OXAZA AND DIOXAZA MEDIUM-SIZED HETEROCYCLES AND BENZ-FUSED DERIVATIVES

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Abstract - This review summarises the preparations and some properties of oxaza and dioxaza medium-ring systems (8-11 membered rings), and their benz-fused derivatives. Classification within each group has been made on the type of operation involved in the ring forming process, viz. ring construction, ring destruction, or ring interconversion.

CONTENTS

I. INTRODUCTION

Medium-sized heterocycles constitute an area of considerable chemical and pharmacological interest. Despite this, relatively few systematic reviews of these systems have appeared and have been largely confined to those rings containing one or more nitrogen atoms. This review is an effort to rectify this situation, at least in part, in the general area of oxaza and dioxaza medium-ring systems (8-11 membered rings), together with their benz-fused derivatives.

Emphasis has been placed on the preparation of these compounds, but some references to chemical, physical, and pharmacological properties are also included. Coverage of the literature has been attempted up to 1980 (Chemical Abstracts, Volume 92), together with a few later references mainly on work from this Department. Systems are reviewed in the order: non-fused oxaza and dioxaza medium-rings, followed by benzoxaza systems and benzodioxaza ring systems. Within each major group, classification has been made on the basis of the type of operation[1] involved in the ring-forming process. i.e. A: ring construction, B: ring destruction, or C: ring interconversion. In some cases, where a choice is possible as a result of the non-isolation or instability of

intermediates, the operation representing the overall transformation is used for classification purposes.

II. OXAZA MEDIUM-RING SYSTEMS

Introduction

All of the four possible position isomers of each of the oxazocine and oxazonine ring systems are known. However only three of the five possible oxazecines, the 1,3-, 1,4-, and 1,5-isomers, and two of the five possible oxaza cycloundecanes, the 1,4- and 1,5-isomers, have been described.

IIA. Preparation of Oxaza Medium Rings by Ring Construction

All but one of the methods reported involved C-heteroatom connections; some used C-O, some C-N, and some both. In a single case an N-O connection was claimed. These bond formations have not been separated, and the systems are considered consecutively on the basis of the relative position of the heteroatoms for oxaza compounds, within each ring size (8 → 11).

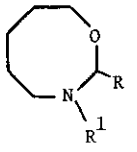
IIA(i) Oxazocines

1,2-Oxazocines [s.a. Sect. II C(i)]

The first claim to the preparation of this ring system was made by Wallach[2] in 1902. He treated ethyl 6-amino-3-isopropylheptanoate with excess iodomethane followed by silver oxide, and the product obtained was assigned an 8-membered ring structure. However it was incompletely characterised, and evidence for a cyclic structure must be regarded as inconclusive.

1,3-Oxazocines

One of the products of the reaction of 1-nitropropane with formaldehyde and ammonia was originally claimed to be a 1,3-oxazocine derivative[3]; however this was later shown to be a 1,3-oxazine[4]. A compound abstracted as a 3-trifluoroethenyl-1,3-oxazocine is listed in the original paper as the 1,4-oxazocine analogue, but appears to be an N-substitution product of morpholine, and hence a 1,4-oxazine[5]. No evidence of structure is given. The only examples of the 1,3-oxazocine system are therefore of the saturated derivatives (1). The hexahydro-2H-1,3-oxazocine (1a) formed in 9% yield by heating N-(5-hydroxypentyl)hexanamide with paraformaldehyde in xylene, in the presence of acid catalysts such as p-toluenesulfonic acid, Bu_4TiO_4 or dry HCl.[6]



(1) a. R=H, $R^1=CO(CH_2)_4CH_3$

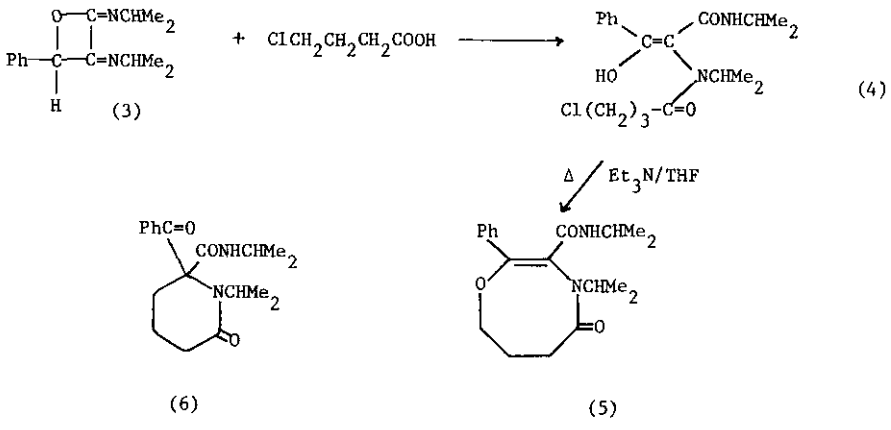
b. R=CF_3, R^1=H

(1b) $\rightleftharpoons$ $F_3C-CH=N(CH_2)_5OH$ (2)

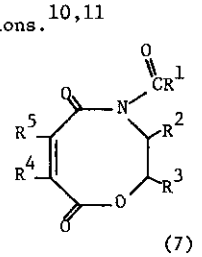
Condensation of trifluorethanal hydrate and 5-aminopentanol in benzene to a Schiff's base, followed by azeotropic removal of water, gave 2-trifluoromethyl-hexahydro-2H-1,3-oxazocine (1b) in 52% yield.[7,8] N.m.r. spectroscopy showed that this compound was in tautomeric equilibrium with its acyclic precursor (2) in a ratio of about 85:15. Some antiinflammatory activity and depression of the CNS was shown by (1b) in mice.[7]

1,4-Oxazocines [s.a. Sect. II B(i)]

Kahbe and Joop[9] reacted the oxetane (3) with 4-chlorobutanoic acid to give the acyclic compound (4) after aqueous work up. Refluxing this intermediate with triethylamine in tetrahydrofuran cyclised it to the 1,4-oxazocin-5-one derivative (5) in 58% overall yield from (3). Assignment of the eight membered ring structure to the product, rather than the 2-piperidone alternative (6), was made on spectroscopic grounds.[9]



Cyclocondensation in xylene of unsaturated esters of type Z-$R^1CONHCHR^2CHR^3OCOCR^4$=CR^5COOH gave the 1,4-oxazocine-5,8-dione derivatives (7). These products form homo or copolymers for use in coating compositions.[10,11]



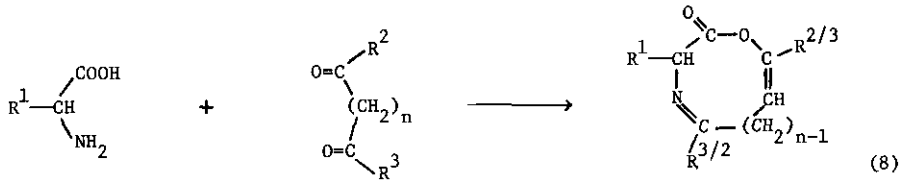
(7)

R^1 = C < 18 branched or linear alkyl

R^2, R^3 = H, C_{1-14} saturated alkyl

R^4, R^5 = H, Cl, Me

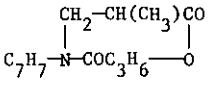
Bodanszky[12] has reported the preparation of several 1,4-oxazocin-2-ones (8, n=2) by condensation of L-α-amino acids with 1,4-dicarbonyl compounds. In some cases mixtures of isomeric products were obtained. (These medium-ring products (8) are not mentioned in Chemical Abstracts).



(8)

1,5-Oxazocines [s.a. Sect. II C(i)]

The first reference to this ring system was in 1892 when the formation of a lactone-lactam designated as (9) was claimed.[13]

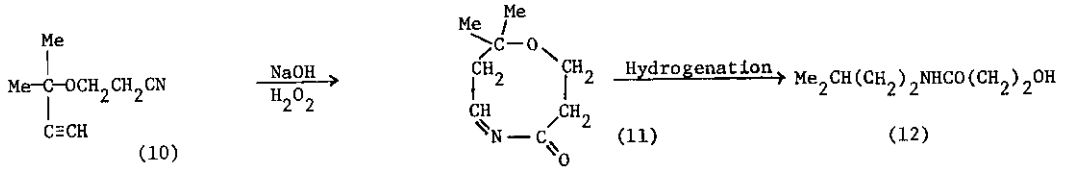


(9) (C_7H_7 = 2- or 4-tolyl)

Heating of 2- or 4-toluidine with ethyl 2-bromo-2-methylpropanoate yielded mixed esters. Hydrolysis of the highest boiling fractions gave products assigned as 3-N-aryl-2-methylpropanoic acids, skeletal rearrangement having previously occurred. Strong heating of these acids gave (9), with elimination of 2- or 4-toluidine. Lower boiling ester fractions on hydrolysis gave isomeric acids which did not cyclise on heating, and were considered the unrearranged substitution products. While the assignment of a 1,5-oxazocine-2,6-dione structure to (9) may be correct it cannot be regarded as conclusively proved.

In 1945 Kost et al.[14] reduced $O(CH_2CH_2CN)_2$ with sodium and butanol with liberation of ammonia, followed by steam distillation to give a product designated as hexahydro-1,5-oxazocine. The active hydrogen content was consistent with this cyclised structure. Several derivatives were prepared.

