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The Present State of the Chemistry of 1,4-Benzodiazepines

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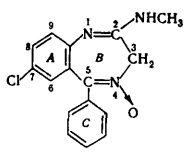
Derivatives of 1,4-benzodiazepines have found wide application as minor tranquilisers. Moreover, compounds of this class are of interest for the investigation of problems in stereochemistry, tautomerism, and mutual effects of atoms in heterocyclic systems and also for the determination of the relation between pharmacological activity and structure. This review deals with the methods of preparation and the chemical properties of 1,4-benzodiazepines and also their dihydro- and tetrahydro-derivatives and the stereochemistry and applications of these substances.
The bibliography includes 195 references.

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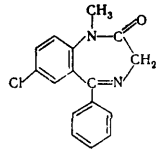
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I. INTRODUCTION

The chemistry of 1,4-benzodiazepines has been attracting increasing interest each year. The reason is that 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide [Chlordiazepoxide, Librium, Elenium†, and Thymosine† (I)],[1,2] 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one [Diazepan, Valium, or seduxene† (II)][3] and their derivatives have proved to be exceptionally effective tranquilisers of a new type[4]:



(I)



(II)

On the other hand, the chemical reactions of these systems and their stereochemistry and tautomerism proved to be unusual. The range of studies carried out so far includes systems resembling (I) and (II) with various substituents in the rings, A, B, and C, systems with non-benzene substituents in the 5-position, tetrahydro-derivatives, and also derivatives of 1,4-benzodiazepine with various functional groups. One review has been published on the chemistry of 1,4-benzodiazepines covering the literature up to 1963.[4] In the general reviews on diazepines[5] and benzodiazepines[6] a number of problems are not dealt with at all, for example the problem of the stereochemistry of 1,4-benzodiazepines and their tautomerism, and extensive new data have now accumulated which were not considered in previous reviews. Moreover, although the first derivative of 1,4-benzodiazepine, namely 4-(*N*-phenylacetamido)-3,4-dihydro-5*H*-1,4-benzodiazepine-3,5-dione was sythesised as early as 1904 by Gärtner[7], the chemistry of these structures has developed essentially only in the last ten years. The present review covers the bibliography up to 1969 inclusive.

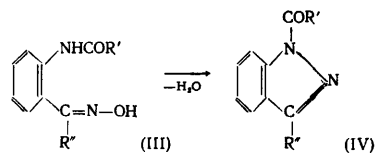
† Tentative spelling (not traced) (Ed. of Translation).

II. METHODS OF SYNTHESIS OF 1,4-BENZODIAZEPINE SYSTEMS

1. 3*H*-1,4-benzodiazepines

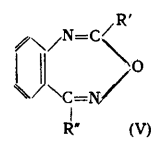
Fully unsaturated 1,4-benzodiazepines were synthesised for the first time in 1959 by Sternbach and coworkers, but the problem has had a fairly long previous history.

In 1891 Auwers and Meyenburg[8] reported that, in the reaction between oximes of *o*-carbamoylaceto- and *o*-carbamoylbenzophenones (III) and a Beckmann mixture, water is split off with formation of acylindazoles (IV). However, these "acylindazoles" were not hydrolysed to indazoles as might have been expected, but were reconverted on hydrolysis into acetamido-oximes, which threw doubt on the proposed structure (IV):



(III) (IV)

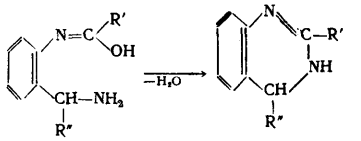
Three years later Bischler[9] proposed formula (V) for these substances, whereby they were assigned to the class of benzoxadiazepines. This formula was adopted by all investigators, including Auwers himself, although the latter believed that the proof of structure (V) was insufficiently vigorous[10].



(V)

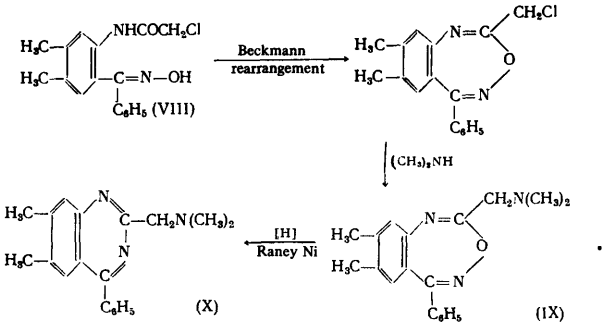
In 1954 Ried and Stahlhofen[11] observed that benzoxadiazepines combine with two molecules of hydrogen over Raney nickel and are converted into dihydroquinazolines.

These investigators suggested that compound (V) is hydrogenated to product (VI), which eliminates water and is converted into dihydroquinazoline (VII):



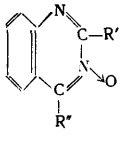
(VI) (VII)

Almost simultaneously Sternbach carried out the following synthesis in order to obtain structures of type (IX), i.e. benzoxadiazepines with basic substituents:



However, on reduction by the method of Ried and Stalhofen the product (IX) gave a high yield of the quinazoline (X) instead of the expected 3,4-dihydroquinazoline of type (VII).

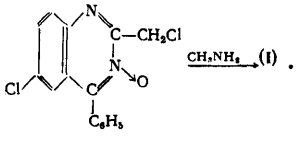
On the basis of the work of Schmitz[12], Katritzky[13], and others in the field of heterocyclic *N*-oxides, Sternbach established that the Auwers compounds have the structure of quinazoline *N*-oxides (XI):



(XI)

This was indicated by the presence of an intense absorption band in the region of 1318–1290 cm^{-1}, which is usually attributed to the N → O bond[14]. Soon structure (XI) was finally proved also chemically[15].

By allowing methylamine to react with 6-chloro-2-chloromethylquinazoline-3-oxide (XII), Sternbach obtained a compound isomeric with the expected 6-chloro-2-methylaminoquinazoline 3-oxide, but differing in its ultraviolet and infrared spectra. A more detailed study showed that this is the 4-oxide of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (I, trivial name—Chlordiazepoxide‡):

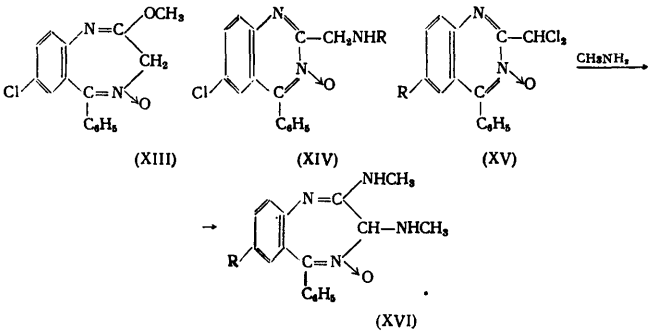


(XII)

According to Sternbach[4], the rearrangement occurring during the reaction of (XII) with methylamine takes place in three stages. The carbon atom in the 2-position of the quinazoline (XII) has a partial positive charge owing to the inductive effect of the N→O group. The first stage is the nucleophilic attack by methylamine on this carbon atom, the second stage includes the dissociation of the C–N bond between the 2-carbon atom and the *N*-oxide nitrogen, and the third stage is the formation of a new C–N bond between the amine oxide nitrogen and the methylene carbon atom with elimination of a chloride ion. The seven-membered ring is in fact formed in this third stage.

A similar rearrangement with ring expansion takes place when (XII) reacts with ammonia, primary aliphatic amines[2,16], hydrazine[17], and sodium methoxide[18]. In the latter case the product is 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (XIII), which is obtained also when diazomethane reacts with compound (XXVIII).[18,19]

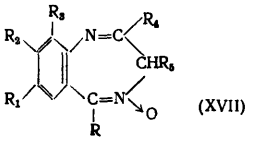
In some cases the reaction of (XII) with primary amines also gives 2-aminomethylquinazolines (XIV) as side products[20]. This type of reaction with secondary amines leads to aminoquinazolines. Only the normal substitution product is formed in the reaction of diethylamine and pyridine. The reaction of 2-dichloromethylquinazolines (XV) with methylamine leads to bismethylamino-derivatives of 1,4-benzodiazepines (XVI):[21]



(XIII) (XIV) (XV)

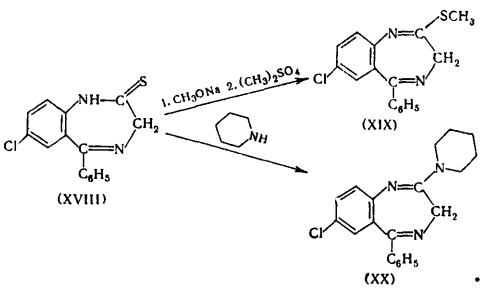
(XVI)

A necessary condition for the rearrangement is the presence of the *N*-oxide group. Without this group, quinazoline reacts with amines to form substitution products. Quinazolines with electron-donating substituents in the 6- and 8-positions also do not undergo the rearrangement. The method described permitted a synthesis of 3*H*-1,4-benzodiazepine *N*-oxides (XVII) with a large number of a wide variety of substituents[1,2,15–37]:



(XVII)

3*H*-1,4-Benzodiazepines without the *N*-oxide group can be obtained by the reduction of the corresponding *N*-oxides or by the reaction of 1,2-dihydro-3*H*-1,4-benzodiazepine-2-thiones with amines or alkylating agents[38]:



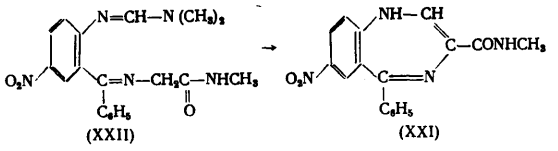
(XVIII) (XIX) (XX)

‡ The names Librium and Elenium were given to the hydrochloride of Chlordiazepoxide.

As already stated, 1,4-benzodiazepine derivatives are distinguished from the isomeric quinazolines by their infrared and ultraviolet spectra. In the infrared spectra of 1,4-benzodiazepine there is an intense absorption band in the region 1620–1605 cm^{-1} and a second intense band in the region 1590–1580 cm^{-1}, while quinazoline has only two weak bands in this region[2], at 1605 and 1550 cm^{-1}.

