

SYNTHESES OF BENZODIAZOCINES

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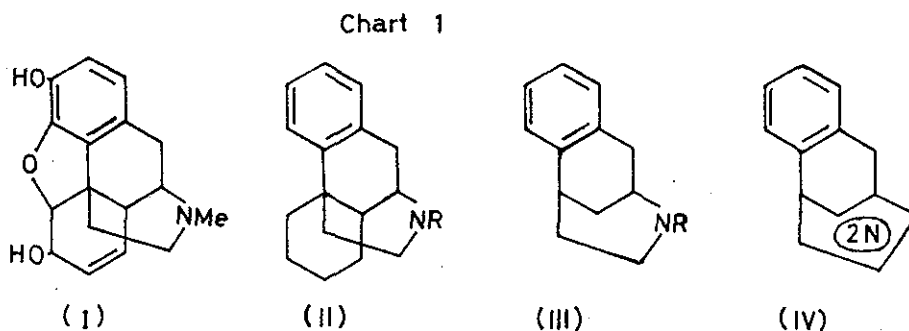
Introduction of an additional nitrogen atom into a benzazocine (6,7-benzomorphan) ring gives a benzodiazocine (azabenzomorphan). The syntheses of twelve types of benzodiazocines are reviewed and some of their analgesic properties are discussed.

CONTENTS

- 1 Introduction
- 2 Condensation of an amino group with a halogen or carbonyl function
- 3 Reaction of aldehydes with two amino groups
- 4 Reductive cyclization
- 5 Mannich reaction
- 6 Beckmann rearrangement
- 7 Pharmacology

1 INTRODUCTION

Chemical and molecular modifications of morphine (I) have been widely investigated in order to obtain an effective analgesic without side effects.¹ Of a series of morphinans (II) and 3-benzazocines (6,7-benzomorphans) (III) that have been synthesized, some exhibited morphine-like analgetic properties, with or without addiction.^{2,3} It was recognized from structure-activity studies,¹ that these morphinans



and the 3-benzazocines probably owed their activity to the fact that they retain the partial structure of morphine with regard to the spacial relationship between the aromatic ring, the cycloalkane ring and the tertiary nitrogen atom. In other words, they contain a structural factor for analgetic activity.

Based on the assumption that replacement of a carbon atom in the 3-benzazocine structure by a nitrogen atom would cause only stereochemical minor changes, a number of benzodiazocines (IV) with two ring nitrogen atoms, either adjacent or separated, have been synthesized.

In this review, the syntheses of benzodiazocines are considered according to the method of cyclization which is the key step in their construction. Accordingly, the preparation of twelve types of benzodiazocines by five cyclization methods are

discussed (Chart 2).

Due to the presence of two nitrogen atoms in the benzodiazocines, cyclization methods⁴ for the synthesis of 3-benzazocine (III) were not generally applicable except for the condensation of an amino group with a halogen or carbonyl function^{4a,4b} (Chapter 2).

Alternatively, cyclizations involving the reaction of aldehydes with two amino groups yielded benzodiazocines containing a ring N-C-N bond (Chapter 3).

Reductive cyclization, initially used for the synthesis of morphine⁵ and physostigmine-type alkaloids,⁶ provided a route to the 1,3-benzodiazocines (Chapter 4) while the Mannich reaction, applied by the present authors for the syntheses of 9-azamorphinan derivatives,⁷ was efficiently employed in the synthesis of a 2-aza analog in which a nitrogen atom is adjacent to a *p*-alkoxybenzyl moiety (Chapter 5). Finally, the Beckmann rearrangement of a suitable oxime generated, non-selectively, two kinds of benzodiazocines (Chapter 6).

2 CONDENSATION OF AN AMINO GROUP WITH A HALOGEN OR CARBONYL FUNCTION

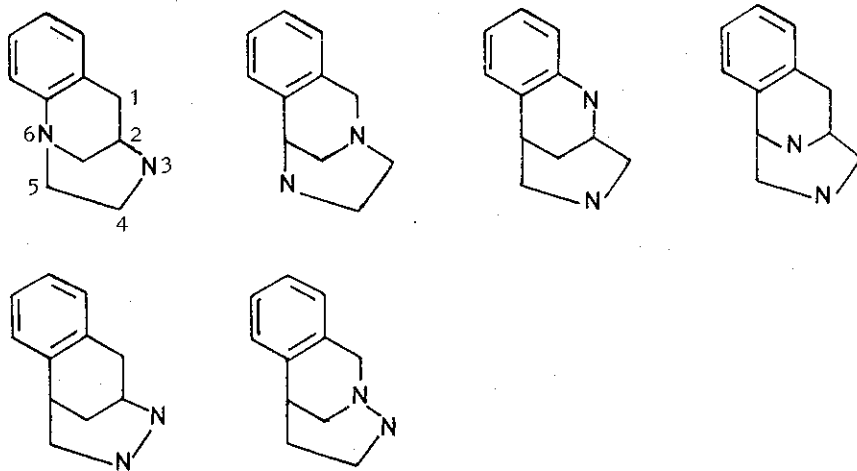
2-1 3,6-Benzodiazocines⁸: In 1964, Kametani⁹ and Mitsuhashi,¹⁰ independently, synthesized the first example of a 2,6-methanobenzodiazocine (XXIII) from 3-aminoquinoline precursors (Chart 3).

Since the bromine atom of 3-bromoquinoline (V)^{11,46} is not as susceptible as the 2- and 4-analogs to substitution reactions, amination of V with ammonia required drastic conditions in an autoclave to give 3-aminoquinoline (VI).¹² Attempted reductions of V and VI to the 1,2,3,4-tetrahydroquinoline with either tin and hydrochloric acid, sodium and ethanol, or formic acid and hydrogenation catalyst were unsuccessful. However, the quaternary ammonium salt (VIII), prepared by benzoylation of VI to VII followed by reaction with ethyl chloroacetate, was catalytically hydrogenated in the presence of platinum oxide to afford 3-benzamido-1-

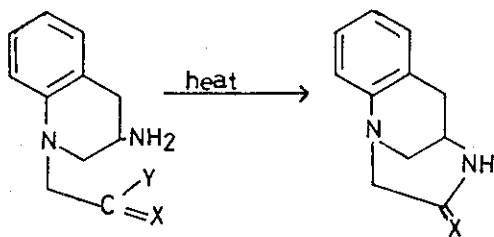
ethoxycarbonylmethyl-1,2,3,4-tetrahydroquinoline (X). Hydrolysis of X in 36 %

Chart 2

a)



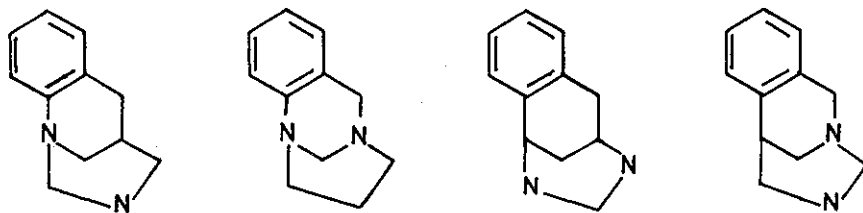
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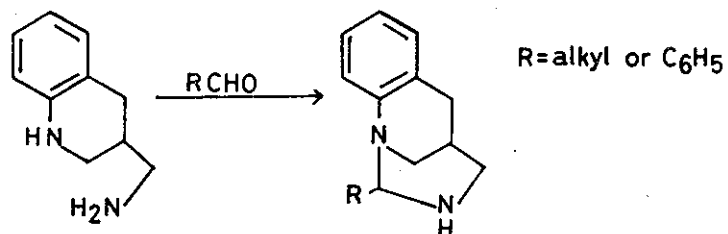
X=O or H₂

Y=OH, Cl or Br

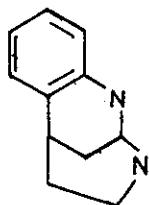
b)



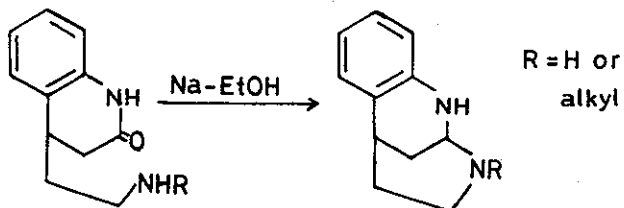
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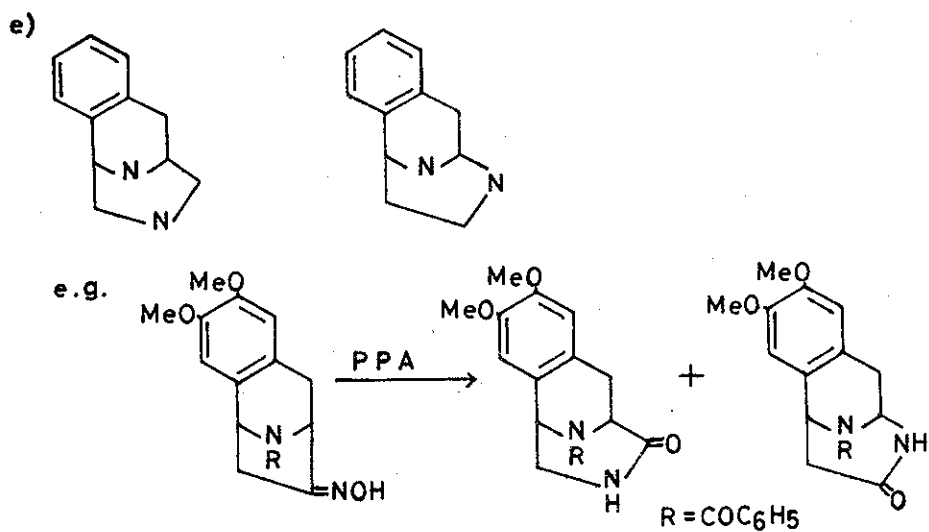
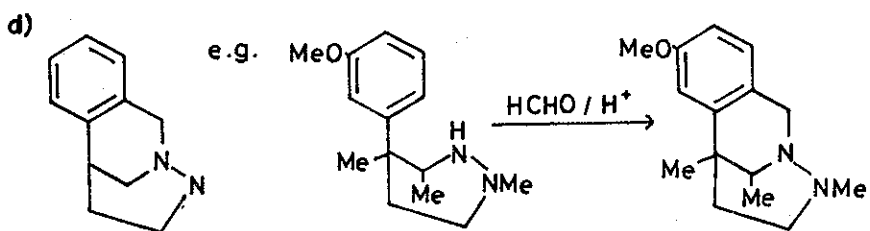


c)



e.g.





hydrochloric acid gave none of the amino acid (XI) but furnished directly the desired ketobenzodiazocine (XV) which was then reduced with lithium aluminum hydride to give 1,2,3,4,5,6-hexahydro-2,6-methano-3,6-benzodiazocine (XXIII).