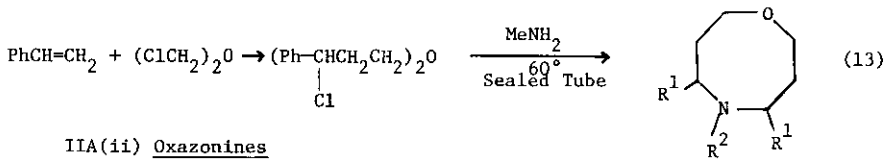
Other Russian workers[15] treated the nitrile (10) with hydrogen peroxide and sodium hydroxide and stated the product was the 1,5-oxazocin-4-one (11). Hydrogenation of (11) cleaved the ring to yield the acyclic amide (12).



(10) (11) (12)

Another condensation reaction from a substituted symmetrical ether was that of a dihalide with methylamine to give the saturated 1,5-oxazocine (13) (R^1 = Ph, R^2 = Me).[16] Analogous

reactions of di-(3-chloropropyl) ethers with primary amines in ethanol, in the presence of sodium carbonate, have been used to prepare a series of perhydro N-substituted 1,5-oxazocines (13) (R^1 = H) in moderate yields.[17,18] One of these derivatives, (13) (R^1 = H, R^2 = $CH_2CH_2OCHPh_2$), was described as showing both antihistaminic and local anaesthetic effects in experimental animals.[19]



(13)

IIA(ii) Oxazonines

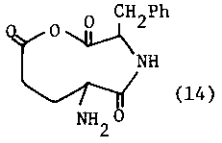
1,3-Oxazonines [s.a. Sect. II B(ii), C(ii)]

A hexahydro-2-methyl-1,3-oxazonine was prepared by heating ethoxyethyne and 6-aminohexanol with elimination of ethanol.[20]

1,4-Oxazonines [s.a. Sect. II B(ii)]

Bodanszky prepared two 1,4-oxazonine derivatives (8) (n = 3) by condensation of glycine or cysteine with 1,5-dialdehydes.[12]

Another preparation of a derivative of this ring system was by cyclisation of the methyl ester of α-L-glutamyl-L-phenylalanine in methanolic ammonia at room temperature for 2 days to the dipeptide anhydride (14).[21]



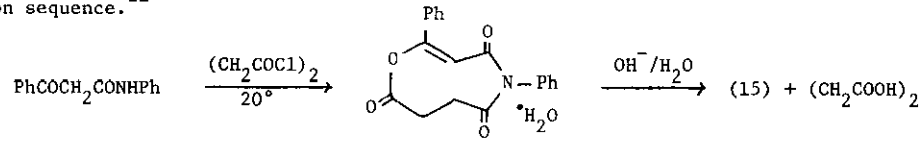
(14)

1,5-Oxazonines

The only mention of a derivative of this ring is to the formation of the unstable lactone (16) by condensation of the anilide (15) with succinoyl chloride.[22] Yields of up to 57% were obtained in dioxane at 20°. Elemental analyses indicated one mole of water of crystallisation was present; decomposition occurred on attempted dehydration by heating in vacuum.

Compound (16) did not form hydrazone nor anilide derivatives, and this, together with infrared and n.m.r. spectroscopic data, was considered to be consistent with the hydrated 1,5-oxazonine structure, rather than that of a seven-membered ring or an acyclic compound.

Reaction of (15) with succinoyl chloride in refluxing solvents, notably chlorobenzene or benzene, did not give (16), but instead yielded a 4-pyrone derivative, a dimer of (15). This did not form in the absence of the acyl halide, which suggested that (16) could be a transient intermediate in this reaction sequence.[22]



(15) (16)

IIA(iii) Oxazecines

1,3-Oxazecines

A derivative of this ring system was prepared by Delaby and Damiens in 1957.[23] Reaction of 7-aminoheptanol with ethylene carbonate gave octahydro-2H-1,3-oxazecin-2-one. The sulfate ester of the amino alcohol heated to 50° with one equivalent of aqueous potassium carbonate gave the same product. Refluxing this 1,3-oxazecine with aniline gave the 1-phenyl derivative of a 1,3-diazecin-2-one.[23]

1,4-Oxazecines [s.a. Sect. II C(iii)]

Bodanszky prepared a derivative of this ring (8) (n = 4) ($R^1 = R^2 = R^3 = H$) by condensation of glycine with 1,6-hexanedial.[12]

IIA(iv) No eleven-membered oxaza rings have been prepared by ring construction methods.

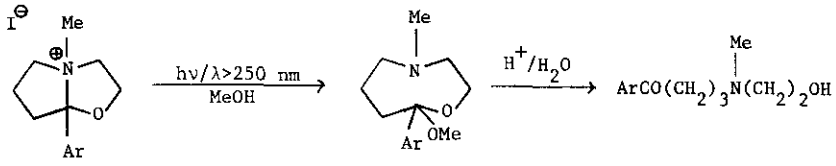
IIB. Preparation of Oxaza Medium Rings by Ring Destruction

IIB(i) Oxazocines

No cases have been reported in the literature of the preparation of an oxazocine ring by this method. However one example has been prepared by a ring destruction technique in this Department.[24]

1,4-Oxazocines

Photo-induced methanolysis of the pyrrolo[2,1-b]oxazole derivative (17) gave the 3,4,5,6,7,8-hexahydro-2H-1,4-oxazocine (18) in 89% yield.[24] The structural assignment of (18) was based largely on spectroscopic data, together with elemental analysis. Acid hydrolysis of (18) afforded the expected hydroxyamino ketone (19) in good yield.



(17) (18) (19)

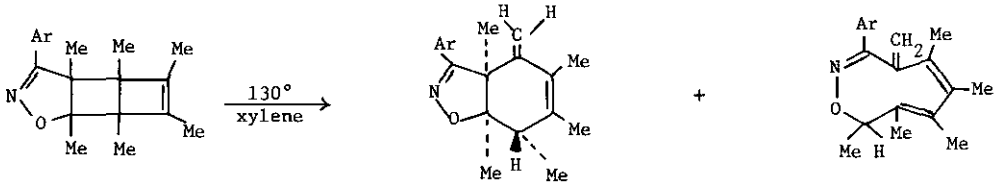
Ar = 3,4-$(MeO)_2$Ph

IIB(ii) Oxazonines

1,2-Oxazonines

The only reported derivative of this ring was prepared by the ring destruction reaction sequence shown below.[25] Hexamethyl-Dewar benzene with $ArC{\equiv}N^{+}\text{-}O^{-}$ gave the tricyclic adduct (20). Thermolysis of (20) in xylene at 130° gave a 20:1 mixture of the bicyclic compound (21) and its monocyclic 1,2-oxazonine isomer (22). This medium ring only formed with (Ar=2,4,6-trimethylphenyl) and not with (Ar=Ph or 4-nitrophenyl). The latter were unaffected under these conditions, but were converted slowly to hexamethylbenzene at 200° in decalin.

The 1,2-oxazonine (22) was a distillable oil which was well characterised spectroscopically.

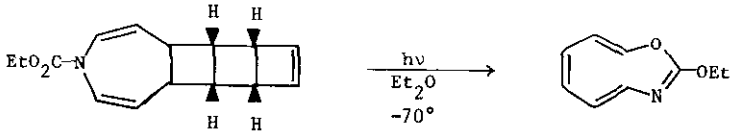


(20) (21) (22)

Ar = $2,4,6\text{-}Me_3C_6H_2$

1,3-Oxazonines

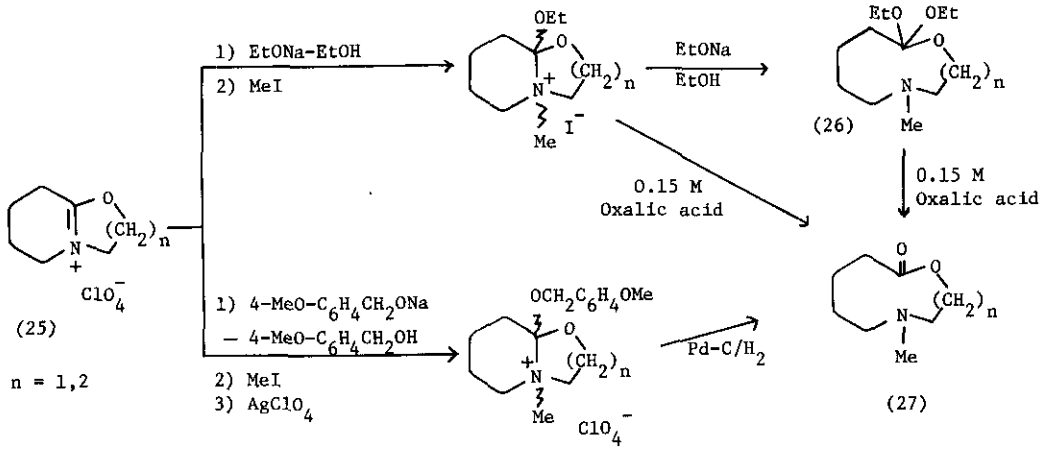
2-Ethoxy-1,3-oxazonine (24) has been isolated as a minor byproduct (~3.5%) of the photolysis of the tetracyclic derivative (23) in diethyl ether with a low pressure UV lamp at -70°[26,27].



(23) (24)

1,4-Oxazonines

The 1,4-oxazonin -9-one (27) (n = 1) and its derivative (26) (n = 1) have been prepared from the azabicyclic immonium ether perchlorate (25) (n = 1).[28] These medium ring lactones (27) were obtained by alternative multistep ring destructive routes as indicated in the reaction sequences.



IIB(iii) 1,5-Oxazecines [s.a. Sect. II C(iii)]

The 1,5-oxazecin -10-one (27) (n = 2) and its derivative (26) (n = 2) were prepared from (25) (n = 2) by analogous sequences to those used for the 1,4-oxazonines above.[28]

IIB(iv) No eleven-membered oxaza rings have been prepared by ring destruction methods.

