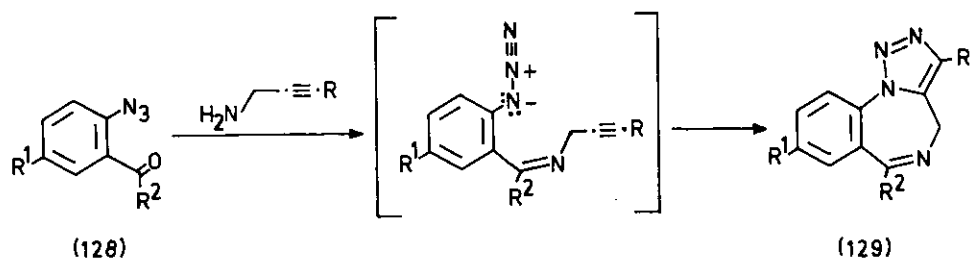
Scheme 23



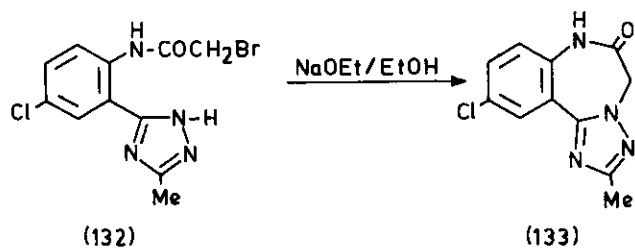
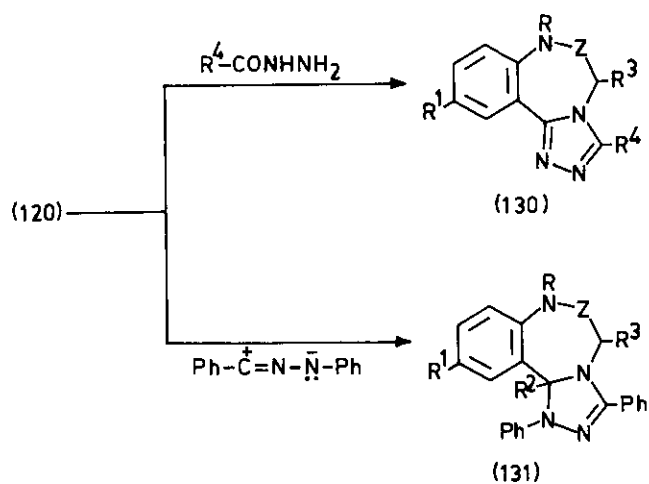
Scheme 24



Scheme 25



Scheme 26



in refluxing tetrahydrofuran¹³⁶. An intermolecular 1,3-dipolar cycloaddition of benzonitrile oxide with diazepam (3) gave [1,2,4]oxadiazolo[4,5-d][1,4]benzodiazepine (138)¹³⁷, (Scheme 27).

5.10 Tetrazolo-1,4-benzodiazepines

Hester¹³⁸ obtained 8-chloro-6-phenyl-4H-tetrazolo[1,5-a][1,4]benzodiazepine (139) by the treatment of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2-yl-hydrazine (89, R = NHNH₂; R¹ = Cl; R² = Ph) with NaNO₂-HCl. Klaubert and his coworkers¹³⁹ prepared 5H-tetrazolo[4,1-c][1,4]benzodiazepine (141) from ethyl 1-(5-chloro-2-nitrobenzyl)-5-tetrazolecarboxylate (140) by reduction of the nitro group followed by ring closure. 5H-Tetrazolo[1,5-d][1,4]benzodiazepines (143, Z = CH₂, CO) were prepared in two different ways by the diazotization of 5-hydrazino-1,4-benzodiazepine (142)¹⁴⁰ and by reacting 5-(2'-aminophenyl)tetrazoles (144) with bromoacetyl bromide¹⁴¹, (Scheme 28).

5.11 Thiatriazolo-1,4-benzodiazepines

Only one type of this system - 1,2,3,5-thiatriazolo[5,4-a][1,4]benzodiazepine-1-oxide (145) is known¹⁴². It was synthesised by the thionyl chloride reaction on benzodiazepinyl hydrazides (89, R = NHNHCOR³; R¹ = Cl; R² = Ph), (Scheme 29).

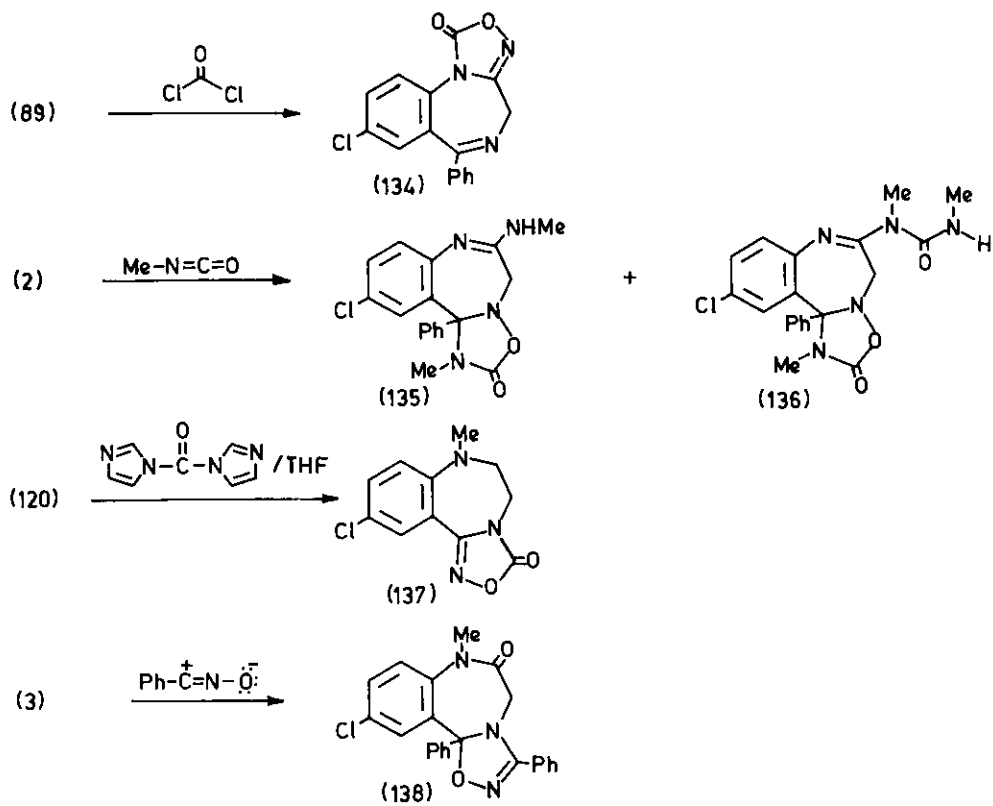
6 Six-membered rings annelated to 1,4-benzodiazepines

A large variety of different six-membered heterocycles fused to 1,4-benzodiazepine at 1,2-, 2,3-, 3,4- and 4,5- positions are reported in literature. These include pyrido, pyrimido, azino (pyrazino, oxazino and thiazino), triazino and oxadiazinobenzodiazepines.

