On the Synthesis of Pyrido[3,2,1-*kl*]phenothiazine, Quino[8,1-*bc*][1,4]benzothiazepine and their Derivatives

P. Catsoulacos* and D. Catsoulacos

University of Patras, School of Health and Sciences, Department of Pharmacy,
Laboratory of Pharmaceutical Chemistry,
Patra, Greece

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This review article comprises tetracyclic rigid analogues of phenothiazine and dibenzothiazepine derivatives. In order to discover new useful drugs, the side chain of the heterocyclic nucleus is incorporated into a ring forming tetracyclic compounds. The text has been divided in thirteen sections.

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Contents.

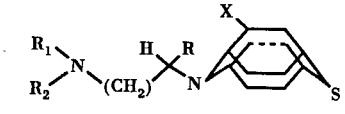
Introduction.

Medicinal agents containing the phenothiazine nucleus, such as phenergan and chloropromazine, drastic in allergic and psychiatric conditions and the dibenzothiazepine nucleus such as clothiapine and metiapine [1] as major tranquilizers, have suggested the extension on the synthesis of this type of compounds with the aim to discover new active pharmacologically, compounds with less side effects.

The physiological properties of phenothiazine and dibenzothiazepine nucleus are dependent mainly of three factors:

a. Various side chains, enhance or detract from activity [2]. The most changes in pharmacological properties involve extension of the side chain that separate the nitrogen of the nucleus from the nitrogen of the side chain.

It should be noted that a certain degree of free rotation of the side chain is necessary. The bulkiness of the R group restricts rotation resulting in less pharmacologically active compounds, while derivatives with a substituent at 2-carbon (R) of the side chain is optically active and the *levo* isomer is by far the more active isomer of the enantiomorphic pair.

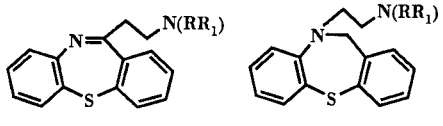


According to hypothesis of Pfeiffer [3], the amount of structural specificity of any given point in a biological active molecule is in proportion to the ratio of activities of the optical isomers.

b. The nature of the substituent X in the 2 position of the nucleus, which influence the resonance forms of the ring system [3].

c. The lack of the coplanarity of the heterocyclic system [4]. In the phenothiazine nucleus the ring which contains two heteroatoms is in the shape of boat.

The pharmacological properties of phenothiazine are maintained in a compound that contains an extra atom on the nitrogen bridge, namely dibenzothiazepines, which have similar physiological properties as the phenothiazines.



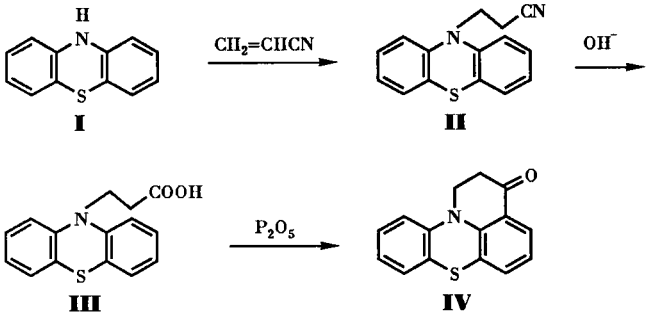
The discovery and clinical acceptance of phenothiazine compounds and the relative chemical accessibility of this group of compounds had led to intensive exploration of dibenzothiazepine.

For extensive reviews of the synthesis [5,6], pharmacology, chemical structure of phenothiazines [3] and dibenzothiazepines, see papers [7,8].

The incorporation of the alkylamino chain present on the heterocyclic nitrogen into a fourth ring, could effect pharmacologically important structural features of the molecules, such as the rotational freedom of the side chain or the stereochemistry of the phenothiazine and dibenzothiazepine ring system and may result in derivatives with interesting properties.