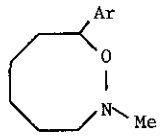
IIC. Preparation of Oxaza Medium Rings by Ring Interconversion

Ring interconversions may be further subdivided into ring enlargements, ring contractions, and ring relocations.[1] All the reactions described in this section are of the first type.

IIC(i) Oxazocines

1,2-Oxazocines

Thermal Meisenheimer rearrangement of hexahydro-1-methyl-2-phenylazepine N-oxide converted it to the saturated 1,2-oxazocine (28) (Ar = Ph)[29] in low yield. An unsaturated hydroxylamine derivative was also produced by a competing Cope elimination. Much of the N-methylazepine precursor was recovered.



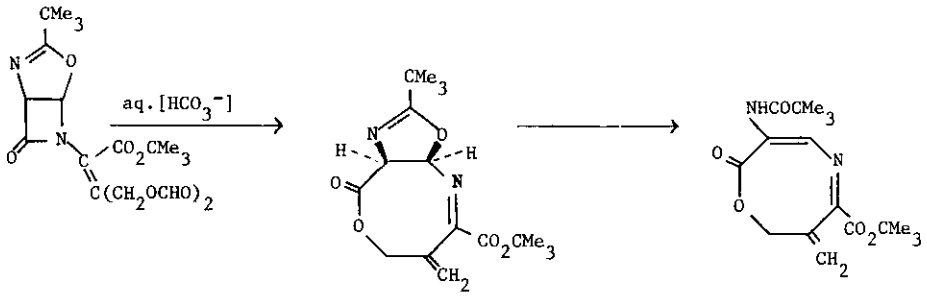
(28)

The mass spectrometric behaviour of the 8-aryl-2-methyl-1,2-oxazocine (28) (Ar = 3-pyridyl) has been compared with that of analogous six- and seven-membered rings.[30]

1,5-Oxazocines

A recent paper described the formation of the unstable fused 1,5-oxazocine derivative (30) from the fused azetidinone (29) by bicarbonate hydrolysis, followed by β-lactam ring opening and dehydration.[31] Chromatographic isolation of (30) on silica was accompanied by rearrangement to the 1,5-oxazocinone (31), as an optically inactive yellow solid. The structure of (31) was established by X-ray crystallographic analysis, but full details of this analysis were not given.[31]

The bis-formate (29) was also converted directly to (31) on alumina.



(29) (30) (31)

IIC(ii) Oxazonines

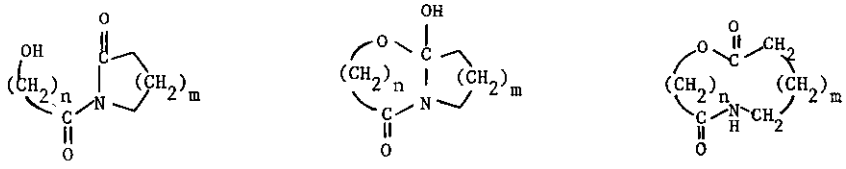
1,3-Oxazonines

2-Ethoxy-1,3-oxazonine (24) [Sect. IIB (ii)] has also been prepared, in 40% yield, by irradiation of 1-carbethoxyazepine in diethyl ether at -80°.[27]

IIC(iii) and IIC(iv) Oxazecines and Oxaazacycloundecanes

All known examples of the 1,4- and 1,5- isomers of these ring systems have been prepared by what is essentially the same general type of reaction; they have therefore been considered under one heading. This is the most intensively studied of the oxaza medium ring areas.

All preparations are examples of the general type of ring interconversion (32) to (34) via the cyclol type intermediates (33).



(32) (33) (34)

m = 2,3

n = 1,2,3

This sequence might possibly be considered as a ring destruction technique for the preparation of the medium rings (34), from the cyclols (33); but as the essential and practical conversion is that from the precursors (32) to the monocycles (34) it has been classified under Section C.

The main interest in these systems lay in their study as models for larger, and related, cyclodepsipetides. Intramolecular interactions of activated amide groups with functional groups

such as (OH, SH, NH_2) had been advanced as the source of certain properties of peptides, cyclodepsipeptides, and related natural products such as ergot alkaloids, in which the formation of unstable 'cyclol' type intermediates (33) had been postulated.[cf. 32] The studies referred to here were mainly done to give experimental backing to this postulate, and not to prepare heterocyclic medium rings, as such.

The earliest major published study in this field, involving the formation of monocyclic rings, was that of Griot and Frey in 1963.[33] At about the same time, Shemyakin and coworkers were independently studying related systems, approached by similar, but not identical, methods.[34-45] An essential feature is the application of the concept of the enhanced activation of N-acylamides, such as (32), towards nucleophilic attack, compared with the non-acylated amides.[eg. 37,39,40] Where sufficient activation exists for cyclisation and steric accessibility is adequate, the actual product formed will depend on the energetic preference for the depsipeptide structure (34), as compared with the initial acylamide (32) or the intermediate cyclol (33).[37] It was also anticipated that solvent polarity and pK values could affect the relative stability of these three tautomeric forms.[33] Detection methods used to distinguish among these three types of structure included ultraviolet,[33,37,46] infrared,[33,35,36,37,42,44] NMR,[33,37,45] and mass spectrometric[37,38] methods, and dipole moments.[44]

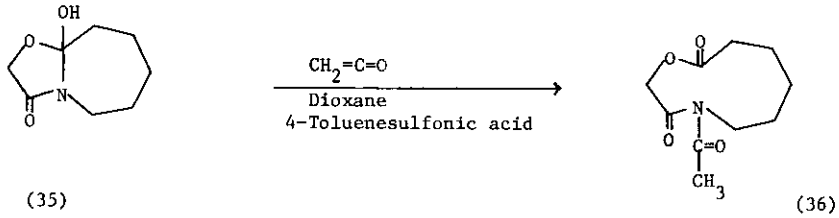
Factors influencing the formation and stability of (33) and (34) have been considered and discussed.[33,37] No such reactions occur with N-substituted 2-pyrrolidones (32) (m = 1). Cyclols (33) form readily from the N-substituted 2-piperidones and caprolactams (32) (m = 2,3). In the cases of reaction of (32) (m = 2,3; n = 1) the cyclols (33) formed, but could not be converted to the medium rings. Shemyakin attributed this to excessive ring strain in the relevant medium ring systems.

Larger oxaza rings ($\geq$11) formed readily, and often spontaneously, from (32), the latter usually being prepared *in situ* by hydrogenolysis of the side chain O-benzyl precursors. Only rarely was heat, or the addition of a base such as triethylamine, necessary to catalyse the cyclisation. There was a tendency for some of the oxazecines to be readily reconverted to cyclols, or to exist in tautomeric equilibrium with them. With eleven-membered, or larger, rings the monocyclic medium or macrocyclic ring structure was favoured.[33,39]

In view of the main aim of preparation of (34) as models for cyclic peptide systems, conformational studies of substituted rings were made[42-45] using spectroscopic methods of analysis. The results suggested that the greater stability of these larger rings was associated with their lower tendency towards transannular interactions; these would encourage reversion to the cyclol form.

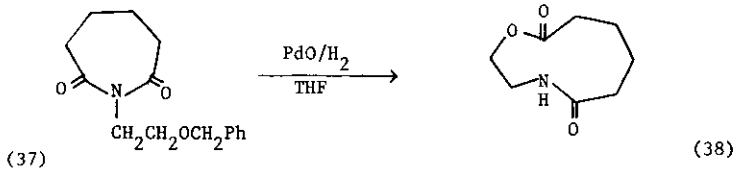
1,4-Oxazecines

It follows from the above established criteria that the 1,4-oxazecine-3,10-dione ring (34) (m = 3, n = 1) could not be formed directly by the route outlined above. Detection of this ring system has, however, been claimed in the mass spectrum of the relevant cyclol precursor (33).[38] A derivative of this ring has also been formed in a case where the reaction was not reversible.[33] Treatment of the cyclol (35) with ketene, as indicated, yielded the N-acetyl-1,4-oxazecine-3,10-dione (36). The UV spectrum of this compound has been reported.[46]



(35) (36)

The 2H-1,4-oxazecine-5,10-dione (38) has been prepared by a somewhat related interconversion reaction.[40] Hydrogenolysis of the N-substituted adipic acid imide (37) yielded the medium ring product (38) directly, presumably via an intermediate cyclol.



(37) (38)

1,5-Oxazecines

Most of the investigations described above have centred on this ring system. The preparation of the unsubstituted perhydro-1,5-oxazecine-4,10-dione (34) (m = n = 2) was reported independently by both groups.[33-36] Derivatives of this compound include the 3-phthalimido,[37] and several substituted with methyl, amide, and/or ester groups at the 2,6, and/or 9 positions,[41-45] which were prepared in attempts to establish the conformation and stereochemistry of the ring.

1-Oxa-4-azacycloundecanes

The only reference to this ring system appears to be to the preparation, by the above route, of 1-oxa-4-azacycloundecane-3,11-dione (34) (m = 4; n = 1).[43]

1-Oxa-5-azacycloundecanes

The preparation of 1-oxa-5-azacycloundecane-4,11-dione (34) (m = 3; n = 2) by the above method was reported by both groups.[33,36] A 3-phthalimido derivative was similarly prepared.[37] An N-acetyl derivative formed normally by the reaction of acetyl chloride and pyridine with the unsubstituted parent compound.[33] Mass spectral,[38] ultraviolet,[46] and conformational studies have been done on this ring system.[42,44,45]

III. *DIOXAZA MEDIUM RINGS*

This area is largely unexplored. The theoretical number of isomeric ring systems is:- eight-membered : 12; nine-membered : 16; ten-membered : 20; eleven-membered : 25 (See Introduction to Section IV). In fact only one isomer is known for each of these four ring sizes, viz: the 1,3,6-dioxazocine,[47-52] 1,4,7-dioxazonine,[53-55] 1,4,7-dioxazecine,[56] and 1,7-dioxa-4-azacyclo-undecane[57] ring systems.