Chart 3

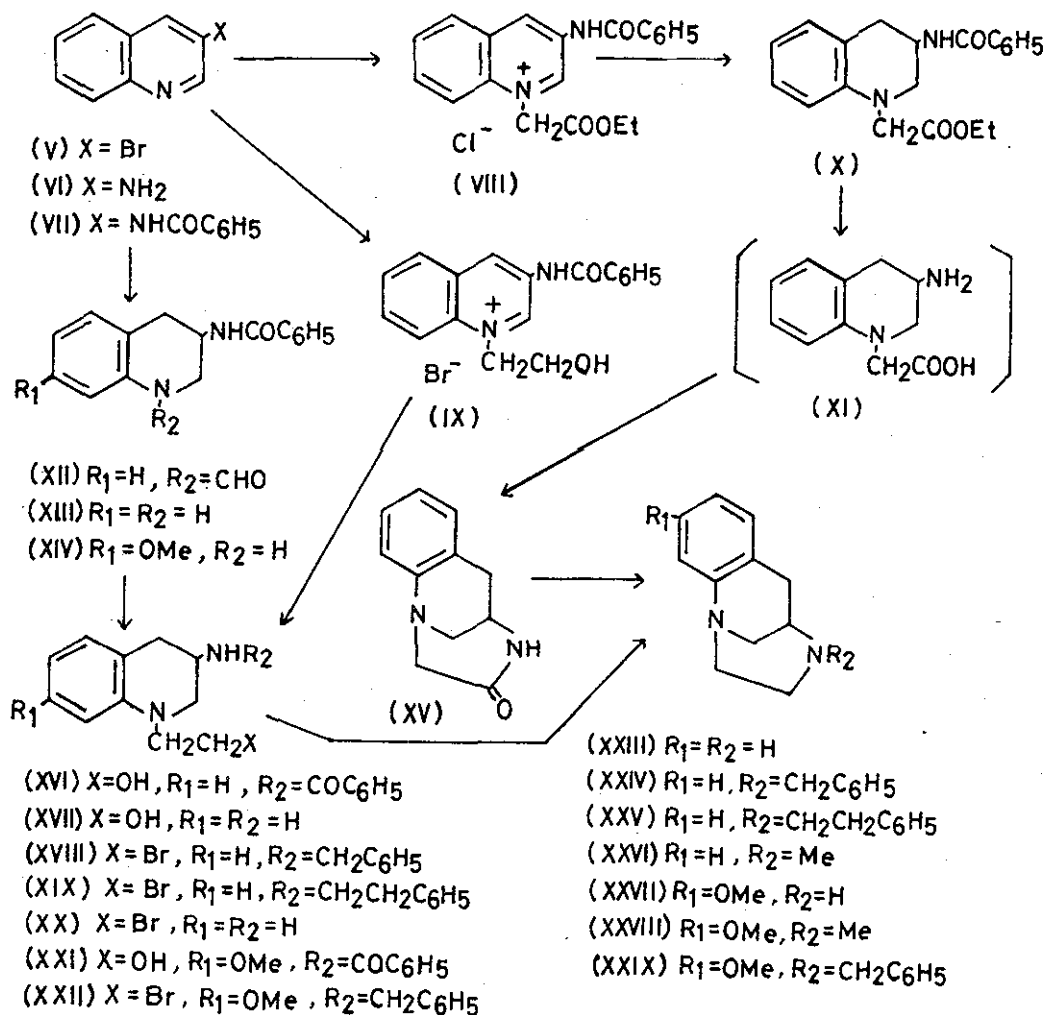
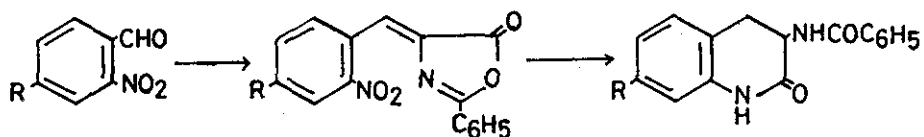


Chart 4



(XXX) R = H

(XXXI) R = OMe

(XXXII) R = H

(XXXIII) R = OMe

(XXXIV) R = H

(XXXV) R = OMe

(XX) ← (XVII) ← (XIII)

(XXII) ← (XXI) ← (XIV)

Attentive reduction of VII with formic acid and formamide¹³ afforded the N-formyltetrahydroquinoline (XII) which was hydrolyzed to the secondary amine (XIII) and treated with ethylene oxide to give 3-benzamido-1,2,3,4-tetrahydro-1-(2-hydroxyethyl)quinoline (XVI). On the other hand, the quaternary salt (IX), prepared by the fusion of VII with ethylene bromohydrin, was also reduced with formic acid and formamide and then hydrolyzed to also give XVI. Debenzylation of XVI in aqueous sulfuric acid afforded the 3-amino compound (XVII) which was converted into the N-benzyl (XVIII) and N-phenethyl (XIX) derivatives by standard methods of alkylation and bromination.

The 7-substituted (XXII) and unsubstituted quinoline (XX) derivatives were obtained from 4-methoxy-2-nitrobenzaldehyde (XXXI)¹⁴ and 2-nitrobenzaldehyde (XXX), respectively (Chart 4). The preparation of the 3,4-dihydrocarbostryls (XXXIV and XXXV) was achieved by catalytic reduction of the azlactones (XXXII and XXXIII), respectively, prepared by condensing the corresponding aldehydes (XXX and XXXI) with hippuric acid. Utilizing these sequences, XXXV was converted via XXXV → XIV → XXI into the N-(2-bromoethyl)quinoline (XXII).

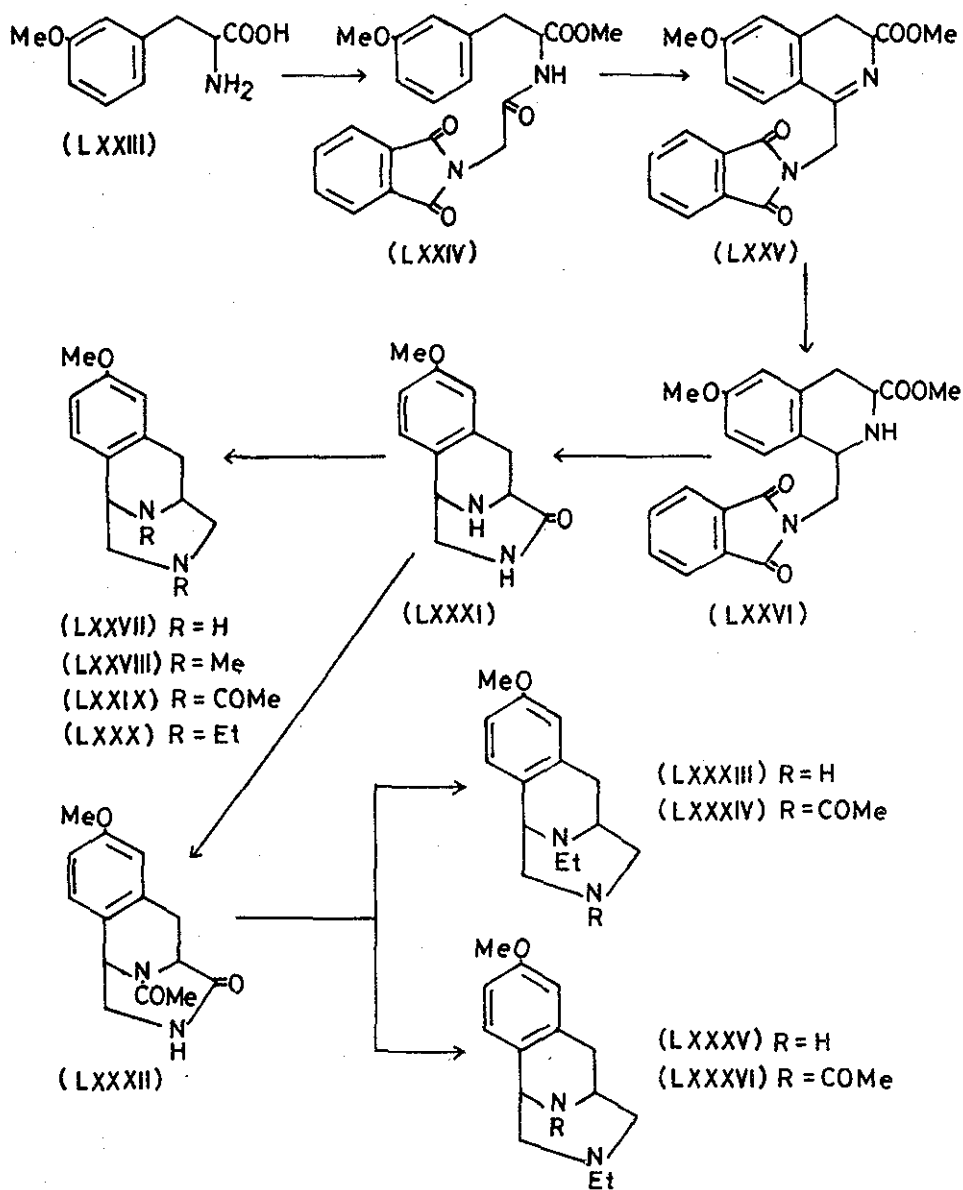
Cyclization was accomplished by heating of the 3-amino-1-(2-bromoethyl)-quinoline derivatives (XVIII, XIX, XX and XXII) in toluene in the presence of potassium carbonate to afford the corresponding 3,6-benzodiazocines (XXIV, XXV, XXIII and XXIX). 8-Methoxy-N-norbenzodiazocine (XXVII) was prepared by the catalytic debenylation of XXIX. Treatment of the N-nor compounds (XXIII and XXVII) with formic acid and formaldehyde produced the corresponding N-methyl derivatives (XXVI and XXVIII).

2-2 2,5-Benzodiazocine^{16,22a}: The synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-2,5-benzodiazocine (XXXVI) from 4-bromoisoquinoline (XXXVII)¹⁷ was achieved by the sequences employed for the preparation of 3,6-benzodiazocines.

Ammonolysis of XXXVII gave 4-aminoisoquinoline (XXXVIII)^{17b} which was converted into its N-acyl derivatives (XXXIX and XL). Treatment of XXXIX with ethylene bromohydrin or ethyl chloroacetate followed by catalytic hydrogenation of the resulting quaternary ammonium salts (XLI and XLV) over platinum oxide furnished the 1,2,3,4-tetrahydroisoquinolines (XLII and XLVI), respectively, which were then reduced with lithium aluminum hydride to afford the same 4-benzylamino-1,2,3,4-tetrahydro-2-(2-hydroxyethyl)isoquinoline (XLVII). The chloro compound (XLIX) was then cyclized by heating in xylene to afford the desired 2,5-benzodiazocine (LVI) which upon catalytic debenylation yielded the N-nor-substituted 2,5-benzodiazocine (XXXVI). The N-ethyl derivative (L), prepared from XL via XLIII → XLIV → XLVIII, was also submitted to similar cyclization conditions to provide the N-ethyl-2,5-benzodiazocine (LVIII).