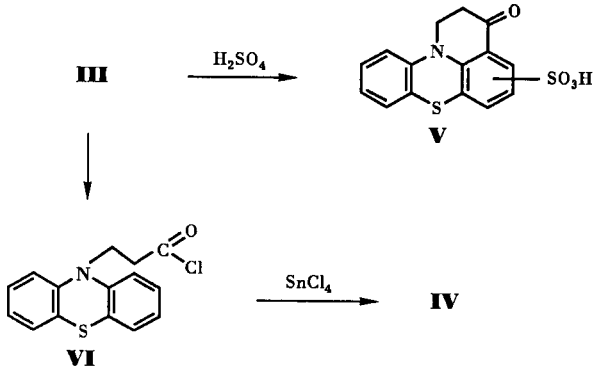
In this review article we will discuss the synthesis, physicochemical and physiological properties of pyrido[3,2,1-*c*]phenothiazine, dibenzo[*c,jk*]pyrido[2,1-*c*]thiazepine and their derivatives, using as substrates the phenothiazine and dibenzothiazepine nucleus.

2,3-Dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazines.

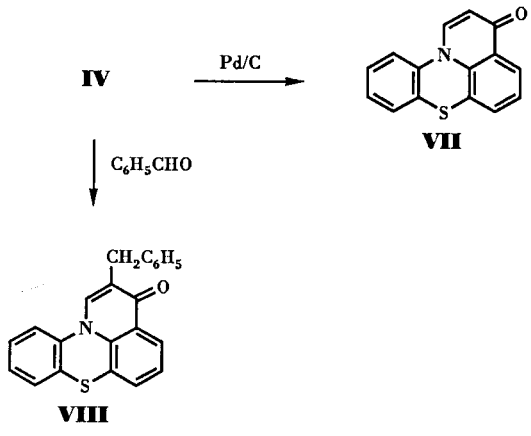


Smith and co-workers [9] have effected the synthesis of β-(10-phenothiazyl)propionic acid (**III**) *via* hydrolysis of the cyanoethylation product of phenothiazine, β-(10-phenothiazyl)propionitrile (**II**). Subsequent cyclization of the substituted propionic acid derivative readily provided 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (**IV**).

An adaptable method for the synthesis of ketone **IV** was developed by Godefroi and Wittle [10] using β-(10-phenothiazinyl)propionyl chloride and catalyst, dimethylcadmium or tin(IV) chloride. The action of warm sulfuric acid resulted in cyclization but this was concomitant with the introduction of a sulfonic acid group into the nucleus.



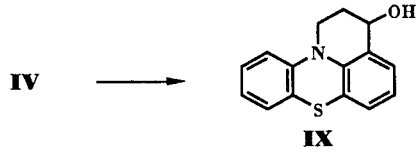
The ketone **IV** may be dehydrogenated with palladium-charcoal to 3*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one (**VII**), while condensation of **IV** with benzaldehyde gives 2-benzyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**VIII**) [11] and not the benzylidene compound suggested by Mackie and Coulter [12].



The ultraviolet spectra of 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one (**IV**) is compared with its dehydrogenated product **VII** and with its condensation product with benzaldehyde **VIII**, their similarity leaves little doubt that the ring has become fully conjugated.

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-ol.

It has been shown that ketone **IV** was reduced to 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-ol (**IX**) with sodium borohydride in wet dioxane [11]. The latter compound has also been prepared by reduction of ketone **IV** with lithium aluminum hydride in ether [10].

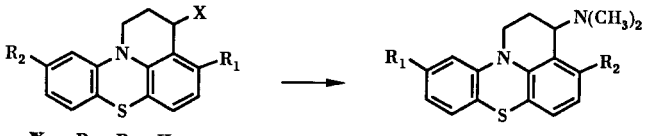


The *in vivo* reduction of ketone **IV** by *Rhizopus arrhizus* Fisher is due to a NADPH-dependent alcohol dehydrogenase.

The bioconversion product **IX** displayed optical activity $[\alpha]_{\Delta}^{20} = -32°$ while the alcohol resulting from chemical reduction was racemate [13].

Synthesis of 2- or 3-Amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]-phenothiazine and their Derivatives.