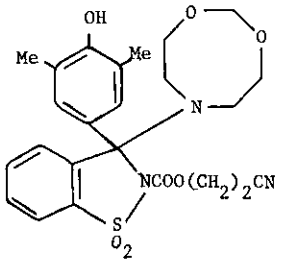
IIIA. Preparation by Ring Construction

IIIA(i) 1,3,6-Dioxazocines [s.a. Sect. III B(i)]

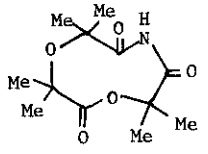
N,N-Bis(2-hydroxyethyl)anilines have been condensed with dihalomethanes in the presence of alkali and quaternary ammonium salt catalysts to give N-aryl-tetrahydro-2H,4H-1,3,6-dioxazocines.[47] The benzisothiazole derivative (39) is mentioned in a patent, from the same source, concerning photographic products and processes employing pH sensitive filter dyes.[48] While no method of preparation of the medium ring in (39) was given it was presumably formed similarly.

IIIA(ii) 1,4,7-Dioxazonines [s.a. Sect. III C(ii)]

In 1941 Ultée claimed that the action of HCl upon acetone cyanohydrin gave as the principal product the 1,4,7-dioxazonine-2,6,8-trione (40).[53]

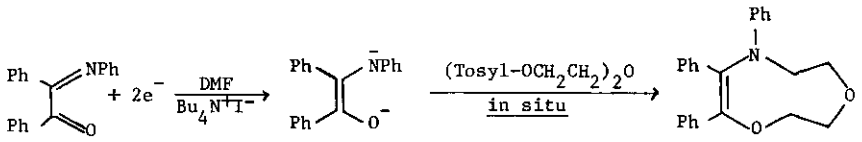


(39)



(40)

Preparation of the 1,4,7-dioxazonine derivative (42) in 10% yield has recently been reported.[54] The ketoimine precursor (41) was converted electrochemically to a dianion, followed by a nucleophilic displacement reaction *in situ* with tosylated diethylene glycol to give (42).



(41) (42)

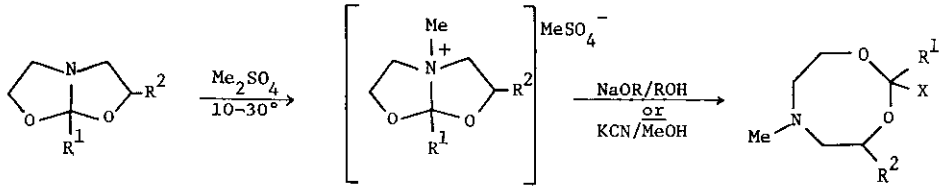
IIIA(iv) 1,7-Dioxa-4-azacycloundecanes

The only reference to this ring is in a patent describing the formation of fogging-resistant polyethylene films by incorporation of triethanolamine mixed esters.[57] Two octadecanoic acid derivatives of 1,7-dioxa-4-azacycloundecane are indexed as being among the compounds prepared,[57] apparently by a ring construction method.

IIIB. Preparation by Ring Destruction

IIIB(i) 1,3,6-Dioxazocines

Feinauer reported the preparation of a series of saturated 1,3,6-dioxazocines (45) by the following ring cleavage reactions.[49-52] The bicyclodioxazaoctanes (43) were treated with dimethylsulfate in inert solvents to give the salts (44). Reaction of these intermediates with either potassium cyanide[50,51] or with sodium alkoxides[49,52] formed the 1,3,6-dioxazocine derivatives (45) (R^1 = lower alkyl; R^2 = H, Me). Some related 2-alkylidene derivatives were also prepared.



(43) (44) (45)

X = OR or CN

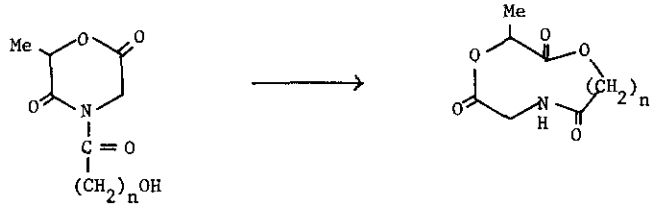
IIIC. Preparation by Ring Interconversion

IIIC(i) No preparations of dioxazocines have been reported by this general method.

IIIC(ii) 1,4,7-Dioxazonines

A derivative of this ring system has also been prepared by an intramolecular rearrangement of the N-hydroxyacyl-2,5-dioxomorpholine (46) (n = 1), analogous to those described under Section II

C(iii and iv), to give the 5H-1,4,7-dioxazonine-3,6,9(2H)-trione (47) (n = 1).[55] The rearrangement was catalysed by the addition of triethylamine. This cyclic tridepsipeptide (47) (n = 1) was readily hydrolysed in mild alkaline or acidic conditions.



(46) (47) n = 1,2

IIIC(iii) 1,4,7-Dioxazecines

The 1,4,7-dioxazecine derivative (47) (n = 2) was similarly prepared by a very slow rearrangement of the N-propanoylmorpholine (46) (n = 2).[56]

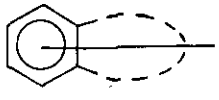
IV. BENZOXAZA MEDIUM-RING SYSTEMS

Introduction

Of the fifteen possible isomeric benzoxazocine ring skeletons, only nine have so far been reported in the literature; these are the 1,4-, 1,5-, 1,6-, 2,3-, 2,4-, 2,5-, 3,1-, 4,1-, and 5,1- systems, including derivatives of the rings. Even fewer benzoxazonines (five out of twenty one; the 1,4-, 2,3-, 2,5-, 2,6- and 4,1- systems) have been described. Only two benzoxazecines (the 2,6- and 3,6- systems) and two benzoxazacycloundecines (the 1,3- and 2,7- systems) are known out of a possible total of twenty eight and thirty six, respectively, for these latter two ring sizes. Obviously there is much scope for further development.

The calculation of the number of isomeric ring systems possible for benzoxaza medium-ring compounds was based on the following equation:

$$T = \left(\frac{A-M}{2}\right) + M$$



(48)

In this equation,

(i) T is the total number of isomeric ring systems for each medium ring size (n);

(ii) A equals $\frac{P!}{P_C!P_N!P_O!}$, where P = (n-2) is the number of possible replacement sites in the medium ring, while P_C, P_N, and P_O are the numbers of carbon, nitrogen and oxygen atoms, respectively, in the ring, excluding those shared with the benzene ring; and

(iii) M is equal to the number of arrangements in the ring in which 'mirror symmetry' is shown

about the central horizontal line in (48).

Hence, in the case of the benzoxazocines, for example, A = 30, M = 0 and T = 15. It should be noted that the above general equation can also be used to calculate the number of possible oxaza and dioxaza medium-ring systems, on replacement of the fused benzene ring by a nitrogen atom in the general diagram (48). In these cases P = (n-1), and $P_N!$ is omitted from the equation.

IVA. Preparation of Benzoxaza Medium Rings by Ring Construction

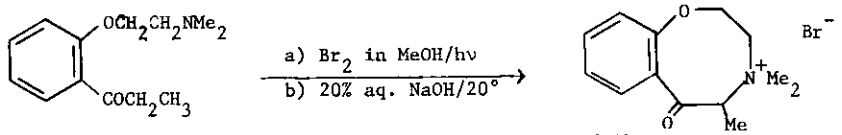
IVA(i) Benzoxazocines

Derivatives of the 1,4-, 1,5-, 1,6-, 2,5-, 5,1-, and 3,1- isomers have been synthesised by ring closures of the C-O and C-N types. A 4,1- isomer has also been reported.

1,4-Benzoxazocines

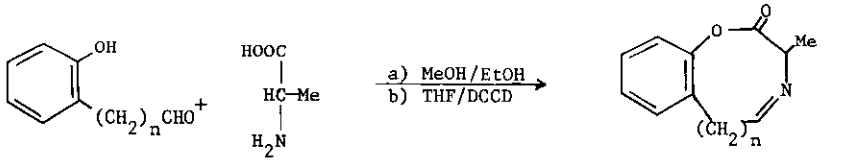
Only two ring construction methods have been reported for this ring system.

The 1,4-benzoxazocin-6-one salt (50) was prepared from the phenylpropanone derivative (49), by side chain bromination followed by C-N ring closure with alkali.[58]



(49) (50)

Bodanszky[12] prepared the 2H-1,4-benzoxazin-2-one (52a) by condensation of the phenolic aldehyde (51a) with L-alanine as shown. Lactones of this and related types are described as useful acylating agents in the preparation of peptides.

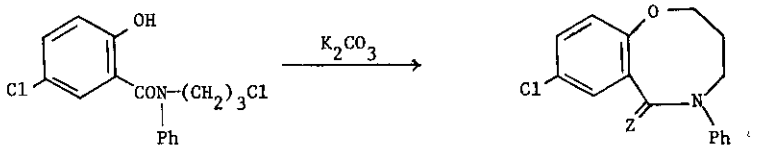


(51) (52)

a. n = 1
b. n = 2

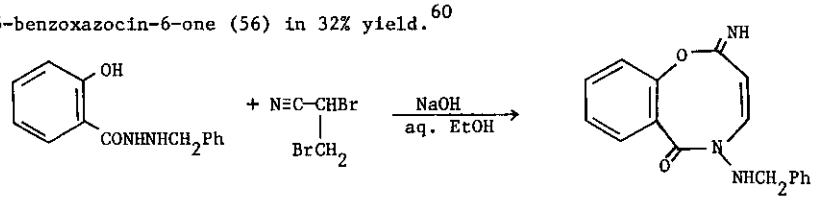
1,5-Benzoxazocines [s.a. Sect. IV C(i)]

This ring system has been prepared by both C-O and C-N type ring closures. The 2H-1,5-benzoxazocin-6-one (54a) was prepared by treating (53) with potassium carbonate; the product was reported to have no psychopharmacological activity.[59] Reduction of (54a) with lithium aluminium hydride gave the 1,5-benzoxazocine derivative (54b).