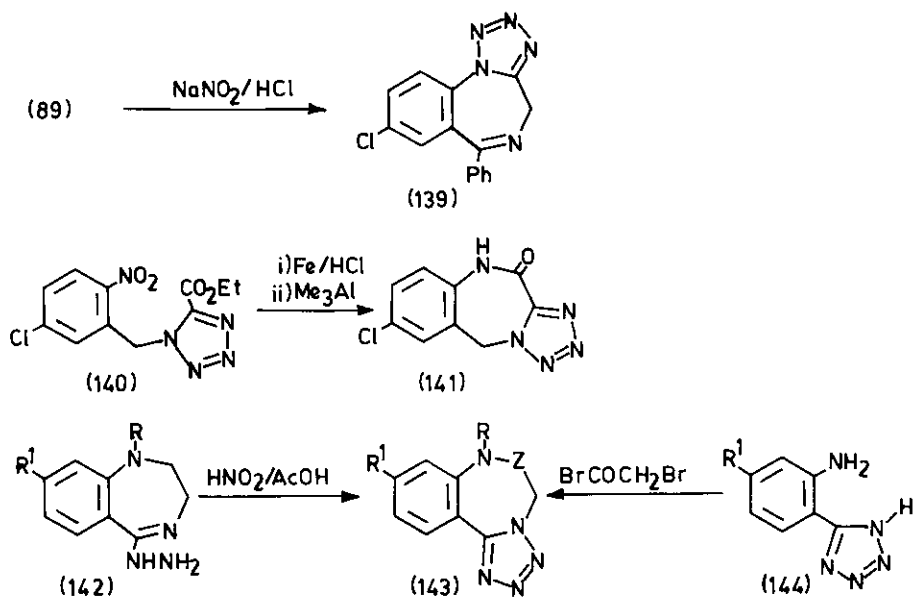
6.1 Pyrido-1,4-benzodiazepines

The known methods of synthesising pyridobenzodiazepines involve the construction of benzodiazepine ring on pyridine derivatives. 5,6-Dihydro-6-oxo-11H-pyrido[2,3-b][1,4]benzodiazepine (147) was thus obtained starting from 2-chloro-3-aminopyridine and 2-nitrobenzoyl chloride^{143,144}. The intermediate nitroamide (146) on reductive cyclization¹⁴⁵ or by heating in 1,3,5-trichlorobenzene¹⁴⁶ at 200°C gave (147). Compound 147 was converted to chloroacetyl derivative by the treatment of chloroacetyl chloride and Et₃N in dioxane, which was refluxed with N-methylpiperazine in benzene and treated with HCl to give pirenzepine (148)¹⁴³, a drug for peptic ulcer. Compound 147 was also obtained in 77% yield by the cyclization of 3-(2'-amino-benzoyl)amino-2-chloropyridine with H₂SO₄¹⁴⁷. The 1-oxides of (147) were also prepared^{148,149}. Sunjic and his coworkers¹⁵⁰ prepared 2,3,4,4a,5,11-hexahydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one (150) by the cyclodehydration of (149), which in turn was synthesised by the reaction of isatoic anhydride (43) and anhydroornithine in refluxing acetonitrile, 150 was also obtained in one-step by reacting 43 with ornithine ethyl ester hydrochloride¹⁵¹. Further, compound 150 on dehydrogenation gave 147. The dehydrohalogenation of 2-alkylaminobenzophenones and 3-(nitro or amino)-2-chloropyridine gave (151, X = NO₂ or NH₂) which on cyclization yielded 152¹⁵²⁻¹⁵⁴. The direct condensation of 2-aminobenzophenones and 3-amino-2-chloropyridine also afforded 152^{155,156}, (Scheme 30).