Heating of the primary amine (LII), obtained by hydrolysis of XLII followed by chlorination of the resulting hydroxy compound (LI), afforded XXXVI which was converted into the N-acyl derivatives (LV and LVII). Alternatively, XXXVI was prepared by intramolecular condensation of 4-amino-1,2,3,4-tetrahydro-2-hydroxycarbonylmethylisoquinoline (LIII) followed by reduction of the resulting

Chart 7



(LXIV). Catalytic hydrogenation of LXIII in acetic acid with platinum oxide gave methyl 2-carbonyl-1,2,3,4-tetrahydrocinchoninate (LXV). Reduction of LXV with lithium aluminum hydride gave a mixture of the desired 2-aminomethyl-1,2,3,4-tetrahydroquinoline-4-methanol (LXVII) and 1,2,3,4-tetrahydroquinoline-4-methanol (LXVI) which were separated by distillation in vacuo. The diamine (LXVII) was characterized as its N,N',O-triacetyl (LXXII) derivative while the monoamine compound (LXVI) was characterized as its N,O-dibenzoyl (LXXI) derivative, and identical with an authentic sample, prepared from the acid (LX) by decarboxylation, esterification and reduction.^{19,21} Chlorination of LXVII with phosphorous oxychloride gave LXVIII as its hydrochloride.

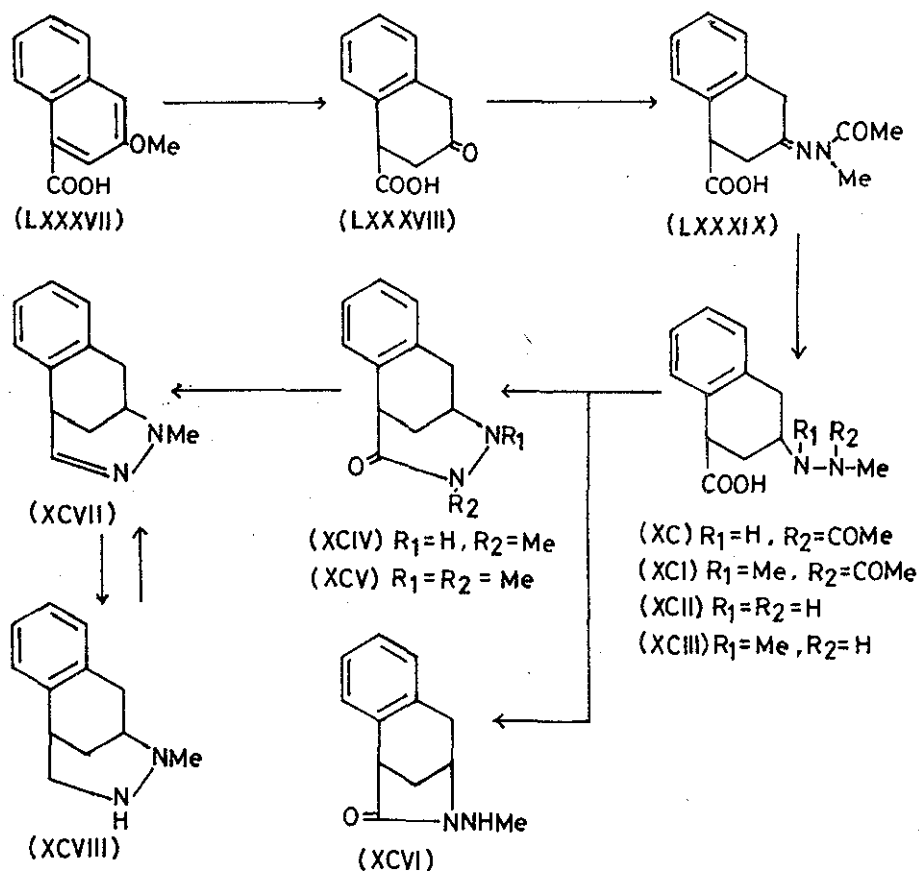
With regard to the stereochemistry of the 1,2,3,4-tetrahydroquinolines (LXV, LXVII, LXVIII and LXXII) the 2- and 4-substituents were assumed to be cis since the compounds gave clear melting points and LXVIII was successfully cyclized in xylene in the presence of potassium carbonate to the intramolecular condensation product 1,2,3,4,5,6-hexahydro-2,6-methano-1,4-benzodiazocine (LXX). The latter was extremely labile and therefore characterized as the stable N-benzoyl derivative (LXX).

2-4 4,11-Benzodiazocine²²: Synthetic pathway for the 4,11-benzodiazocines is summarized in Chart 7.

Methyl 3,4-dihydro-6-methyl-1-phthalimidomethylisoquinoline-3-carboxylate (LXXV), which was obtained by the condensing 3-(3-methoxyphenyl)alanine (LXXIII)²³ with phthalimidoacetyl chloride²⁴ and esterifying the resulting amide (LXXIV) followed by Bischler-Napieralski reaction, was catalytically hydrogenated to give the 1,2,3,4-tetrahydroisoquinoline (LXXVI). While the stereochemistry of LXXVI was not confirmed, its cis-configuration was indicated by treating with hydrazine hydrate and then hydrochloric acid to produce the 3-keto-4,11-benzodiazocine (LXXXI). Reduction of LXXXI with lithium aluminum hydride afforded 1,2,-

3,4,5,6-hexahydro-2,6-imino-9-methoxy-4,11-benzodiazocine (LXXVII). The corresponding N,N'-dimethyl (LXXVIII), N,N'-diacetyl (LXXIX), and N,N'-diethyl (LXXX) derivatives were prepared from LXXVII by standard methods.

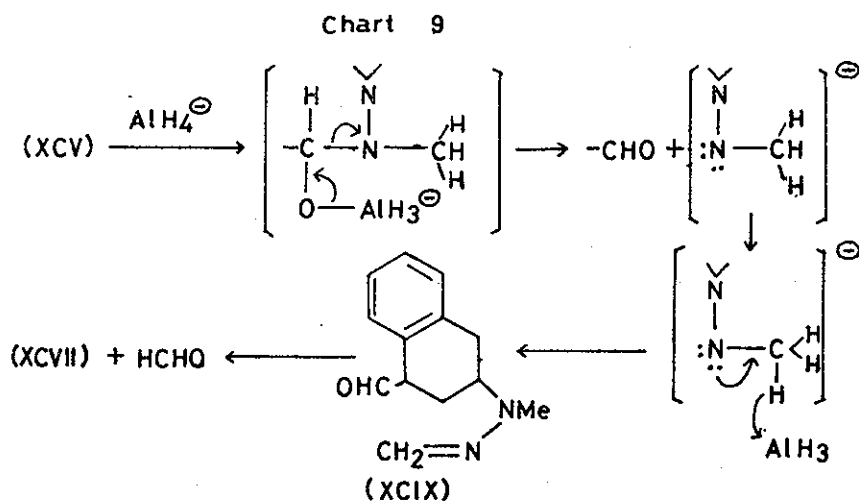
Chart 8



In the reduction of the N-monoacetyl derivative (LXXXII) with lithium aluminum hydride, two isomeric N-ethyl compounds (LXXXIII and LXXXV) were obtained. The latter (LXXXV) was the N→N' acetyl group migrated product²⁵ since acetylation of the isomers gave LXXXIV and LXXXVI, respectively, which were converted by reduction with lithium aluminum hydride into the same N,N'-diethyl derivative (LXXX).

2-5 3,4-Benzodiazocine²⁶: Reduction of 3-methoxy-1-naphthoic acid (LXXXVII)²⁷ with one molar equivalent of 3 % sodium amalgam gave 1,2,3,4-tetrahydro-3-oxo-1-naphthoic acid (LXXXVIII) which was condensed with N-acetyl-N-methylhydrazine²⁸ to give the hydrazone (LXXXIX). Catalytic reduction of LXXXIX over Adams' catalyst yielded the hydrazine derivative (XC) which was then N-methylated to provide XCI.

Cyclization of XCIII was effected by esterification followed by heating to give the 5-keto-3,4-benzodiazocine (XCV), whereas, the same treatment of XCII produced the desired 1,2,3,4,5,6-hedahydro-5-keto-2,6-methano-3-methyl-3,4-benzodiazocine (XCIV) together with 1,2-dihydro-5H-2,5-methano-3-methylamino-4-oxo-3-benzazepine (XCVI).

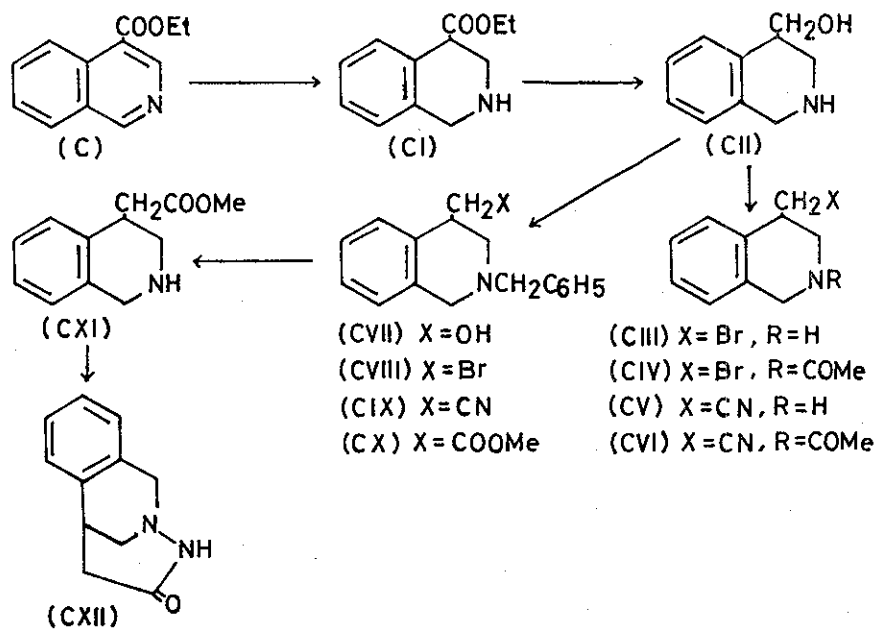


Reduction of XCV with lithium aluminum hydride gave the unexpected compound (XCVII) which on further reduction afforded XCVIII. It would be reasonable to assume that XCVII was formed by abnormal cleavage of the lactam (XCV) followed by recyclization of the intermediate (XCIX).²⁹