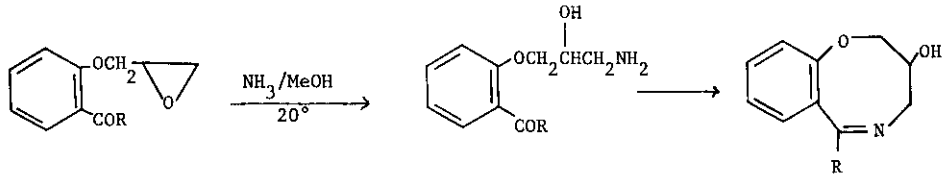
(53) (54) a. Z = O b. Z = 2H

The condensation of the hydrazide (55) with 2,3-dibromopropanenitrile, gave the N-substituted 5,6-dihydro-2H-1,5-benzoxazocin-6-one (56) in 32% yield.[60]



(55) (56)

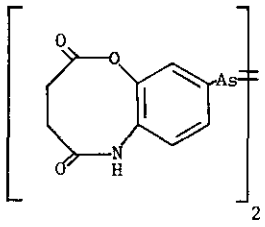
A series of 3,4-dihydro-3-hydroxy-2H-1,5-benzoxazocines (59) has been prepared by treatment of the appropriate oxirane derivatives, e.g. (57), with methanolic ammonia at room temperature for several days.[61] The cyclisations proceeded slowly in low to moderate yields via the assumed intermediate amino alcohols (58). Distinction from possible isomeric 3-hydroxymethyl-1,4-benzoxazepines was made on the basis of n.m.r. evidence. Some chemical interconversions were reported, giving twenty four benzoxazocines with a variety of substituents. 3,4-Dihydro-3-hydroxy-6-methyl-2H-1,5-benzoxazocine (59, R = Me) had high sympathetic β-receptor blocking activity.[61] Further pharmacological studies have been reported on this compound.[62]



(57) (58) (59)

1,6-Benzoxazocines [s.a. Sect. IV C(i)]

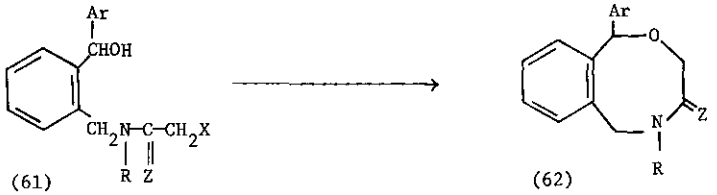
This ring system is usually prepared by ring enlargement methods. However a dimeric arsenic derivative (60) has been reported to form by condensing 3-amino-4-hydroxybenzene-arsonic acid with succinic anhydride, and reducing the product with sodium hyposulfite.[63]



(60)

2,5-Benzoxazocines

The ring closure of compounds (61a) (X = Cl) with potassium t-butoxide in dimethyl sulfoxide gave the lactams (62a), which were reduced with lithium aluminium hydride to 3,4,5,6-tetrahydro-1H-2,5-benzoxazocines (62b) (R = Me, Et).[64] Ring closure of the amines (61b) (X = OH) with p-toluenesulfonic acid in xylene[64] or in benzene,[65] or with aqueous hydrobromic acid in chloroform,[66,67] gave (62b) (R = H; Me) directly.



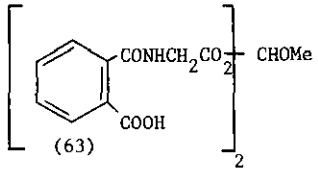
(61) (62)

a. Z = O; b. Z = 2H

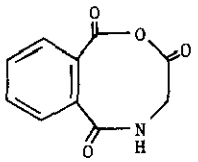
The most important member of this series is the 1H-2,5-benzoxazocine derivative Nefopam (62b) (R = Me; Ar = Ph), which, as its hydrochloride salt, is used as an analgesic. Pharmacological studies on Nefopam have been reported, but are not covered by this review.[cf. 68,69] Nefopam could also be prepared by treatment of 2-benzoylbenzoyl chloride with 2-methylaminoethanol followed by reduction and cyclisation.[70]

The action of acrylonitrile on (62b) (R = H; Ar = Ph), followed by reduction of the product with 5% palladium on charcoal gave the related central nervous system depressant (62b) (R = $(CH_2)_3NH_2$; Ar = Ph).[71] Several active derivatives of this compound were also prepared.

Condensation of phthaloylglycine with dichloromethyl methyl ether formed (63), which on heating gave a product which was incorrectly indexed as the 1H-2,5-benzoxazocine-1,3,6-trione derivative (64),[72] instead of as a diphthalimido compound.



(63)



(64)

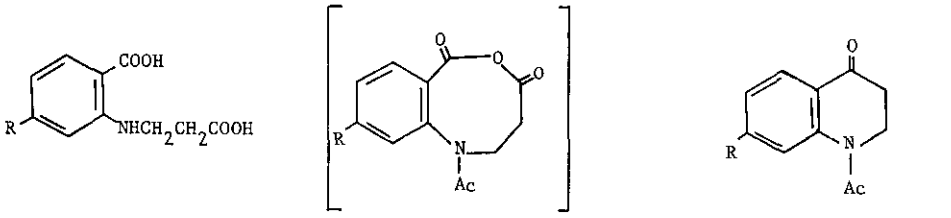
Claims to the preparation of 1H-2,5-benzoxazocine-1,6-diones from phthalic anhydride derivatives[73-75] have not been substantiated by more recent work.[76]

5,1-Benzoxazocines

The diarylketones (65) (R = H, Cl, Me, NO_2; R^1 = H, Me), reduced with $NaBH_4$, were stated to give unspecified intermediates, which when dissolved in methanol and treated with sodium gave a series of 2H-5,1-benzoxazocin-2-one derivatives (66), with chemotherapeutic activity.[77]

(65) (66)

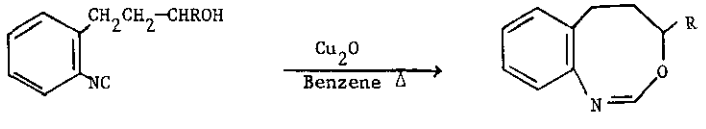
Bekhli and coworkers[78] claimed that cyclisation of the diacids (67) to the quinolin-4-ones (69) in the presence of potassium acetate-acetic anhydride proceeded through the eight-membered cyclic anhydrides (68). These 2H-5,1-benzoxazocine-4,6-dione derivatives were not isolated, and their formation was only assumed on the basis of infrared data.



(67) (68) (69)

3,1-Benzoxazocines

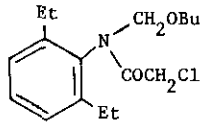
Ito et al[79] reported the formation of the 4H-5,6-dihydro-3,1-benzoxazocines (71) (R = Me, Et) in low to moderate yields, by intramolecular cyclisation of the isonitriles (70) (R = Me, Et) respectively, in the presence of cuprous oxide.



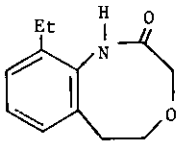
(70) (71)

4,1-Benzoxazocines

The 1H-4,1-benzoxazocin-2(3H)-one derivative (73) was claimed to be a minor metabolite formed from butachlor (72) by the action of the soil fungus Chaetomium globosum.[80] Identification was by gas chromatography-mass spectroscopy only.



(72)



(73)

IVA(ii) Benzoxazonines

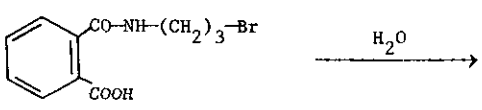
Derivatives of the 1,4- and 2,6-benzoxazonine ring systems have been synthesised using ring construction procedures; these procedures involve, in the penultimate step, both C-O and C-N bond formation in the former case and C-O bond formation in the latter.

1,4-Benzoxazonines [s.a. Sect. IV B(ii)]

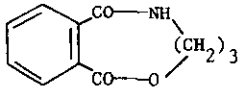
As part of his work on lactone intermediates useful in peptide synthesis [see also Sections IIA(i) and IVA(i)], Bodanszky has described[12] the preparation of the 1,4-benzoxazonin-2-one derivative (52b) from L-alanine and the phenolic propionaldehyde (51b).

2,6-Benzoxazonines

In 1905, Gabriel reported[73] the preparation of an intermediate 2,6-benzoxazonine-1,7-dione (75) by cyclization of the carboxylic acid (74). However, some doubt is cast on this structural assignment in view of the recent results of Wicks[76] on a related reaction.

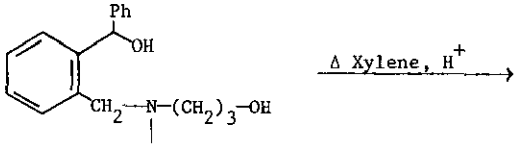


(74)

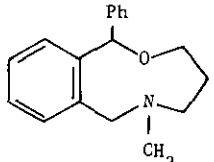


(75)

An alternative preparation of this ring system was achieved,[64] in an analogous fashion to the 2,5-benzoxazocines, by acid-catalysed dehydration of the amino alcohol derivative (76). The product (77) was characterized as the oxalate salt.