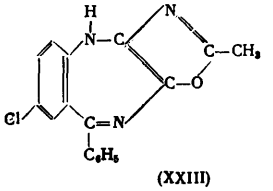
2. 1*H*-1,4-Benzodiazepines

Only two compounds of this series are known. One of these, compound (XXI), was obtained by the cyclisation of the corresponding di-imine (XXII):[39]



(XXII) (XXI)

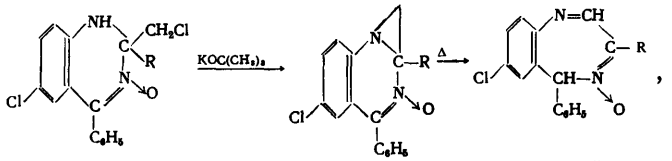
The second derivative (XXIII) is obtained as a side product in the acetylation of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide:



(XXIII)

3. 5*H*-1,4-Benzodiazepines

When acted upon by potassium t-butoxide, the 3-oxides of dihydroquinazolines of type (XXIV) form the *N*-oxides of aziridinoquinazolines (XXV),[40,41] which readily isomerise on heating to derivatives of 5*H*-1,4-benzodiazepines (XXVI):

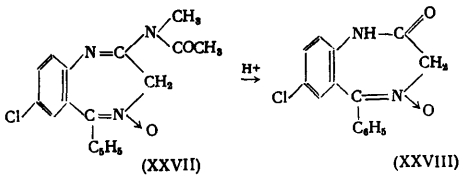


(XXIV) (XXV) (XXVI)

where R = H or CH_3.

4. 1,2-Dihydro-3*H*-1,4-Benzodiazepines

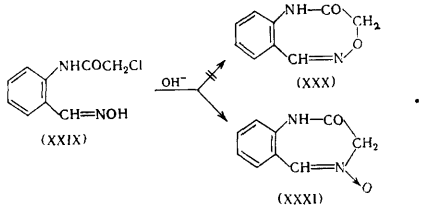
When an inorganic acid is allowed to react with an acetyl derivative of Chlordiazepoxide (XXVII) under mild conditions, the hydrolysis product (XXVIII)[22] is identical with the substance formed when a solution of the hydrochloride of compound (I) is allowed to stand in the cold for a long time§. Alkaline hydrolysis of the acetyl derivative yields the initial 1,4-benzodiazepine (I):



(XXVII) (XXVIII)

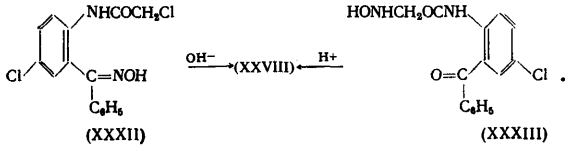
Similar compounds are readily obtained by the reaction of the 3-oxide of 6-chloro-2-chloromethyl-4-phenylquinazolines with alkali[44,45]. This process resembles the rearrangement (described above) which occurs in the course of the synthesis of compounds of type (I) from the corresponding quinazolines. Here the attacking nucleophilic agent is the hydroxide ion[45].

By treating 2-chloroacetamidobenzaldehyde β-oxime (XXIX) with alkali, Auwers[42] obtained a substance, to which he attributed the structure of benzoxadiazocine (XXX), but later it was shown that the substance is in fact the 4-oxide of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (XXXI):[47]



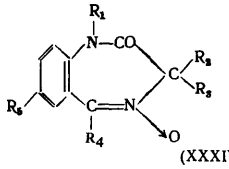
(XXIX) (XXX) (XXXI)

Under these conditions 5-chloro-2-chloracetamidobenzophenone β-oxime (XXXII) cyclises to the *N*-oxide (XXVIII),[42] which is also formed from the hydroxylamine derivative (XXXIII) in an acid medium[48–51]:



(XXXII) (XXVIII) (XXXIII)

A number of homologues and analogues of compound (XXVIII) having the general formula (XXXIV) have been synthesised by these methods[22,44–53]:



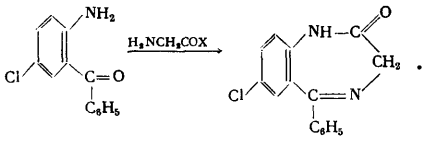
(XXXIV)

The reduction of the 4-oxide of 7-chloro-1-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one yielded compound (II), which also proved to be a tranquiliser and was given the trivial name Diazepam. The high activity of compounds of this kind stimulated the synthesis of analogues and homologues of compound (II).

Several methods are known for the preparation of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-one from aromatic and

§ Like the 4-oxide of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine, this compound is a product of the metabolism of Librium in the human and dog organisms[43].

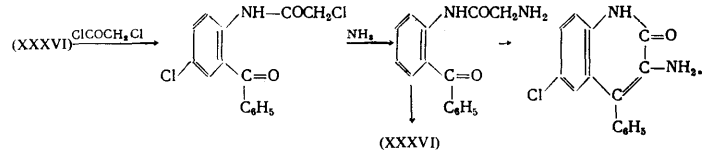
aliphatic-aromatic *o*-aminoketones. The simplest synthesis is based on the condensation of *o*-aminobenzophenones with glycine or its hydrochloride or the hydrochloride of the ethyl ester of glycine[3,54-56]:



(XXXV) (XXXVI)

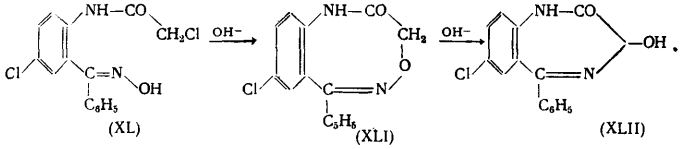
Sometimes the amino-group in glycine is protected by a benzyloxycarbonyl or phthaloyl group[44,57-60]. Syntheses have been described where one obtains initially halogenoacetamidobenzophenone (XXXVII), which is then converted into the amino-derivative (XXXVIII) and cyclised to (XXXVI).[3,23,44,61] Sometimes the dihydroquinolone (XXXIX) is then obtained as a side product.

3-Hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones may be obtained by treating 2-chloroacetamidobenzophenone α-oximes (XL) with alkali, with the intermediate formation of the benzoxadiazocine (XLI), which is readily converted into benzodiazepine:



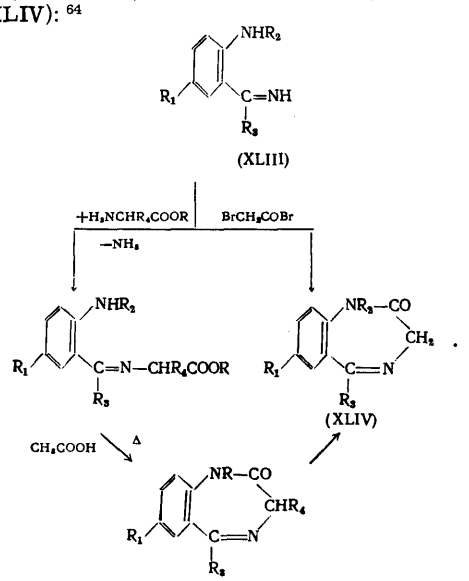
(XXXVII) (XXXVIII) (XXXIX)

7-Chloro-3-hydroxy-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (XLII) [the active principle of the medicinal preparation Oxazepam (or Adumbran)] was synthesised in this way[62]:



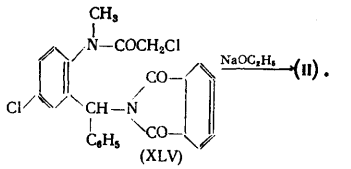
(XL) (XLI) (XLII)

Together with *o*-aminophenones, *o*-aminoketimines (XLIII) may be employed as the starting materials for the synthesis of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones.[63] Another way involves the reaction of the ketimines with bromoacetyl bromide, which leads directly to compounds of type (XLIV):[64]



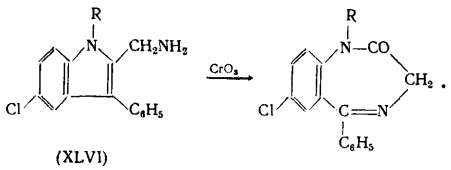
(XLIII) (XLIV)

The reaction of alkaline agents with phthalimido-derivatives of type (XLV) also leads to 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones[65]:



(XLV)

The 1,2-dihydro-3*H*-1,4-benzodiazepine system is formed on oxidation of aminoindoles (XLVI) with chromium trioxide[66]:

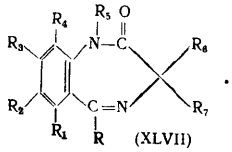


(XLVI)

1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones can also be obtained by the reduction of *N*-oxides of type (XXVIII) or by oxidising tetrahydro-1,4-benzodiazepines or 1,2-dihydro-3*H*-1,4-benzodiazepines.

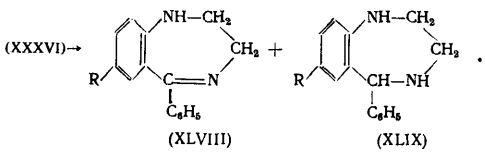
Substituents in the 1-position are usually introduced by alkylating the benzodiazepinone.

Recently many analogues and homologues of compound (II) having the general formula (XLVII) have been obtained[3,23-25,44,57-94]:



(XLVII)

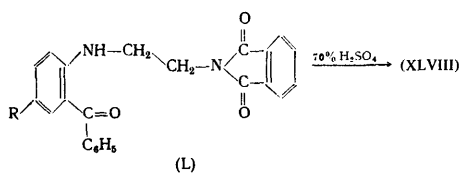
The conversion of the carbonyl group in 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones into a methylene group leads to 1,2-dihydro-3*H*-1,4-benzodiazepines[82,95-98]. However, when the initial lactams are reduced by lithium, aluminium hydride or hydrogen in the presence of a Raney nickel, tetrahydro-1,4-benzodiazepines (XLIX) are formed in addition to the dihydro-derivatives of type (XLVIII):



(XLVIII) (XLIX)

A more convenient method is the reduction over Raney nickel of the thiones (XVIII),[99,100] which are readily obtained from the corresponding carbonyl compounds.

1,2-Dihydro-3*H*-1,4-benzodiazepine (XLVIII, R = H) may be obtained by the cyclisation of phthalimidoethylaminobenzophenone (L):[95]

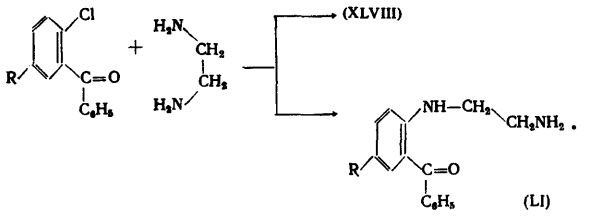


(L)

where R = H.