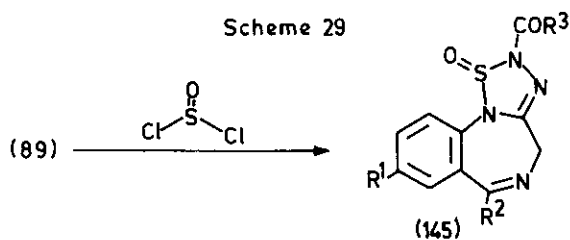
Scheme 27



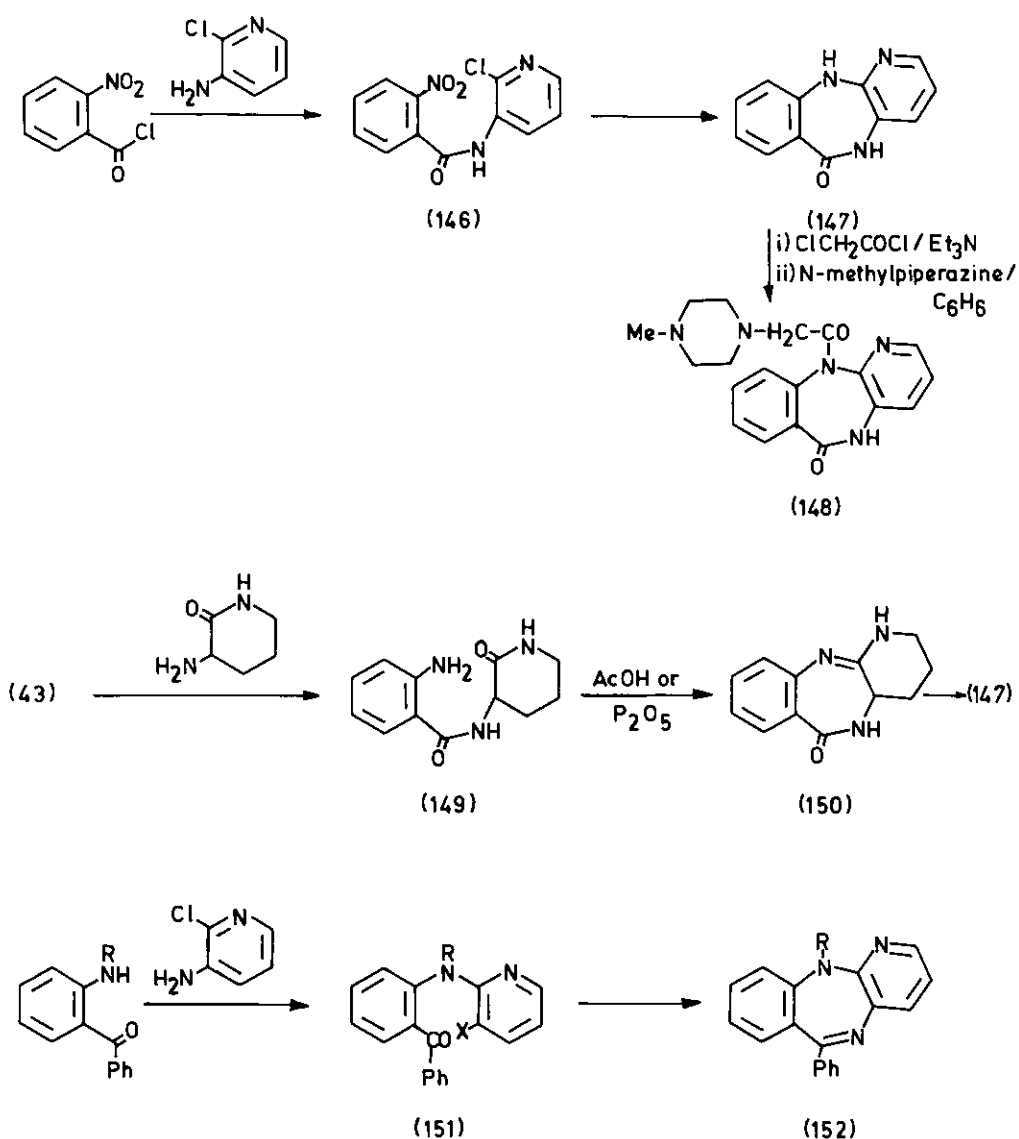
Scheme 28



Scheme 29



Scheme 30



1,2,3,11,12,12a-Hexahydro-4H,6H-pyrido[1,2-c] [1,4]benzodiazepin-12-one (154)¹⁵⁷ has been prepared starting from 2-nitrobenzyl chloride and ethyl pipercolinate through the intermediate 153. Pyrido[1,2-d] [1,4]benzodiazepine (156) was obtained by catalytic hydrogenation of the quaternary salt (155)^{158,159}, (Scheme 31). The benzo analog of 154, isoquinolino[3,2-c] [1,4]benzodiazepine (157, X = H, Cl, Z = CH₂, CO), was prepared starting from 2-nitrobenzoyl chloride or 2-nitrobenzyl chloride and ethyl (-) 1,2,3,4-tetrahydroisoquinoline-3-carboxylate¹⁶⁰⁻¹⁶³. Isoquinolino[2,1-d] [1,4]benzodiazepine (158), on the other hand, was synthesised starting from 2-chlorobenzoyl chloride and phenethylamine¹⁶⁴. Compound 158 was also obtained in one-step from 1-(2'-aminophenyl)isoquinoline derivatives^{165,166}. 6,7,8,13-Tetrahydro[1]benzopyrano[4,3-b] [1,4]benzodiazepine-6,8-dione (159) has been prepared from 2-[(3-nitro-2-oxo-2H-1-benzopyran-4-yl)amino]benzoic acid¹⁶⁷, (Scheme 31).

6.2 Pyrimido-1,4-benzodiazepines

Pyrimido[1,2-a] [1,4]benzodiazepines are prepared from 2-substituted 1,4-benzodiazepines. Thus 7-chloro-2-amino-5-phenyl-3H-1,4-benzodiazepine (89, R¹ = Cl; R = NH₂; R² = Ph) on reaction with alkyne carboxylates afforded 7-phenylpyrimido[1,2-a] [1,4]benzodiazepin-3(5H)-ones (160) in a single step¹⁶⁸. 2-Acetoacetamidobenzodiazepines (89, R = -NHCOCH₂COCH₃) also gave 160 when treated with HCl-MeOH¹⁶⁹. On the other hand, 89 (R = NHCOCH₂COCH₃) underwent a novel acyl migration and cyclization when heated in toluene to give the isomer (161), (Scheme 32).

Tetrahydropyrimido[1,2-a] [1,4]benzodiazepines (163) are easily prepared¹⁷⁰ from the corresponding benzodiazepinones (162), (Scheme 33).

In the Vilsmeier-Haack reaction of the benzodiazepinone (70, R¹ = Cl, R² = Ph) a pyrimidine derivative (165) is formed through an imidine intermediate, instead of the expected α,β -unsaturated β -chloroaldehyde (164). The pyrimidine derivative (165) underwent cyclization in alkaline medium to give pyrimido[4,5-b] [1,4]benzodiazepines (166)¹⁷¹, (Scheme 34).

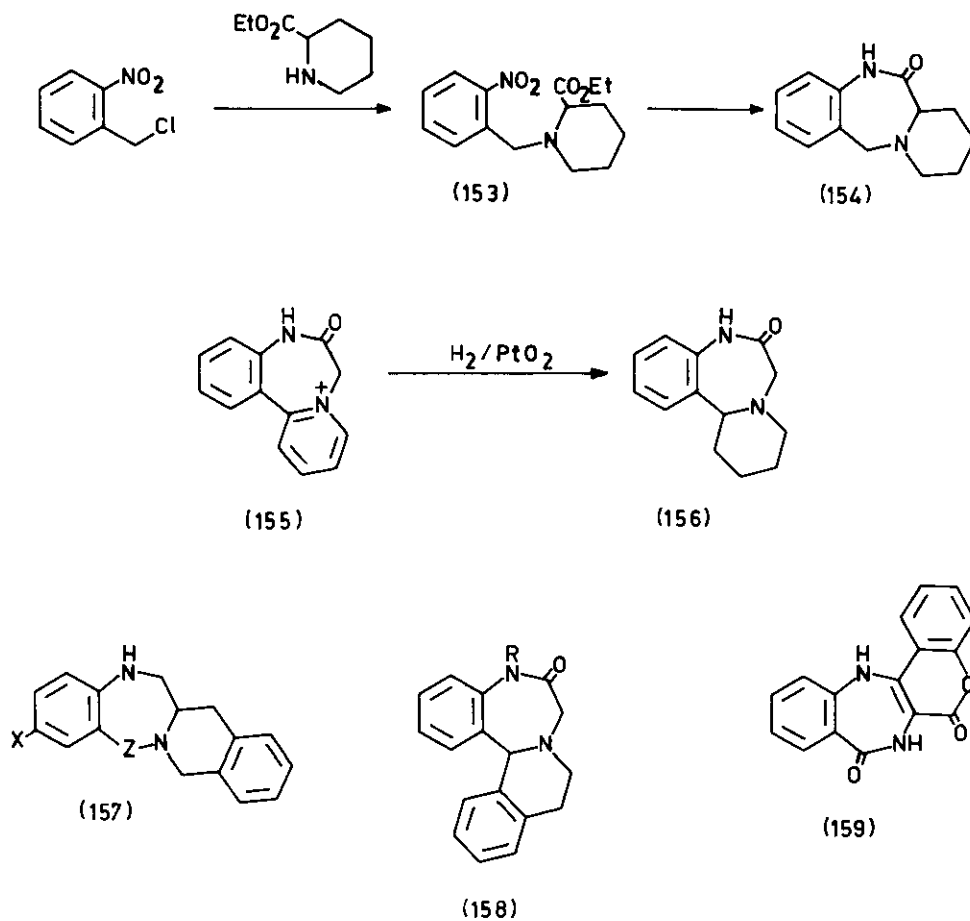
The synthesis of quinazolino[3,2-a],[3,2-d] and [3,4-d] [1,4]benzodiazepines (167, 168 and 169) is also described in literature^{140,172-176}, (Scheme 35).