(76)



(77)

No ten-or eleven-membered benzoxaza rings have been prepared by ring construction techniques.

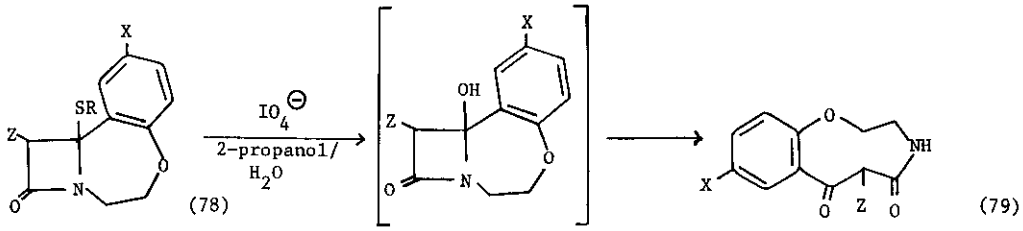
IVB. Preparation by Ring Destruction

Somewhat surprisingly, no benzoxazocines appear to have been prepared by the ring destruction strategy. However, this approach has been applied effectively in the preparation of nine- and ten-membered benzoxaza systems, and in one case, to a benz-fused eleven-membered oxaza ring system.

IVB(ii) Benzoxazonines

1,4-Benzoxazonines

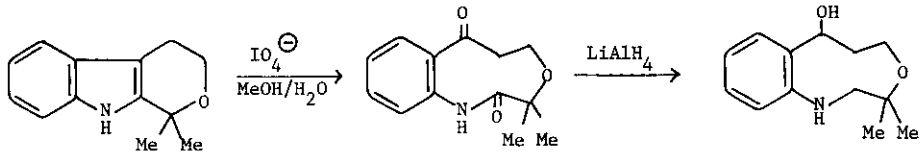
A ring destruction reaction which provides access to the 3,4-dihydro-1,4-benzoxazonine-5,7-(2H,6H)-diones (79) has been described[81] by Bose and coworkers. This reaction involved oxidative removal of the alkyl thioether group in (78) followed by ring expansion of the resultant hydroxy-amide intermediate; yields, however, were low.



X = H, Z = OMe or N_3; X = Cl, Z = OMe; R = Me, Et or i-Pr.

4,1-Benzoxazonines

Another type of oxidative cleavage reaction has been utilised[82] in the preparation of the 4,1-benzoxazonine-2,7(1H,3H)-dione (81) from the pyranoindole derivative (80). In this case the yield was high. Further functional group manipulations by standard methods led readily to other derivatives of the basic ring system, for example (82).

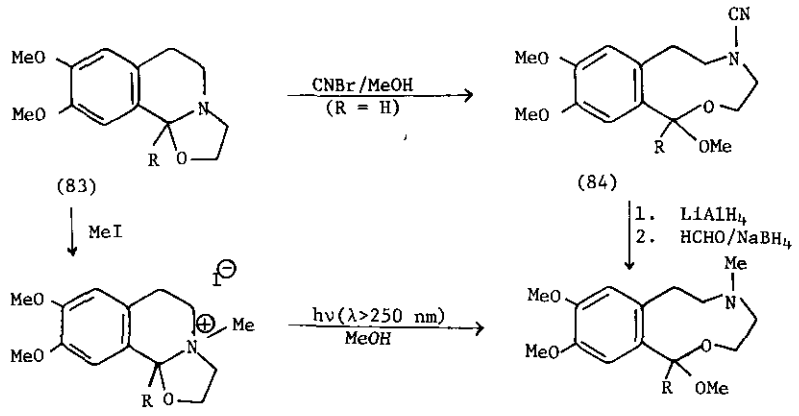


Other substituted 4,1-benzoxazonine-2,7(1H,3H)-diones have also been prepared by the above reactions and are reported[83] to be useful as antihypertensives, bactericides and fungicides.

2,5-Benzoxazonines [s.a. Sect. IV C(ii)]

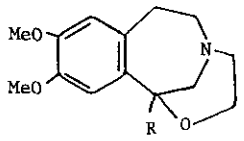
Two complementary ring-destruction routes to this ring system have been developed recently.

These routes are based on cyanogen bromide-induced solvolysis,[84] or on photosolvolysis,[85] of reduced oxazolo-isoquinoline substrates. Thus reaction of (83a) with cyanogen bromide in methanol/chloroform in the presence of potassium carbonate gave the tetrahydro-2,5-benzoxazonine-5(1H)-carbonitrile (84a) in 97% yield, while photolysis of the methiodide salt (85a) of (83a) in methanol afforded the related product (86a) (55% yield) after neutralisation of the photolysate. Conversion of (84a) to (86a) was readily achieved[86] by reduction of the secocyanamide with lithium aluminium hydride followed by N-methylation of the resultant secondary amine.



a) R = H b) R = Me

In the case of the bridgehead amine (83b), the reaction with cyanogen bromide and methanol took a different course, resulting in the novel 1,5-methano-bridged 2,5-benzoxazonine derivative (87a) as the major product;[87] a small amount of (87b) was also produced. Although this transformation is formally a ring interconversion, it was considered more appropriate to include it at this point rather than in Section IVC. Photolysis of the corresponding quaternary salt (85b) in methanol proceeded normally to give (86b) in high yield. Structural assignments for all the above medium-ring products rest on analytical and spectroscopic data, together with an X-ray structural analysis[85] on the methiodide salt of (86b).



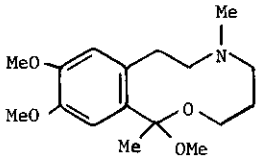
(87) a) R = OMe
b) R = CN

IVB(iii) Benzoxazecines

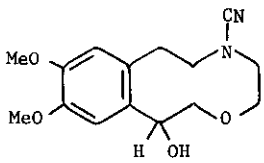
2,6- and 3,6-Benzoxazecines [s.a. Sect. IV C(iii)]

Representatives of these ring systems have been prepared[84,85] by ultraviolet light- or cyanogen bromide - induced solvolytic ring destruction procedures, analogous to those described in the

previous Section for 2,5-benzoxazonine derivatives. Examples include the hexahydro-1H-2,6-benzoxazecine (88) and the tetrahydro-2H-3,6-benzoxazecine-6(1H)-carbonitrile (89), derived from tetrahydro[1,3]oxazino- and hexahydro[1,4]oxazino-isoquinoline precursors, respectively.



(88)



(89)

IVB(iv) Benzoxazacycloundecines

1,3-Benzoxazacycloundecines

Tetrahydro-1,3-benzoxazacycloundecine-2,4,7(3H)-triones (91) have been prepared[88] from the tetrahydro-benzoquinolines (90) by reaction with m-chloroperbenzoic acid in refluxing dichloromethane. A ring destruction is involved together with an apparent Baeyer-Villiger-type expansion to include oxygen in the medium-ring of the products. These eleven-membered ring compounds show anti-inflammatory activity.

(90) R = H, OMe; R^1 = H, Me (91)

IVC. Preparation by Ring Interconversion

Four benzoxazocine ring systems (1,5-, 1,6-, 2,3- and 2,4-) have been prepared by ring interconversion. However only two benzoxazonines (2,3- and 2,5-), one benzoxazecine (2,6-), and one benzoxazacycloundecine (2,7-), have been made in this manner.

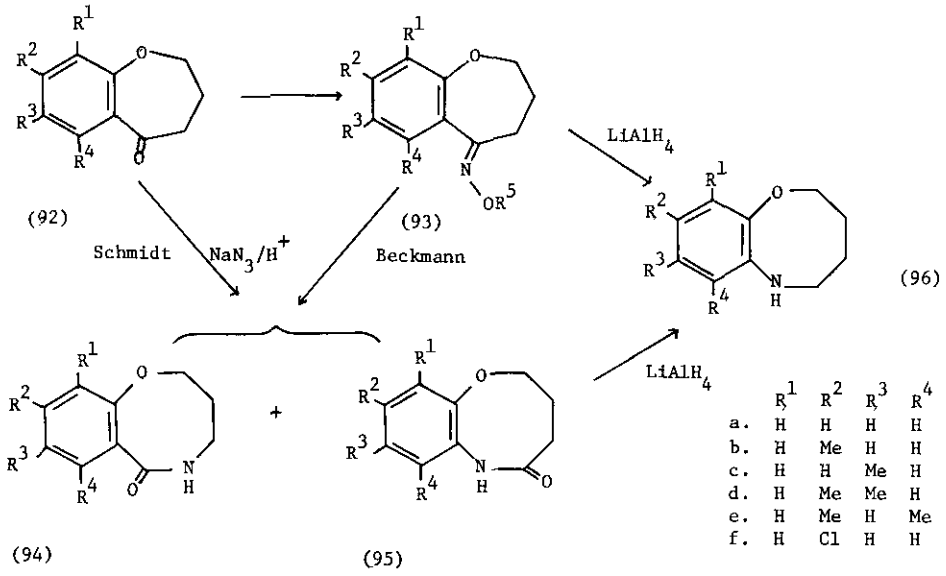
IVC(i) Benzoxazocines

Ring interconversion has been less extensively used than ring construction methods to prepare eight-membered rings. The Beckmann and Schmidt rearrangements have been employed to synthesise 1,5- and 1,6-benzoxazocines, mixtures of the two isomers usually being obtained.[89-96] Otherwise a 2,3-benzoxazocine derivative has been prepared by a Meisenheimer rearrangement,[97] and a 2,4-derivative by the ring expansion of an isoquinoline.[98]

1,5- and 1,6-Benzoxazocines

In most cases reported of both the Beckmann rearrangement and Schmidt reaction on derivatives of 1-benzoxepin-5-ones (92), mixtures of 1,5- and 1,6-benzoxazocines [(94) and (95) respectively]

were obtained. The latter generally predominated, indicating that aryl migration was favoured over alkyl migration.