After Michael addition of acrylonitrile to phenothiazine or to 2-chlorophenothiazine, the nitrile formed was converted to the methyl ester, followed by hydrolysis. The ring closure of the carboxylic acid with zinc chloride in acetic acid [14] produces 4- and 10-chloroisomers while were separated by repeated fractional crystallization or with preparative hplc [15-16].

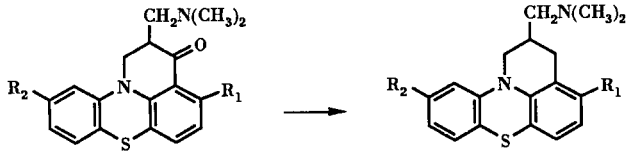


X, $R_1 = R_2 = H$
Xa, $R_1 = H, R_2 = Cl$
Xb, $R_1 = Cl, R_2 = H$
X = OH, Br

XIa, $R_1 = R_2 = H$
XIb, $R_1 = H, R_2 = Cl$
XIc, $R_1 = Cl, R_2 = H$

The structures of compounds **Xa** and **Xb** were confirmed by nmr spectroscopy.

The pyridophenothiazine **X** (X = Br) was obtained by reduction of the ketone, conversion to the bromide with phosphorus tribromide followed by substitution with dimethylamine [15-16].



XII, $R_1 = R_2 = H$
XIIa, $R_1 = H, R_2 = Cl$
XIIb, $R_1 = Cl, R_2 = H$

XIII, $R_1 = R_2 = H$
XIIIa, $R_1 = H, R_2 = Cl$
XIIIb, $R_1 = Cl, R_2 = H$

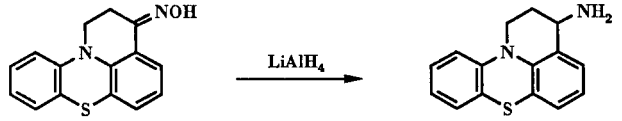
The aminoketone **XII** was prepared with a variant of Mannich reaction [16], using *N,N*-dimethyl(methylene)-ammonium chloride in acetonitrile.

In order to reduce the aminoketone diborane was employed.

These amino compounds did not show neuroleptic activity from the pharmacological data [16].

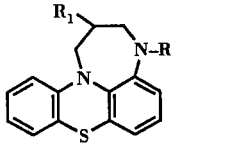
The concept to design and to synthesize compounds with antiallergic, psychotherapeutic, antihistaminic activity and others is due to the similar structure of useful drugs such as 3-(10-phenothiazinyl)propylamine.

In 1956 Godefroi and Wittle [10] reported that oxime **XIV** has been reduced to the corresponding amine **XV** by means of lithium aluminum hydride.



XIV **XV**

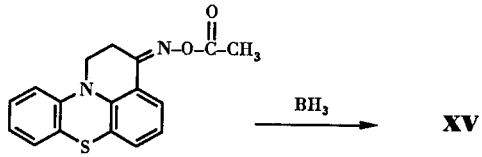
In 1958 Harfenist and Magnien [17] showed that the reduction of oxime **XIV** has produced the Beckmann rearrangement product, namely homopiperazino[3,2,1-*kl*]phenothiazine (**XVI**).



XVI, $R = R_1 = H$
XVIa, $R = C_2H_5, R_1 = H$
XVIb, $R = H, R_1 = C_2H_5$

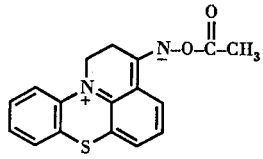
The latter was converted to the amide with acetic anhydride, which upon reduction with lithium aluminum hydride gave 4-ethyl homopiperazino[3,2,1-*kl*]phenothiazine (**XVIa**). The same authors have used Bouveault-Blanc method for the preparation of 3-amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine (**XV**), but the product obtained was contaminated by an impurity. They have succeeded in preparing of amine **XV** using the Leuckart reaction.