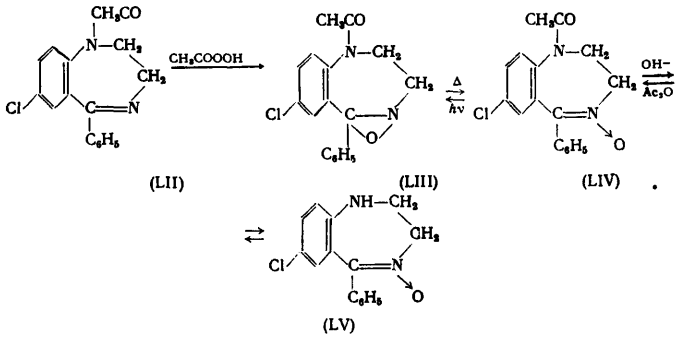
Another version of the reaction considered is the condensation of *o*-aminobenzophenones with aziridine in the presence of aluminium chloride. This reaction has a very low yield[95].

Finally, yet another procedure whereby compounds with a methylene group in the 2-position may be obtained is based on the reaction of *o*-chlorobenzophenones with diamines[101]. Then the yields of the dihydro-derivatives are higher when a nitro-group or CF_3 group is present in the *para*-position relative to the chlorine atom. With 2,5-dichlorobenzophenone, the yield is only 10%. The open-chain compounds (LI) may be formed in this reaction together with 1,4-benzodiazepines (XLVIII):



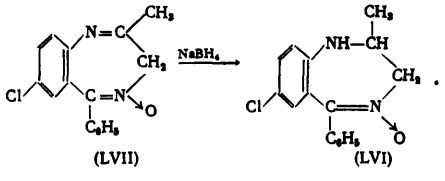
(LI)

The 4-oxides of 1,2-dihydro-3*H*-1,4-benzodiazepines were synthesised from the 1-acetyl derivatives (XLVIII). Thus, when 1-acetyl-7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine (LII) is treated with peracetic acid, an oxaziridine derivative (LIII) is obtained and then converted on heating into the isomeric *N*-oxide form (LIV). The acetyl group may be eliminated in an alkaline medium[102]:



(LII) (LIII) (LIV) (LV)

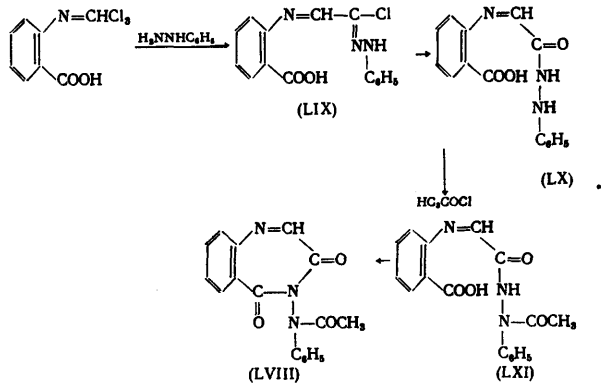
The formation of compound (LVI) on reduction of 7-chloro-2-methyl-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (LVII) with sodium borohydride has been described[41]:



(LVII) (LVI)

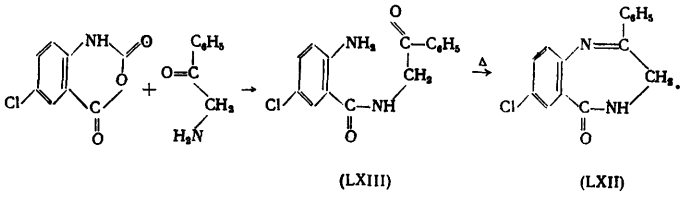
5. 3,4-Dihydro-5*H*-1,4-benzodiazepines

As stated above, the first 1,4-benzodiazepine synthesised was 4-(*N*-phenylacetamido)-3,4-dihydro-5*H*-1,4-benzodiazepine-3,5-dione (LVIII). Trichloroethylidene-anthranilic acid was converted into the phenylhydrazide (LIX) by condensation with phenylhydrazine and then by treatment with water into compound (LX), which reacted with acetyl chloride to give the acetyl derivative (LXI). Its vacuum distillation gave compound (LVIII):[7]



(LIX) (LX) (LVIII) (LXI)

7-Chloro-5-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (LXII) is formed by the cyclisation of compound (LXIII), obtained by the reaction of 5-chloroisatoic anhydride with aminoacetophenone[103,104]:

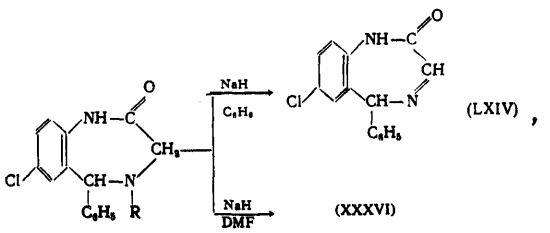


(LXIII) (LXII)

Similarly 2-(*o*-chlorophenyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one is obtained from ω-amino-*o*-chloroacetophenone and isatoic anhydride[105]. Another method for the preparation of 3,4-dihydro-5*H*-1,4-benzodiazepines consists in the reduction of the homologues and analogues of Chlordiazepoxide with lithium aluminium hydride.

6. 1,2-Dihydro-5*H*-1,4-benzodiazepines

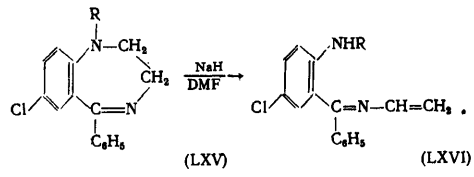
Representatives of this system are fairly unstable, i.e. they readily isomerise to 1,2-dihydro-3*H*-1,4-benzodiazepines. They are obtained by treating 4-tosyl(or-methanesulphonyl)tetrahydro-1,4-benzodiazepin-2-ones with sodium hydride[106] or ethoxide[50] in an anhydrous non-polar solvent:



(LXIV) (XXXVI)

where R = *p*-tosyl, methanesulphonyl, or $OCOCH_3$. When the reaction is carried out in a polar solvent or aqueous solution, the more stable isomer (XXXVI) is formed.

When treated with sodium hydride in dimethylformamide, 1-tosyl(or methanesulphonyl)-1,2-dihydro-3*H*-1,4-benzodiazepines (LXV) form the vinylimines (LXVI) and not the 1,4-benzodiazepine derivatives:

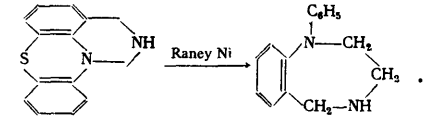


(LXV) (LXVI)

7. 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepines

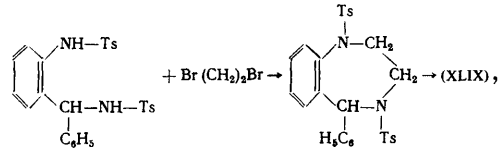
These compounds are largely obtained by the reduction of the corresponding carbonyl derivatives and *N*-oxides by complex metal hydrides or hydrogen in the presence of catalysts (palladium, nickel, and platinum).[95,98,103,107] When acted upon by $LiAlH_4$ and $NaBH_4$, the N→O group is converted into N–OH.

Diazepinophenothiazine (LXVII) undergoes reductive desulphuration on Raney nickel with formation of compound (LXVIII):[108]



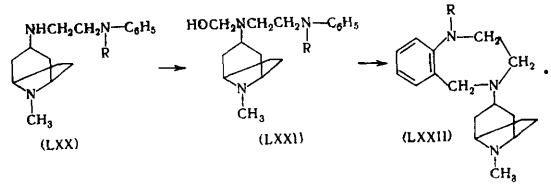
(LXVII) (LXVIII)

By allowing ethylene bromide to react with the diamide (LXIX), a ditosyl derivative was obtained, which on treatment with sulphuric acid was converted into (XLVIII, R = H).[109]



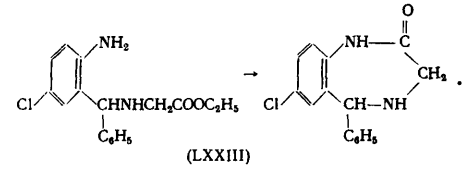
where R = H.

The reaction of formaldehyde and formic acid with tropanylethylenediamine (LXX) gave tropanyl derivatives of 1,4-benzodiazepine[110,111]. It is suggested that compound (LXXI) is formed as an intermediate, the intramolecular rearrangement of which gives tetrahydro-1,4-benzodiazepine (LXXII):



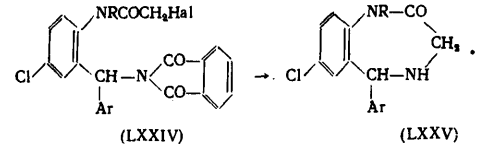
(LXX) (LXXI) (LXXII)

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-2-ones are obtained from aminoesters of type (LXXIII), which are formed when [*o*-aminophenyl(phenyl)]methylamines are treated with bromoethyl acetate or *o*-aminobenzyl chlorides are treated with glycine ethyl ester[112–115]:



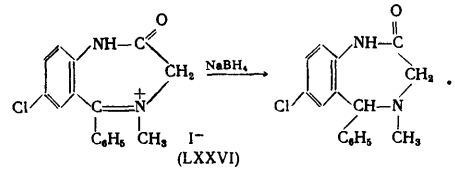
(LXXIII)

Derivatives of tetrahydro-1,4-benzodiazepin-2-one (LXXV) were synthesised by heating phthalimide derivatives of type (LXXIV) in aqueous potassium carbonate solution and subsequent treatment of the product with hydrobromic acid in acetic acid[116]:



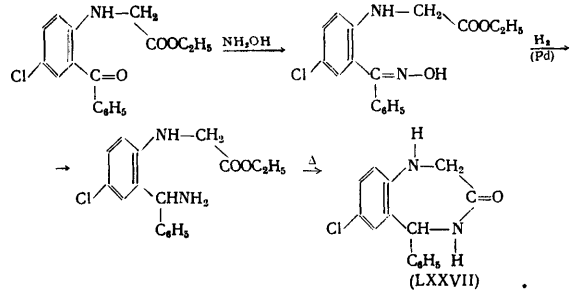
(LXXIV) (LXXV)

The reaction of $NaBH_4$ with the quaternary salt (LXXVI) leads to the selective reduction of the C=N bond (the carbonyl group is then retained)[44]:



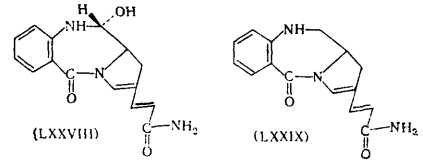
(LXXVI)