	R^1	R^2	R^3	R^4
a.	H	H	H	H
b.	H	Me	H	H
c.	H	H	Me	H
d.	H	Me	Me	H
e.	H	Me	H	Me
f.	H	Cl	H	H

The course of the Beckmann rearrangements of the anti-oximes (93a-e) (R^5 = H) with both polyphosphoric acid and phosphorus pentachloride-ether gave low yields of (95a,b,d,e) as the major products, together with much smaller amounts of (94a,b,d,e); cyclic products were not obtained from (93c).[89] Nmr, uv, and ir spectroscopy, and hydrolysis, were used to distinguish between the isomers. The rearrangement was found to be influenced by both electronic and steric effects, and possible mechanisms were discussed. Reduction of (95a) with lithium aluminium hydride gave 2H-3,4,5,6-tetrahydro-1,6-benzoxazocine (96a). Lockhart et al.[90] had earlier described the unexpected formation of the 1,6-benzoxazocine derivative (95e) on attempted Neber rearrangement of the oxime derivative (93e) (R^5 = tosyl). The 1,5- isomer (94e) was not detected in this case. On the other hand Beckmann rearrangement of the oxime (93f) (R^5 = H) with phosphorus pentachloride in ether-benzene had given a trace of cyclic product assigned the 1,5-benzoxazocine structure (94f) on the basis of infrared spectroscopy only.[91]

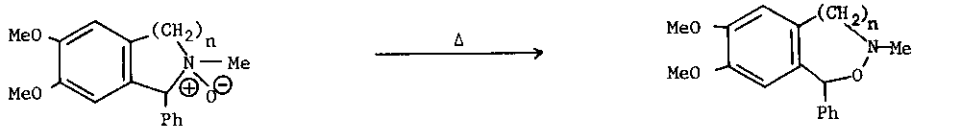
Orlova and coworkers[92] reported the formation of the reduced 1,6-benzoxazocine (96a) directly, by treatment of the oxime (93a) (R^5 = H) with lithium aluminium hydride; the major product was 5-amino-2,3,4,5-tetrahydrobenzoxepin. However the formation of this primary amine could be suppressed by reduction of either the oxime or its tosyl derivative with lithium aluminium hydride-aluminium chloride. Analogously, Schmidt reaction of the ketone (92a) with sodium azide in sulfuric acid-acetic acid gave the 1,6-benzoxazocine (95a) in 54% yield, plus only 5% of the

1,5- isomer (94a).[93] In addition small amounts of a benzoxazole, and of a tetrazolo[5,1-e]-1,6-benzoxazocine were isolated. A related tetrazole derivative was the only identified product of a Schmidt reaction on the seven-ring ketone (92f).[91]

Kawamoto and coworkers[94] reported the formation of the 1,5- and 1,6-isomers, (94a) and (95a), in a ratio of 3:7 when the ketone (92a) underwent the Schmidt reaction in trichloroacetic acid. Tandon et al.,[95] on the other hand, reported that the Schmidt reaction of (92a,c) yielded only the 1,6-benzoxazocines (95a,c). Reduction of these lactams with lithium aluminium hydride gave the 3,4,5,6-tetrahydro-2H-1,6-benzoxazocines (96a,c). Reduction of the oximes (93a,c,d) (R^5 = H) with lithium aluminium hydride gave approximately equal amounts of the cyclic amines (96a,c,d) and 5-aminobenzoxepin derivatives.[95] The 8-methyl-1,6-benzoxazocine (96c) was converted to several 6-substituted derivatives, none of which showed any significant pharmacological activity.[96]

2,3-Benzoxazocines

Meisenheimer rearrangement of the tetrahydro-1H-2-benzazepine-N-oxide (97) (n = 3), on brief heating alone or in ethanenitrile, gave high yields of 3,4,5,6-tetrahydro-8,9-dimethoxy-3-methyl-1-phenyl-1H-2,3-benzoxazocine (98) (n = 3).[97] The crystal and molecular structure of the product was determined by X-ray crystallographic analysis. Reductive cleavage of this benzoxazocine with zinc in acetic acid followed by N-methylation gave the expected product, [2-{3-dimethylamino)propyl}-4,5-dimethoxyphenyl]phenylmethanol.

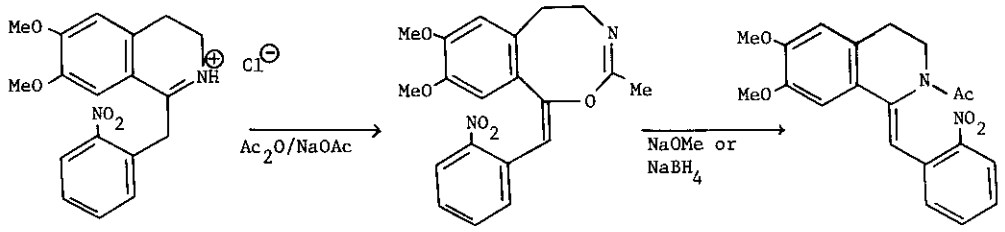


(97) (98) n = 3,4

2,4-Benzoxazocines

Acetylation of the 3,4-dihydroisoquinoline salt (99) with acetic anhydride and sodium acetate gave three products, of which the major one (60% yield) was assigned the cis-1-benzylidene-1H-2,4-benzoxazocine structure (100).[98] Treatment of (100) with the bases shown, converted it to the trans-1-benzylidene-1,2,3,4-tetrahydroisoquinoline derivative (101), which was also the main product of acetylation of (99) with acetic anhydride alone or with pyridine. Ring contraction also occurred on catalytic reduction of (100), or on reduction with hydrazine hydrate and Raney nickel, to yield the 1-(2-aminobenzylidene) analogue of (101). Heating (100) with formic acid and formamide reduced the exocyclic double bond only to give the 1-benzyl analogue of (100).

The o-nitro group seems to be important for the ring expansion; it may play a steric role or be more actively involved.



(99) (100) (101)

IVC(ii) Benzoxazonines

2,3-Benzoxazonines

The Meisenheimer rearrangement of benz-fused cyclic amine N-oxides has been extended[97] to include the synthesis of the 1,3,4,5,6,7-hexahydro-2,3-benzoxazonine (98, n = 4). The yield, however, was low, possibly due to a competing Cope elimination.

2,5-Benzoxazonines

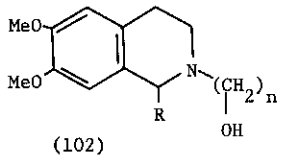
Cyanogen bromide-induced intramolecular O-alkylation provides[99,100] a convenient route to some members of this heterocyclic family, and related larger ring systems, which complements the analogous ring-destruction approach discussed in Section IV B(ii). Thus reaction of cyanogen bromide with the readily accessible tetrahydro-isoquinolinyl ethanols (102a-c) gave the tetrahydro-2,5-benzoxazonine-5(1H)-carbonitriles (103a-c) in yields ranging from 66-72%. Structural assignments rest heavily on spectroscopic data. The presence of the secocyanamide moiety was confirmed by an infrared absorption band in the region of 2200 cm^{-1}, while a diagnostic low-field singlet for H-1 was observed at δ values ranging from 5.60 to 5.52 in the ^1H n.m.r. spectra of (103a-c). Preliminary mechanistic evidence, based on substituent effects and on stereochemical studies, suggest that a stabilised carbonium ion intermediate is involved in the formation of (103a-c), after initial cyanation of the nitrogen in (102a-c).

IVC(iii) and (iv) Benzoxazecines and Benzoxazacycloundecines

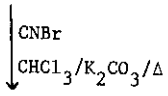
2,6-Benzoxazecines and 2,7-Benzoxazacycloundecines

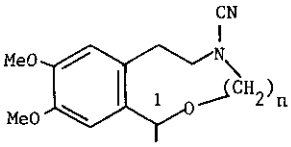
Reduced derivatives of these ring systems have been prepared by the ring-interconversion procedure described in the previous Section, although yields were generally lower. The 4,5,7,8-tetrahydro-1H-2,6-benzoxazecine-6(3H)-carbonitriles (103d) and (103e), for example, were obtained[99] in yields of 65% and 15% respectively, while yields for the 3,4,5,6,8,9-hexahydro-2,7-benzoxazacycloundecine-7(1H)-carbonitriles (103f), (103g), and (103h)[101] were 21%, 15%, and 9%. Conversion of (102g)

to (103g) could be improved by replacement of the nucleophilic bromide ion in the intermediate N-cyanoammonium salt by tetrafluoroborate ion (with silver tetrafluoroborate); this exchange procedure did not help, however, in the case of (103e). The low yield of (103h) can be accounted for, in part, by the occurrence of a competing elimination reaction to give a ring opened product.[101]



(102)

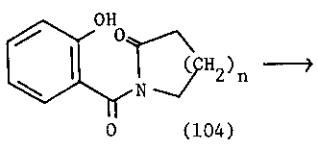




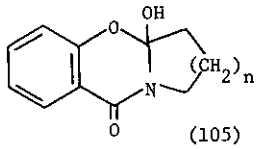
(103)

(102), (103)	R	n
a	Ph	2
b	3,4-$(MeO)_2$Ph	2
c	3,4-(OCH_2O)Ph	2
d	Ph	3
e	H	3
f	Ph	4
g	H	4
h	Me	4

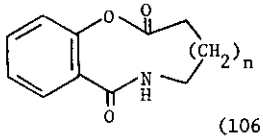
Finally, it is of interest to note the report[37] by Shemyakin et al. that the N-salicyl lactams (104a,b) formed stable cyclols which did not interconvert with the corresponding 1,7-benzoxazecine-2,8-dione (106a) or 1,8-benzoxazacycloundecine-2,9-dione (106b) derivatives. Stabilisation of the cyclols (105a,b) was attributed to the flattening effect of the fused benzene ring (see also Section II C (iii) and (iv)).