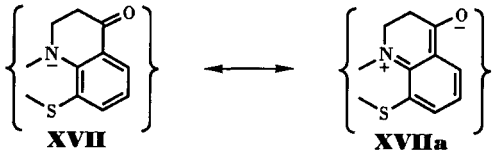
Since it is known that oxime acetates can be reduced by diborane to the corresponding amines [18-19], the reduction of oxime acetate **XVII** into the amine **XV** by diborane was attempted.



XVII

The unsuccessful reduction even with a prolonged reflux temperature is due to the existence of a charge separated resonance from, which weakens the double bond character of the C=N bond and inhibits hydride transfer from BH_3 to this functional group.



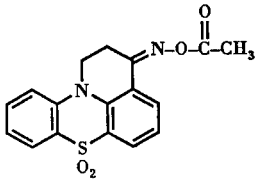


XVII **XVIIa**

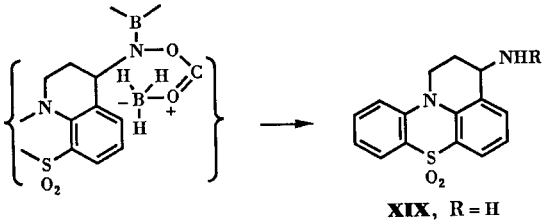
VanAllan *et al.* [11] have provided spectroscopic evidence for the existence of charge separated forms (**XVII** < – > **XVIIa**) in ketones of analogous to **XVII** structures of benzologs of phenothiazine. Evidently, the oxime acetate function is expected to exert an even more power-

ful pull on the electrons and further promote the formation of charge-separated resonance forms.

When sulfur is present as a sulfone its strong inductive effect exerts a powerful pull on the electrons of the heterocyclic nitrogen and inhibits the formation of charge-separated resonance forms. The C=N bond retains its double bond character and reduction of the oxime acetate may proceed by the well established mechanism [18] given in the following figure.

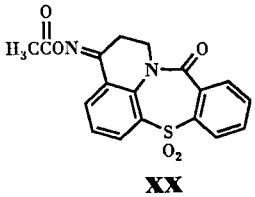


XVIII

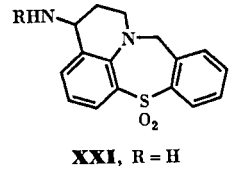


XIX, R = H

In accordance to the above, after 20 hours of reflux of **XVIII** with BH_3-THF and subsequent basic hydrolysis of the reaction mixture, gave the desired amine **XIX** (R = H) in high yield and the amide (R = $COCH_3$) after acetylation [20]. In addition a dihydrodibenzothiazepine derivative of related structure, bearing oxidized sulfur as well, the 7,7-dioxo-1,2-dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*]-[1,4]thiazepin-3,12-dione oxime acetate (**XX**) [21] was reduced to the corresponding amine **XXI** in high yield [20] (simultaneous reduction of the tertiary amide group to tertiary amine took place) [22].

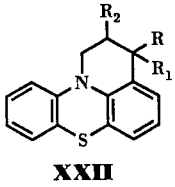


XX

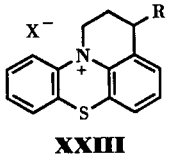


XXI, R = H
R = CH_3CO

Formation of pyrido[3,2,1-*kl*]phenothiazinium Salts and 1,2-Dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazines.



XXII



XXIII

Sunagawa and Ichii [23] reported the synthesis and identification of 3-substituted pyrido[3,2,1-*kl*]phenothiazinium salts **XXIII** by treatment of 3-methyl or 3-phenyl-1,2-dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazines with concentrated hydrochloric acid in acetic acid.

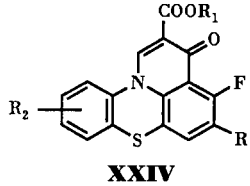
The delicate work of Martin and co-workers [24], showed that 1,2-dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazines (**XXII**): R_1 = OH, R_2 = H, R = CH_3, C_6H_5 and 1*H*-pyrido[3,2,1-*kl*]phenothiazines (R_1R_2 = bond) undergo acid transfer to form pyrido[3,2,1,-*kl*]phenothiazinium salts **XXIII** and 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazines (**XXII**, R_1 = R_2 = H).