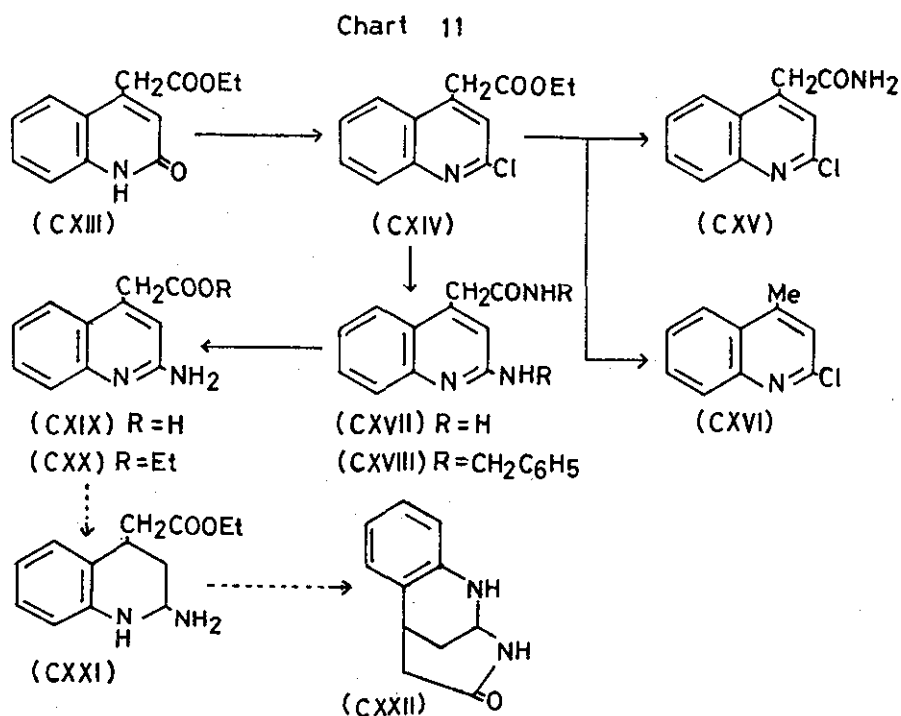
2-6 2,3-Benzodiazocine³⁰: The attempted synthesis of 2,3-benzodiazocine involved N-amination followed by cyclization as shown in Chart 10.

Ethyl 1,2,3,4-tetrahydroisoquinoline carboxylate (CI),³ prepared by the hydrogenation of C, was reduced with lithium aluminum hydride to the hydroxy compound (CII) followed by bromination to furnish (CIII). However neither CIII nor its N-acyl derivative (CIV) could be converted into the cyano compounds (CV and CVI). Similar difficulty was experienced in the cyanation of 4-bromomethyl-3,4-dihydrocarbostryl (CXXIII)³⁴ as described in Chapter 2-7.

Chart 10



In contrast, the N-benzyl bromide (CVIII), obtained from CIII via CVII, was readily transformed into the cyanide (CIX). Treatment of CIX with methanol, sulfuric acid and a calculated amount of water in a sealed tube provided the intermediate (CX) which was then catalytically debenzylated to CXI while nitrosation of CXI followed by reduction with zinc and acetic acid gave 1,2,3,4,5,6-hexa-



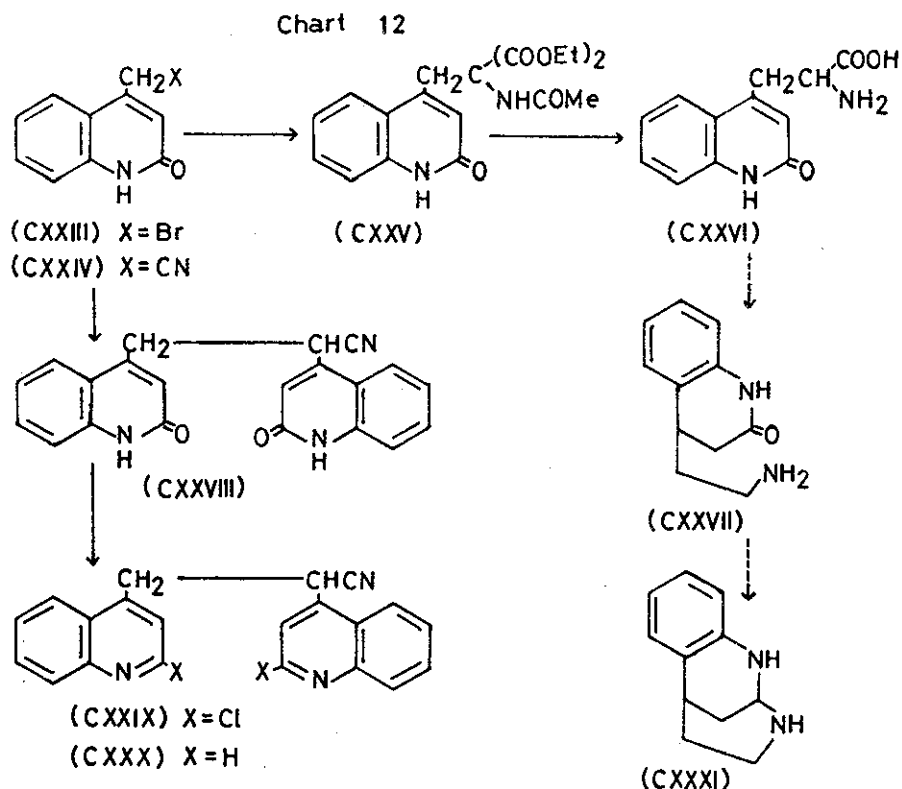
hydro-2,6-methano-4-oxo-2,3-benzodiazocine (CXII). Attempts to reduce the carbonyl group of CXII were as unsuccessful as encountered in the reduction of some acylhydrazines.³²

2-7 Intermediates for 1,3-Benzodiazocine^{33,34}: Synthesis of the 1,3-benzodiazocine structure was attempted as outlined in Chart 11 and 12.

Treatment of ethyl 1,2-dihydro-2-oxo-4-quinolineacetate (CXIII)³⁵ with phos-

phorous oxychloride gave ethyl 2-chlorocinchoninate (CXIV) which was reacted with benzylamine to afford the 2-benzylamino-derivative (CXVIII). In contrast, reaction of CXIV with ammonia or aqueous ammonia in a sealed tube furnished CXV and CXVI,³⁶ respectively, instead of the desired 2-amino compound (CXVII). Debenzylation of CXVIII with 48 % hydrobromic acid gave 2-amino-4-quinoline-acetic acid (CXIX) which was esterified to give CXX. In order to obtain the 1,3-benzodiazocine (CXXII) via its tetrahydro precursor (CXXI) hydrogenation of CXX under a variety of conditions was examined in failure.

Alternatively, the synthesis of 1,3-benzodiazocine (CXXXI) was examined as shown in Chart 12. Cyanation of the bromide (CXXIII)³⁷ did not give the desired



compound (CXXIV) which would be the precursor of the amine (CXXVII), but the unexpected dimeric-type⁵⁵ (CXXVIII), characterized as its chloro (CXXIX) and dechlorinated (CXXX) derivatives. On the other hand, reaction of diethyl acetamidomalonate with the bromide (CXXIII) gave the condensation product (CXXV) which was hydrolyzed, with loss of carbon dioxide and the acetyl group, to the amino acid (CXXVI). However, attempts to decarboxylate CXXVI to the desired amine (CXXVII) were unsuccessful.

3 REACTION OF ALDEHYDES WITH TWO AMINO GROUPS

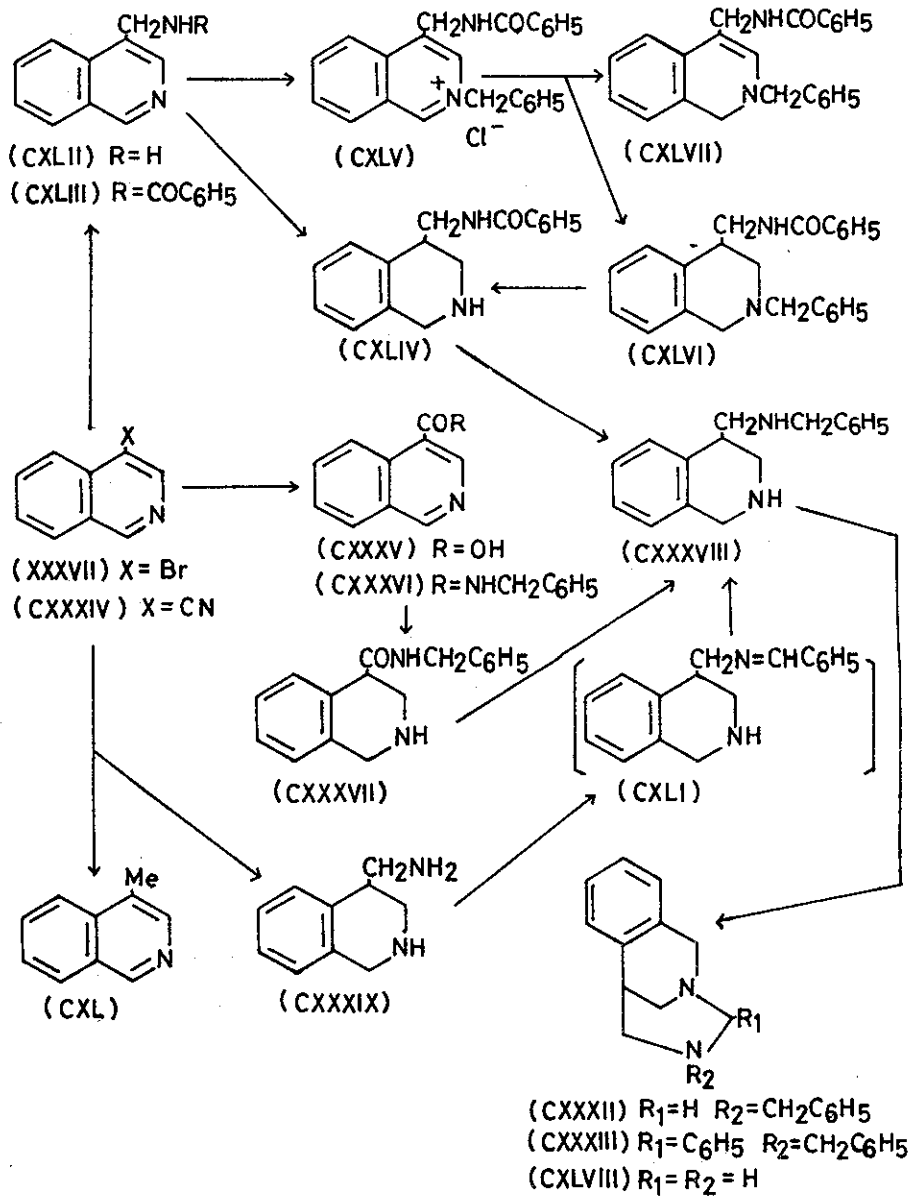
3-1 2,4-Benzodiazocines: Kametani and his co-workers³⁸ reported on the synthesis of the 2,4-benzodiazocines (CXXXII and CXXXIII) by forming the N-C-N bond between the two amino groups of 4-benzylamino-1,2,3,4-tetrahydroisoquinoline (CXXXVIII) which in turn was prepared by three methods.