6.3 Azino-1,4-benzodiazepines

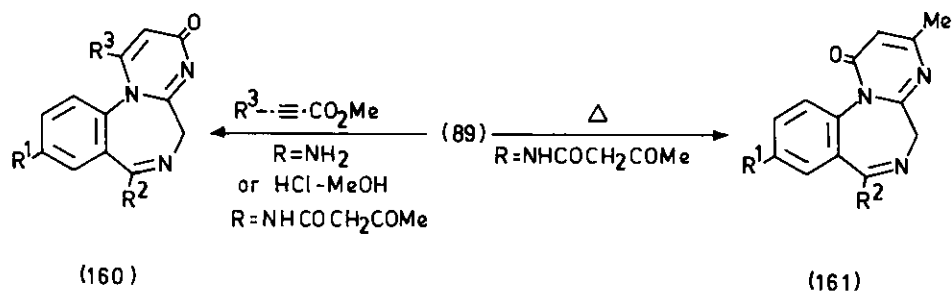
A number of oxazino, thiazino, pyrazino-1,4-benzodiazepines, fused at different bonds are known in literature. The reactions leading to the formation of these derivatives are closely related and hence are discussed together. 7-Phenyl-1H-[1,3]azino[3,2-a] [1,4]benzodiazepine-1,3(2H)-dione (171, X = O, S) were prepared by treating the appropriate benzodiazepines (170, X = O, S) with α,α -dimethylmalonyl chloride¹⁷⁷. 1-(β -Chloroethyl)-2-chloromethyl-5-aryl-2,3-dihydro-1H-1,4-benzodiazepines (172) were cyclized with NaOH, H₂S or NH₃ to yield the corresponding 7-aryl[1,4]azino[4,3-a] [1,4]benzodiazepines (173, X = O, S, NH)^{178,179}, (Scheme 36).

The anti-anxiety agent Ketazolam (15), which is a 1,3-oxazino[3,2-d] [1,4]benzodiazepine derivative, was obtained by condensing diazepam (3) with acetyl chloride in the presence of triethylamine^{9,180} or diketene

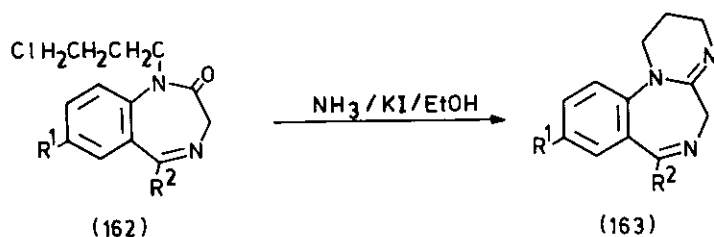
Scheme 31



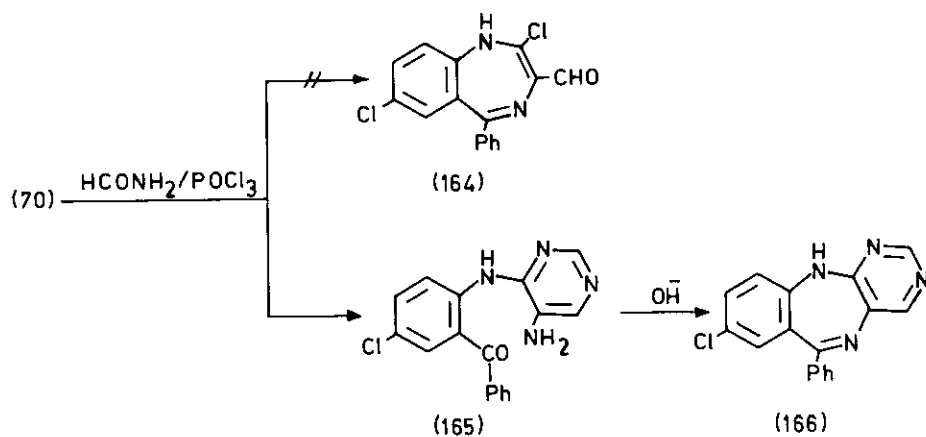
Scheme 32



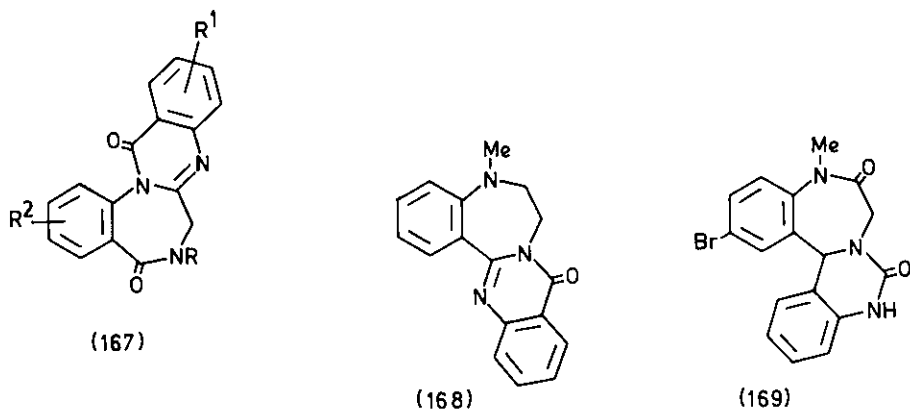
Scheme 33



Scheme 34



Scheme 35



in pyridine¹⁸¹ or diketene in acetone^{9,180}. In another experiment the 2-oxo derivatives of (15) were prepared by cyclizing the respective benzodiazepines (170, X = O, H₂) with malonic acid^{182,183}. The eneamino ester (89, R = -CH(NH₂)CO₂Me, R¹ = Cl, R² = 2-Cl-C₆H₄) on treatment with chloroacetyl chloride in methylene chloride gave (174) which underwent base catalyzed dehydrohalogenation to give methyl 9-chloro-7-(2'-chlorophenyl)-2-oxo-1,2,3,5-tetrahydropyrazino[1,2-a] [1,4]benzodiazepine-4-carboxylate (175)¹⁸⁴ in 74% yield.

