BENZODIAZOCINES

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Abstract - Synthesis and stereochemistry of benzodiazocines are reviewed.

CONTENTS:

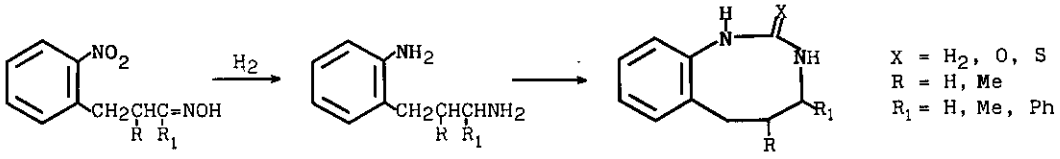
1. INTRODUCTION

Benzodiazocines are benzannelated eight-membered unsaturated heterocycles containing two nitrogen atoms interesting for their biological activity. Diverse activities as central nervous system depressant[36,41,95], muscle relaxant[38-40], antispasmodic[49], anticonvulsant[11,22,25,27,37,86,93,98], antiaggressive[46], antianxiety[38,42], sedative[39,40,57,88], hypnotic[27,39,40,57], analgesic[27,59,88,89,100], antipyretic[88], antitussive[88], antiinflammatory[27,57,59], antidepressant[91,93,97], anorexic[93,95,96,113,114], diuretic[57], cardiovascular[9,25,113,114], etc., have been found to be associated with benzodiazocine derivatives.

In the present paper the synthesis and the stereochemistry of this important group of heterocyclic compounds are reviewed, of which very little data concerning their reactivity are available.

2. 1,3-BENZODIAZOCINES

Only few papers concerning the synthesis of 1,3-benzodiazocines have appeared. The first compound (3) of this series have been synthesized [1,2] in 1975 from 3-(2-nitrophenyl)propionaldehyde oxime derivatives (1) by reduction to 2 and subsequent cyclocondensation with formaldehyde, phosgene or carbon disulfide.



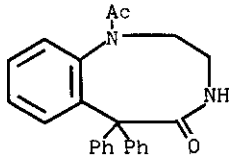
1 2 3

The preparation of 1,3-benzodiazocine-2,6-dione derivative (5) was carried out by Saito and co-workers [3] by the Rose bengal-sensitized photooxygenation of pyrroloindole (4) in methanol.

4 5

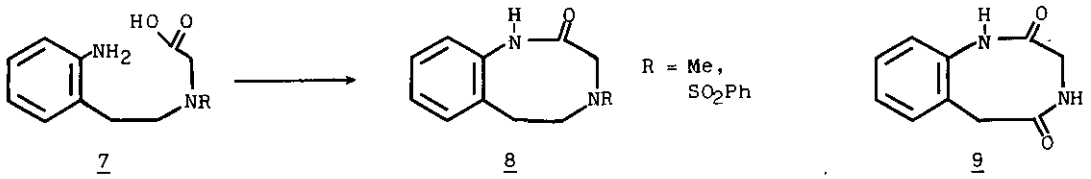
3. 1,4-BENZODIAZOCINES

The 1,4-benzodiazocine system was synthesized in 1965 [4]. The 1-acetyl-6,6-diphenyl-1,2,3,4-tetrahydro-1,4-benzodiazocin-5(6H)-one (6) was prepared by condensation of benzylic acid ß-(N-phenylacetamido)ethylamido with sulfuric acid in AcOH.



6

Other preparative routes available to 1,4-benzodiazocine system were reported by Muchowski: hexahydro-1,4-benzodiazocin-2-one derivatives (8) were synthesized [5] by the dicyclohexylcarbodiimide induced cyclization of the appropriate N-2-(2-aminophenyl)ethylglycines (7), while hexahydro-1,4-benzodiazocine-2,5-dione (9) was obtained [6] from isatin with a three step synthesis.

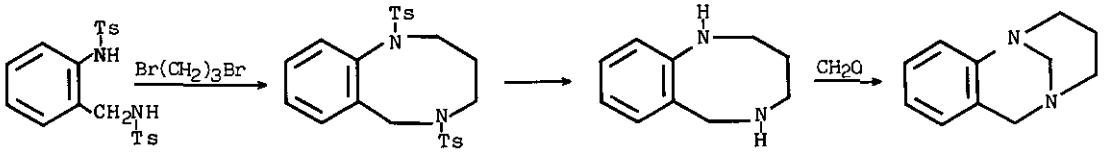


7 8 9

4. 1,5-BENZODIAZOCINES

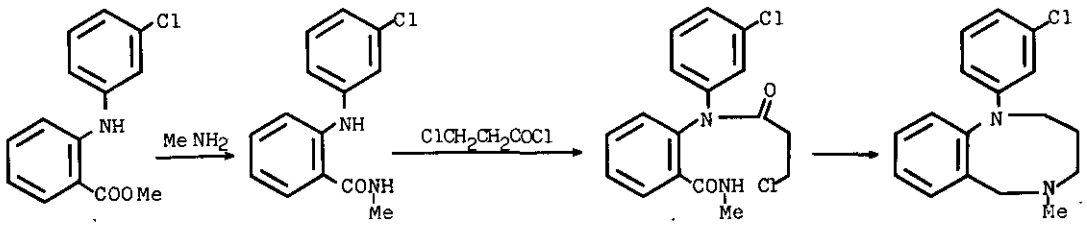
1,5-Benzodiazocines have received intensive study and several synthetic routes have been described.

The earliest approach was reported by Shiotani and co-workers [7,8] in 1964 to obtain hexahydro-1,5-benzodiazocine (12). A solution of 2-aminobenzylamine in pyridine was treated with p-tosyl chloride to give N,N'-ditosyl-2-aminobenzylamine (10), which was refluxed in a solution of Na in butanol and then with 1,3-dibromopropane to give 11 from which 12 was obtained. The benzodiazocine 12, warmed in methanol with 35% formalin, gave 3,4-dihydro-2H,6H-1,5-methano-1,5-benzodiazocine (13).



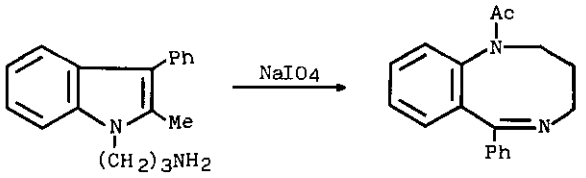
10 11 12 13

1-(m-Chlorophenyl)-1,2,3,4,5,6-hexahydro-5-methyl-1,5-benzodiazocine (17) was prepared [9] by the route shown below. Methyl N-(m-chlorophenyl)anthranilate (14) in isopropanol and methylamine gave 2-(m-chlorophenylamino)-N-methylbenzamide (15). This was refluxed in benzene with 3-chloropropionyl chloride to give 2-[N-(m-chlorophenyl)-3-chloropropionylamino]-N-methylbenzamide (16). Treatment of 16 with diborane in THF and heating with acetic anhydride led to 1,5-benzodiazocine 17.