7-Chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-3-one (LXXVII)[117] was synthesised from 5-chloro-2-ethoxycarbonylmethylaminobenzophenone according to the following mechanism:



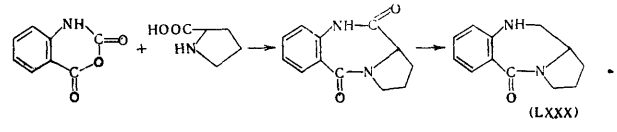
(LXXVII)

The 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one system is a component of the structure of the cytotoxic antibiotic anthramycin (LXXVIII) and its simpler analogue (LXXIX):



(LXXVIII) (LXXIX)

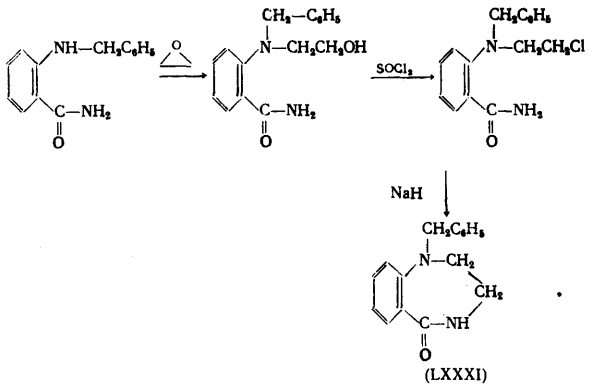
The structures of these compounds, their stereochemistry, and intramolecular transformations have been investigated in very great detail and described in a number of papers by Leimgruber and coworkers[118,119]. Compound (LXXX) was synthesised by these investigators as a model using the following procedure:



(LXXX)

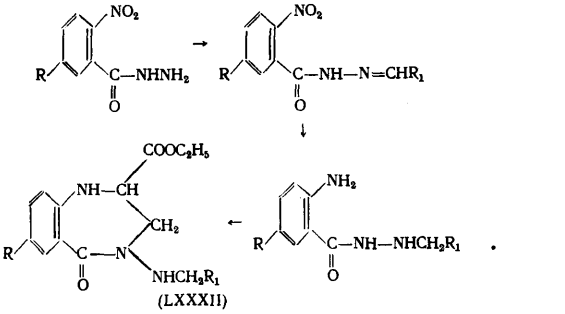
The synthesis of a compound in the 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one series was first described by Santilli and Osdene[103]. However, later it was established that the substance which they assumed to be 1-tosyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one has in fact the structure of the isomeric oxazoline[104,120]. The same investigators[121] achieved the synthesis of compound (LXXXI)

from the amide of *N*-benzylanthranilic acid according to the mechanism



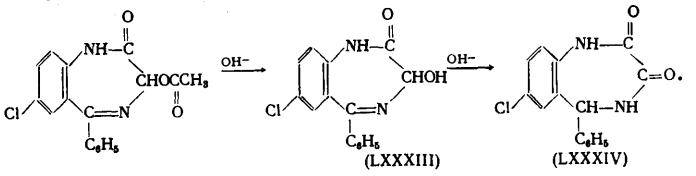
(LXXXI)

A number of various derivatives of 4-arylalkylamino-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-ones (LXXXII) were synthesised from *o*-nitrobenzoylhydrazines [122]:



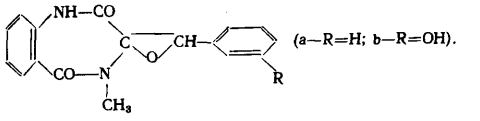
(LXXXII)

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-2,3-diones are formed when 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines and their 2-carbonyl derivatives are oxidised with CrO_3 and also on treatment with alkali of 3-acetoxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one via the intermediate 3-hydroxy-derivative [123]:



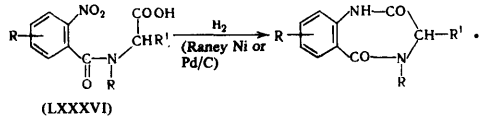
(LXXXIII) (LXXXIV)

Cyclopenin (LXXXVa) and cyclopenol (LXXXVb), metabolites of the fungi *Penicillium cyclopium* Westling and *Penicillium viridicatum* Westling [124,125], are derivatives of 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-2,5-dione [126]. The structure of (LXXXVa) was confirmed by synthesis [127,128]:



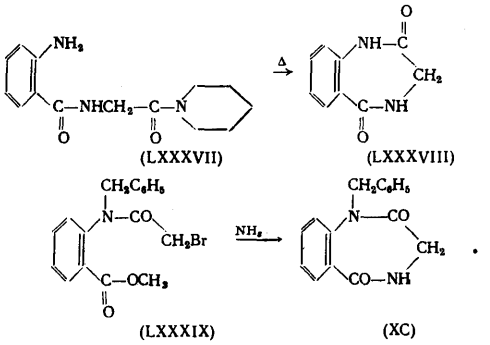
(LXXXV)

There are several synthetic procedures for the preparation of the 2,5-diones. One of these consists in the reductive cyclisation of *o*-nitrobenzamides of type (LXXXVI): [129-133]



(LXXXVI)

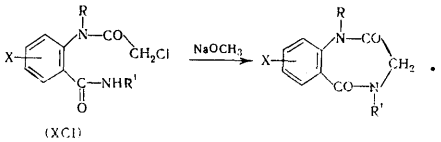
The amide of *o*-aminohippuric acid (LXXXVII) splits off piperidine on heating in acetic acid and is converted into the 2,5-dione (LXXXVIII). Its 1-benzyl derivative (XI) is obtained by treating with ammonia the methyl ester of *N*-benzyl-*N*-bromoacetylanthranilic acid (LXXXIX): [134,135]



(LXXXVII) (LXXXVIII)

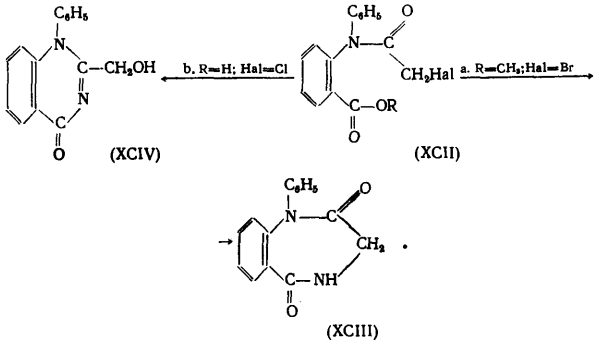
(LXXXIX) (XC)

A similar process takes place when *o*-chloroacetamidobenzamides (XCI) are treated with bases such as sodium methoxide and potassium carbonate [136-138]:



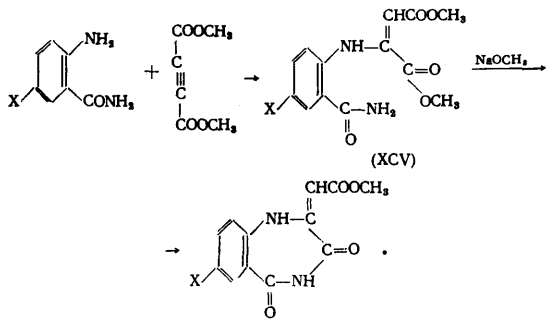
(XCI)

However, it has been observed [139,140] that in certain cases the reaction yields a quinazoline and not a benzodiazepine derivative. Thus, like compound (LXXXIX), the methyl ester (XCII, R = CH_3, Hal = Br), gives 1-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (XCIII), while *N*-acetyl-*N*-phenylanthranilic acid (XCII, R = H, Hal = Cl) cyclises to the isomeric quinazolinone (XCIV):



(XCIV) (XCII) (XCIII)

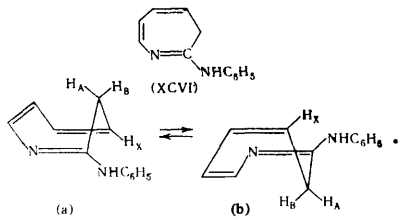
1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-3,5-diones were obtained by the Michael reaction from anthranilic acid amides and the dimethyl ester of acetylenedicarboxylic acid via the intermediate compound (XCV): [141,142]



(XCV)

III. STEREOCHEMISTRY OF 1,4-BENZODIAZEPINES

In 1967 Mannschreck et al.[143] investigated by NMR the intramolecular mobility of various azepines and diazepines, including 2-phenylamino-3*H*-1,4-azepine [Dibenzamil (XCVI) and similar compounds]. According to their data, in deuterated acetone compound (XCVI) (and similar substances) exist in the boat form, which undergoes inversion at a temperature as low as $-55° \pm 7°C$ between two conformations (a) and (b) 258 times per second. The free energy of activation for the process (a)⇌(b) proved to be 10.2 ± 0.4 kcal mole^{-1}. An approximately the same barrier (17 kcal mole^{-1}) was found also for 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one:



(XCVI)

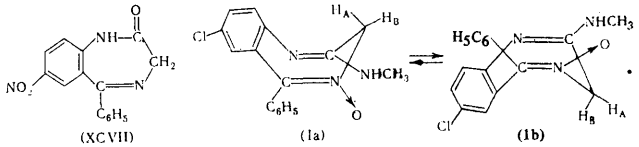
(a) (b)

Somewhat later Nuhn and Bley[144,145] found that at room temperature the methylene protons located near the 3-C atom of compound (II) gives rise in the spectrum to a typical AB-quartet with $\Delta\nu = 144$ Hz (spectrometer with $\nu_0 = 100$ MHz) and $J_{HH'} = 10.5$ Hz. At a temperature as low as 32°C the lines of the quartet begin to blur and at 127°C the protons of the methylene group contribute to a singlet peak.

Thus at room temperature the Diazepam (II) molecule exists in a conformation which does not undergo inversion and the conformational inversion of the system begins only at 32°C. The conformational stability of compounds (XCVII) and (I) is lower. The inversion of their conformations begins at −65° and −10° respectively.

The values of ΔH^* are respectively 15.9 ± 0.4 kcal mole^{-1} for (II), 10.9 ± 1.1 kcal mole^{-1} for (I), and 11.0 ± 0.3 kcal mole^{-1} for (XCVII), while the ΔS^* are 5.1 ± 1.0 kcal mole^{-1} deg^{-1} for (II), 3.4 ± 4.5 kcal mole^{-1} deg^{-1} for (I), and 13.3 ± 0.9 kcal mole^{-1} deg^{-1} for (XCVII).