(104)



(105)



(106)

a. n = 2
b. n = 3

V. BENZODIOXAZA MEDIUM-RING SYSTEMS

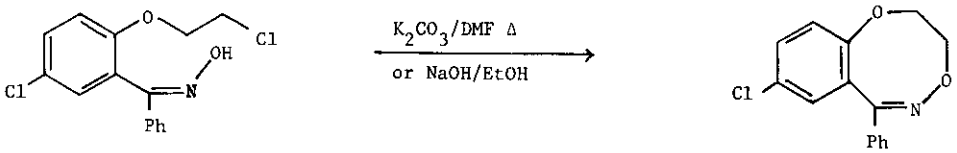
Many ring systems are possible in this category, but very few have so far been described. Of the thirty possible benzodioxazocines (calculated from the equation given in Section IV - Introduction), only two representatives, the 1,4,5- and 2,5,3-systems, have been reported. The larger ring systems are represented by a 1,7,4-benzodioxazonine derivative and a 2,8,5-benzodioxazacyclo-undecine, while a reference to a third system, a 1,5,6-benzodioxazonine, has only recently been published. No benzodioxazecines have been described. For the nine-membered heterocycles fifty four basic systems are theoretically possible, while there are eighty four and one hundred and

twenty eight possible for the fused ten- and eleven-membered rings respectively.

VA. Preparation of Benzodioxaza Medium Rings by Ring Construction

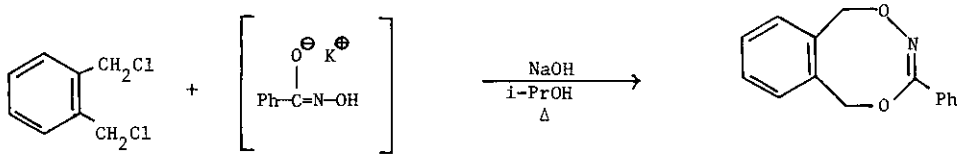
VA(i) Benzodioxazocines

Luts prepared[102] a derivative (108) of the 1,4,5-benzodioxazocine ring system in low yields by cyclisation of the ketoxime (107) which was either pre-formed or generated in situ.



(107) (108)

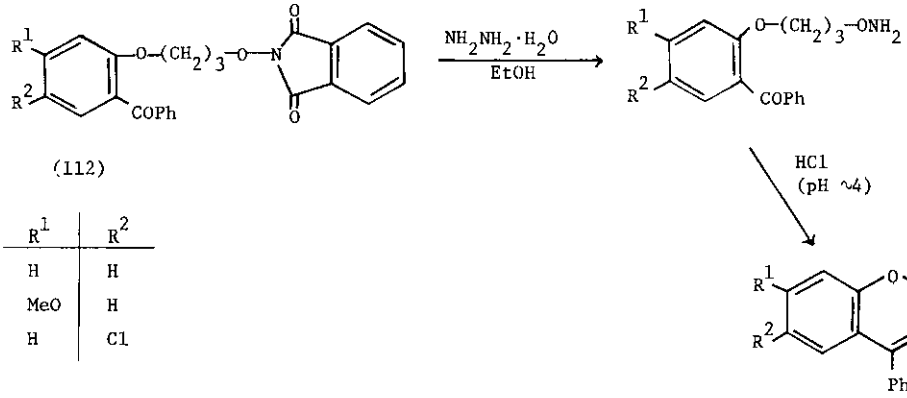
Reaction of o-bis(chloromethyl)benzene (109) with potassium benzohydroxamate (110) yielded the dihydro-2,5,3-benzodioxazocine (111) by a double displacement.[103] Compound (111) showed antilipemic activity in animals.



(109) (110) (111)

VA(ii) and (iv) Benzodioxazonines and a Benzodioxazacycloundecine

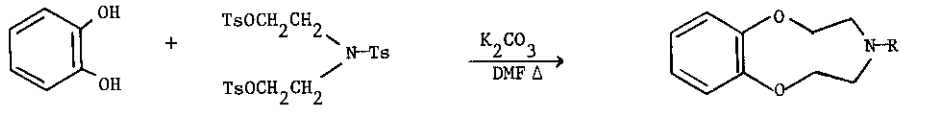
Derivatives (113a-c) of the 2H-1,5,6-benzodioxazonine ring system were prepared[104] in low to moderate yields by hydrazinolysis of the phthalimido-ketones (112a-c), and cyclisation of the assumed intermediate O-substituted hydroxylamines under mildly acidic conditions. Later work has also revealed the formation of small amounts of cyclic dimers from these reactions.



(112) (113)

	R^1	R^2
a.	H	H
b.	MeO	H
c.	H	Cl

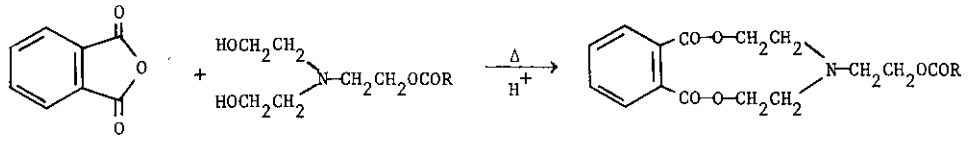
Two derivatives (115a,b) of the 1,7,4-benzodioxazonine system were prepared[105] incidentally by Högberg and Cram, during work aimed at the development of simpler syntheses of some benzocrown amino ethers. Reaction of catechol with the tosylated derivative (114) under basic conditions afforded (115a) in 35% yield; detosylation of (115a) gave (115b) in 50% yield.



(114) (115)

a) R = Ts. b) R = H

A similar ring construction procedure resulted[57] in the preparation of a hexahydro-5H-2,8,5-benzodioxazacycloundecine-1,9-dione derivative (117). In this case, it is presumed from the abstract that phthalic anhydride was condensed with triethanolamine monostearate (116) in the presence of p-toluenesulfonic acid. Compounds such as (117) were claimed to improve the fogging resistance of polyethylene films (see also Section III A(iv)).



(116) (117)

$R = -(CH_2)_{16}CH_3$

No ring destruction or ring interconversion procedures for the preparation of benzodioxaza medium-ring systems appear to have been reported.

VI. CONCLUSION

In the Table following an attempt has been made to bring together various aspects of this review. The basic ring skeletons or systems of which derivatives have been reported are listed and compared with the numbers theoretically possible, emphasis being placed on the large number of systems still undescribed.

The 8-membered oxaza and benzoxaza systems have been the most explored from a preparative point of view, although there is still scope for the development of complementary ring-destruction and ring-interconversion methods for these systems.

Table: Total Numbers of Different Oxaza, Dioxaza, Benzoxaza, and Benzodioxaza Medium-Ring Systems Possible and Reported.

Ring Size	8		9		10		11	
Heteroatoms	O,N	O,O,N	O,N	O,O,N	O,N	O,O,N	O,N	O,O,N
No. of Systems Possible	(4)[a] [15][c]	(12)[b] [30][d]	(4)[a] [21][c]	(16)[b] [54][d]	(5)[a] [28][c]	(20)[b] [84][d]	(5)[a] [36][c]	(25)[b] [128][d]
Preparation by Ring Construction	(1,2) (1,3) [(1,4)] [(1,5)] [1,6] [2,5] [3,1] [4,1] [5,1]	(1,3,6) [1,4,5] [2,5,3]	(1,3) [(1,4)] (1,5) [2,6]	(1,4,7) [1,5,6] [1,7,4]	(1,3) (1,4)			(1,7,4) [2,8,5]
Preparation by Ring Destruction	(1,4)	(1,3,6)	(1,2) (1,3) [(1,4)] [4,1] [2,5]		(1,5) [2,6] [3,6]		[1,3]	
Preparation by Ring Interconversion	(1,2) [(1,5)] [1,6] [2,3] [2,4]		(1,3) [2,3] [2,5]	(1,4,7)	(1,4) (1,5) [2,6]	(1,4,7)	(1,4) (1,5) [2,7]	
No. of Systems Reported	(4) [9]	(1) [2]	(4) [5]	(1) [2]	(3) [2]	(1) [0]	(2) [2]	(1) [1]
No. of Systems Still Undescribed	(0) [6]	(11) [28]	(0) [16]	(15) [52]	(2) [26]	(19) [84]	(3) [34]	(24) [127]

a,b - (Oxaza) and (dioxaza) ring systems.

c,d - [Benzoxaza] and [benzodioxaza] ring systems.

While enough has been done to establish the feasibility of obtaining a number of the other related medium-ring systems, many opportunities for further preparative work are apparent. This is especially so for the benzoxaza and fused and non-fused dioxaza systems, both in terms of the general methods and skeletal types.

There is also a need to broaden the range of derivatives of the ring skeletons already known, both for biological screening purposes and to enable greater study of their chemistry. Some areas which could be of interest include the study of transannular interactions, chelating properties, and the use of medium rings as intermediates in the preparation of macro-heterocyclic compounds.

Acknowledgements

We thank Mrs. J.M. Watson, Department of Mathematics, University of Tasmania, for her valuable assistance in the calculation of the numbers of possible ring systems; we also thank Mrs. B.A. Thomson and Mrs. H.G. Hen of the Department of Chemistry for their patient help in the preparation of the manuscript. Support for this work from the Australian Research Grants Committee and the Upjohn Company is gratefully acknowledged.

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Received, 24th September, 1981