Firstly, hydrolysis of 4-cyanoisoquinoline (CXXXIV),³⁹ obtained by Rosemund-von Braun reaction of XXXVII,⁴⁰ gave the isoquinoline-4-carboxylic acid (CXXXV) which was hydrogenated as the amide (CXXXVI) over platinum oxide to provide the tetrahydroisoquinoline (CXXXVII). Reduction of CXXXVII with lithium aluminum hydride afforded the 4-aminomethyl derivative (CXXXVIII).

Secondly, catalytic hydrogenation of CXXXIV in acetic acid over platinum oxide furnished the amine (CXXXIX) in low yield along with the deaminated product (CXL).⁴² Further hydrogenation of CXXXIX over platinum catalyst in the presence of benzaldehyde yielded CXXXVIII via the Schiff base (CXLI).

The third procedure to synthesize CXXXVIII started with the catalytic hydrogenation of CXXXIV over Raney nickel to afford 4-aminomethylisoquinoline (CXLII)⁴¹ whose N-benzoyl derivative (CXLIII) was hydrogenated over platinum oxide to CXLIV followed by lithium aluminum hydride reduction to afford CXXXVIII. Compound CXLIV was also obtained from the quaternary ammonium salt (CXLV) by hydrogenation over platinum oxide or reduction with sodium borohydride followed by

Chart 13

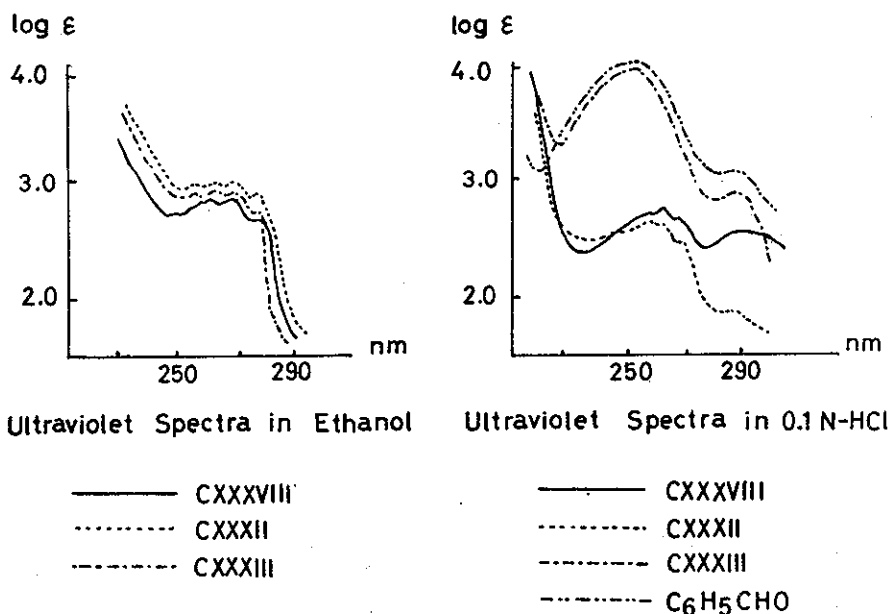


debenzylation of the resulting compound (CXLVI). In the latter reaction, the 1,2-dihydroisoquinoline (CXLVII) was also produced.

Ring closure of the diamine (CXXXVIII), thus obtained, was carried out with paraformaldehyde or benzaldehyde to afford the desired 1,2,3,4,5,6-tetrahydro-2,6-methano-2,4-benzodiazocine (CXXXII) or CXXXIII, respectively. However, all attempts to obtain the N-nor compound (CXLVIII) by catalytic hydrogenation of CXXXII and CXXXIII with palladium-charcoal, palladium oxide, platinum oxide or Raney nickel resulted in recovery of the starting materials.

In view of the known acid lability of methylenediamine-type compounds such as imidazolines and hexahydropyrimidines⁴³ which is enhanced by the presence of an aromatic substituent on the carbon atom of the N-C-N bond,^{43b} basification with sodium hydroxide of a solution of CXXXII in 0.1 N hydrochloric acid furnished partly the ring-opened compound (CXXXVIII). Similar treatment of CXXXIII also

Fig. 1

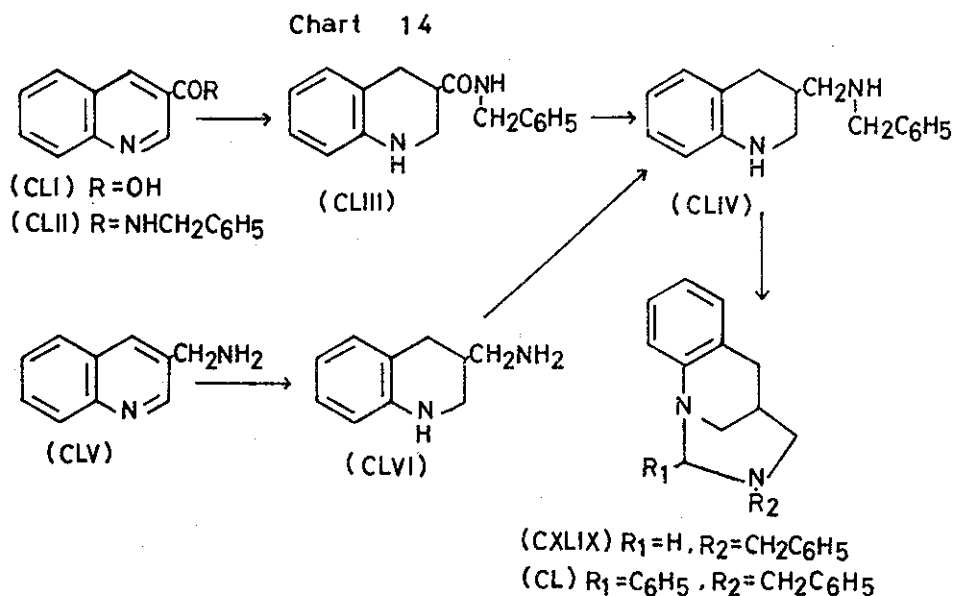


gave a mixture of CXXXVIII and benzaldehyde. Further, treatment of CXXXVIII with picric acid effected decomposition to the picrate of CXXXVIII.

In this connection, the ultraviolet spectra of both CXXXVIII and CXXXII in ethanol and 0.1 N hydrochloric acid showed almost the same curve while the absorption curve of CXXXIII in 0.1 N hydrochloric acid was similar to that of benzaldehyde but differed from that in ethanol.

3-2 4,6-Benzodiazocines⁴⁴: Synthesis of the 4,6-benzodiazocines (CXLIX and CL) was investigated according to the procedures reported for the synthesis of imidazolidine,⁴³ hexahydropyrimidine,⁴³ 1,3-diazaadamanthane,⁴⁵ and 2,4-benzodiazocine (CXXXII).³⁸ The synthetic route is shown in Chart 14.

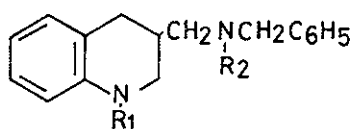
The key intermediate, 3-benzylaminomethyl-1,2,3,4-tetrahydroquinoline (CLIV) was prepared by two procedures. Quinoline-3-carboxylic acid (CLI)⁴⁷ was condensed with benzylamine to give the amide (CLII). Catalytic hydrogenation of



CLII over platinum oxide afforded the tetrahydroquinoline (CLIII), which was reduced with lithium aluminum hydride to give CLIV. On the other hand, catalytic hydrogenation of 3-aminomethylquinoline (CLV) with platinum oxide gave CLVI, which was further hydrogenated with the same catalyst in the presence of benzaldehyde to afford CLIV.

Reaction of the diamine (CLIV) with paraformaldehyde or benzaldehyde afforded the N-substituted 4,6-benzodiazocines (CXLIX and CL), respectively. However, catalytic debenylation of CXLIX over palladium oxide in methanol gave, after absorption of one molar equivalent of hydrogen, the ring opened N-methyl diamine (CLVII) instead of the desired N-nor-4,6-benzodiazocines.

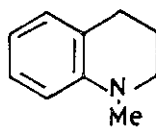
Chart 15



(CLVII) $R_1 = H$, $R_2 = Me$

(CLVIII) $R_1 = Me$, $R_2 = H$

(CLX) $R_1 = R_2 = Me$



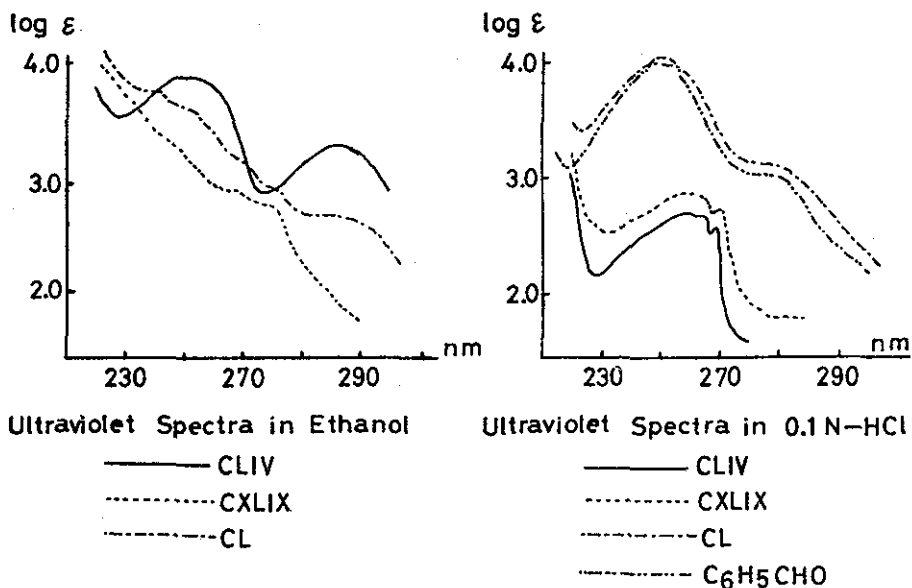
(CLIX)

The structure of CLVII was indicated by its nmr spectrum where the chemical shift of the N-methyl group appeared at a rather high field of 2.18 ppm compared with that of 2.82 ppm for 1,2,3,4-tetrahydro-1-methylquinoline (CLIX),⁴⁸ thus ruling out the possibility of the isomeric structure CLVIII. Further, N-methylation of CLVII afforded the di-tertiary amine (CLX). On the other hand, catalytic hydrogenation of CL over palladium oxide gave a mixture of CLIV and toluene after absorption of two molar equivalents of hydrogen.