The higher conformational stability of compound (II) compared with (XCVII) and (I) can be accounted for by an increase in the rigidity of the system on introduction of a methyl substituent in the 1-position of the benzodiazepine ring:

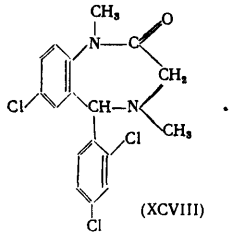


(XCVII) (Ia) (Ib)

It is also interesting that the lowest entropy of activation is observed for compound (I), which indicates a lower probability of the formation of a transition state in this case, probably because the nature of the transition state for substance (I) differs significantly from that of the transition state formed on conformational inversion of compounds(II) and (XCVII). It is not difficult to see that in the transition state formed by the inversion of conformation (I) considerable electrostatic repulsion may occur, which evidently effects the probability of the formation of such a system.

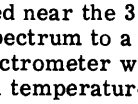
By comparing the spectra with Dreiding's models, Nuhn and Bley concluded that the most probable conformation of the above systems is the boat form¶. Consequently the above investigators arrived at the general conclusion that compounds (I), (II), and (XCVII) have a non-polar conformation, which is probably the boat form, and inversion of the type (Ia)⇌(Ib) is observed after definite temperature barriers have been overcome.

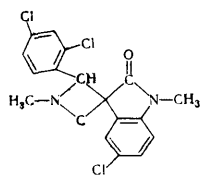
Karle and Karle[147] showed by X-ray diffraction that 7-chloro-5-(2,4-dichlorophenyl)-1,4-dimethyl-4,5-dihydro-3*H*-1,4-benzodiazepin-2-one (XCVIII) crystallises in the triclinic space group with two molecules in the unit cell, the dimensions of which are as follows: $a = 8.84$ Å; $b = 10.18$ Å; $c = 10.80$ Å; $\alpha = 93°51'$; $\beta = 112°31'$; $\gamma = 101°39'$.



(XCVIII)

The nitrogen atom in the 1-position is planar while that in the 4-position is pyramidal, which contributes to the difference between their basicities.

The  group is almost planar but is rotated by 50°C relative to the condensed benzene ring. On the basis of the above calculations of the bond lengths and valence angles in the molecule, the authors[147] assert that the configuration of the compound corresponds to a distorted "boat", the 5-phenyl and 4-methyl groups being in the *trans*-positions with respect to one another:



It follows from the above that only the first steps have been taken in the study of the stereochemistry of the systems under consideration. Despite the valuable information obtained recently, important problems such as the question of the preferred conformation of the ring and the factors influencing the stability of the conformation have still not been resolved unambiguously. Further study of the problem will help in the development of the chemistry of 1,4-benzodiazepines and will undoubtedly promote further development of modern stereochemistry.

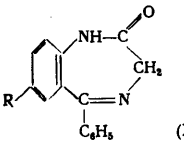
IV. PROPERTIES OF 1,4-BENZODIAZEPINES

1. Certain Characteristics of the Structure and Tautomerism of 1,4-benzodiazepine

The study of the infrared spectra of lactams of type (XCIX) leads to the conclusion that in the crystalline state and in concentrated solutions these compounds form association complexes via intermolecular hydrogen bonds.

¶ 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one and its *N*-oxide exist in the same preferred conformation[146].

The interaction of (XCIX) with the molecules of polar solvents (chloroform, pyridine) also has a distinctive effect. The electronic influence of the substituent in the 7-position on the absorption frequency of the carbonyl group can be readily traced in the spectra of crystalline specimens of compound (XCIX).



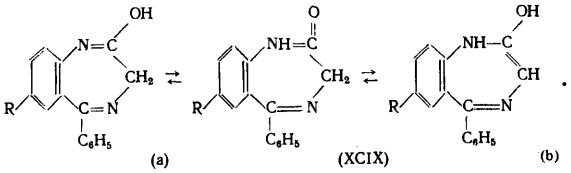
(XCIX)

The carbonyl band in the spectrum of the compound with R = NO_2 is displaced by 20 cm^{-1} towards higher wave numbers compared with the spectrum of the compound with R = CH_3 and by about 10 cm^{-1} compared with the spectrum of the compound where R = Cl.[148]

An electron-accepting substituent, for example a nitro-group, increases the polarisation of the carbonyl group and displaces the carbonyl absorption band towards higher wave numbers, as happens in other examples known from the chemistry of the aromatic series[149]. An electron-donating substituent causes the opposite shift of the absorption band, while substituents with $-J$ and $+C$ effects (halogens) have an intermediate influence. It has been found that the relative changes in the shift of the carbonyl absorption bands as a function of the substituent in the 7-position are satisfactorily correlated with Hammett's σ constants.

Usually investigators[2] regard the bands at 1620–1605 cm^{-1} and 1580–1590 cm^{-1} as characteristic of this system, but this assertion is so far insufficiently supported by evidence although empirically it is probably reliable.

Three tautomeric forms may be suggested for compounds of type (XCIX):



(a) (XCIX) (b)

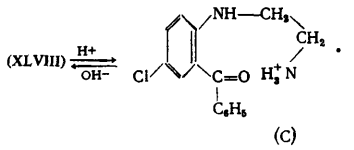
In the crystalline state and in acid and neutral solutions, (XCIX) exists in the lactam form, as shown by the infrared spectra and the chemical properties of the compound. In the presence of bases the lactim or enol forms may be produced, which has been demonstrated by ultraviolet spectroscopy at different pH of the medium. The changes in the position of the long-wavelength absorption band (λ_{max} = 320–370 nm) are of greatest interest. The bathochromic shift of this band in alkaline and acid media (to λ_{max} = 350–370 nm) compared with the neutral medium (λ_{max} = 320 nm) may be accounted for by an increase in the conjugation chain, which occurs as a result of the quaternisation of the fourth nitrogen atom (in an acid medium) and the formation of the lactim form (XCIXa) (in an alkaline medium).

The choice of structure (a) in preference to (b) was made on the basis of the finding that the ultraviolet spectra of 1-substituted and unsubstituted benzodiazepines are identical in neutral and alkaline media.

2. Hydrolysis of 1,4-Benzodiazepines

Acid hydrolysis under mild conditions of the *N*-oxides of 3*H*-1,4-benzodiazepines or their acetyl derivatives leads to the *N*-oxides of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones.[22,150]. Under more severe conditions, 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine is hydrolysed to 2-amino-5-chlorobenzophenone, glycine, and methylamine[2].

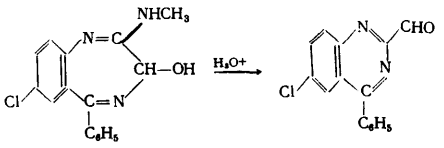
The acid hydrolysis of 1,2-dihydro-3*H*-1,4-benzodiazepines (XLVIII) takes place with the opening of the seven-membered ring and the formation of the salt (C), which on treatment with alkali cyclises to the initial compound[95]:



(C)

where R = Cl.

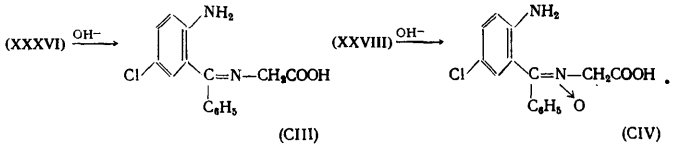
7-Chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (CI) is hydrolysed by acids to quinazolinealdehyde (CII):[151]



(CI) (CII)

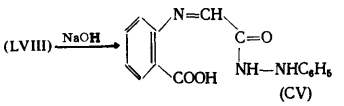
When treated with hot 75% sulphuric acid, the 2,5-dione (LXXXVIII) is converted into anthranilic acid[134].

Alkaline hydrolysis of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (XXXVI) and their 4-oxides (XXVIII) leads to the aminoacid salts (CIII) and (CIV) respectively, which, however, react differently with acids: compound (CIII) decomposes into *o*-aminobenzophenone and glycine and compound (CIV) cyclises to the initial product[22,44]:



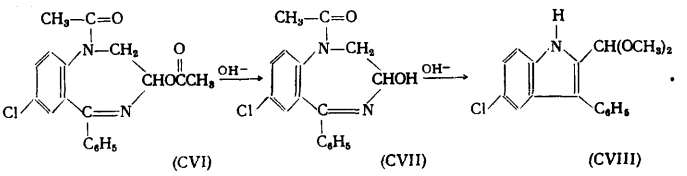
(CIII) (CIV)

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepine-2,5-diones (LXXXVIII) are not decomposed by alkali, in contrast to the 3,5-dione (LVIII), which is readily cleaved by a hot sodium hydroxide solution to the phenylhydrazide (CV):[7,134]



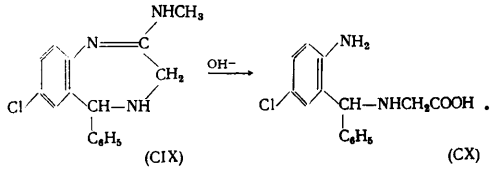
(CV)

The alkaline hydrolysis of 3-acetoxy-1-acetyl-1,4-benzodiazepine (CVI) gives the 3-hydroxy-derivative (CVII), while under more severe conditions it rearranges to the indole derivative (CVIII):[153]



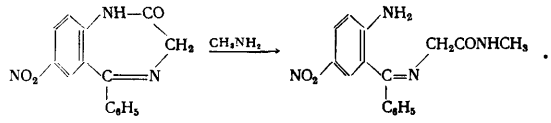
(CVI) (CVII) (CVIII)

When an aqueous alcoholic solution of compound (CIX) is refluxed with barium hydroxide, an aminoacid derivative (CX) is formed[2]:



(CIX) (CX)

It has been shown for 7-nitro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (XCVII) that the seven-membered ring is opened when acted upon by methylamine[39]†:

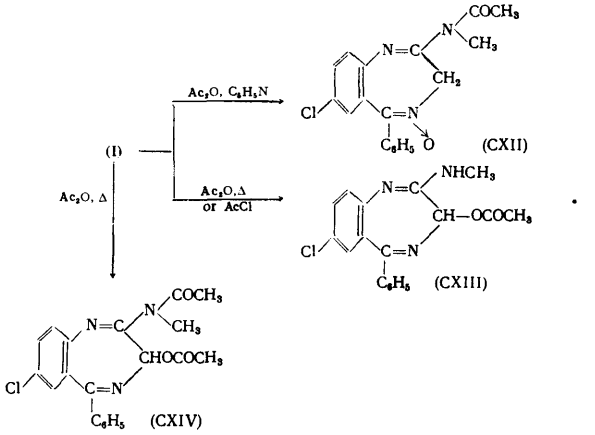


(CXI)

The heterocyclic ring in the 2,5-dione (LXXXVIII) is cleaved under the same conditions[134].