Reduction with sodium borohydride of 3-methyl or 3-phenylpyrido[3,2,1-*kl*]phenothiazinium salts produces 3-methyl or 3-phenyl-1*H*-pyrido[3,2,1-*kl*]phenothiazines.

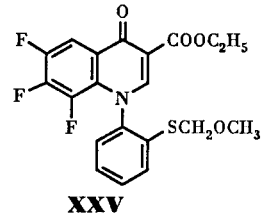
In the presence of proton source, sodium borohydride reduction of pyrido[3,2,1-*kl*]phenothiazinium fluoroborate or 3-chloropyrido[3,2,1-*kl*]phenothiazine, gives 1,2-dihydro-3*H*-pyrido[3,2-*kl*]phenothiazine, while 1*H*-pyrido[3,2,1-*kl*]phenothiazine is formed in aprotic solvents with pyridine present.

3*H*-Pyrido[3,2,1-*kl*]phenothiazine-2-carboxylates.

In 1985 Abbott Laboratories [25-26] have synthesized compounds of the general structure **XXIV** as bactericidal, (R = unsubstituted, substituted, saturated, heterocyclic; R_1 = H, protective group; R_2 = H, alkyl, haloalkyl, hydroxyalkyl, carboxyl, cyano, halo, amino, nitro, methylenedioxy).



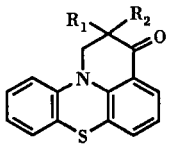
XXIV



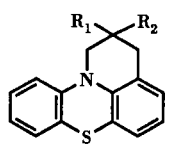
XXV

The compound **XXIV** was synthesized from 2,3,4,5-tetrafluorobenzoic acid which was converted into its acid chloride and condensed with succinic ethyl ester to produce 2,3,4,5-tetrafluorophenylacetoacetic ethyl ester. The latter was treated with ethyl orthoformate and 2-aminophenyl thioether and cyclized by heating with sodium hydride to produce phenylquinolinecarboxylate **XXV**. The thioether group was cleaved with boron trichloride and the compound cyclized with sodium hydride to give **XXIV**, which was saponified and condensed with piperazine derivative **XXIV** (R = 1-piperazinyl, R_1 = R_2 = H).

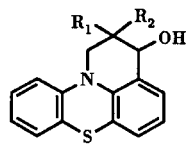
Reduction of 1,2-Dihydroketo-3*H*-pyrido[3,2,1-*kl*]phenothiazine Derivatives [27].



IV, $R_1 = R_2 = H$
XXVIa, $R_1 = H$, $R_2 = SC_6H_5$
XXVIb, $R_1 = R_2 = SC_6H_5$
XXVIc, $R_1 = H$, $R_2 = COOC_2H_5$
XII, $R_1 = H$, $R_2 = CH_2N(CH_3)_2$

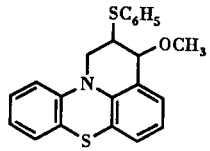


X, $R_1 = R_2 = H$
XXVIIa, $R_1 = H$, $R_2 = SC_6H_5$
XXVIIb, $R_1 = R_2 = SC_6H_5$
XXVIIc, $R_1 = H$, $R_2 = CH_2OH$
XIII, $R_1 = H$, $R_2 = CH_2N(CH_3)_2$



IX, $R_1 = R_2 = H$
XXVIII, $R_1 = H$, $R_2 = SC_6H_5$
XXVIIIa, $R_1 = R_2 = SC_6H_5$
XXVIIIb, $R_1 = H$, $R_2 = CH_2OH$
XXVIIIc, $R_1 = H$, $R_2 = CH_2N(CH_3)_2$

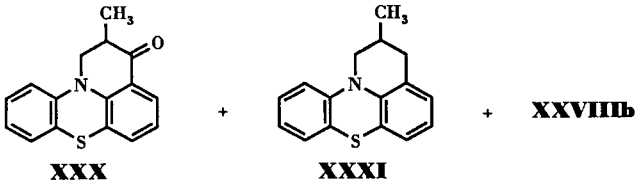
Diborane reduction of **IV** affords **X**, while aminoketone **XII** is reduced to **XXVIIIc**. Reduction of dithiophenyl ketone **XXVIb** with borane gave a partial reduction product, the alcohol **XXVIIIa**, with trace of hydrocarbon **XXVIIIb**. The reduction of **XXVIa** produces **XXVIII** as a major product and **XXVIIa**, **XXIX** as minor ones.