Both of the 4,6-benzodiazocines (CXLIX and CL) were unstable to acid and decomposed to CLIV. In addition, CL hydrolyzed merely by refluxing in aqueous

ethanol to also give CLIV. Comparison of the uv spectra of CXLIX and CL in ethanol and 0.1 N hydrochloric acid suggested that the latter is more unstable than CXLIX to acid since the absorption curve of CL in 0.1 N hydrochloric acid is very similar to that of benzaldehyde, a potential cleaved product of CL. Further-

Fig. 2

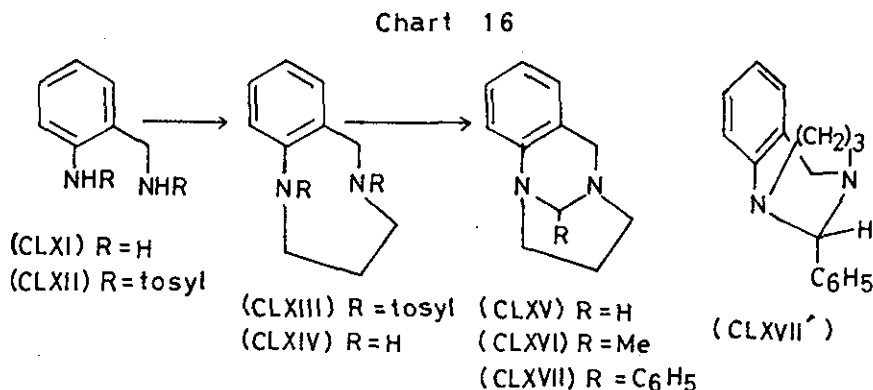


more, the hypsochromic shift of these compounds in acidic solution suggests the presence of a phenyl-N-C-N bond.^{60a,60e,61} This acid lability of CL could be explained by the electron withdrawing character of the phenyl group which decreases the stability of the N-C-N bond toward hydrolysis.

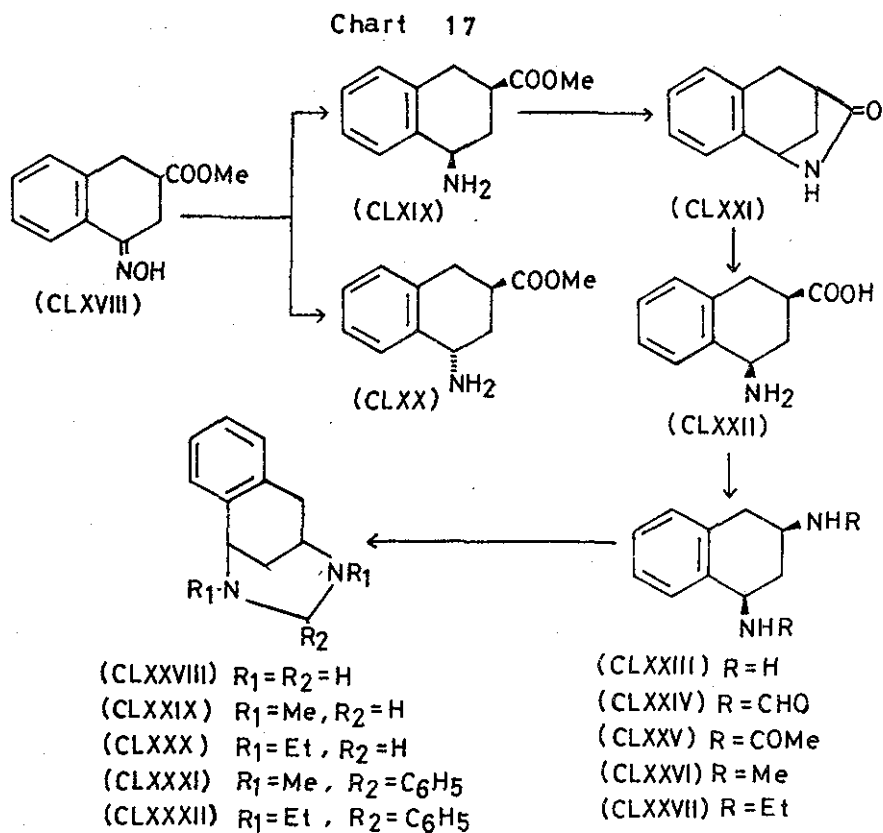
3-3 2,6-Benzodiazocines⁴⁹: The 2,6-benzodiazocines (CLXV, CLXVI and CLXVII) were easily synthesized (Chart 16).⁵⁴

The N,N'-ditosyl derivative (CLXII) of 2-aminobenzylamine (CLXI) was treated with sodium butoxide and 1,3-dibromopropane to afford 1,2,3,4,5,6-hexahydro-2,5-ditosyl-2,6-benzodiazocine (CLXIII). Reaction of the detosylated compound (CLXIV)⁵⁰ with formaldehyde, acetaldehyde and benzaldehyde afforded the corres-

ponding 2,6-methano-2,6-benzodiazocines (CLXV, CLXVI and CLXVII), respectively. The conformation of CLXVII (indicated by CLXVII') was suggested by its nmr spectra as well as Dreiding model considerations.⁵¹ Interestingly enough, while CLXV was unaffected by 0.1 N hydrochloric acid, CLXVII decomposed to CLXIV and benzaldehyde.



3-4 3,5-Benzodiazocines⁵²: Catalytic reduction of methyl 1,2,3,4-tetrahydro-4-hydroxyimino-2-naphthoate (CLXVIII)⁵³ over Adams' catalyst afforded a mixture of cis- (CLXIX) and methyl trans-4-amino-2-naphthoate (CLXX). By heating this mixture, cis-isomer (CLXIX) was cyclized to the lactam (CLXXI) while the trans-isomer (CLXX) remained unchanged. The resulting neutral amide (CLXXI) was hydrolyzed to the amino acid (CLXXII) followed by a Schmidt reaction to afford the cis-1,3-diamino-1,2,3,4-tetrahydronaphthalene (CLXXIII). Since condensation of CLXXIII with formaldehyde did not form the 3,5-benzodiazocine (CLXXVIII), the N,N'-dialkylamines (CLXXVI and CLXXVII) were prepared by reduction of the corresponding N,N'-diacyl compounds (CLXXIV and CLXXV) with lithium aluminum hydride. Cyclization of CLXXVI and CLXXVII with formaldehyde and benzaldehyde furnished the desired 3,5-benzodiazocines (CLXXIX, CLXXX, CLXXXI and CLXXXII), respectively.

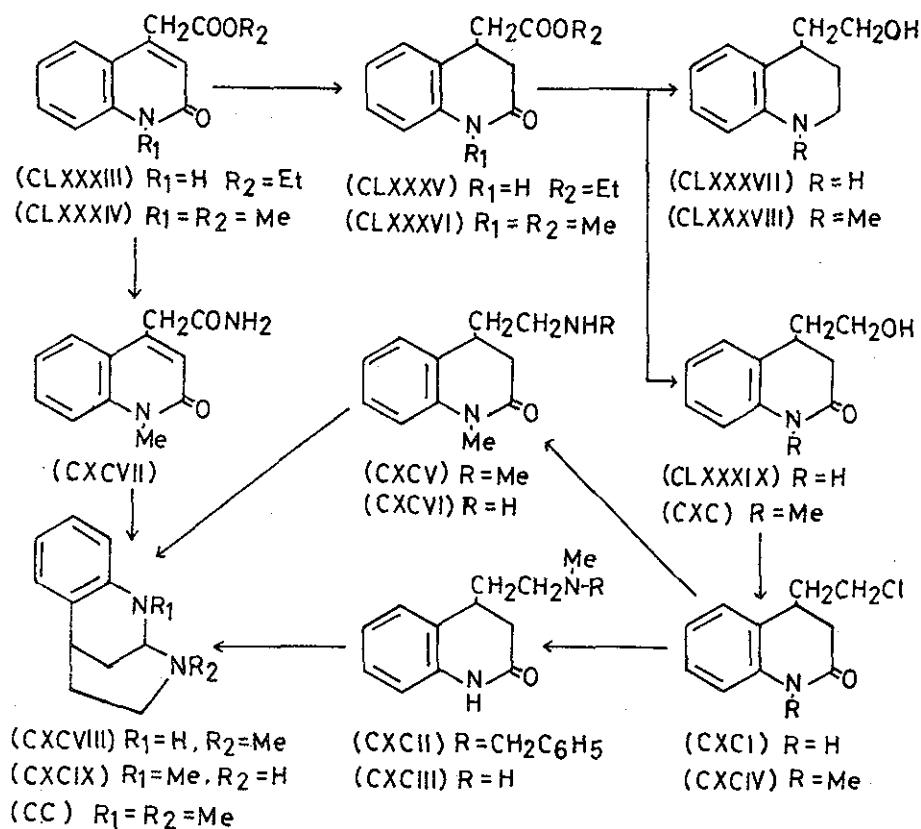


4 REDUCTIVE CYCLIZATION

4-1 1,3-Benzodiazocines^{56,57}: In contrast to the lack of success in forming 1,3-benzodiazocines via a lactam precursor (Section 2-7), their synthesis could be achieved by reductive cyclization (Chart 18).

4-Ethoxycarbonylmethyl-3,4-dihydrocarbostyryl (CLXXXV),³³ which was obtained by hydrogenation of CLXXXIII over platinum catalyst, was reduced with lithium aluminum hydride to afford the tetrahydroquinoline (CLXXXVII) and partially reduced carbostyryl (CLXXXIX). The former product (CLXXXVII) was identical with an

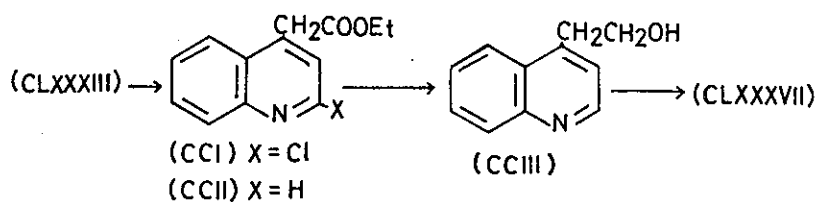
Chart 18



authentic sample synthesized by an alternative procedure (CLXXXIII \rightarrow CCI \rightarrow CCH \rightarrow CCHII \rightarrow CCHIII \rightarrow CLXXXVII)⁵⁸ as shown in Chart 19.