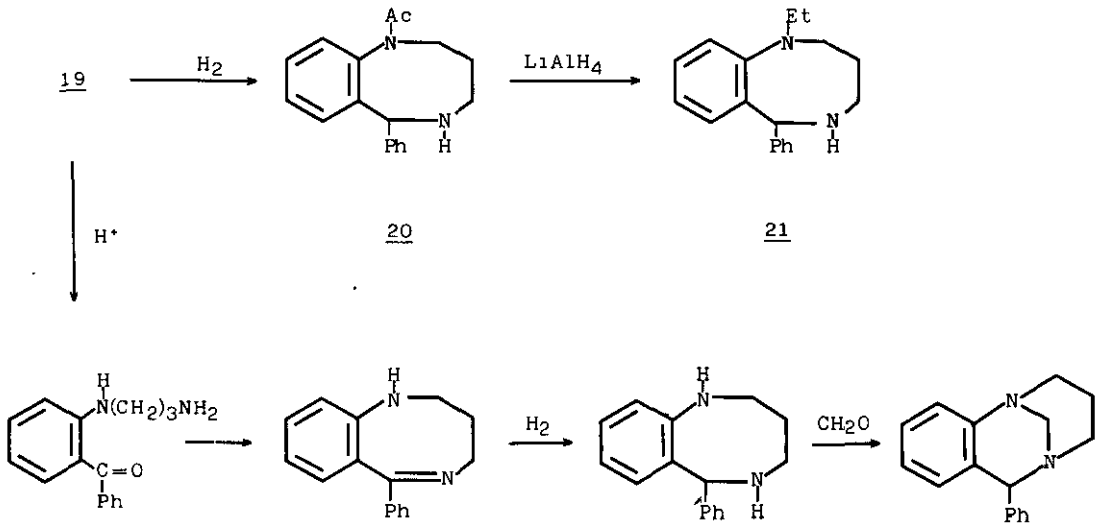
14 15 16 17

Another route to 1,5-benzodiazocines was reported [10] by Gatta and co-workers who prepared 6-phenyl-1,5-benzodiazocines, e.g. 19-21 and 23-24 by oxidative fission of the double bonds in indole derivatives. The oxidative ring opening of 1-(3-aminopropyl)-2-methyl-3-phenylindole (18), using sodium periodate in aqueous methanol at room temperature, and subsequent thermal cyclodehydration in pyridine of the resulting compound, afforded the 1-acetyl-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (19).



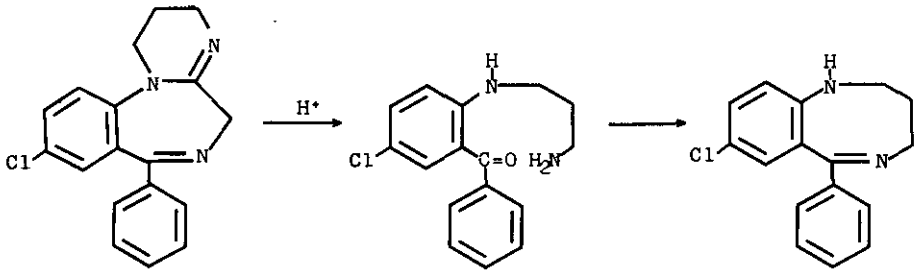
18 19

From 19, by catalytic reduction, was obtained 1-acetyl-1,2,3,4,5,6-hexahydro-6-phenyl-1,5-benzodiazocine (20) which can be converted to 1-ethyl derivative (21) by reduction with $LiAlH_4$. Sulfuric acid hydrolysis of 19 yielded 2-(3-aminopropyl)-aminobenzophenone (22) intermediate which cyclized, refluxing in pyridine, to 6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (23). The catalytic reduction of 23 afforded 1,2,3,4,5,6-hexahydro-6-phenyl-1,5-benzodiazocine (24) which reacted quite readily with formaldehyde to give 3,4-dihydro-6-phenyl-2H,6H-1,5-methano-1,5-benzodiazocine (25).



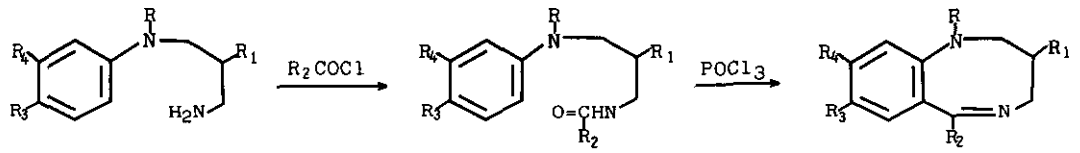
20 21 22 23 24 25

8-Chloro-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine can be prepared from a benzodiazepine derivative [11,12]. Treatment of 9-chloro-1,2,3,5-tetrahydro-7-phenylpyrimido[1,2-a][1,4]benzodiazepine (26) with HCl and ethanol resulted in ring opening to give 2-(3-aminopropylamino)-5-chlorobenzophenone (27). By intramolecular dehydration, the product undergoes cyclization to 8-chloro-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (28). 1-Acetyl-, 1-methyl- and 1-p-tosylderivatives of 28 were obtained by corresponding benzophenones.

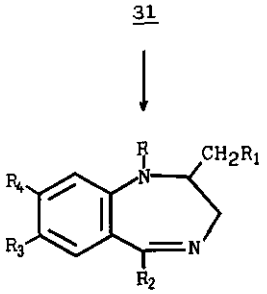


26 27 28

Reaction between 3-aminopropylanilines (29) and acyl chloride had been used in the synthesis of derivatives 30 which, after treatment with $POCl_3$, led to 6-aryl-1,2,3,4-tetrahydro-1,5-benzodiazocines (31) [13-22]. The benzodiazocines 31 can be converted with ring contraction to corresponding benzodiazepines 32 [13,15, 19-23].