Pyrazino[2,3-b] [1,4]benzodiazepine (176) is obtained when 90 (R = CH₃; R¹ = R³ = Cl; R² = Ph) was reacted with ethylenediamine⁷², (Scheme 37).

6.4 Triazino-1,4-benzodiazepines

s-Triazino[1,2-a] [1,4]benzodiazepine-1,3(2H,5H)-dione (177) was obtained by the cyclization of benzodiazepinylurea derivative (89, R = -NH-CONH-CO₂Et; R¹ = Cl; R² = Ph)¹⁸⁵.

Szmuszkowicz^{186,187} prepared a number of 7-aryl-3,4-dihydro-s-triazino[4,3-a] [1,4]benzodiazepin-2(1H)-ones (179) by refluxing the respective benzodiazepin-2-thiones (178) with aliphatic hydrazines (Scheme 38). The other methods of synthesising as-triazinobenzodiazepines and their oxo derivatives (181, 182 & 183) involve the cyclization of benzodiazepinylhydrazine derivatives (180, R = -CO₂CH₃, -COCH₃, -CH₂Cl) under acidic and thermal conditions¹⁸⁸⁻¹⁹⁰, (Scheme 38).

The reaction of aminotriazinethione with isatoic anhydride (20) gave a novel 1,2,4-triazino[5,6-b] [1,4]benzodiazepinone (184) in a single step¹⁹¹. The cyclocondensation of the imidoyl chloride (120, Z = CO; X = R = Cl; R¹ = Me; R² = H) with 4-morpholinoglyoxylic acid hydrazide in DMF at 100°C gave 84% yield of as-triazino[4,3-d] [1,4]benzodiazepine-3,4,7-trione (185)^{192,193}, (Scheme 39).

6.5 Oxadiazino-1,4-benzodiazepines

Wasler¹⁹⁴ cyclized 7-chloro-5-(2'-fluorophenyl)-3H-1,4-benzodiazepine-2-carboxaldoxime (89, R = -CH=NOH; R¹ = Cl; R² = 2-F-C₆H₄) with paraformaldehyde alone or with paraformaldehyde in pivalic acid catalyst¹⁹⁵ to yield the corresponding 1,2,5-oxadiazino[5,4-a] [1,4]benzodiazepine (186), (Scheme 40).

7. Seven-membered rings annelated to 1,4-benzodiazepines

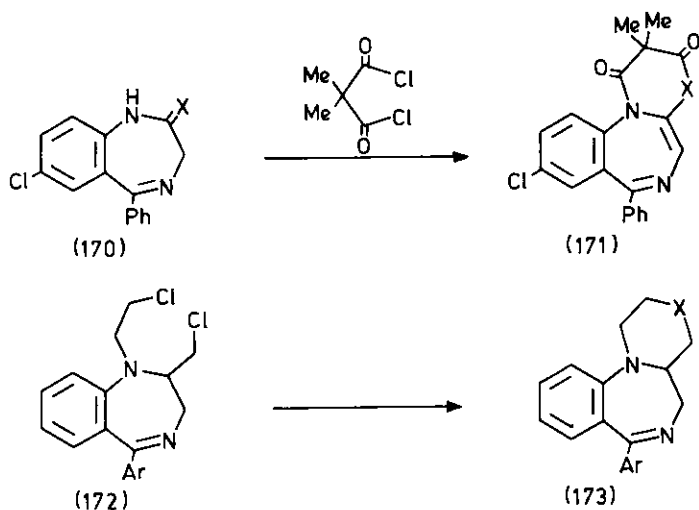
Only one derivative of this category is known so far. Fryer and Coffen^{196,197}, obtained 1,5,3-oxathiazepino[3,4-a] [1,4]benzodiazepine (187) by the oxidation of the benzodiazepine (76; Z = CH₂) with manganese dioxide and subsequent reactions with thioglycol and formaldehyde.

Recently, a novel 1,4-benzodiazepino[4,5-d] [1,4]benzoxazepine (189) has been synthesised¹⁹⁸ via a preformed benzoxazepine (188), (Scheme 41).

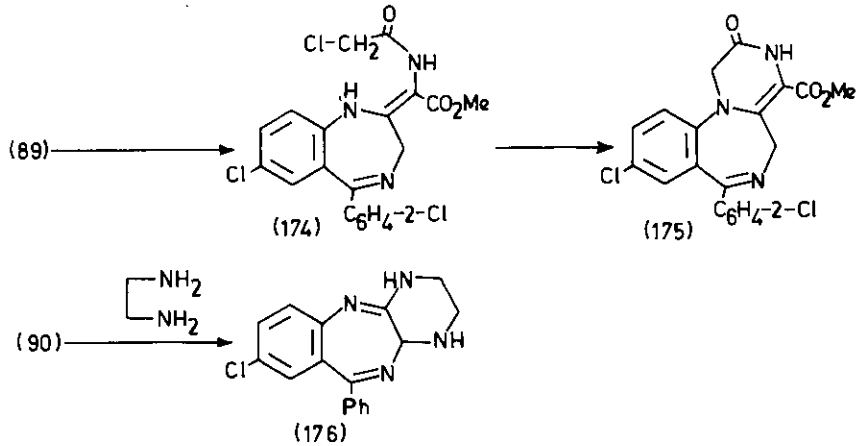
8. Di-annelated-1,4-benzodiazepines

A number of 1,4-benzodiazepines fused to different heterocycles at more than one bond are also known in literature. These di-annelated benzodiazepines possessing three, four, five and six-membered heterocycles at [1,2]-[3,4] and [1,2]-[4,5] positions are particularly important in view of their hypnotic, anticonvulsive, sedative, CNS depressant, tranquilizer and muscle relaxant activity.