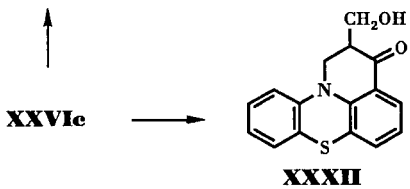
XXIX

The formation of compound **XXIX** is due to the decomposition of borane complex with methanol.

Reduction of **XXIVc** with tenfold excess of aluminum hydride produces **XXX**, **XXXI** and **XXVIIIb**.



XXX + **XXXI** + **XXVIIIb**

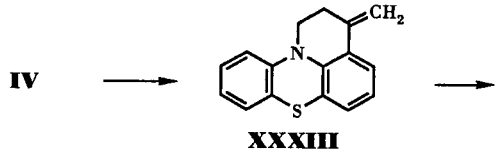


XXVIc → **XXXII**

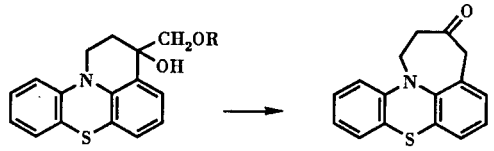
The alcohol **XXXII** was obtained with stoichiometric amount of aluminum hydride.

The reduction of 1,2-dihydro-dimethylaminomethyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**XII**) with aluminum hydride produces **XIII** and **XXVIIIc** as a minor product.

Synthesis of 1,2,3,4-Tetrahydroazepino[3,2,1-*kl*]phenothiazine-4-one, 1,2,3,4-Tetrahydroazepino[3,2,1-*kl*]phenothiazine-3-one and 3-Dimethylamino-1,2,3,4-tetrahydroazepino[3,2,1-*kl*]phenothiazine.



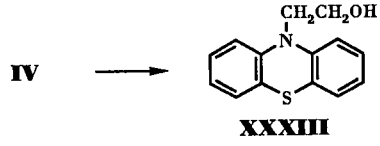
IV → **XXXIII**



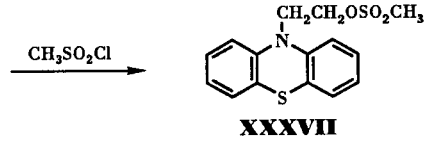
XXXIV, R = H
XXXIVa, $R = SO_2C_6H_4CH_3$

XXXV

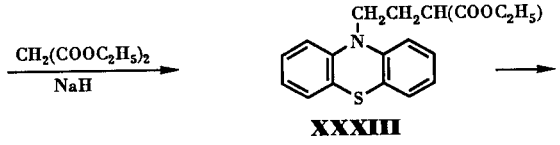
The 1,2-dihydro-3-methylidenyl-3*H*-pyrido[3,2,1-*kl*]-phenothiazine (**XXXIII**) was obtained by the action of methyltriphenylphosphonium bromide on ketone **IV** and in the presence of phenyl lithium. Compound **XXXIII** was reacted with osmium tetroxide in pyridine and the mixture treated with pyridine-sodium bisulfite to produce



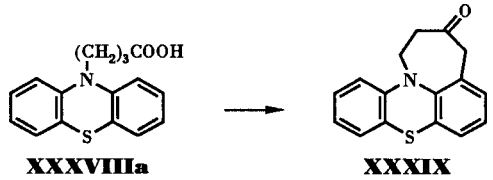
IV → **XXXIII**



XXXVII



XXXIII



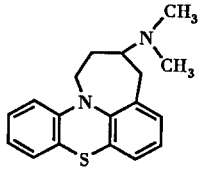
XXXVIIIa → **XXXIX**

1,2-dihydro-3-hydroxy-3-hydroxymethyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**XXXIV**). The glycol was converted into the unstable monotosylate **XXXIVa** which rearranged to the desired compound **XXXV**, after chromatography on neutral alumina [28].