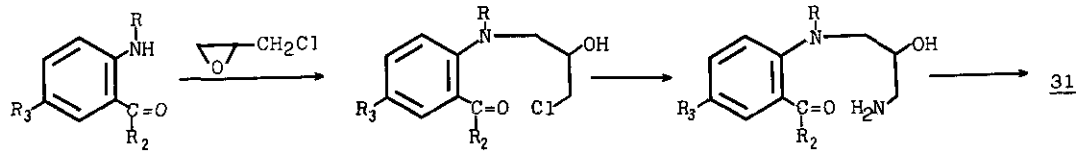
29 30 31



32

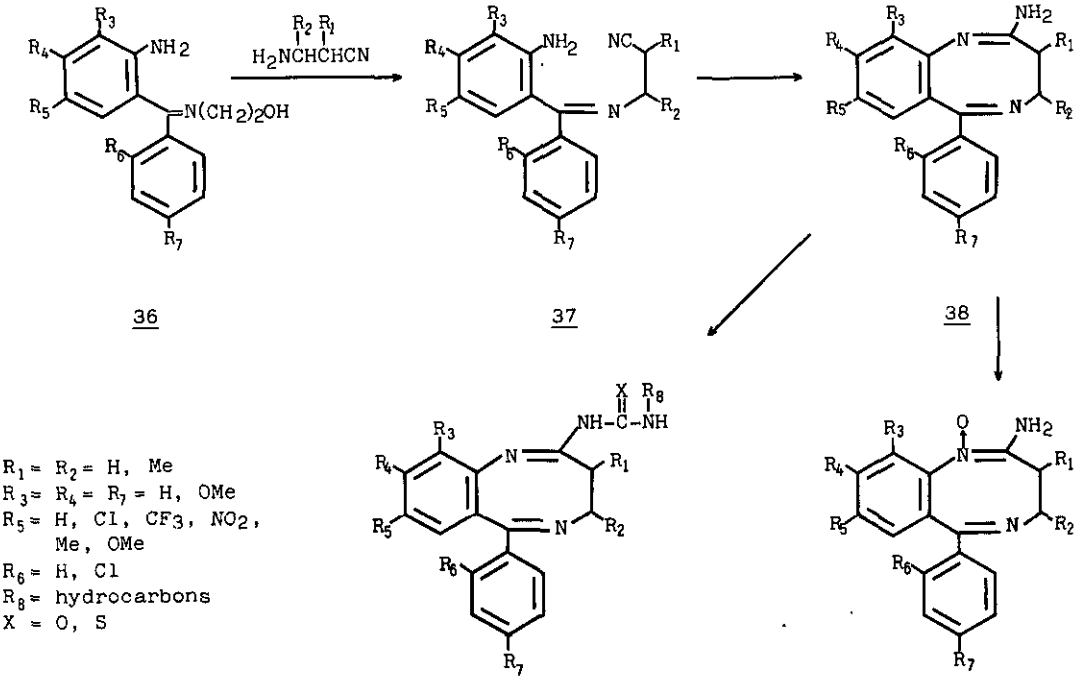
R = H, C_{1-6} alkyl, cycloalkyl, benzyl
R_1 = halogen, OH, OAc, OBz
R_2 = Ph, halo-, nitro-, trifluoromethyl-, alkyl-, or alkoxyphenyl, 2-furyl, 2-thienyl, 3-thienyl
R_3, R_4 = H, halogen, CF_3, NO_2, alkyl, alkoxy, alkylthio

Compounds 31 were also prepared [22,24] by the cyclization of 35. Thus, 2-amino-5-chlorobenzophenone (33) reacted with epichlorohydrin to give 34, which was treated with sodium hydroxide and then with ammonia to give 35. This was heated with methanol and ammonium chloride to afford 31.



33 34 35

2-Amino-3,4-dihydro-6-phenyl-1,5-benzodiazocine derivatives (38) were synthesized [25,26] by cyclization of 3-(2-amino-α-phenylbenzylideneamino)propionitriles (37), obtained by an exchange reaction of 2-aminobenzophenones Shiff bases (36) with the 3-aminopropionitriles in the presence of acetic acid. By reacting 38 with iso(thio)cyanates, were prepared benzodiazocine derivatives 39 [27]. When the compounds 38 were treated with m-chloroperbenzoic acid, oxidation occurred selectively at the 1-position giving the corresponding 1-oxides (40) [28].

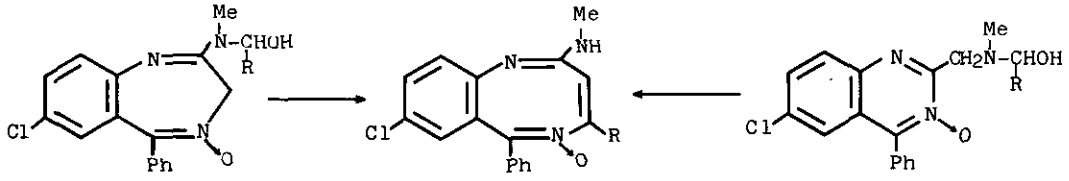


36 37 38

R_1 = R_2 = H, Me
R_3 = R_4 = R_7 = H, OMe
R_5 = H, Cl, CF_3, NO_2, Me, OMe
R_6 = H, Cl
R_8 = hydrocarbons
X = O, S

39 40

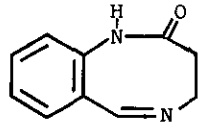
Some 1,5-benzodiazocine 5-oxides (43), which are structurally related to the antianxiety agent chlorodiazepoxide, have been synthesized [29-33]. Treatment of 1,4-benzodiazepine 4-oxides (41) or quinazoline 3-oxides (42) with sodium hydroxide, ammonia or with a basic ion exchange resin, or treatment of 41 with nucleophiles, e.g. sodium methoxide, induced a very unusual ring expansion and gave 43.



41 43 42

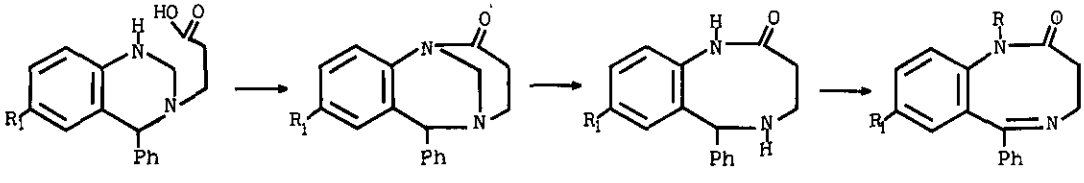
R = H, Me, Et, Pr, Ph, 2-furyl

The only 3,4-dihydro-1,5-benzodiazocin-2(1H)-one (44) without substituent on C(6) was reported by Bogatskii and co-workers [34]. Polarographic reduction of 44 gave hydrogenated derivative which exists in its tautomeric lactam form.



44

A method [35-37] for preparation of 6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-ones (47) was realized bridging the two nitrogen atoms of a 4-phenyl-1,2,3,4-tetrahydroquinazoline derivative (45) to a 3,4-dihydro-6-phenyl-6H-1,5-methano-1,5-benzodiazocin-2-ones (46) followed by removal of the methylene bridge with an acid to form a 6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocin-2(1H)-ones (47), which can be also oxidized to 6-phenyl-3,4-dihydro-1,5-benzodiazocin-2(1H)-ones (48) and then N-methylated to 48a.



45 46 47 48 R = H

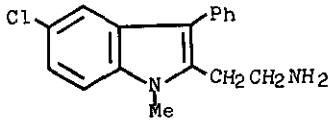
48a R = Me

R_1 = H, Cl

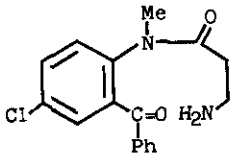
These compounds are structurally related to diazepam and have received an intensive study. The synthesis of 48a was also achieved[38,39] by treatment of 1-methyl-2-(2-aminoethyl)-3-phenyl-5-chloroindole hydrochloride (49) in acetic acid with CrO_3 as oxidizing agent. From mixture was extracted with chloroform a yellow powder which was refluxed in pyridine to give 48a.

Another route to obtain 48a is via N-methyl-N-(2-aminoethylcarbonyl)-2-benzoyl-4-chloroaniline (50) which was refluxed in pyridine containing a small amount of HCl[40] or in toluene[11,12,42].

Cyclization of N-demethyl derivative of 50 did not give 48, as had been claimed by Sulkowski[41], but afforded a dimer as reported by Derieg and co-workers[12].