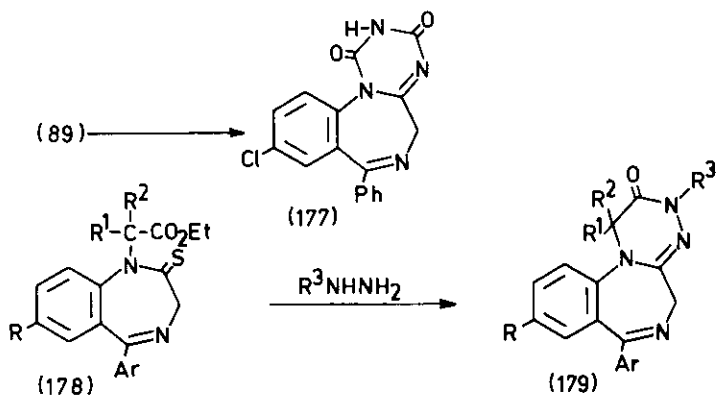
Scheme 36



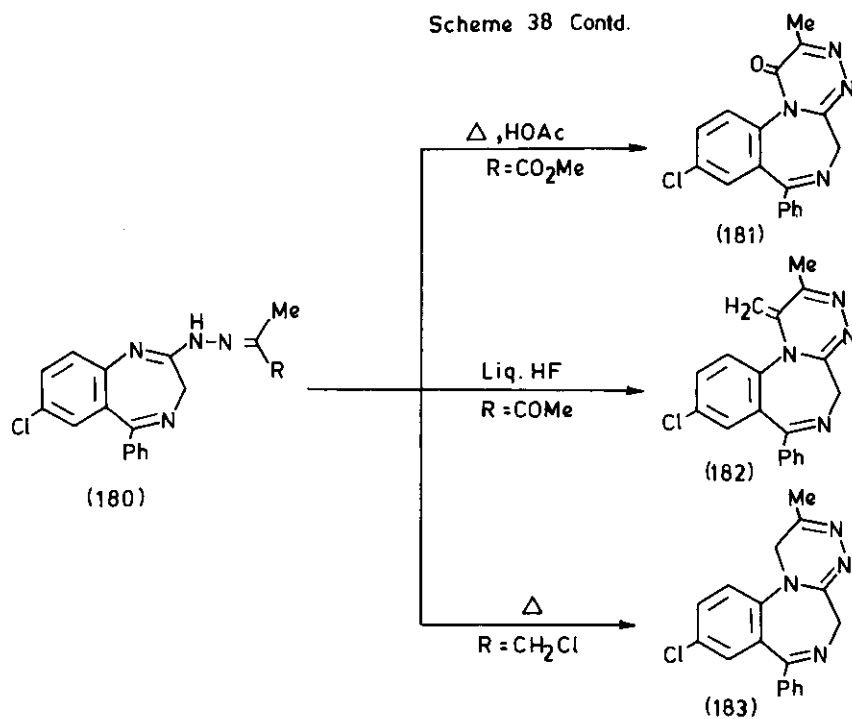
Scheme 37



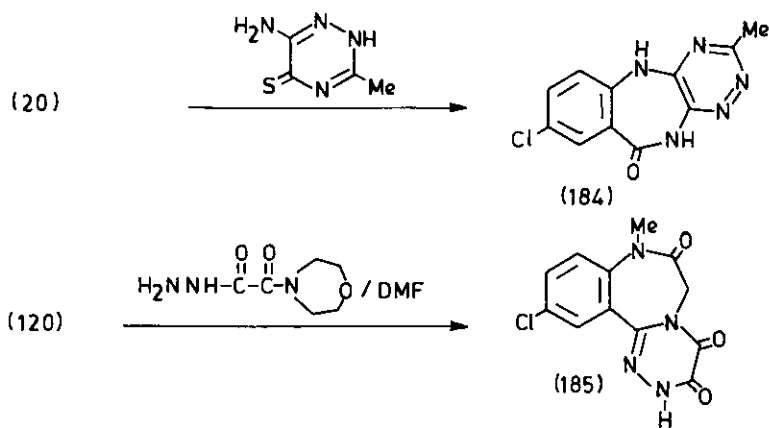
Scheme 38



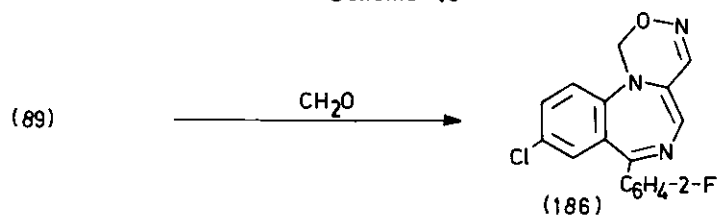
Scheme 38 Contd.

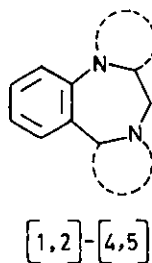
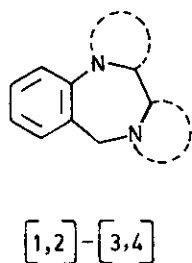


Scheme 39



Scheme 40





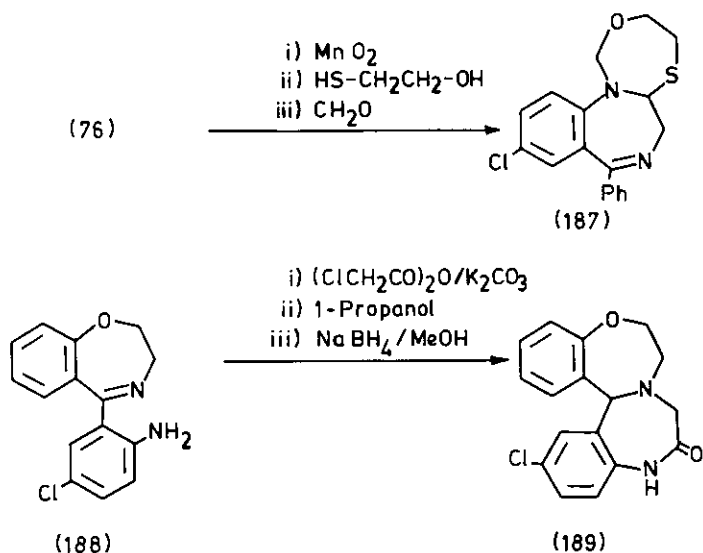
They are generally obtained through two distinct routes.

- i) From preformed mono-annelated 1,4-benzodiazepines by reaction with suitable reagents to construct the second heterocycles thereon.
- ii) By preparing suitably substituted hetaryl benzophenones and cyclizing them. Generally, the reagents employed to build the different heterocycles on 1,4-benzodiazepines are similar to those employed in the synthesis of mono-annelated benzodiazepines described in the preceding sections.