The tetrahydroazepino[3,2,1-*kl*]phenothiazine-4-one (**XXXIX**) was obtained by cyclization of phenothiazine-10-butanoic acid **XXXVIIIa** [29].

Using as starting material compound **XXXIX**, a rigid analogue of promazine, namely, 3-(dimethylamino)-1,2,3,4-tetrahydroazepino[1,2,3-*kl*]phenothiazine (**XL**) was obtained by reductive amination [30].

The X-ray crystallographic study revealed that the seven member ring exist as a half chair form, while the amino function is in an equatorial position.



XL

This analogue of promazine was approximately one-half as active as promazine as an inhibitor of [^{3}H]spiperone binding in rat corpus striatal homogenates.

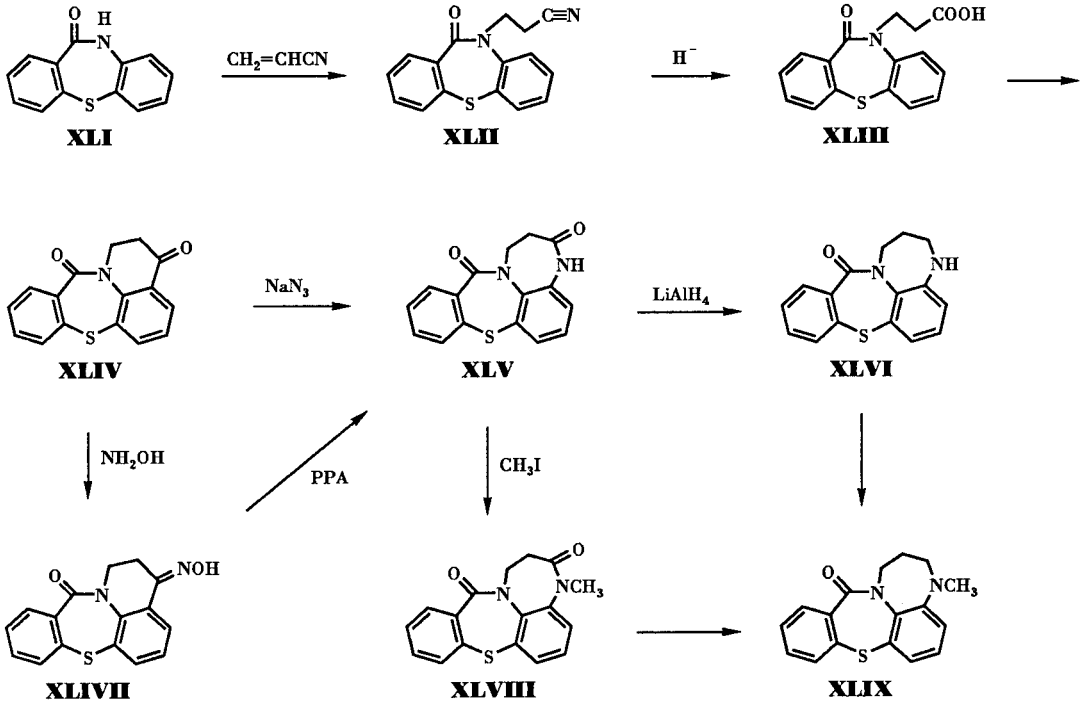
Electron Impact Promoted Mass Spectral Fragmentation of some Pyrido[3,2,1-*kl*]phenothiazines.