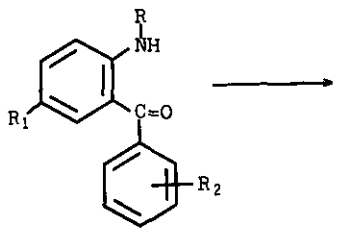


49

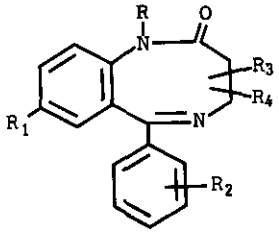


50

Derivatives of 48 were also obtained by reaction of 2-aminobenzophenones (51) with 3-chloropropionyl chloride followed by cyclization with ammonia[43], by cyclocondensation of 51 with ß-amino acids[44] or with ß-alanyl chloride hydrochloride[45,46], or by reaction with dimethylcyanoacetyl chloride followed by reduction and the subsequent cyclization[42].



51



48 deriv.

R = H, Me, Et, Pr, Bu, CF_3, CH_2CF_3, allyl, benzyl, p-$BrC_6H_4CH_2$, p-$Et_2NC_6H_4$

R_1 = H, Cl, Br, Me, NO_2, NH_2, NHAc, CF_3, OCF_3, CHF_2, $OCHF_2$, $SCHF_2$

R_2 = H, o-, m-, p-Cl, Br, F, Me, CF_3, NO_2

R_3 = H, CF_3, Me, Et, Pr, at position 3 or 4

R_4 = H, Me at position 3

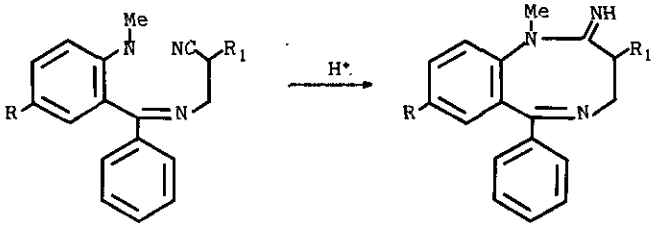
Two strains of Actinomyces roseochromogenes were able to dealkylate 1,5-benzodiazocin-2-ones 48 in a liquid synthetic medium containing starch, corn meal and glucose[47].

A Russian group reported mass spectra[48] of trisubstituted 3,4-dihydro-1,5-benzodiazocin-2(1H)-ones and crystal and molecular structure of 8-bromo and 8-chloro-3,4-dihydro-1-methyl-6-phenyl-1,5-benzodiazocin-2(1H)-one (48a)[49,50].

X-ray structure determination has shown that the eight-membered ring has a boat conformation: the main difference between the two compounds is the orientation of the phenyl ring at position 6.

Diffractometric data of 3,4-dihydro-1,8-dimethyl-4,6-diphenyl-1,5-benzodiazocin-2(1H)-one were also reported [51]. The eight-membered heterocycle ring has a deep boat conformation. The presence of the 4-Ph substituent leads to significant distorsion of the C(2)-C(3)-C(4)-N(5) torsional angle.

3,4-Dihydro-1-methyl-1,5-benzodiazocin-2(1H)-imines (53) were prepared [52] by treatment of 2-methylaminobenzophenone cyanoethylimines (52) in anhydrous benzene with a dry mineral acid.



R = Cl, CF_3, NO_2
R_1 = H, Me

52 53

Gatta and co-workers [53] prepared 1,5-benzodiazocin-6-ones using the synthetic approach reported below: N-substituted 2-amino-N-(3-chloropropyl)benzamides (54), obtained by corresponding 2-nitroderivatives, were refluxed in DMF with potassium carbonate to give 1,2,3,4-tetrahydro-1,5-benzodiazocin-6(5H)-ones (55), from which in ethyl ether with lithium aluminum hydride the corresponding hexahydro-1,5-benzodiazocines were obtained.

R = Ph, Bz

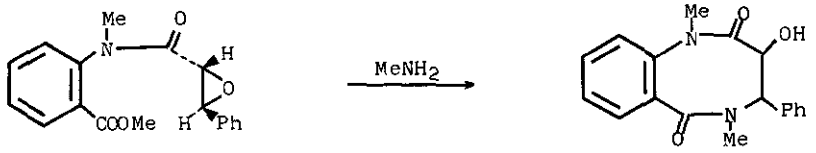
54 55

Similarly, the same authors obtained [54] 3,4-dihydro-1,5-benzodiazocine-2(1H),6(5H)-diones (57) by cyclization of 2-amino-N-(2-carboxyethyl)benzamides (56) via the mixed anhydride method. From 57, the corresponding N-methyl derivatives and hexahydro-1,5-benzodiazocines were obtained with methyl iodide and lithium aluminum hydride respectively.

R = Ph, Bz

56 57

3,4-Dihydro-1,5-benzodiazocine-2(1H),6(5H)-dione derivative (59) was synthesized[55] by the reaction of methyl trans-2-(N-methyl-2,3-epoxy-3-phenylpropionylamido)benzoate (58), prepared via a Darzen's reaction, with methylamine. Conversion of 59 to the p-toluensulfonate and subsequent base-catalyzed elimination afforded the corresponding 3,4-ene-2,6-dione.

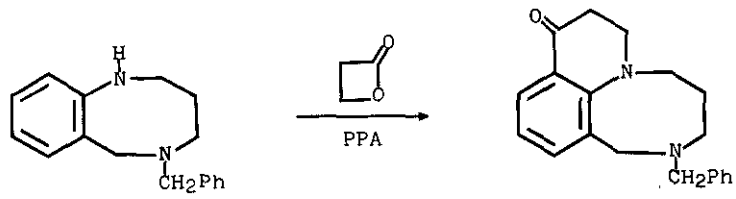


58 59

5. 1,5-Benzodiazocines with heterocyclic fused rings

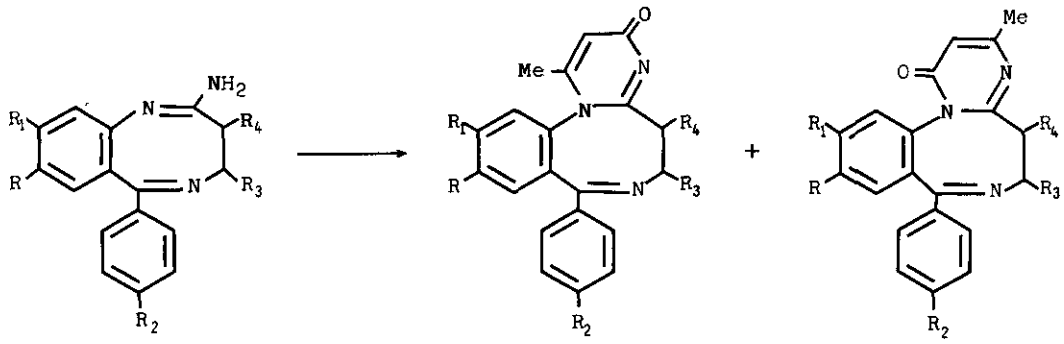
In the hope of finding agents that would be specific for the various kinds of CNS disturbances, cyclofunctionalization of 1,5-benzodiazocines, by building a new heterocyclic ring at the various positions of the 8-membered ring, have been carried out.