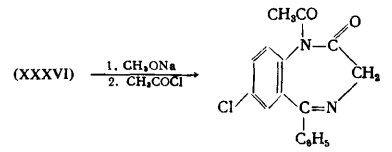
3. Acylation of 1,4-Benzodiazepines

When benzodiazepines of the "Chlordiazepoxide" type are acetylated, various derivatives are obtained depending on the reaction conditions[151,154]. Thus the acetylation of compound (I) with acetic anhydride in pyridine at room temperature leads to the 2-acetyl derivative (CXII). When Chlordiazepoxide is treated with hot acetic anhydride or acetyl chloride in dimethylformamide, a rearrangement of the Polonovskii type takes places with formation of the 3-acetoxy-derivative (CXIII). Prolonged heating of compound (I) with acetic anhydride gives the 3-acetoxy-2-acetyl derivative (CXIV):



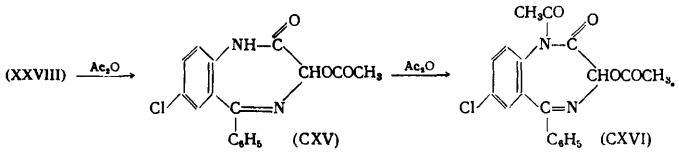
(CXII) (CXIII) (CXIV)

1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones are capable of being acetylated when their sodium salts are acted upon by acetyl chloride[155]:



† The corresponding amidine is also formed as a side product in this reaction[152].

Like compound (I), on treatment with acetic anhydride the *N*-oxides of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (XXVIII) undergo a rearrangement in which the *N*-oxide oxygen atom migrates to the carbon atom in the 3-position forming 3-acetoxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (CXV). Further reaction with acetic anhydride leads to compound (CXVI): [123,156]

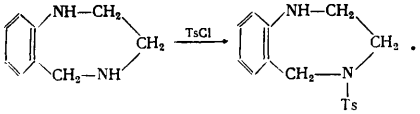


(CXV) (CXVI)

When 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (XXXVI) are treated wtih a mixture of acetic and peracetic acids and acetic anhydride, 3-acetoxy-derivatives (CXVI) are immediately obtained[157].

Other reactions of compounds of type (XXXVI) on treatment with acylating agents will be discussed below.

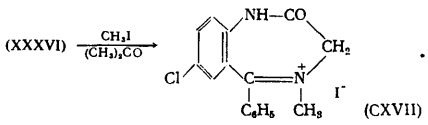
1,2-Dihydro-3*H*-1,4-benzodiazepines are acylated in the 1-position by acid anhydrides and chlorides[92,98,153]. It is interesting that the acylation of 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine with *p*-toluenesulphonyl chloride in pyridine gives only the 4-tosyl derivative[105], which indicates a higher basicity of the nitrogen atom in the 4-position:



4. Alkylation and Alkoxylation of 1,4-Benzodiazepines

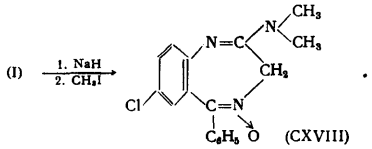
1,4-Benzodiazepines are alkylated preferentially in the 1- and 4-position when they or their sodio-derivatives are treated with the usual alkylating agents[3,22,44]. The methylation of the 2,5-dione (LXXXVIII) gives a mixture of the 1-methyl and 1,4-dimethyl derivatives[107].

Owing to the different basicities of the two nitrogen atoms in 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-2-ones, 1- or 4-alkyl or 1,4-dialkyl derivatives may be obtained depending on the reaction conditions[76]. The reaction of compound (XXXVI) with methyl iodide gives the quaternary salt (CXVII): [44]



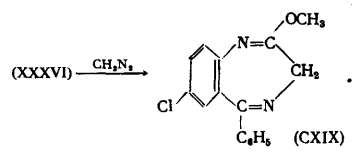
(CXVII)

On treatment with methyl iodide in the presence of sodium hydride, Chlordiazepoxide (I) is converted into the 2-dimethylamino-derivative (CXVIII): [158]

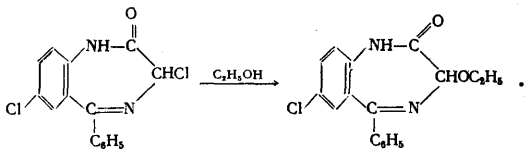


(CXVIII)

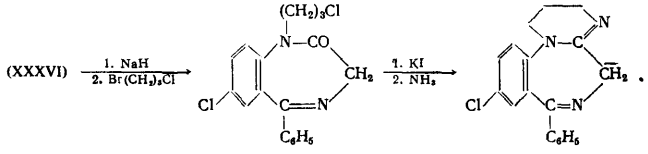
When compounds (XXVIII) and (XXXVI) react with diazomethane, the *O*-methyl derivatives of the 3*H*-1,4-benzodiazepine system (CXIX) are formed: [17,159]



3-Halogeno-derivatives of 1,4-benzodiazepines are converted into the 3-ethoxy-derivatives when acted upon by ethanol [45]:



By alkylating 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones unsubstituted in the 1-position, a large number of compounds of this series with various substituents at the N_1 atom‡ were obtained. In many cases this method is used to synthesise more complex condensed systems. For example dihydroimidazo- and tetrahydropyrimido-[1,2-*a*]-1,4-benzodiazepines were obtained in this way [161,162]:



5. Oxidation of 1,4-Benzodiazepines

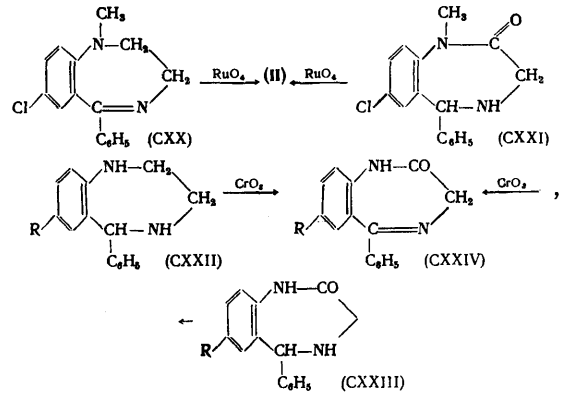
Several examples of the oxidation of these substances by peroxides have been described. 1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones may be converted into the 4-oxides by treatment with hydrogen peroxide [22]. 1,4-Benzodiazepin-2-ones unsubstituted in the 1-position (XXVI, CXIV) react with peracetic acid to form the 4-oxides.

Under these conditions, 1-acetyl-7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine (LII) forms the oxaziridino derivative (LIII), which on heating is converted into the *N*-oxide (LIV).

2-Acetylmethylamino-3*H*-1,4-benzodiazepines are oxidised by peracetic acid to compounds of type (XXVIII). [150]

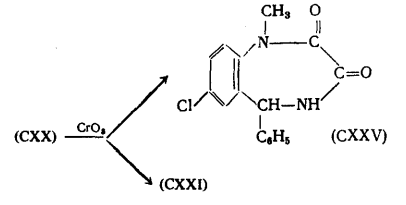
Mercury(II) oxidises 4,5-dihydro-3*H*-1,4-benzodiazepin-4-ols to *N*-oxides of type (I). [163]

When acted upon by RuO_4, CrO_3, SeO_2, or AgO, dihydro- and tetrahydro-1,4-benzodiazepines (CXX and CXXI) and tetrahydro-1,4-benzodiazepin-2-ones (CXXII and CXXIII) are converted into dihydro-1,4-benzodiazepinones (II) and compound (CXXIV) [112,164,165] respectively:



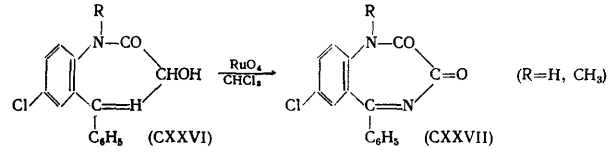
where R = H.

However, it should be noted that 1-alkyltetrahydro-1,4-benzodiazepines are oxidised to the dihydrobenzodiazepinones only by RuO_4, while CrO_3, SeO_2, and AgO oxidise compounds (CXX) to the monocarbonyl (CXXI) or dicarbonyl (CXXV) derivatives of tetrahydro-1,4-benzodiazepines:

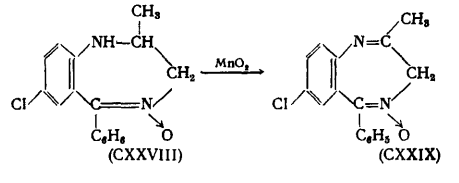


where R = CH_3.

3-Hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (CXXVI) are oxidised by ruthenium tetroxide to the unstable α-dicarbonyl derivatives (CXXVII): [165]



When 7-chloro-2-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine 4-oxide (CXXVIII) is oxidised with MnO_2, the 4-oxide of 7-chloro-2-methyl-5-phenyl-3*H*-1,4-benzodiazepine (CXXIX) is obtained:



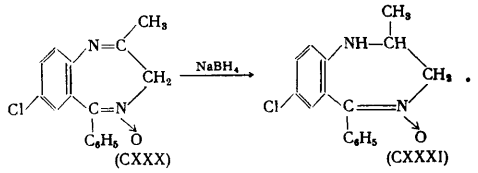
6. Reduction of 1,4-Benzodiazepines

The *N*-oxides of 1,4-benzodiazepines are reduced to the corresponding deoxy-compounds by phosphorus trichloride or hydrogen in the presence of Raney nickel [2].

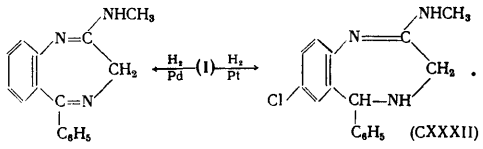
‡ It proved possible to synthesise in this way all the metabolites of 7-chloro-1-(diethylaminoethyl)-5-(2-fluorophenyl)1,2-dihydro-3*H*-1,4-benzodiazepin-2-one observed previously in the urine of patients receiving this preparation [160,161].

The N-oxide group is reduced to N–OH by complex hydrides [$LiAlH_4$, $NaBH_4$, $(CH_3)_4NBH_4$], hydrogen on a platinum catalyst and in the presence of Raney nickel, and also by Grignard reagents. Apart from the N-oxide group, the adjacent C=N double bonds are also reduced and in the case of N-oxides of 1,4-benzodiazepines $LiAlH_4$ reduces the carbonyl group to the methylene group[2,98,163].