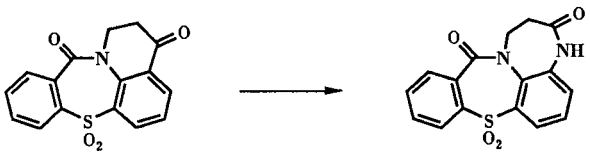
Vishwakarma and Martin [31] have described the mass spectral fragmentation pattern of the 2-, 3-, 2,2- and 2,3-substituted pyrido[3,2,1-*kl*]phenothiazines. From this study they have concluded that the initial major fragmentations occur in the pyrido ring leaving phenothiazine moiety intact.

Synthesis of 1,2-Dihydro-3*H*-dibenzo[*c,kj*]pyrido[2,1-*c*]-1,4-thiazepin-3,12-dione its Dioxide-7,7 and their Derivatives.

Cyclization of 3-[10-(11-oxodibenzo[*b,f*]-1,4-thiazepinyl]-propionic acid (**XLIII**) (obtained by hydrolysis of 10-(β-cyanoethyl)dibenzo[*b,f*][1,4]thiazepin-11-one (**XLII**) with concentrated hydrochloric acid) with phosphorus pentoxide afforded 1,2-dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*][1,4]-thiazepin-3,12-dione (**XLIV**). The Schmidt reaction of **XLIV** gave 1,2,3,4-tetrahydrodibenzo[*c,kl*]-1,4-diazepino-[2,1-*c*]-1,4-thiazepin-3,13-dione (**XLV**) and subsequent methylation of **XLV** gave **XLVIII**. The latter was reduced with lithium aluminum hydride to 4-methyl-1,2,3,4-tetrahydrodibenzo[*c,kl*][1,4]diazepine (**XLIX**). 3-Hydroxyimino-1,2-dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*][1,4]thiazepin-12-one (**XLVII**) produced compound **XLV** [32] by a Beckmann rearrangement.

Under similar reaction conditions, the 1,2-dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*]thiazepin-3,12-dione 7,7-dioxide (**L**), afforded the 1,2,3,4-tetrahydrodibenzo[*c,kl*][1,4]thiazepin-3,13-dione 8,8-dioxide (**LI**) [33].





L LI

Pyrrolo[3,2,1-*kl*]phenothiazine.

Pyrrolo[3,2,1-*kl*]phenothiazine is prepared by cyclization of phenothiazine-10-acetaldehyde with polyphosphoric acid in chloroform [34].

Martin and his co-workers [35] cyclized phenothiazine-10-acetaldehyde in high yield at room temperature using molecular sieves in toluene.

LII LIII

Hollins and Pinto [34] have investigated some electrophilic substitution reactions of **LIII**, such as Mannich condensation and the Vilsmeier formylation, in which 2-substituted derivatives of **LIII** could be isolated. Martin and co-workers [36] reported the lithiation of pyrrolo[3,2,1-*kl*]phenothiazine and subsequent reactions of the lithio intermediate giving 1- and 10-mono and 1,10-disubstituted derivatives.

Construction of the pyrido[3′,4′:4,5]pyrrolo[3,2,1-*kl*]-phenothiazine ring system *via* selective metallation of a 2-substituted pyrrolo[3,2,1-*kl*]phenothiazine has been effected [37].

Assignment of ^{1}H nmr spectra of pyrrolo[3,2,1-*kl*]phenothiazine has been reported by Martin and co-workers [38].

Conclusion.

The lack of the coplanarity of the tricyclic heterocyclic nucleus in phenothiazine and dibenzothiazepine and a certain degree of free rotation of the side chain is necessary for activity.

The rigid molecules of tetracyclic compounds of pyrido-[3,2,1-*kl*]phenothiazine and dibenzo[*c,jk*]pyrido[2,1-*c*]thiazepine do not show pharmacological activity as do phenothiazine derivatives. This is due to the lack of the free side chain. On the other hand, in this tetracyclic system the fourth new ring in keto form **IV** exist partially in the charge separated form **XVIIa**.

Rigid molecule are the most appropriate to study the drug-receptor topography.

Further pharmacological studies of these compounds and newer groups on the fourth nucleus are warranted to refine structure activity relationships and to identify promising drugs.

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