2-Benzyl-2,3,4,5,7,8-hexahydro-1H,9H-pyrido [3,2,1-kl][1,5] benzodiazocin-9-one (61) was synthesized [56] by treating 5-benzyl-1,2,3,4,5,6-hexahydro-1,5-benzodiazocine (60) with β-propiolactone and cyclizing with polyphosphoric acid (PPA). The pyrido-benzodiazocin-9-one 61 was reduced to corresponding pyridobenzodiazocin-9-ol or pyridobenzodiazocine with sodium borohydride or hydrazine respectively.



60 61

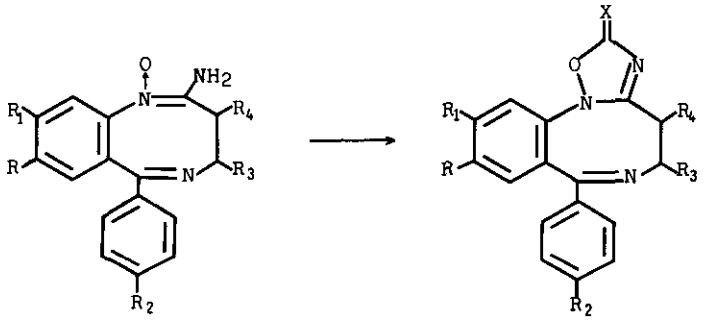
The reaction of 2-amino-1,5-benzodiazocines (62) with diketene gave two isomeric acetoacetylated derivatives which, with HCl or thionyl chloride, afforded, by condensation-cyclization, the fused pyrimido[1,2-a][1,5]benzodiazocines 63 and 64 [57,58].



62 63 64

R = H, Cl, Me, MeO; R_1 = H, MeO; R_2 = H, Cl; R_3 = R_4 = H, Me

The fusion of an oxadiazole ring on benzodiazocine system has been object of study: twelve 4,5-dihydro-7-phenyl-2H-[1,2,4]oxadiazolo[2,3-a][1,5]benzodiazocin-2-thiones (66) were prepared [59] from the 1,5-benzodiazocine N_1-oxides 65 by treating with methyl isocyanate, phosgene or thiophosgene. The N_1-oxides 65 were obtained by reaction of 2-amino-3,4-dihydro-1,5-benzodiazocines (62) with m-chloroperoxybenzoic acid.



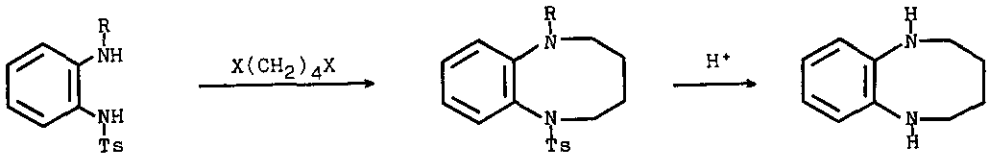
X = O, S
R = H, Cl, Me, MeO
R_1 = H, MeO
R_2 = H, Cl, MeO
R_3 = H, Me
R_4 = H, Me, Et

65 66

6. 1,6-BENZODIAZOCINES

1,6-Benzodiazocines have received attention since the early 1950s. For their preparation a number of methods have been reported which utilize o-phenylenediamine as starting compound.

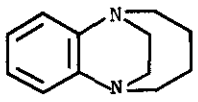
Refluxing N,N'-ditosyl- or N-phenyl-N'-tosyl-o-phenylenediamine (67), in butanol containing sodium, with 1,4-dibromo- or 1,4-diiodobutane were obtained the 1,6-ditosyl- or 1-phenyl-6-tosyl derivatives 68 which, by successive hydrolysis afforded 1,2,3,4,5,6-hexahydro-1,6-benzodiazocine (69) [60-62].



67 68 69

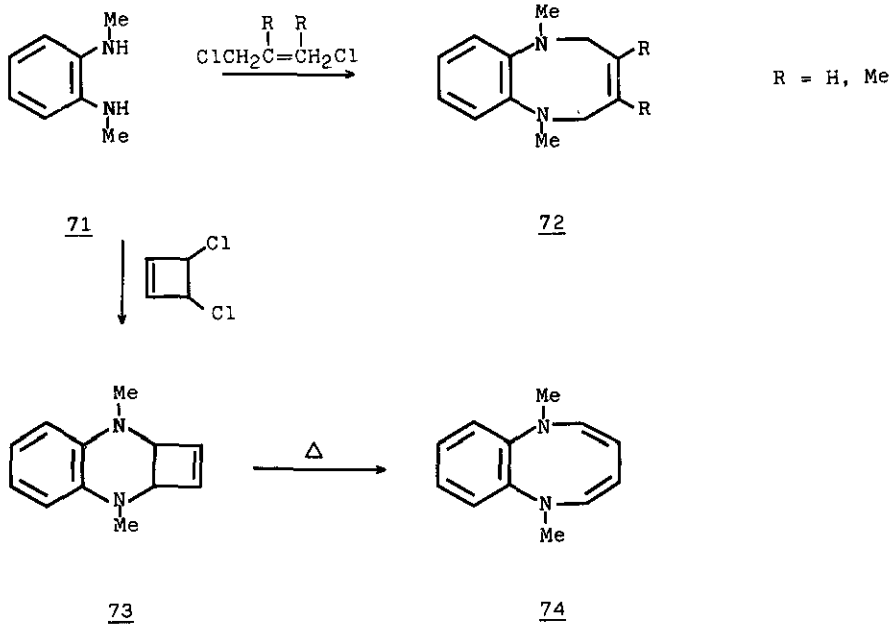
R = Ts, Ph X = Br, I

The N,N'-dimethyl derivative was prepared [63] from 69 by the action of formaldehyde in presence of cyanoborohydride. *N*-Acetyl- *or* N-tosylderivatives of 69 were also obtained [64] and by hydroxyethylation with ethylene oxide and successive cyclization gave 2,3,4,5-tetrahydro-1,6-ethano-1,6-benzodiazocine (70).



70

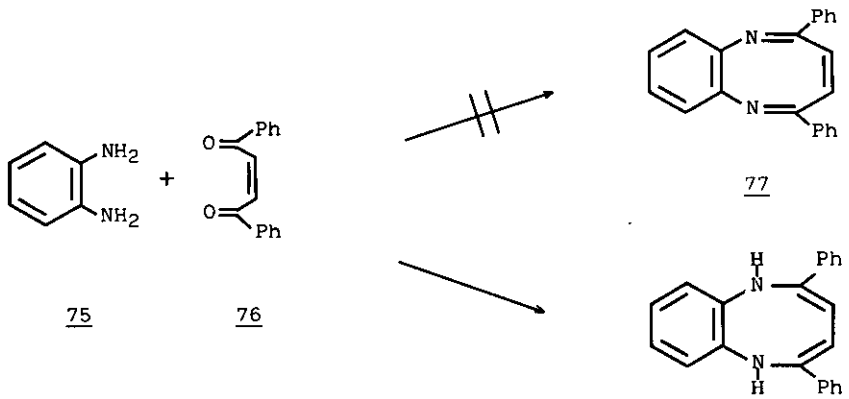
1,6-Dimethyl-1,2,5,6-tetrahydro-1,6-benzodiazocines (72) were obtained by reaction of N,N'-dimethyl-o-phenylenediamine (71) with cis-1,4-dichloro-2-butene derivatives [65] or via the Hinsberg-Stetter reaction from 67 [60] . Instead, the treatment of 71 with cis-3,4-dichlorocyclobutene, *in the presence of* butyllithium, yielded 73 which, heated at 285°C, afforded 1,6-dihydro-1,6-dimethyl-1,6-benzodiazocine (74) [66] .