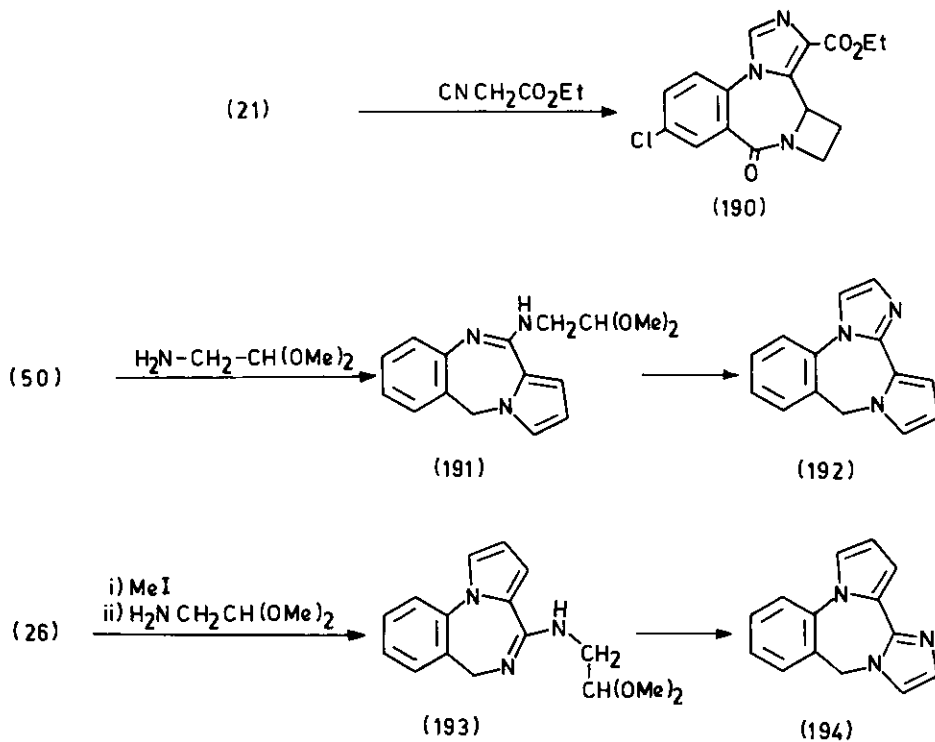
Imidazo-azetobenzodiazepindiones (190) prepared by the treatment of 21 with ethyl isocyanoacetate³⁰. 11-Amino-5H-pyrrolo[2,1-c][1,4]benzodiazepine (50, R = NH₂) on treatment with aminoacetaldehyde dimethyl acetal gave 191 which on cyclization with HCl yielded 9H-imidazo[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine (192)^{54,199}. Duceppe and Gauthier³⁵ obtained 5H-imidazo[2,1-c]pyrrolo[1,2-a][1,4]benzodiazepine (194) by refluxing in 2N HCl a solution of N-(2-dimethoxyethyl)-6H-pyrrolo[1,2-a][1,4]benzodiazepine-4-amine (193) which in turn was prepared from (26, R, R¹ = S) by MeI and H₂NCH(OMe)₂ treatment. Amino compound (50, R = NH₂) on condensation with diethyl ethoxymethylenemalonate gave 195. This underwent cyclization by the treatment of sodium ethoxide to give ethyl 10H-pyrimido[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate (196)⁵⁴. Amino ester (48) on reaction with chloroacetyl chloride and 40% aqueous methylamine afforded 10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepin-1,4-dione (197)⁵², (Scheme 42). The 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine derivative (38), after debenzoylation with H₂, Pd/C in AcOH, could be cyclized with diethyl oxalate to give 1,14b-dihydro-2-methyl-10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine-3,4-dione (198)⁴³. The diketo compound (198) on diborane reduction afforded 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine (199)^{43,200}. The synthesis of 199 was also accomplished from phthalimide in nine steps²⁰¹, (Scheme 43).

Oxazirino[2,3-d]-s-triazolo[4,3-a][1,4]benzodiazepines (201, R = CH₂OH, Me) were prepared by U.V. irradiation of 4H-s-triazolo[4,3-a][1,4]benzodiazepine-5-N-oxides (200, R = CH₂OH, Me)²⁰². Oxidative cyclization of (202) also afforded 201 (R = Me) along with 200, (R = Me)²⁰³. The 2-triazolylbenzophenone derivative 125 (Y = Cl), when treated with ethylenediamine gave imidazo[3,2-d]-s-triazolo[4,3-a][1,4]benzodiaze-