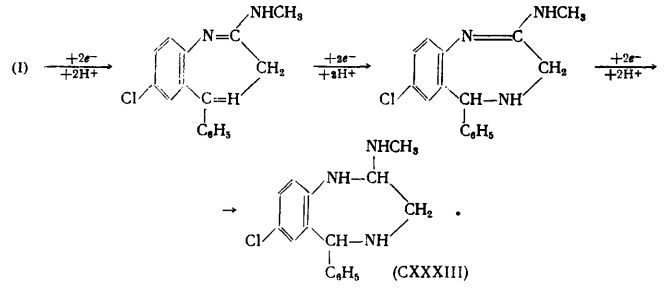
The 4-oxides of 5H-1,4-benzodiazepines are reduced by complex hydrides to 1,2,3,4-tetrahydro-5H-1,4-benzodiazepines[41]. In contrast to other 1,4-benzodiazepine N-oxides, compound (CXXX) is reduced by sodium borohydride to (CXXXI), i.e. in this case a selective reduction of the C=N bond in the 1,2-position without involvement of the N→O group is observed[41]:



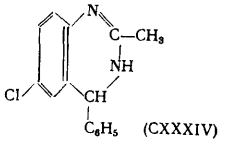
Chlordiazepoxide (I) is reduced in different ways by hydrogen on palladium and platinum catalysts: in the first case the reduction proceeds with elimination of chlorine from the 7-position and the oxygen from the N→O group, while in the second case the N→O group and the adjacent C= N bond are reduced[2]:



The attempts to reduce further compound (CXXXII) by hydrogen in the presence of platinum were unsuccessful. Compound (I) is reduced at a dropping mercury electrode in three stages, which corresponds to three polarographic waves[166]:



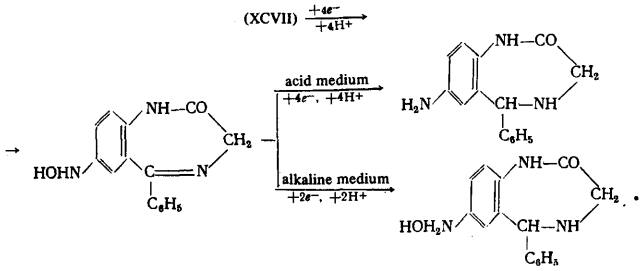
In the first stage the N-oxide group is reduced, in the second stage the azomethine bond in the 4,5-position, and in the last case the double bond in the 1,2-position. However, it proved impossible to isolate compound (CXXXIII) by the preparative electrochemical reduction of (CXXXII) owing to its instability and ready conversion into the dihydroquinazoline (CXXXIV) with elimination of methylamine[167]:



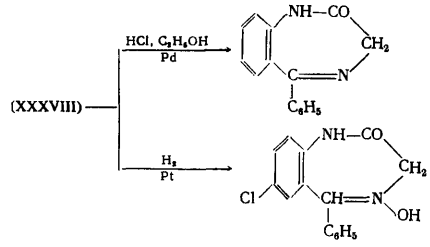
The azomethine group is reduced polarographically in 1,2-dihydro-3H-1,4-benzodiazepin-2-ones of type (II).[168-171]

The mechanism of the reduction of 7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (CXVII)§ is more complex, since this compound contains another polarographically active group (NO_2). In the first stage, corresponding to the first wave, the nitro-group is reduced to the hydroxyamino-group. In the second stage (second wave) in an acid medium the azomethine bond and the hydroxyamino groups are reduced, the latter to the amino-group.

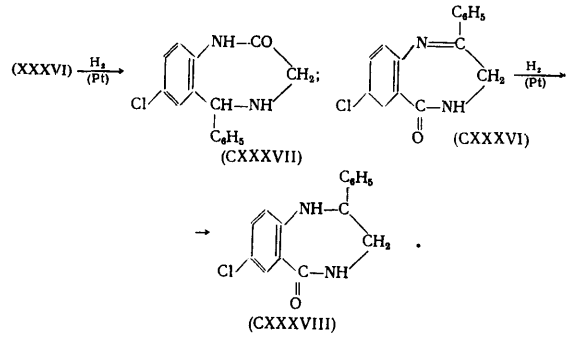
In an alkaline medium only the azomethine bond is reduced in this stage[169,170]:



The benzodiazepinone (XXVIII) is also reduced on a palladium catalyst with elimination of chlorine and N-oxide oxygen atoms, whereas treatment with hydrogen in the presence of platinum results in the formation of compound (CXXXV):[22,44,172]



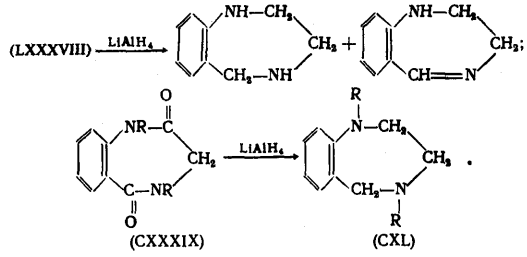
Compounds (XXXVI) and (CXXXVI) are reduced on a platinum catalyst to the 1,2,3,4-tetrahydro-5H-1,4-benzodiazepinones (CXXXVII) and (CXXXVIII) respectively[22,103]:



When compounds (XXXVI) and (LXXXVIII) are reduced with lithium aluminium hydrides, a mixture of dihydro- and

§ The active ingredient of the familiar sedative "Mogadon" ["Mogadan", "Nitrazepam", "Eunoctine" (tentative spelling—Ed. of Translation)].

tetrahydro-derivatives is formed, while 1,4-disubstituted diones give only the tetrahydro-derivatives (CXL): [95,107,134]



(LXXXVIII) (CXXXIX) (CXL)

Dihydro-derivatives of 1,4-benzodiazepines of type (XLVIII) are reduced to tetrahydro-1,4-benzodiazepines by lithium aluminium hydride and hydrogen on platinum and palladium catalysts [95].

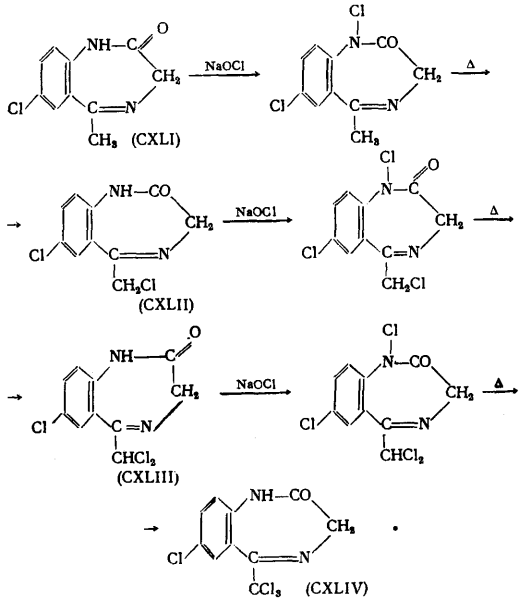
7. Nitration of 1,4-Benzodiazepines

Benzodiazepines unsubstituted in ring *A* are nitrated in the 7-position. When 7-substituted 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones are nitrated, derivatives with the nitro-group in ring *C* occupying the *meta*-positions are obtained [173]. Consequently the 1,4-benzodiazepine system behaves as an electron acceptor in relation to the benzene ring. Further nitration leads to the substitution of hydrogen by a nitro-group in the 9-position [174] and in the nitration of tetrahydro-1,4-benzodiazepines substitution also takes place in ring *C*, but this time in both the *meta*- and *para*-positions and not the *meta*-position only.

8. Halogenation of 1,4-Benzodiazepines

1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones with a very mobile chlorine atom in the 1-position can be obtained by the reaction of the lactams (CXLI) with organic or mineral hypochlorites [175].

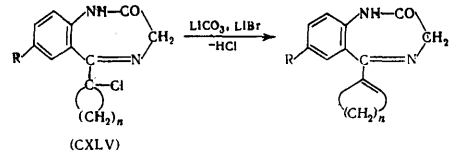
The chlorine atom readily migrates to the carbon atom of the substituent in the α-position relative to the seven-membered ring provided that there is at least one hydrogen atom at this carbon atom. If there are two or three such hydrogen atoms, they are all successively substituted by chlorine atoms:



(CXLI) (CXLII) (CXLIII) (CXLIV)

The chlorine atoms in compounds of type (CXLII), (CXLIII), and (CXLIV) can be readily replaced, by the usual procedures, by a CN group or amino-residues.

When chloro-derivatives of type (CXLV) in solution in dimethylformamide are refluxed with lithium carbonate or bromide, a molecule of HCl is split off with formation of a double bond in the $\alpha\beta$-position of the substituent at C_5:

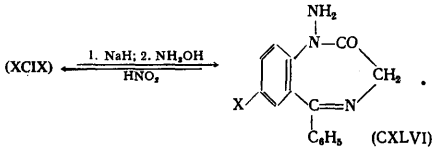


(CXLV)

There are data showing the successful halogenation of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones by *N*-halogeno-compounds [176]. However, according to Bell's results [50], the bromination of compound (XXXVI) by *N*-bromosuccinimide does not give the required 3-bromo-derivative. The latter was obtained by the action of *N*-bromosuccinimide on an isomer of compound (XXXVI)—7-chloro-5-phenyl-1,2-dihydro-5*H*-1,4-benzodiazepin-2-one [50].

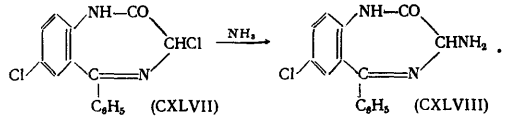
9. Amination of 1,4-Benzodiazepines

The sodium salts of lactams of type (XCIX) can react with chloramine to form 1-amino-derivatives (CXLVI), [177] which are readily deaminated by nitrous acid:



(XCIX) (CXLVI)

3-Amino-derivatives (CXLVIII) are obtained when solutions of 3-chloro-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (CXLVII) are treated with ammonia:



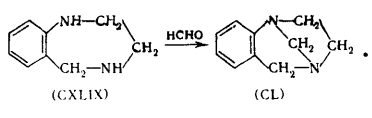
(CXLVII) (CXLVIII)

1,4-Benzodiazepines with an amino-group in the 7-position are obtained from the 7-nitro-derivatives by reduction with hydrogen in the presence of Raney nickel [25] and also by the Hofmann degradation of 7-carbamoyl-1,4-benzodiazepines. Aminobenzodiazepines may be converted into the corresponding hydroxy-, cyano-, and halogeno-derivatives via diazo-compounds.