71 72 R = H, Me

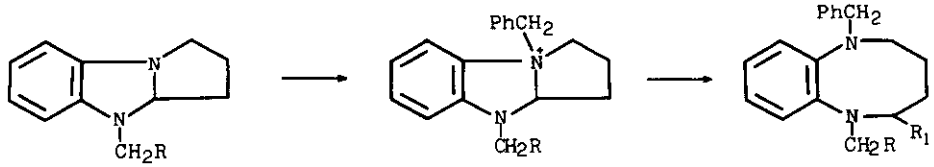
73 74

The condensation [67] of o-phenylenediamine (75) with 1,2-dibenzoylethylene (76) resulted in the formation of 1,6-dihydro-2,5-diphenyl-1,6-benzodiazocine (78), whose formation proceeded via intermediates that undergo oxidation-reduction reactions. Precedently [68] the structure 77 had been assigned to the product of this reaction.



75 76 77 78

A different synthetic route [69] was used by Meth-Cohn and Grantham to prepare the 1,6-dibenzyl-1,2,3,4,5,6-hexahydro-1,6-benzodiazocines (81): 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazoles (79) gave quaternary salts (80) with benzyl chloride, which reacted readily with nucleophiles (hydride, cyanide and hydroxide ions) to give 81.



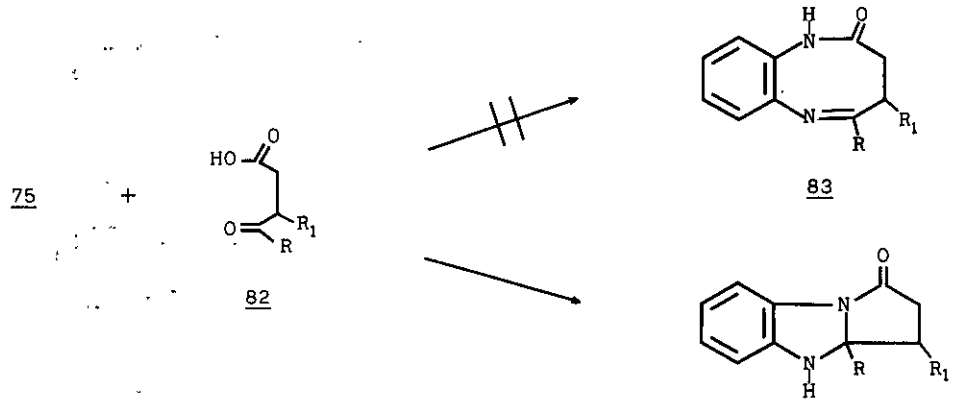
79 80 81

R = Ph, o-$NO_2C_6H_4$ R_1 = H, OH, CN

The delocalization energies, free valence indexes, the superdelocalizabilities and aromaticity of some 1,6-dihydro-1,6-benzodiazocines were calculated [70].

Photoelectron spectra of hexahydro-1,6-benzodiazocines were reported [71], but they do not appear to be useful for the determination of their conformation because of the strong interaction between the effects of bending and twisting at nitrogen on ionization potentials.

The reaction of o-phenylenediamine (75) with acylpropionic acids (82) was studied both by Sulkowski [72] and by Aubagnac and co-workers [73], who reached different conclusions. Under the same synthetic conditions, the former author suggested the possibility to obtain a 3,4-dihydro-5-phenyl-1,6-benzodiazocin-2(1H)-one (83), while the latters proposed for the same compound a more probable pyrrole[1,2-a]-benzimidazolic structure 84.

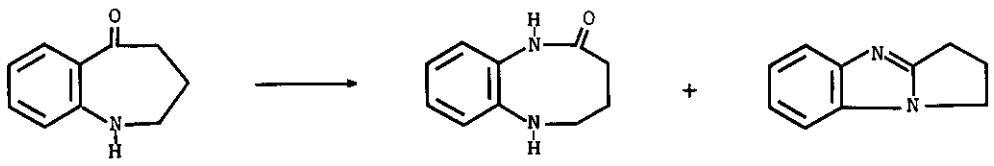


75 + 82 → 83 / 84

R = Me, Ph R_1 = H, Me

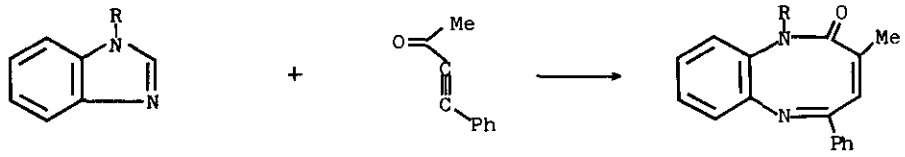
Recently the authors of the present review reported [74] NMR and X-ray analysis of the reaction product of o-phenylenediamine with β-benzoylpropionic acid and solved the ambiguity: the obtained adduct is 3a-phenyl-2,3,3a,4-tetrahydropyrrolo[1,2-a]-benzimidazol-1-one (84).

Schmidt reaction of the ketone 85 gave [75] 3,4,5,6-tetrahydro-1,6-benzodiazocin-2(1H)-one (86) and 2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (87) via a carbonium ion intermediate.



85 → 86 + 87

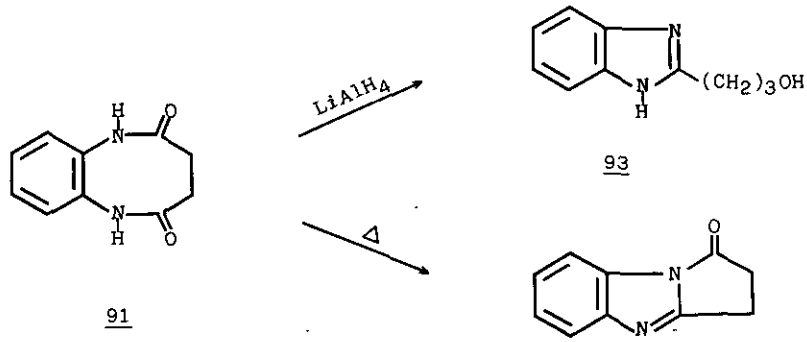
Other 1,6-benzodiazocin-2(1H)-ones (90) were obtained [76] treating benzimidazoles 88 with 1-phenyl-1-butyn-3-one (89).



88 89 90

R = Me, Et, CH_2Ph

The condensation of o-phenylenediamine (75) with diethylsuccinate yielded [77] 3,4-dihydro-1,6-benzodiazocine-2(1H),5(6H)-dione (91), which was thermally rearranged to 2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (92) or reduced with lithium aluminum hydride to 2-(γ-hydroxypropyl)benzimidazole (93) [73].