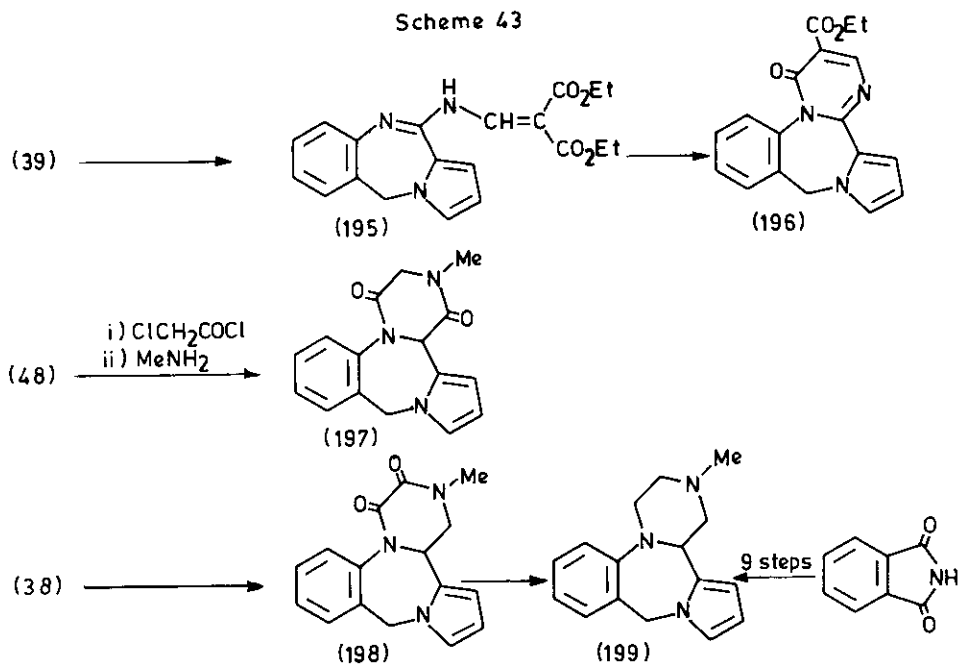
Scheme 41



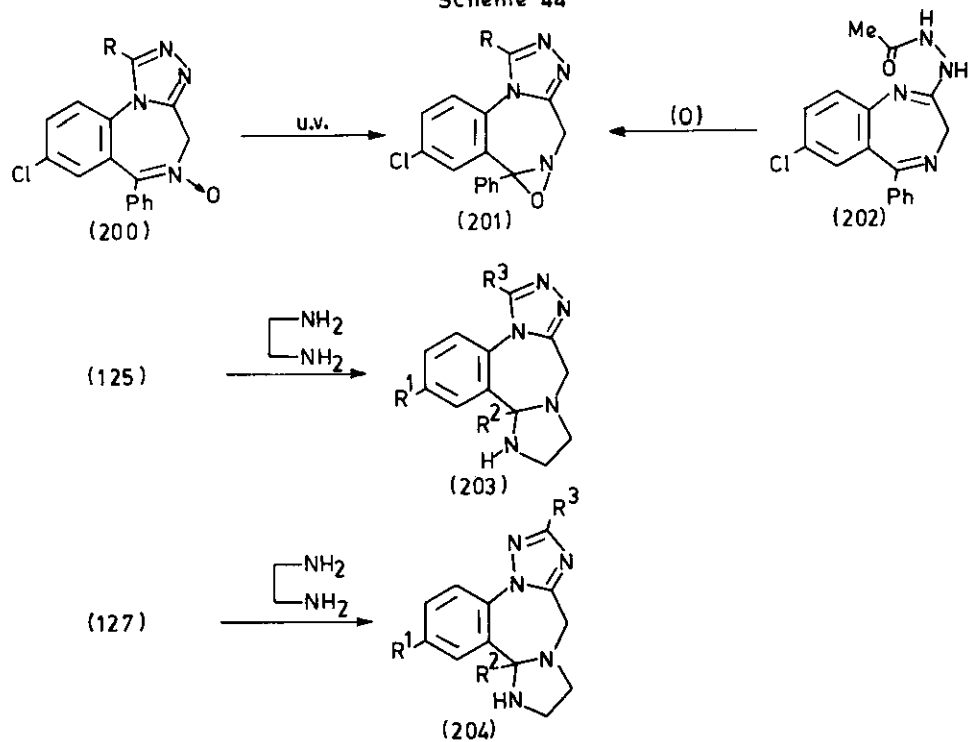
Scheme 42



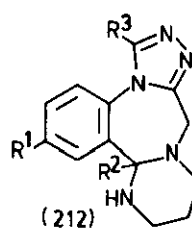
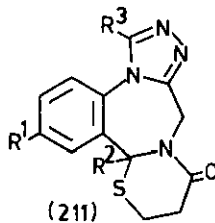
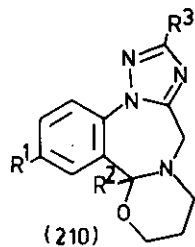
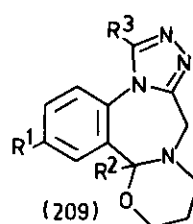
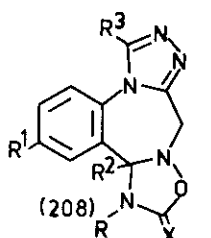
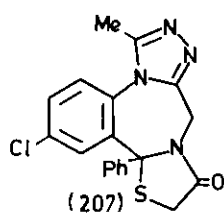
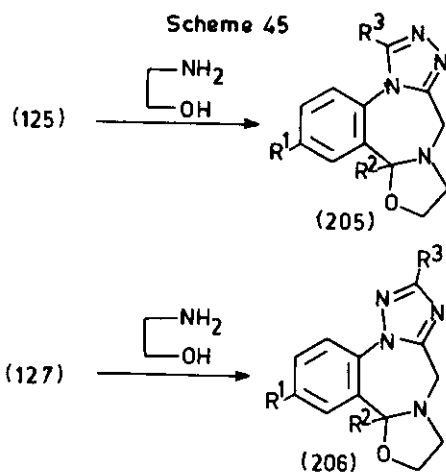
Scheme 43



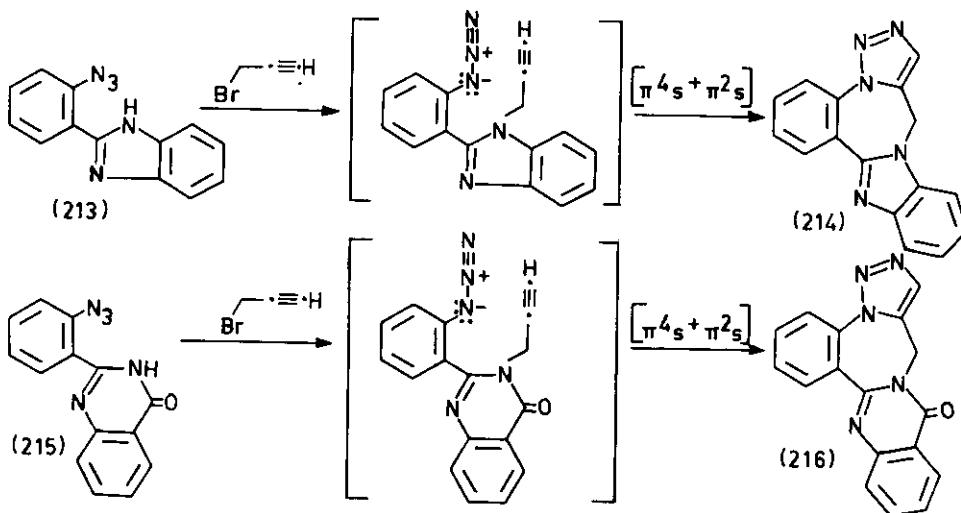
Scheme 44



Scheme 45



Scheme 46



pine (203)^{204,205}. The isomeric s-triazolo[1,5-a] compound (204)^{206,208} was also prepared similarly from 127, (Y = Cl), (Scheme 44).

Use of ethanolamine in these reactions gave the corresponding oxazolo[3,2-d]-s-triazolo[4,3-a] and [1,5-a]-[1,4]benzodiazepines (205 & 206)²⁰⁴⁻²¹³. In these reactions intermolecular dehydrochlorination and intramolecular dehydration seem to occur in one-step to give the tetracyclic system.

Cyclocondensation of 122, ($R^1 = Cl$, $R^2 = Ph$, $R^3 = Me$) with thioglycolic acid in xylene gave thiazolo-[2,3-d]-s-triazolo[4,3-a]-[1,4]benzodiazepin-11(12H)-one (207)^{215,216}.

1,2,4-oxadiazolo[2,3-d]-s-triazolo[4,3-a]-[1,4]benzodiazepin-12-ones (208, X = O) and thiones (208, X = S) were prepared by treating 200 with alkyl (thio) isocyanates²¹⁴. Formation of 208 may be visualised through an intermolecular 1,3-dipolar cycloaddition of the N-oxide (200) and C = N of alkyl (thio) isocyanates. Triazolo-oxazino[1,4]benzodiazepines (209, 210) were prepared by reacting 125, (Y = Cl) and isomeric triazolyl benzophenones with 3-aminopropanol. However, use of β -thiopropionic acid and 1,3-diaminopropane gave the corresponding thiazino (211) and pyrimido (212)-1,4-benzodiazepines²⁰⁴, (Scheme 45).

Novel pentacyclic systems viz. 9H-benzimidazo[1,2-d]-[1,2,3]triazolo[1,5-a]-[1,4]benzodiazepines (214) have been prepared by the propargylation of 2-(2'-azidophenyl)-benzimidazole (213) in excellent yield. Similarly 2-(2'-azidophenyl)-4-(3H)-quinazolinones (215) afforded 9H,11H-quinazolino[3,2-d]-[1,2,3,]triazolo[1,5-a]-[1,4]benzodiazepin-11-ones (216), (Scheme 46). In these reactions dehydrobromination followed by an intramolecular 1,3-dipolar cycloaddition[$\pi 4s + \pi 2s$] between azido and acetylene moieties have been proposed²¹⁷.

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