10. Other Reactions

The reaction of 1,4-benzodiazepin-2-ones with P_2S_5 (in boiling pyridine) leads to the substitution of carbonyl oxygen by sulphur, i.e. to the formation of 1,4-benzodiazepine-thiones, from which methylthio-derivatives have been obtained by reaction with dimethyl sulphate [38,158].

Tetrahydro-1,4-benzodiazepine (CXLIX) undergoes condensation with formaldehyde, forming a bridge-type compound (CL): [110]

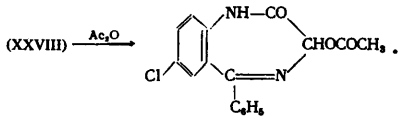


(CXLIX) (CL)

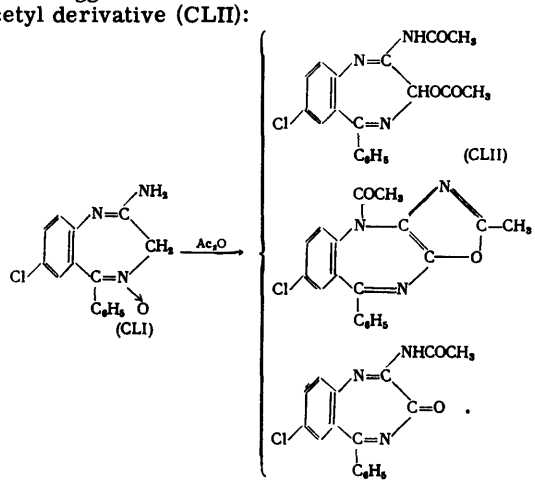
1,4-Benzodiazepines readily form coordination compounds with Lewis acids. Thus it has been observed that 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones react with SiF_4 to give 1 : 1 adducts. The SiF_4 molecule is probably coordinated to the 4-N atom [178].

11. Rearrangements and Isomerisation

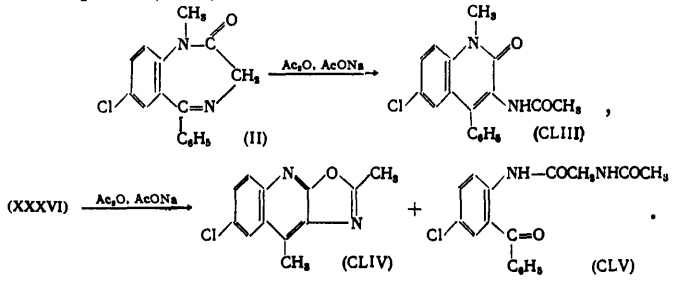
The rearrangement of *N*-oxides of 1,4-benzodiazepines of the Polonovskii type¶ under the influence of acetic anhydride leads to the formation of derivatives with the acetoxy-group in the α-position relative to the nitrogen atom of the *N*-oxide group [123]:



Benzoyl chloride and diacetyl sulphide behave analogously [181]. Bell and coworkers showed [151] that the 4-oxide of 2-amino-7-chloro-3*H*-1,4-benzodiazepine (CLI) forms three compounds on heating with acetic anhydride; the authors suggest that the last two are formed from the diacetyl derivative (CLII):

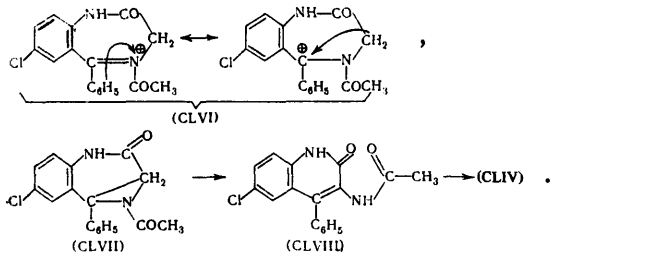


The reaction of acetic anhydride with 7-chloro-1-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (II) in the presence of sodium acetate leads to an intramolecular rearrangement with formation of 3-acetamido-6-chloro-1-methyl-4-phenyl-2-(1*H*)-quinolone (CLIII). [182] The corresponding 1,4-benzodiazepinone without the methyl group at the nitrogen atom rearranges under these conditions to the tricyclic compound (CLIV) and at the same time the seven-membered ring is cleaved with formation of compound (CLV):

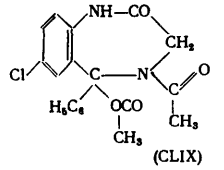


¶ The mechanism of the rearrangement has been discussed in a number of papers (see, for example, Refs. 179 and 180).

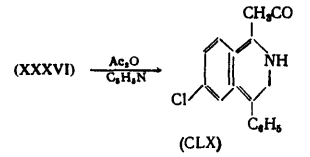
The formation of compound (CLIV) can be accounted for as follows. The mesomeric acetylated ion (CLVI), formed when acetic anhydride reacts with compound (XXXVI) via the unstable intermediate (CLVII), is converted into acetamidoquinolone (CLVIII), which is cyclodehydrated under the reaction conditions to compound (CLIV):



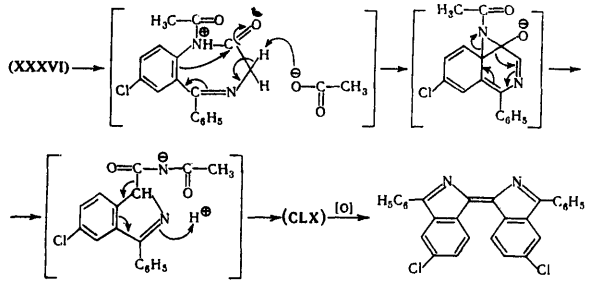
The formation of compound (CLIII) from (II) can be explained similarly. The second intermediate (CLIX) is postulated to account for the formation of compound (CLV) and the mesomeric acetylated ion (CLVI):



When acted upon by acetic anhydride in the presence of pyridine, compounds of type (XXXVI) are converted into isoindole derivatives (CLX): [183]

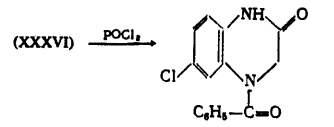


It is suggested that this reaction also proceeds via a stage involving the formation of an acetylated ion:



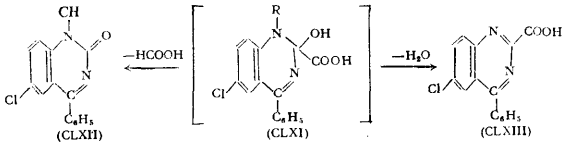
A certain amount of the "dimer" is formed as a result of the oxidative dimerisation of the isoindole.

1-Alkyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones also rearranges to isoindoles when acted upon by bases in an anhydrous medium [184]. When compounds (XXVIII) are treated with phosphorus oxychloride or *p*-toluenesulphonyl chloride, a rearrangement of the Beckmann type takes place with formation of 4-benzoyl-6-chloro-3,4-dihydro-1*H*-quinoxalin-2-one: [185]



1,2-Dihydro-3*H*-1,4-benzodiazepine-2,3-diones rearrange to the quinozoline derivatives in the presence of acids[165].

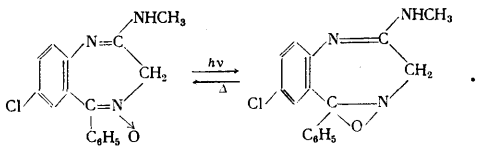
It is suggested that the rearrangement of compound (CXXX) in the presence of acids takes place with participation of an intermediate (CLXI), which splits off formic acid (R = CH_3) or water (R = H) and gives 6-chloro-1-methyl-4-phenyl-1,2-dihydroquinazolin-2-one (CLXII) or 6-chloro-4-phenylquinazolinecarboxylic acid (CLXIII) respectively:



where R = CH_3 or H.

When 1,2-dihydro-5*H*-1,4-benzodiazepin-2-ones are acted upon by bases (alkalis, alkoxides, or triethylamine), they isomerise to 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones[50].

The photoisomerisation of 1,4-benzodiazepines has been described[186]. When a dilute solution of compound (I) in isopropyl alcohol is illuminated, the two absorption maxima in the ultraviolet spectra at λ_{max} = 245 and 265 nm characteristic of the substance disappear and are replaced by a band with a lower intensity at λ_{max} = 278 nm. It is suggested that this involves the formation of an epoxide, as happens in the conversion of nitrones into oxaziridines[187,188]:



V. APPLICATIONS OF 1,4-BENZODIAZEPINES

The development of the chemistry of 1,4-benzodiazepine systems is in many ways due to their practical applications. We may recall that the first studies by Sternbach of compounds of this class were undertaken to find substances acting on the central nervous system. The first preparation of this class—Chlordiazepoxide (Librium or Elenium) (I)—already proved to be an unusually effective tranquiliser[189]. Apart from this effect, compound (I) exhibits a muscle relaxing and anticonvulsive activity.

The tranquilising action of 1,4-benzodiazepines is not only accompanied by the inhibition of the central nervous system but there is at the same time a stimulating effect. All these factors led to the isolation of 1,4-benzodiazepines as a new important group of psychotropic preparations—minor tranquilisers.

All derivatives of the Chlordiazepoxide type, i.e. 4-oxides of 3*H*-1,4-benzodiazepine, and also 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones exhibit an effect on the central nervous system similar to that of Librium. The presence or absence of basic groups in the 2-position of the ring and also of the amine oxide group does not involve a loss of psychopharmacological activity[4].

Probably the 1,4-benzodiazepine ring itself and possibly also its conformation play the most significant role in physiological activity[190].

As effective tranquilisers, 1,4-benzodiazepines have found wide application in the treatment of epilepsy, alcoholism[191], various psychological disorders[4], and tetanus; their use before and after operations as sedatives has been indicated. Among the widely employed preparations enumerated above, Valium (Diazepam), which gives excellent results in 50% of psychotic and 80% of psychoneurotic cases[192] may be particularly recommended. The latest published data suggest that the above effects are not optimal, since the study of this series of physiologically active substances has only just begun[193].

Unfortunately so far other applications of these preparations have been little investigated, although, in view of the presence of an interesting conjugated system in their molecules, they are not without interest for the chemistry of dyes and possibly also in other practical fields. Certain data on this problem have been published recently[194]: a series of cyanine dyes derived from 1,4-thiazepines, diazepines, and selenazepines have been obtained.

Probably 1,4-benzodiazepine derivatives are capable of giving rise to new possibilities in both theory and practice, which will be discovered in further investigations of this interesting group of substances[195].

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