91 93 92

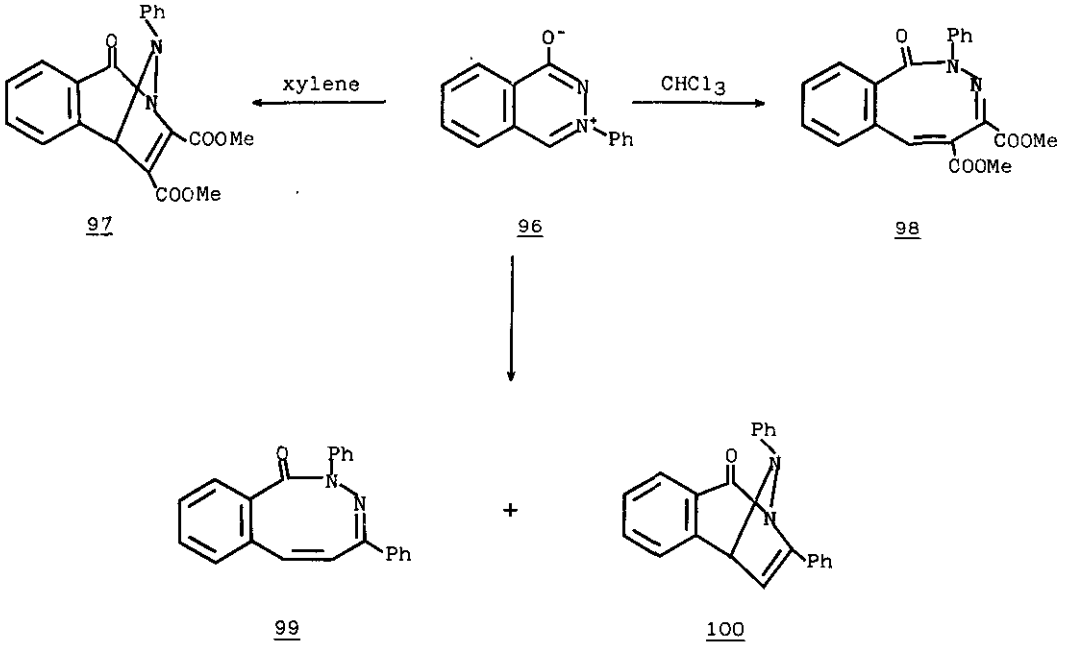
^{1}H nmr conformational studies [78] of N,N'-dimethylderivative of 91 and of its 3-methyl analogue showed that the eight-membered ring has a boat conformation and an interconversion barrier slightly over 100 kJ/mole.

Another condensation of 75 with 3,4-bis(diphenylmethylene)-1,2-cyclobutanedione under ionic and radical reaction conditions gave the dihydrocyclobuta[b]quinoxaline (94) and 3,4-bis(diphenylmethylene)-3,4-dihydro-1,6-benzodiazocine-2(1H),5(6H)-dione (95), respectively [79].

94 95

7. 2,3-BENZODIAZOCINES

The only preparative routes to the 2,3-benzodiazocines have been developed by Dennis and co-workers[80,81]. 1-Oxido-3-phenylphtalazinium (96) reacted with dimethyl acetylenedicarboxylate in refluxing xylene to produce the cycloadduct 97, while use of chloroform as solvent afforded the ring expanded product 98. Reaction of 96 with phenylacetylene gave, in refluxing xylene, two isomeric compounds 99 (75%) and 100 (10%).



Catalytic hydrogenation of the cycloadduct 99 gave the 2,4-diphenyl-3,4,5,6-tetrahydro-2,3-benzodiazocin-1(2H)-one. Bromine in chloroform converted the 99 into the monobromo derivative.

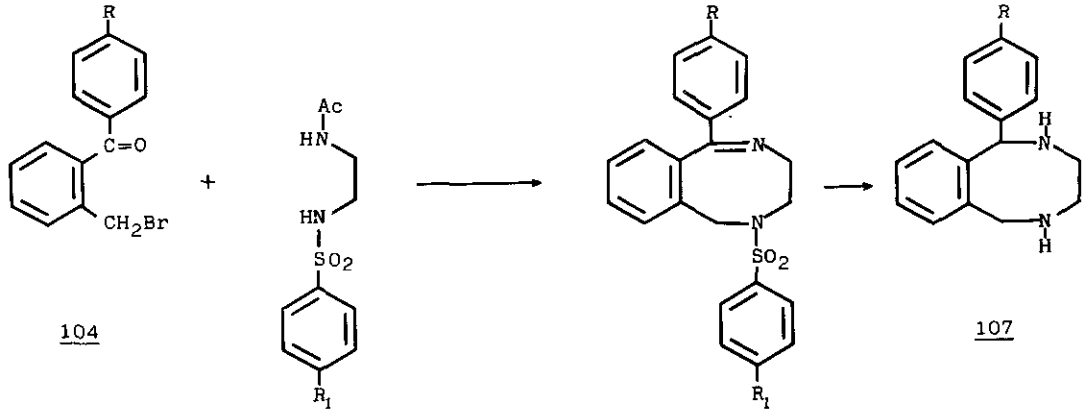
The structure of 2,4-diphenyl-2,3-benzodiazocin-1(2H)-one (99) was determined by X-ray analysis [81,82]. The eight-membered ring assumes a quite distorted tub conformation because of the conjugation within the amide group and the presence of the benzo moiety.

8. 2,5-BENZODIAZOCINES

2,5-Benzodiazocines have received more attention than their 2,3-isomers and good preparative routes have been developed to the fully and partially saturated systems When 3,4,5,6-tetrachloro-o-xylylene dibromide (101) reacted with 2-dimethylamino-ethylamine (102) afforded[83] 2,2-dimethyl-1,2,3,4,5,6-hexahydro-7,8,9,10-tetra-chloro-2,5-benzodiazocinium bromide (103) which, by treatment with silver nitrate yielded the corresponding nitrate, while with methyl bromide, gaseous or in DMF, gave 2,2,5-trimethyl- or 2,2,5,5-tetramethyldibromide products respectively. *2,2,5,5-Tetramethyl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocinium* dibromide was formed[84] when N,N,N',N'-tetramethylethylenediamine reacted with o-xylylene dibromide in acetonitrile.

101 102 103

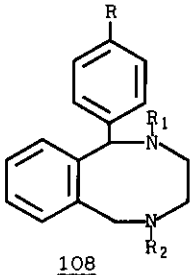
1-Aryl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocines (107) were prepared[85-87] by condensing 2-(bromomethyl)benzophenones (104) with an N-acetyl-N'-arylsulfonyl-ethylenediamines (105). By deacylating, neutralizing and cyclodehydrating the reaction product were obtained 1-aryl-5-arylsulfonyl-3,4,5,6-tetrahydro-2,5-benzodiazocines (106), which by hydrogenation and desulfonylation gave 107.



104 105 106 107

R = H, Br, Cl, CF_3, OMe, NO_2, NH_2; R_1 = H, Br, Me, C_3H_7, OEt

Many 2,5-substituted 1-aryl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocines (108) (about 200) were obtained[88,89] by treating 1-aryl derivatives with acyl chlorides followed by reducing with lithium aluminum hydride. Attempted alkylation of 107 led to isoindole or 1,3-dihydroisoindole[90].