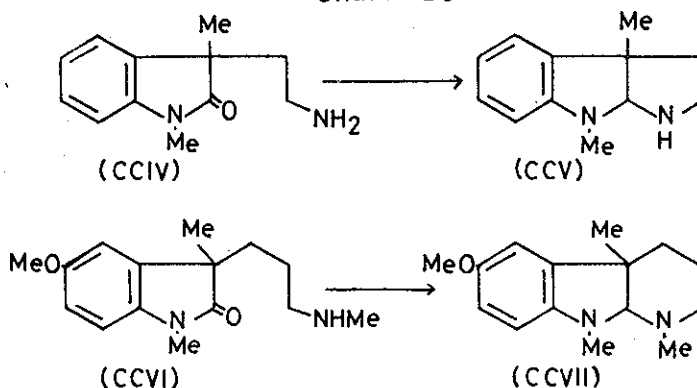
The chloride (CXC I) of CLXXXIX was condensed with benzylmethylamine and then catalytically debenzylated to give the secondary amine (CXC III). The rationale for preparing this key intermediate was the formation of the N-C-N bond in pyrrolo- or piperidino(2,3-b)indole derivatives by reductive cyclization using

Chart 19



sodium in alcohol^{6,59} or lithium aluminum hydride.⁶⁰ For example, Julian and his co-workers^{59a} synthesized CCV from CCIV and Sugasawa and his associate^{59f} prepared CCVII from CCVI.

Chart 20



Based on this approach, Kametani and collaborators^{56,57} treated the preceding dihydrocarbostyryl (CXCIII) with metallic sodium in ethanol to afford the expected 1,2,3,4,5,6-hexahydro-2,6-methano-3-methyl-1,3-benzodiazocine (CXCVIII), whose uv spectrum in ethanol showed two maxima at 250 and 302 nm which shifted to 241 and 291 nm in 1 % hydrochloric acid. This hypsochromic shift is characteristic for compounds containing a phenyl-N-C-N bond.^{60a,60e,61}

The 1-methyldihydrocarbostyryls (CXCIV and CXCVI) were prepared through an

analogous route as stated above (CLXXXIV → CLXXXVI⁶² → CXC → CXCIV → CXCXV). In the preparation of CXC, the tetrahydroquinoline (CLXXXVIII) was also obtained. Compounds CXCVI and CXCXV were also reduced with sodium in ethanol to give the 1,3-benzodiazocines (CXCIX and CC), respectively.

Alternatively, the N-nor-1,3-benzodiazocine (CXCIX) was conveniently synthesized by the reductive cyclization of 4-carbamoylmethyl-1-methylcarbostyryl (CXCXVII) which was easily prepared by ammonolysis of CLXXXIV.

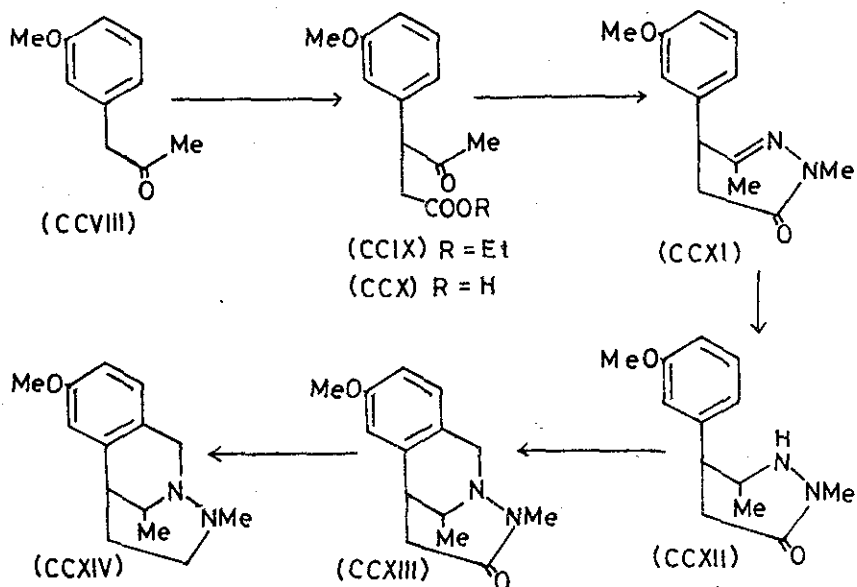
5 MANNICH REACTION

5-1 8-Methoxy-11-methyl-2,3-benzodiazocine³⁰: Condensation of 3-methoxyphenylacetone (CCVIII)⁶³ with ethyl bromoacetate gave the ketoester (CCIX) which upon saponification followed by condensation of the resulting acid (CCX) with methylhydrazine gave the dihydropyridazinone (CCXI). Catalytic hydrogenation of CCXI over Adams' catalyst afforded the tetrahydropyridazinone (CCXII) followed by a Mannich reaction with formaldehyde under acidic condition to furnish the 4-keto-2,3-benzodiazocine (CCXIII) which was then reduced with lithium aluminum hydride to afford 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-3,11-dimethyl-2,3-benzodiazocine (CCXIV).

5-2 8-Hydroxy-6-phenyl-2,3-benzodiazocine⁶⁴: The pharmacological activity of a number of 3-benzodiazocines was examined, by the result of which the presence of 8-hydroxy-, 6-alkyl or phenyl and 11-alkyl groups seems to be important for their analgetic activity.⁶⁵

Kametani and his co-workers⁶⁴ synthesized 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-methyl-6-phenyl-2,3-benzodiazocine (CCXXVI) as follows (see Chart 22). 1-(3-Methoxyphenyl)phenylacetone nitrile (CCXV), readily available by a benzyne reaction⁶⁶ of 1-chloroanisole with phenylacetone nitrile, was hydrolyzed followed by esterification to afford the phenylacetate (CCXVI).⁶⁷ Condensation of

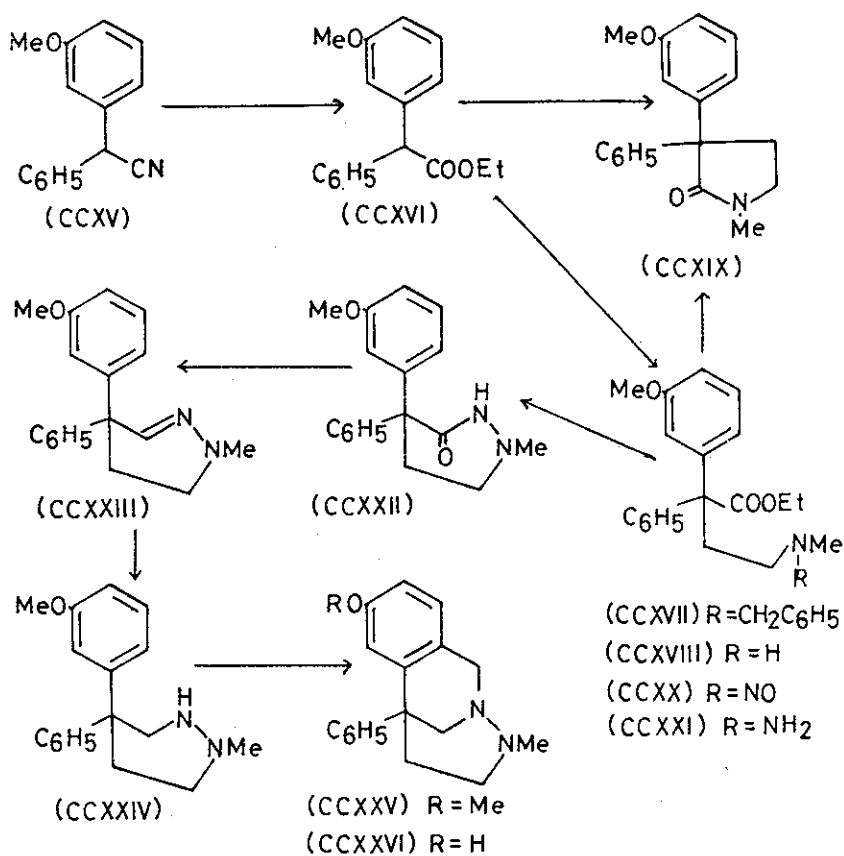
Chart 21



CCXVI with *N*-benzyl-*N*-methylaminoethyl chloride gave ethyl 2-(*N*-benzyl-*N*-methylaminoethyl)-2-(3-methoxyphenyl)phenylacetate (CCXVII) which was reductively debenzylated to afford the secondary amine (CCXVIII). On the other hand, condensation of CCXVI with *N*-methylaminoethyl chloride in the presence of sodium hydride gave 3-(3-methoxyphenyl)-1-methyl-3-phenylpyrrolidin-2-one (CCXIX) which was also obtained by heating of CCXVIII, and no formation of CCXVIII was observed.

Nitrosation of CCXVIII provided CCXX which was reduced with zinc powder in acetic acid to the 4-phenylpyridazin-3-one (CCXXII), probably via the intermediate CCXXI. The pyridazinone (CCXXII) was then reduced with lithium aluminum hydride to give the tetrahydropyridazine (CCXXIII) which was hydrogenated over platinum oxide catalyst to afford the hexahydroindolizidine (CCXXIV) followed by a Mannich reaction with formaldehyde under acidic condition to give the expected

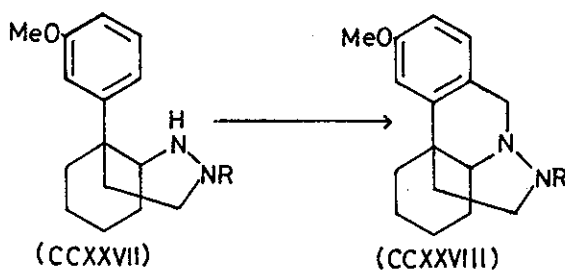
Chart 22



8-methoxy-2,3-benzodiazocine (CCXXV) whose nmr spectrum indicated that cyclization had involved the para position to the methoxy group. A similar type cyclization has been reported for the conversion of the decahydrocinnoline (CCXXVII) into the 3-methoxy-9-azamorphinan (CCXXVIII).⁷

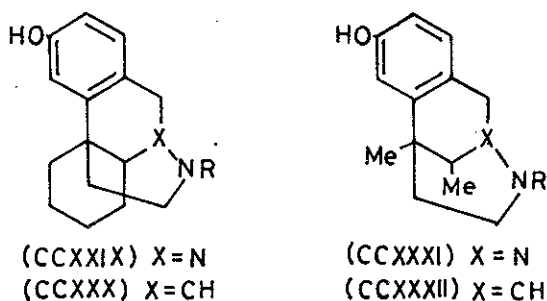
Finally, treatment of CCXXV with 47% hydrobromic acid afforded the desired phenolic base (CCXXVI).