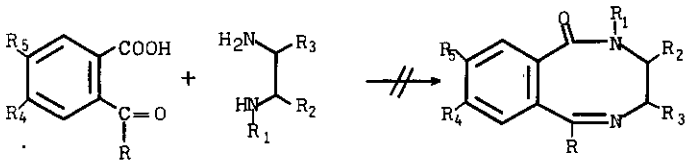


108

R = H, Cl, F, MeO
R_1 = H, Me, cycloalkyl, etc.
R_2 = alkyl, cycloalkyl, phenethyl, etc.

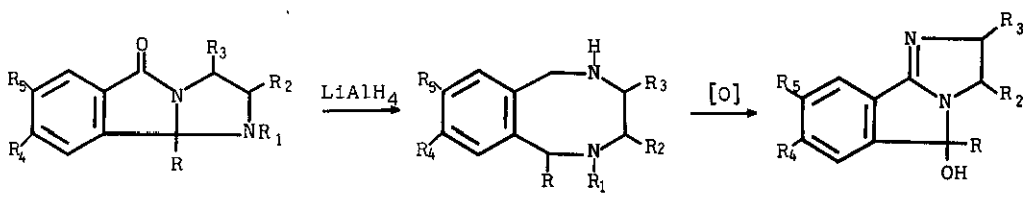
From 107 were also obtained the 5-carbethoxyderivative[91], with ethyl chloroformate in the presence of a mild base, and the 2,5-dimethylderivative[92] by reductive methylation.

A wide range of compounds, to which 2,5-benzodiazocin-1-one structure (111) was assigned and from which were obtained, with lithium aluminum hydride, hexahydro-2,5-benzodiazocines, has been reported by Sulkowski[93]. The sysnthesis was carried out by condensation of acylbenzoic acids (109) with ethylenediamines (110) at 75-200°C. Later, the same author reported[94-96] and confirmed by the IR and NMR spectroscopy[94], that the above condensation afforded 9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-ones (112), which by reduction with lithium aluminum hydride gave[94-100] 1,2,3,4,5,6-hexahydro-2,5-benzodiazocine derivatives (113) whose oxidation afforded imidazoisoindolols 114[101-106], also obtained from 112 via 2-imidazolinylbenzophenones.



109 110 111

R = Ph, substituted Ph, Bz, 2-thienyl
R_1 = H, Me, Et
R_2, R_3 = H, Me, Ph
R_4 = H, Cl, Me, OMe, OH, OBz
R_5 = H, Me

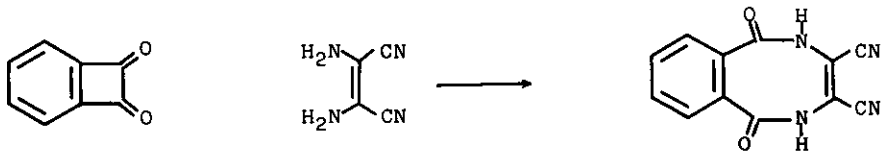


112 113 114

2,3,4,5-Tetrahydro-2,5-benzodiazocine-1,6-dione (117) was obtained[107] by condensation of o-phthaloyl dichloride (115) with ethylenediamine (116).

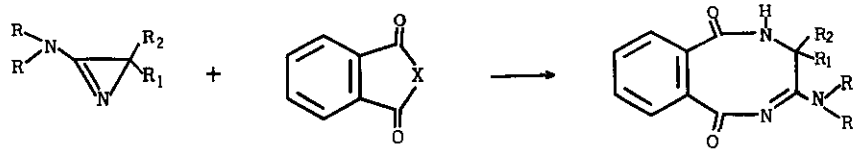
115 116 117

Condensation of benzocyclobutene-1,2-dione (118) with diaminomaleonitrile (119) gave 3,4-dicyano-2,5-benzodiazocine-1(2H),6(5H)-dione (120)[108].

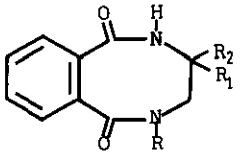


118 119 120

The reactions of azirines (121) with phthalimide[109] and phthalic anhydride[110] (122) were used in the preparation of 2,3-dihydro-3,3-dimethyl-4-dimethylamino-2,5-benzodiazocine-1,6-dione (123) and 2,3,4,5-tetrahydro-2,5-benzodiazocine-1,6-dione 3-(N-phenyl)-carboxamide (124) respectively.



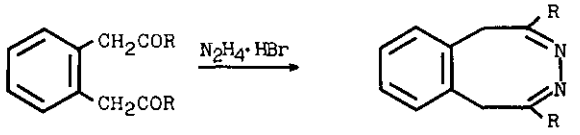
121 122 X = NH, O 123 R = R_1 = R_2 = Me



124 R = R_1 = H R_2 = CONHPh

9. 3,4-BENZODIAZOCINES

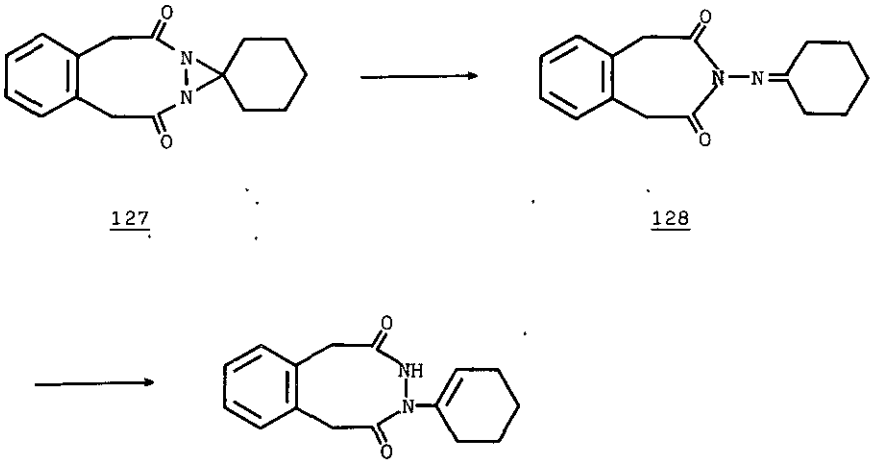
The first preparation of 3,4-benzodiazocine derivatives was carried out by Allinger and Youngdale[111] to obtain 126. Treatment of o-phenylenediacetic acid, obtained from o-phenylenediacetonitrile, with acyl chlorides led to the acylderivatives (125) which reacted with hydrazine hydrobromide to give the 1,6-dihydro-3,4-benzodiazocines 126. Quantum mechanics studies of 3,4-dihydro-3,4-benzodiazocine have been reported [70,111].



125 126

R = Ph, 2,4-$(CH_3)_2C_6H_3$

The 3-(1-cyclohexenyl)-3,4-dihydro-3,4-benzodiazocin-2(1H),5(6H)-dione (129) was obtained [112] from the fused diaziridine (127) which isomerized in refluxing benzene into benzazepinedione (128) and rearranged into 129.



127 128

129

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