Chart 23



5-3 8-Hydroxy-6,11-dimethyl-2,3-benzodiazocine⁶⁸: Recently, Kametani and co-workers⁷ reported on the synthesis of some N-alkyl derivatives of 9-azamorphinan (CCXXIX) which showed potent analgesic activity. Molecular modification of 9-azamorphinan (CCXXIX) afforded the 2,3-benzodiazocine (CCXXXI) which was expected to retain analgesic activity as was reported for the transformation

Chart 24



of the morphinan (CCXXX) into the 3-benzazocine (CCXXXII).^{1,2}

As shown in Chart 25, condensation of 3-(3-methoxyphenyl)-2-butanone (CCXXXIII)⁶⁹ with ethyl bromoacetate in the presence of sodium amide afforded a mixture of the two isomeric γ -ketoesters (CCXXXIV and CCXLI) which were not separated but hydrolyzed to the γ -ketocarboxylic acids (CCXXXV and CCXLII) followed by condensation with methylhydrazine to give 4,5-dihydro-5-(3-methoxy-

phenyl)-2,5,6-trimethylpyridazine-3(2H)-one (CCXXXVI) and 4,5-dihydro-6-(3-methoxy- α -methylbenzyl)-2-methylpyridazin-3(2H)-one (CCXLIII). The former pyridazinone (CCXXXVI) was separated from its isomer (CCXLIII) and reduced with lithium aluminum hydride to furnish the hexahydropyridazine (CCXXXVIII) which was readily oxidized in air to the dehydro base (CCXXXVII) and was therefore characterized as its stable hydrochloride. A similar lability to air oxidation has been observed for the hydroxyridazine-type compounds^{26,64} and also in the hydrocinnoline series.^{7a,7b}

Mannich reaction of CCXXXVIII with formaldehyde in ethanol and hydrochloric acid gave 8-methoxy-2,3-benzodiazocine (CCXXXIX) which was O-demethylated with 47 % hydrobromic acid and acetic acid to afford 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-2,3-benzodiazocine (CCXL).

Compound CCXL showed a weak analgesic activity compared with that of the 3-benzazocine (CCXXXII, R = Me).

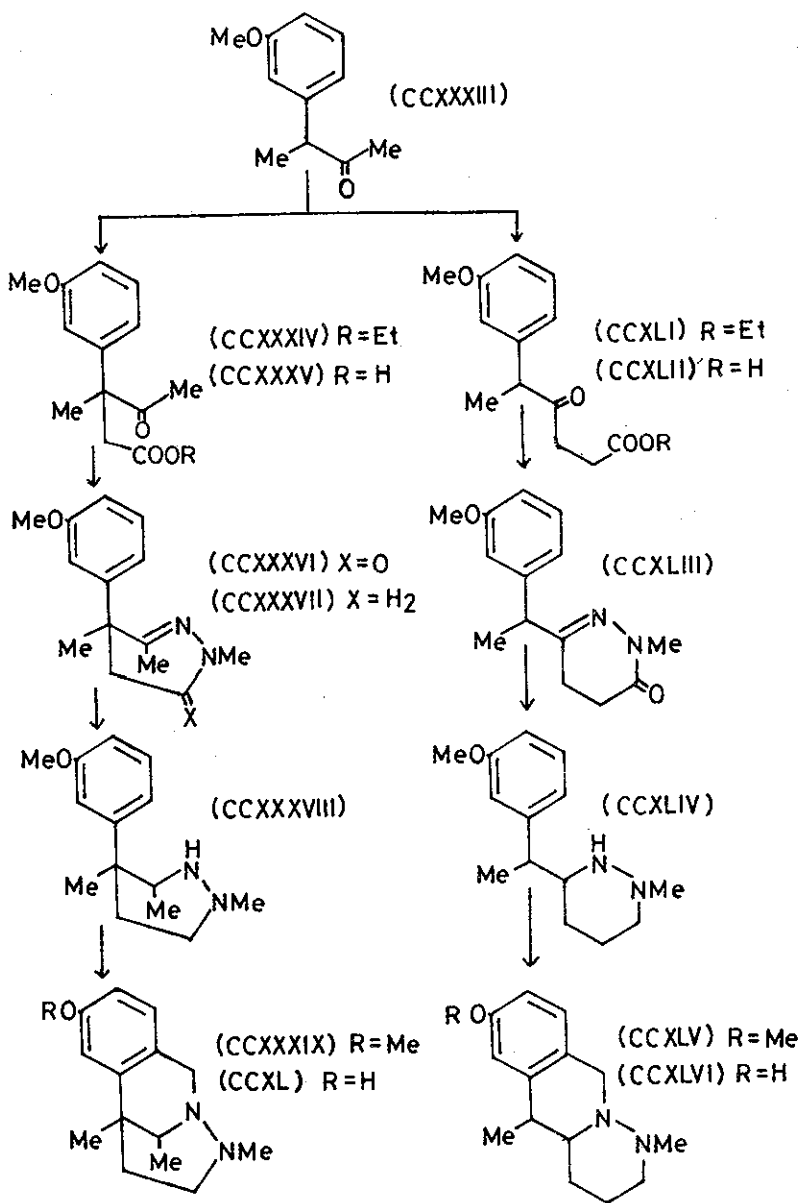
By similar procedures as the synthesis of CCXL, the isomeric pyridazinone (CCXLIII) was converted via CCXLIV and CCXLV into the 10-hydroxypyridazino-2,3-b isoquinoline (CCXLVI).

6 BECKMANN REARRANGEMENT

A synthetic method leading to two isomeric benzodiazocines by the Beckmann rearrangement was reported by Mitsuhashi and co-workers.⁷⁰

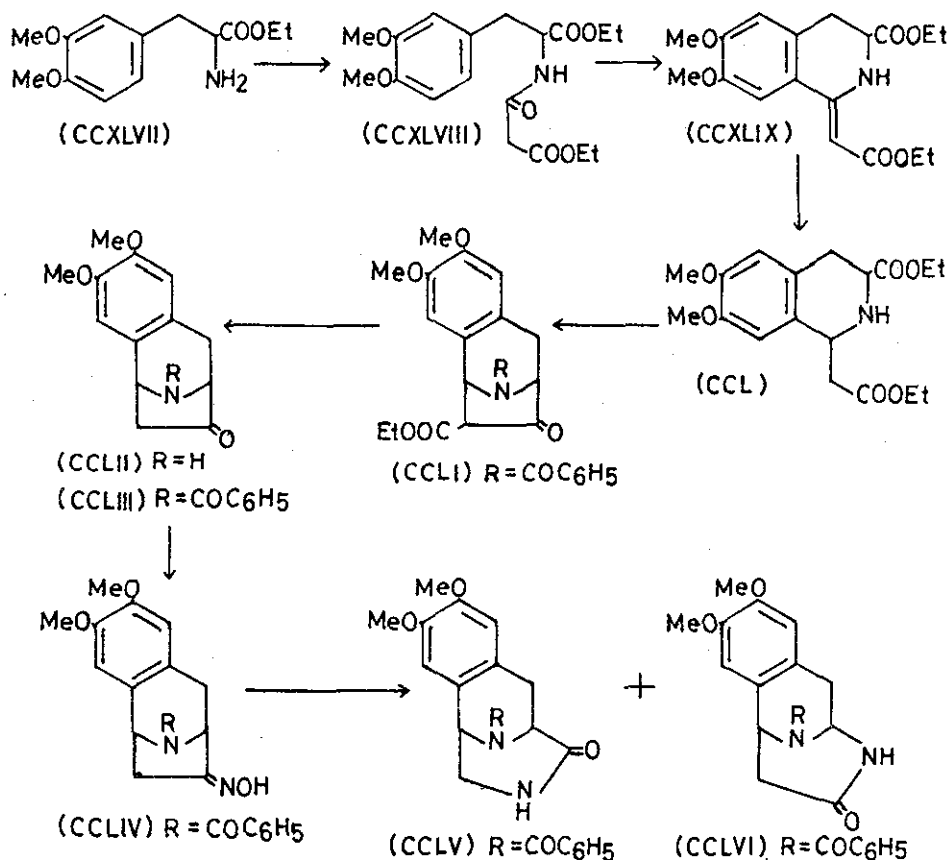
Condensation of 3-(3,4-dimethoxyphenyl)alanine ethyl ester (CCXLVII)⁷¹ with diethyl malonate followed by Bischler-Napieralski reaction of the resulting amide (CCXLVIII) with phosphorous oxychloride gave the 1-carbethoxymethylene-1,2,3,4-tetrahydroisoquinoline (CCXLIX) in which the newly created double bond is exocyclic.¹⁵ Hydrogenation of CCXLIX over Adams' catalyst gave the tetrahydroisoquinoline (CCL) whose N-benzoyl derivative was cyclized by Dieckmann con-

Chart 25



denation²⁰ to the tricyclic β -ketoester (CCLI). While the stereochemistry of CCL was not mentioned in the original paper,⁷⁰ it can be inferred to be the *cis*-isomer because of the homogeneity of CCL and the fair yield of CCLI. Treatment of CCLI with dilute hydrochloric acid afforded 4,5-dihydro-1H-1,4-imino-7,8-dimethoxybenzocyclohepten-3(2H)-one (CCLII) and its *N*-benzoyl derivative (CCLIII). Finally, conversion of CCLIII into its oxime (CCLIV) followed by Beckmann rearrangement using polyphosphoric acid afforded a mixture of 11-

Chart 26



benzoyl-1,2,3,4,5,6-hexahydro-2,6-imino-8,9-dimethoxy-3-oxo-4,11-benzodiazocine (CCLV) and its isomer CCLVI.

7 PHARMACOLOGY

The pharmacological activities of most of the benzodiazocines described in this review have been examined by one of the co-workers in Grelan Pharmaceutical Company. Some of them, particularly the 2,3-benzodiazocines bearing 8-hydroxy group, showed some analgesic activity. For example, compounds CCXXVI and CCXL had approximately one-third of the analgesic potency of the des-N analog, benzazocine (CCXXXII, R = Me) in the rat tail-flick test.⁷² Removal of the 8-hydroxy function in the benzodiazocine decreased activity and such change was also observed in the benzazocine (CCXXXII) series.¹

In addition, the stability of the compounds is an important factor in evaluating the pharmacological tests. For example, the lability of the benzodiazocines containing a N-C-N bond (see Chapter 3 and 4) to acid hydrolysis would be disadvantageous for the preservation of activity.

Generally speaking, introduction of an additional nitrogen atom into the benzazocine ring appears to have an unfavorable effect on the analgesic activity. However, until a large number of benzodiazocines (e.g. their N-alkyl derivatives) are prepared and evaluated, this conclusion can only be regarded as tentative.

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